ORIGINAL ARTICLE

Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia

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ABSTRACT

BACKGROUND

The prognosis for adults with relapsed acute lymphoblastic leukemia is poor. We sought to determine whether inotuzumab ozogamicin, an anti-CD22 antibody conjugated to calicheamicin, results in better outcomes in patients with relapsed or refractory acute lymphoblastic leukemia than does standard therapy.

METHODS

In this phase 3 trial, we randomly assigned adults with relapsed or refractory acute lymphoblastic leukemia to receive either inotuzumab ozogamicin (inotuzumab ozogamicin group) or standard intensive chemotherapy (standard-therapy group). The primary end points were complete remission (including complete remission with incomplete hematologic recovery) and overall survival.

RESULTS

Of the 326 patients who underwent randomization, the first 218 (109 in each group) were included in the primary intention-to-treat analysis of complete remission. The rate of complete remission was significantly higher in the inotuzumab ozogamicin group than in the standard-therapy group (80.7% [95% confidence interval {CI}, 72.1 to 87.7] vs. 29.4% [95% CI, 21.0 to 38.8], P<0.001). Among the patients who had complete remission, a higher percentage in the inotuzumab ozogamicin group had results below the threshold for minimal residual disease (0.01% marrow blasts) (78.4% vs. 28.1%, P<0.001); the duration of remission was longer in the inotuzumab ozogamicin group (median, 4.6 months [95% CI, 3.9 to 5.4] vs. 3.1 months [95% CI, 1.4 to 4.9]; hazard ratio, 0.55 [95% CI, 0.31 to 0.96]; P=0.03). In the survival analysis, which included all 326 patients, progression-free survival was significantly longer in the inotuzumab ozogamicin group (median, 5.0 months [95% CI, 3.7 to 5.6] vs. 1.8 months [95% CI, 1.5 to 2.2]; hazard ratio, 0.45 [97.5% CI, 0.34 to 0.61]; P<0.001); the median overall survival was 7.7 months (95% CI, 6.0 to 9.2) versus 6.7 months (95% CI, 4.9 to 8.3), and the hazard ratio was 0.77 (97.5% CI, 0.58 to 1.03) (P=0.04). In the safety population, the most frequent grade 3 or higher nonhematologic adverse events with inotuzumab ozogamicin were liver-related. Veno-occlusive liver disease of any grade occurred in 15 patients (11%) who received inotuzumab ozogamicin and in 1 patient (1%) who received standard therapy.

CONCLUSIONS

The rate of complete remission was higher with inotuzumab ozogamicin than with standard therapy, and a higher percentage of patients in the inotuzumab ozogamicin group had results below the threshold for minimal residual disease. Both progression-free and overall survival were longer with inotuzumab ozogamicin. Veno-occlusive liver disease was a major adverse event associated with inotuzumab ozogamicin. (Funded by Pfizer; INO-VATE ALL ClinicalTrials.gov number, NCT01564784.)

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An estimated 2650 adults in the United States received a new diagnosis of acute lymphocytic leukemia (ALL) in 2015; the prognosis for these patients remains poor.[1] Current therapies for adults with newly diagnosed B-cell ALL are associated with rates of complete remission of 60 to 90%.[2-9] However, many of the patients with complete remission will have a relapse, and only approximately 30 to 50% will have disease-free survival lasting 3 years or longer.[5-9] Current standard chemotherapy regimens for adults with relapsed or refractory B-cell ALL are associated with rates of complete remission of 31 to 44% when they are the first salvage therapy administered after an early relapse and 18 to 25% when they are the second salvage therapy.[10-13] Because complete remission is typically a prerequisite for subsequent allogeneic stem-cell transplantation, the low rates of complete remission associated with current chemotherapy regimens mean that few adults with relapsed or refractory B-cell ALL (5 to 30%) proceed to transplantation, which is considered to be the main goal after salvage treatment because it is the only potentially curative treatment option.[10-12,14]

The cell-surface glycoprotein CD22 is expressed in more than 90% of patients with B-cell ALL, is not shed into the extracellular matrix,[15-20] and has emerged as an attractive therapeutic target for B-cell cancers.[21-23] Inotuzumab ozogamicin (CMC-544) is a humanized anti-CD22 monoclonal antibody conjugated to calicheamicin, a cytotoxic antibiotic agent.[24-26] After the conjugate binds to CD22, the CD22–conjugate complex is rapidly internalized, and calicheamicin is released. Calicheamicin binds to the minor groove of DNA and thus induces double-strand cleavage and subsequent apoptosis.[24,26-29] A previous phase 2 study of inotuzumab ozogamicin, administered on either a weekly or a monthly schedule, for the treatment of patients with relapsed or refractory B-cell ALL showed antitumor activity.[30] Here, we present results of the ongoing, global, phase 3 INO-VATE ALL trial, which is designed to assess the clinical activity and safety of single-agent inotuzumab ozogamicin, as compared with standard intensive chemotherapy, when it is administered as the first or second salvage treatment in adults with relapsed or refractory B-cell ALL.

Methods

Trial Design and Patients

In this open-label, two-group, randomized, phase 3 trial, patients 18 years of age or older were eligible for enrollment if they had relapsed or refractory (≥5% bone marrow blasts on local morphologic analysis), CD22-positive, Philadelphia chromosome (Ph)–positive or Ph-negative ALL and were scheduled to receive their first or second salvage treatment. Additional information about eligibility criteria is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Patients were randomly assigned, in a 1:1 ratio, to receive either inotuzumab ozogamicin or the investigator's choice of standard therapy; no crossover between groups was allowed. Stratification factors at randomization were the duration of the first remission (<12 months vs. ≥12 months), the salvage-treatment phase (first vs. second), and age (<55 years vs. ≥55 years). Patients who achieved complete remission could undergo stem-cell transplantation at the investigator's discretion.

Trial Oversight

The protocol was approved by the independent ethics committee or the institutional review board at each trial center. Written informed consent was obtained in accordance with the provisions of the Declaration of Helsinki. The trial was designed through a collaboration of the sponsor (Pfizer) and the lead investigators. Pfizer collected and held the data included in this report. Generated data tables were freely accessible to all the authors, who, together with Pfizer representatives, were responsible for the analyses of the data. Two employees of Complete Healthcare Communications, who were funded by Pfizer, developed the first draft of the manuscript under the direction of the authors. All the authors contributed to the drafting and critical review of the manuscript, approved the final draft, and made the decision to submit the manuscript for publication. All the authors vouch for the accuracy of the data and analysis and the adherence of the trial to the protocol, which is available at NEJM.org.

Treatments

Patients in the inotuzumab ozogamicin group received the trial drug intravenously at a starting dose of 1.8 mg per square meter of body-surface

area per cycle; they received 0.8 mg on day 1 of each cycle and 0.5 mg on days 8 and 15. Cycle 1 lasted for 21 days and the subsequent cycles each lasted for 28 days; the patients received treatment for up to six cycles. Once a patient achieved complete remission or complete remission with incomplete hematologic recovery, the dose that was administered on day 1 of each cycle was reduced to 0.5 mg for the duration of the trial.

Patients in the standard-therapy group received the investigator's choice of one of the following three regimens: FLAG (fludarabine, cytarabine, and granulocyte colony-stimulating factor) therapy for up to four 28-day cycles (with cytarabine at a dose of 2.0 g per square meter per day on days 1 through 6, fludarabine at a dose of 30 mg per square meter per day on days 2 through 6, and granulocyte colony-stimulating factor at a dose of 5 μg per kilogram of body weight per day or at the institutional standard dose), cytarabine plus mitoxantrone for up to four 15-to-20-day cycles (with cytarabine at a dose of 200 mg per square meter per day on days 1 through 7 and mitoxantrone at a dose of 12 mg per square meter per day on days 1 through 3; for mitoxantrone, dose reduction to 8 mg was allowed on the basis of age, coexisting conditions, and previous anthracycline use), or high-dose cytarabine for up to one 12-dose cycle (at a dose of 3 g per square meter every 12 hours, or a dose of 1.5 g per square meter for patients ≥55 years of age). These three regimens are commonly used for the treatment of relapsed or refractory ALL and were chosen for the control group to provide investigators latitude to tailor the regimen to the patient's condition and treatment history and to standard practice. Modifications to the dose schedules are described in the Supplementary Appendix.

OUTCOMES

The two primary end points were complete remission (including complete remission with incomplete hematologic recovery) and overall survival. Secondary end points included safety measures, the duration of remission, progression-free survival, the rate of subsequent stem-cell transplantation, and the percentage of patients, among those who achieved complete remission, who had results below the threshold for minimal residual disease. The threshold for minimal residual disease was specified as 0.01% bone marrow blasts and was assessed at a central laboratory with the use of multicolor, multiparameter flow cytometry.

For all patients, bone marrow aspiration (or bone marrow biopsy, if clinically indicated) and a disease assessment were performed at screening; between days 16 and 28 of cycles 1, 2, and 3 and every 1 to 2 cycles thereafter; at the end-of-treatment visit; during planned follow-up visits; and as clinically indicated. Complete remission and disease progression were defined according to the modified criteria of Cheson et al.[31] (see the Supplementary Appendix). Complete remission with incomplete hematologic recovery was defined as complete remission but with an absolute neutrophil count of less than 1000 per microliter, a platelet count of less than 100,000 per microliter, or both. Definitions of overall survival, progression-free survival, and duration of remission among patients with complete remission or complete remission with incomplete hematologic recovery are provided in the Supplementary Appendix.

Adverse events (of any cause) occurring during treatment were defined as any event that occurred between the first dose and 42 days after the last dose, all treatment-related adverse events that occurred after the last dose, and all cases of veno-occlusive liver disease or the sinusoidal obstruction syndrome (of any cause) that occurred within 2 years after randomization. Veno-occlusive disease and the sinusoidal obstruction syndrome were assessed and diagnosed by the investigators and evaluated according to previously defined clinical criteria (for details, see the Supplementary Appendix).

STATISTICAL ANALYSIS

The sample size was calculated to allow adequate independent assessments of between-group differences in the rate of complete remission and in overall survival by splitting the one-sided alpha level of 0.025 evenly between the two primary end points. We calculated that a sample size of 218 patients would give the trial at least 88.5% power to detect a difference in the rate of complete remission (including complete remission with incomplete hematologic recovery) of 24 percentage points between the two groups (61% in the inotuzumab ozogamicin group vs. 37% in the standard-therapy group), at a one-sided alpha level of 0.0125. We also calculated that accrual

of at least 325 patients and 248 overall survival events would give the trial 80% power to detect an increase in overall survival of at least 50% (median, 6.45 months in the inotuzumab ozogamicin group and 4.30 months in the standard care group; hazard ratio, 0.67), at a one-sided alpha level of 0.0125. All reported P values are two-sided.

RESULTS

PATIENTS AND TREATMENT

Between August 27, 2012, and a data cutoff date of October 2, 2014 (see Fig. S1 in the Supplementary Appendix), a total of 279 patients (141 in the inotuzumab ozogamicin group and 138 in the standard-therapy group) from 18 countries underwent randomization. Of those patients, 259 (139 in the inotuzumab ozogamicin group and 120 in the standard-therapy group) received at least one dose of the assigned regimen and were included in the safety population; the remaining 20 patients underwent randomization but did not receive treatment by the cutoff date. An additional 47 patients underwent randomization after the cutoff date, for a total of 326 patients, so that additional survival data could be obtained. The prespecified requirement of at least 248 events to conduct the final analysis of overall survival was achieved on March 8, 2016, when 252 events had been observed. Therefore, survival data as of March 8, 2016, are presented for the 326 patients included in the intention-to-treat population. Data were based on an analysis of a snapshot of the trial database.

In the safety population, 369 treatment cycles were initiated in the inotuzumab ozogamicin group and 152 in the standard-therapy group (including 106 cycles of FLAG, 29 cycles of cytarabine plus mitoxantrone, and 17 cycles of high-dose cytarabine). Patients in the inotuzumab ozogamicin group received treatment for a median of 3 cycles (range, 1 to 6), and those in the standard-therapy group received treatment for a median of 1 cycle (range, 1 to 4). Fewer patients in the standard-therapy group than in the inotuzumab ozogamicin group received treatment for 2 or more cycles (22% vs. 73%), a finding that was expected.

Over the duration of the trial, in the safety population, dose reductions were more common in the inotuzumab ozogamicin group than in the standard-therapy group (in 12% vs. 3% of patients), whereas dose interruptions were less common (in 3% vs. 15% of patients). More patients in the inotuzumab ozogamicin group than in the standard-therapy group discontinued treatment because of complete remission (35% vs. 15%), whereas fewer patients in the inotuzumab ozogamicin group discontinued treatment because of treatment-resistant disease (10% vs. 40%) (see Fig. S1 in the Supplementary Appendix). Currently, no patients are actively receiving an assigned regimen.

EFFICACY

The final primary analysis of complete remission or complete remission with incomplete hematologic recovery was prespecified to include the first 218 patients (109 in the inotuzumab ozogamicin group and 109 in the standard-therapy group) who underwent randomization in the intention-to-treat population (remission-analysis population); complete remission or complete remission with incomplete hematologic recovery was assessed by an independent, central end-point adjudication committee whose members were unaware of treatment assignments. (This end point was not adjudicated in patients who underwent randomization subsequently.) The baseline patient characteristics in the remission-analysis population were well-balanced between treatment groups (Table 1). In the remission-analysis population, the rate of complete remission or complete remission with incomplete hematologic recovery was significantly higher in the inotuzumab ozogamicin group than in the standard-therapy group (80.7% [95% confidence interval {CI}, 72.1 to 87.7] vs. 29.4% [95% CI, 21.0 to 38.8], P<0.001). Thirteen patients in the standard-therapy group declined to start treatment; because the rate of complete remission or complete remission with incomplete hematologic recovery in the standard-therapy group could have been skewed by their inclusion in the denominator, we performed an as-treated analysis, which did not include these 13 patients (i.e., included 109 patients in the inotuzumab ozogamicin group and 96 patients in the standard-therapy group). In this population, the rate of complete remission or complete remission with incomplete hematologic recovery was still significantly higher in the inotuzumab ozogamicin group than in the standard-therapy

Table 1. Baseline Patient Characteristics in the Remission-Analysis Population.*

Characteristic	Inotuzumab Ozogamicin Group (N=109)	Standard-Therapy Group (N=109)
Age		
Median (range) — yr	47 (18–78)	47 (18–79)
Distribution — no. (%)		
<55 yr	66 (61)	69 (63)
≥55 yr	43 (39)	40 (37)
Male sex — no. (%)	61 (56)	73 (67)
Race — no. (%)†		
White	76 (70)	79 (72)
Asian	17 (16)	17 (16)
Black	1 (1)	2 (2)
Other	15 (14)	11 (10)
ECOG performance-status score — no. (%)‡		
0	43 (39)	45 (41)
1	50 (46)	53 (49)
2	15 (14)	10 (9)
Missing data	1 (1)	1 (1)
Salvage-treatment phase — no. (%)		
First	73 (67)	69 (63)
Second	35 (32)	39 (36)
Missing data	1 (1)	1 (1)
Duration of first remission — no. (%)		
<12 mo	62 (57)	71 (65)
≥12 mo	47 (43)	38 (35)
Previous stem-cell transplantation — no. (%)	17 (16)	22 (20)
No. of previous induction therapies — no. (%)		
1	75 (69)	69 (63)
2	33 (30)	39 (36)
3	1 (1)	1 (1)
Response to most recent previous induction therapy — no. (%)		
Complete response	78 (72)	74 (68)
Partial response	9 (8)	7 (6)
Treatment-resistant disease	17 (16)	18 (17)
Progressive or stable disease	4 (4)	10 (9)
White-cell count — per mm^3		
Median	3500	3800
Range	0–47,400	100–51,000
Peripheral-blast count§		
Median — per mm^3	175.4	39.3
Range — per mm^3	0–42,660	0–31,500
Missing data — no. (%)	1 (1)	1 (1)
No circulating peripheral blasts — no. (%)	42 (39)	48 (44)

Table 1. (Continued.)

Characteristic	Inotuzumab Ozogamicin Group (N=109)	Standard-Therapy Group (N=109)
Bone marrow blasts — no. (%)		
<50%	30 (28)	29 (27)
≥50%	77 (71)	78 (72)
Missing data	2 (2)	2 (2)
CD22 expression — no. (%)¶		
<90%	24 (22)	24 (22)
≥90%	74 (68)	63 (58)
Missing data	11 (10)	22 (20)
Karyotype — no. (%)‖		
Normal**	27 (25)	23 (21)
Ph-positive	14 (13)	18 (17)
t(4;11)-positive	3 (3)	6 (6)
Other abnormalities	49 (45)	46 (42)
Unknown or missing data	16 (15)	16 (15)

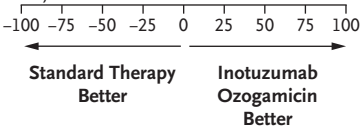
* The remission-analysis population includes the first 218 patients who underwent randomization in the intention-to-treat population.
† Data on race were provided by the trial center.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing symptoms.
§ The peripheral-blast count is the product of the number of peripheral blasts multiplied by 0.01 and the number of white cells multiplied by 1000.
¶ CD22 expression was assessed at a central laboratory.
‖ Karyotype was assessed at a local laboratory, although Philadelphia chromosome (Ph) positivity could be assessed at a central laboratory or local laboratory or through medical history.
** For 20 patients in the inotuzumab ozogamicin group and 20 patients in the standard-therapy group, the assessment of normal karyotype was based on a minimum of 20 metaphases.

group (80.7% [95% CI, 72.1 to 87.7] vs. 33.3% [95% CI, 24.0 to 43.7], P<0.001). In subgroup analyses of the remission-analysis population, performed according to stratification factors at randomization and patient characteristics at baseline, the rate of complete remission or complete remission with incomplete hematologic recovery as determined by the end-point adjudication committee was significantly higher in the inotuzumab ozogamicin group than in the standard-therapy group (P≤0.004) for all factors examined, except for baseline Ph-positive or t(4;11)-positive status (Fig. 1). In both treatment groups, most patients who achieved complete remission or complete remission with incomplete hematologic recovery did so at the end of cycle 1 (64 of 88 patients [73%] in the inotuzumab ozogamicin group and 29 of 32 patients [91%] in the standard-therapy group). Among the patients who achieved complete remission or complete remission with incomplete hematologic recovery, the percentage who had bone marrow blast results below the threshold for minimal residual disease was significantly higher in the inotuzumab ozogamicin group than in the standard-therapy group (78.4% [95% CI, 68.4 to 86.5] vs. 28.1% [95% CI, 13.7 to 46.7], P<0.001) (Table 2).

Among the patients in the remission-analysis population who had complete remission or complete remission with incomplete hematologic recovery as determined by an investigator's assessment (85 patients in the inotuzumab ozogamicin group and 31 in the standard-therapy group), with or without subsequent stem-cell transplantation, the median duration of remission was 4.6 months (95% CI, 3.9 to 5.4) in the inotuzumab ozogamicin group versus 3.1 months (95% CI, 1.4 to 4.9) in the standard-therapy group (hazard

A Rate According to Stratification Factors at Randomization

Subgroup	No. of Patients		Complete Remission		Between-Group Difference (97.5% CI)	P Value
	Inotuzumab Ozogamicin Group	Standard-Therapy Group	Inotuzumab Ozogamicin Group	Standard-Therapy Group		
			% (95% CI)		percentage points	
All patients	109	109	80.7 (72.1 to 87.7)	29.4 (21.0 to 38.8)	51.4 (38.4 to 64.3)	<0.001
Duration of first remission						
<12 mo	71	71	77.5 (66.0 to 86.5)	23.9 (14.6 to 35.5)	53.5 (37.6 to 69.4)	<0.001
≥12 mo	38	38	86.8 (71.9 to 95.6)	39.5 (24.0 to 56.6)	47.7 (25.8 to 69.0)	<0.001
Salvage-treatment phase						
First	73	73	87.7 (77.9 to 94.2)	28.8 (18.8 to 40.6)	58.9 (44.2 to 73.6)	<0.001
Second	36	36	66.7 (49.0 to 81.4)	30.6 (16.3 to 48.1)	36.1 (11.5 to 60.7)	0.002
Age						
<55 yr	66	69	80.3 (68.7 to 89.1)	31.9 (21.2 to 44.2)	48.4 (31.7 to 65.1)	<0.001
≥55 yr	43	40	81.4 (66.6 to 91.6)	25.0 (12.7 to 41.2)	56.4 (36.1 to 76.7)	<0.001



B Rate According to Patient Characteristics at Baseline

Subgroup	No. of Patients		Complete Remission		Between-Group Difference (97.5% CI)	P Value
	Inotuzumab Ozogamicin Group	Standard-Therapy Group	Inotuzumab Ozogamicin Group	Standard-Therapy Group		
			% (95% CI)		percentage points	
All patients	109	109	80.7 (72.1 to 87.7)	29.4 (21.0 to 38.8)	51.4 (38.4 to 64.3)	<0.001
Peripheral blasts						
0	42	48	90.5 (77.4 to 97.3)	41.7 (27.6 to 56.8)	48.8 (29.9 to 67.7)	<0.001
>0 to 1000	32	35	71.9 (53.3 to 86.3)	20.0 (8.4 to 36.9)	51.9 (28.5 to 75.3)	<0.001
>1000	34	25	76.5 (58.8 to 89.3)	20.0 (6.8 to 40.7)	56.5 (32.2 to 80.7)	<0.001
Bone marrow blasts						
<50%	30	29	86.7 (69.3 to 96.2)	41.4 (23.5 to 61.1)	45.3 (20.5 to 70.1)	<0.001
≥50%	77	78	77.9 (67.0 to 86.6)	24.4 (15.3 to 35.4)	53.6 (38.4 to 68.8)	<0.001
CD22 expression						
<90%	24	24	79.2 (57.8 to 92.9)	25.0 (9.8 to 46.7)	54.2 (27.0 to 81.3)	<0.001
≥90%	74	63	82.4 (71.8 to 90.3)	36.5 (24.7 to 49.6)	45.9 (29.1 to 62.8)	<0.001
Karyotype						
Normal	20	20	95.0 (75.1 to 99.9)	30.0 (11.9 to 54.3)	65.0 (39.6 to 90.4)	<0.001
Ph-positive	14	18	78.6 (49.2 to 95.3)	44.4 (21.5 to 69.2)	34.1 (−1.8 to 70.1)	0.08
t(4;11)-positive	3	6	33.3 (0.8 to 90.6)	33.3 (4.3 to 77.7)	0.0 (−74.7 to 74.7)	1.00
Other abnormalities	49	46	85.7 (72.8 to 94.1)	26.1 (14.3 to 41.1)	59.6 (41.3 to 78.0)	<0.001
Previous stem-cell transplantation						
Yes	17	22	76.5 (50.1 to 93.2)	27.3 (10.7 to 50.2)	49.2 (17.8 to 80.6)	0.004
No	92	87	81.5 (72.1 to 88.9)	29.9 (20.5 to 40.6)	51.6 (37.4 to 65.9)	<0.001

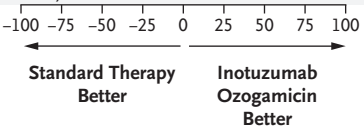


Figure 1 (facing page). Subgroup Analyses of the Rate of Complete Remission.

The rate of complete remission (including complete remission with incomplete hematologic recovery) is shown according to stratification factors at randomization (Panel A) and patient characteristics at baseline (Panel B). The analyses were performed in the remission-analysis population, which included the first 218 patients who underwent randomization in the intention-to-treat population. The two-sided P values were determined by means of the chi-square test or Fisher's exact test (if any cell count was <5). Data are missing for patients in the following subgroups: peripheral blasts (for 1 patient in each treatment group), bone marrow blasts (for 2 patients in each treatment group), CD22 expression (for 11 patients in the inotuzumab ozogamicin group and 22 patients in the standard-therapy group), and karyotype (for 16 patients in each treatment group). CD22 expression was assessed at a central laboratory. Karyotype was assessed at a local laboratory, although Philadelphia chromosome (Ph) positivity could be assessed at a central laboratory or local laboratory or through medical history. The assessment of complete remission or complete remission with incomplete hematologic recovery in patients with a normal karyotype required a minimum of 20 analyzed chromosomes.

ratio for disease progression or death, 0.55 [95% CI, 0.31 to 0.96]; P=0.03) (Fig. 2A). The duration of remission according to minimal residual disease status is shown in Figure S2 in the Supplementary Appendix. Significantly more patients proceeded to stem-cell transplantation directly after treatment in the inotuzumab ozogamicin group than in the standard-therapy group (41% [45 of 109 patients] vs. 11% [12 of 109 patients], P<0.001); more of these patients received a myeloablative conditioning regimen (71% [32 of 45 patients] in the inotuzumab ozogamicin group and 75% [9 of 12 patients] in the standard-therapy group) than a reduced-intensity conditioning regimen (29% [13 of 45 patients] and 17% [2 of 12 patients], respectively). More patients achieved complete remission or complete remission with incomplete hematologic recovery (as determined by investigator's assessment) and proceeded to stem-cell transplantation directly after treatment in the inotuzumab ozogamicin group than in the standard-therapy group (48% [41 of 85 patients] vs. 32% [10 of 31 patients], P=0.12); the duration of remission for these patients was 5.5 months (95% CI, 4.9 to 8.0) in the inotuzumab ozogamicin group versus 5.7 months (95% CI, 0.8 to not reached) in the standard-therapy group.

In the intention-to-treat survival analysis (which included 164 patients in the inotuzumab ozogamicin group and 162 patients in the standard-therapy group), progression-free survival was significantly longer in the inotuzumab ozogamicin group than in the standard-therapy group (median, 5.0 months [95% CI, 3.7 to 5.6] vs. 1.8 months [95% CI, 1.5 to 2.2]; hazard ratio for disease progression, starting new induction therapy or stem-cell transplantation without achieving complete remission, or death, 0.45 [97.5% CI, 0.34 to 0.61]; P<0.001) (Fig. 2B). Median overall survival was 7.7 months (95% CI, 6.0 to 9.2) in the inotuzumab ozogamicin group and 6.7 months (95% CI, 4.9 to 8.3) in the standard-therapy group, and the hazard ratio for death was 0.77 (97.5% CI, 0.58 to 1.03) (P=0.04); the rate of 2-year overall survival was 23% (95% CI, 16 to 30) in the inotuzumab ozogamicin group and 10% (95% CI, 5 to 16) in the standard-therapy group (Fig. 2C). The second primary objective of this trial — to show significantly longer overall survival in the inotuzumab ozogamicin group than in the standard-therapy group, at a prespecified boundary of P=0.0208 (see the Supplementary Appendix) — was not met. However, data for overall survival appeared to depart from the proportional-hazards assumption; therefore, an exploratory post hoc analysis of restricted mean survival time was applied[32] (truncation time, 37.7 months) to alternatively define the clinical benefit of inotuzumab ozogamicin. In this analysis, mean overall survival was longer in the inotuzumab ozogamicin group than in the standard-therapy group (mean [±SE], 13.9±1.10 months vs. 9.9±0.85 months; P=0.005).

SAFETY

In the safety population, in both treatment groups, the most common hematologic adverse events of any cause that occurred during treatment were cytopenias (Table S1 in the Supplementary Appendix). The percentage of patients with grade 3 or higher thrombocytopenia was lower in the inotuzumab ozogamicin group than in the standard-therapy group (37% vs. 59%); fewer patients received platelet transfusions in the inotuzumab ozogamicin group than in the standard-therapy group (64% vs. 95%; median length of transfusion, 5 days [range, 1 to 51] vs.

Table 2. Trial End Points in the Remission-Analysis Population.*

End Point	Inotuzumab Ozogamicin Group		Standard-Therapy Group		Between-Group Difference (97.5% CI)	P Value†
	no./total no.	*% (95% CI)*	*no./total no.*	*% (95% CI)*	*percentage points*	
Complete remission or complete remission with incomplete hematologic recovery						
Total	88/109	80.7 (72.1–87.7)	32/109	29.4 (21.0–38.8)	51.4 (38.4–64.3)	<0.001
Bone marrow blast results below threshold for minimal residual disease	69/88	78.4 (68.4–86.5)	9/32	28.1 (13.7–46.7)	50.3 (29.9–70.6)	<0.001
Complete remission						
Total	39/109	35.8 (26.8–45.5)	19/109	17.4 (10.8–25.9)	18.3 (5.2–31.5)	0.002
Bone marrow blast results below threshold for minimal residual disease	35/39	89.7 (75.8–97.1)	6/19	31.6 (12.6–56.6)	58.2 (31.9–84.4)	<0.001
Complete remission with incomplete hematologic recovery						
Total	49/109	45.0 (35.4–54.8)	13/109	11.9 (6.5–19.5)	33.0 (20.3–45.8)	<0.001
Bone marrow blast results below threshold for minimal residual disease	34/49	69.4 (54.6–81.7)	3/13	23.1 (5.0–53.8)	46.3 (16.2–76.4)	0.004

* The remission-analysis population includes the first 218 patients who underwent randomization in the intention-to-treat population. Confidence intervals for rates were calculated by means of the Clopper–Pearson method, and confidence intervals for between-group differences were calculated by means of the asymptotic method.

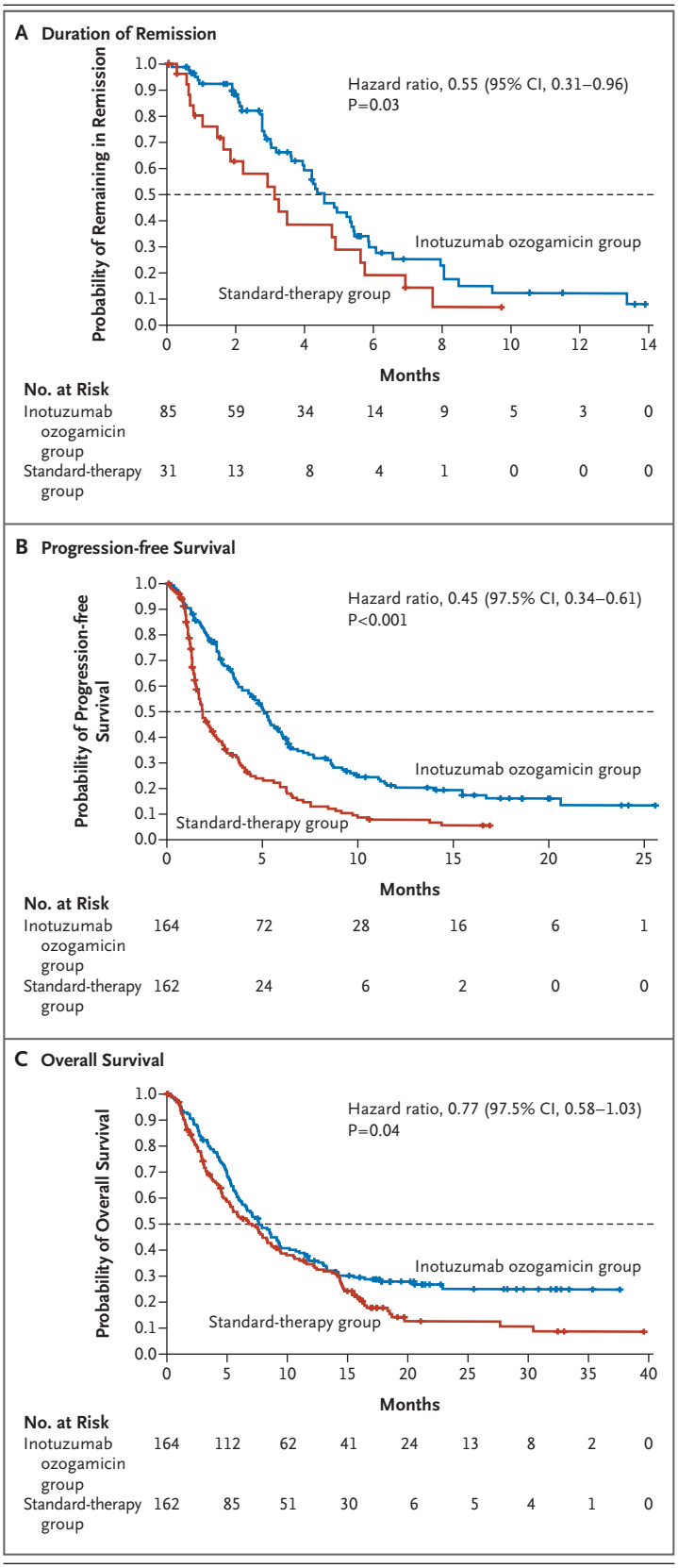
† The two-sided P values for between-group differences were determined by means of the chi-square test or Fisher's exact test (if any cell count was <5).

7 days [range, 1 to 26]). Grade 3 or higher febrile neutropenia occurred in 24% of patients in the inotuzumab ozogamicin group and in 49% of patients in the standard-therapy group. In the inotuzumab ozogamicin group, common nonhematologic adverse events that occurred during treatment included nausea (any grade, in 32% of patients; grade ≥3, in 2% of patients), headache (any grade, in 28%; grade ≥3, in 1%), and pyrexia (any grade, in 27%; grade ≥3, in 4%); in the standard-therapy group, the most common nonhematologic adverse events that occurred during treatment were nausea (any grade, in 47% of patients; grade ≥3, in 0% of patients), pyrexia (any grade, in 43%; grade ≥3, in 5%), and diarrhea (any grade, in 40%; grade ≥3, in 1%). The percentage of patients who had serious adverse events was similar in the inotuzumab ozogamicin group and the standard-therapy group (48% and 46%, respectively); febrile neutropenia was the most frequently reported serious adverse event in both treatment groups (in 12% of patients in the inotuzumab ozogamicin group and 18% in the standard-therapy group) (Table 3).

Liver-related adverse events were more common in the inotuzumab ozogamicin group than in the standard-therapy group (Table S1 in the Supplementary Appendix); the most frequent liver-related adverse events of any grade that occurred during treatment were an increased aspartate aminotransferase level (in 20% of patients in the inotuzumab ozogamicin group and 10% of patients in the standard-therapy group), hyperbilirubinemia (in 15% and 10%, respectively), and increased alanine aminotransferase level (in 14% and 11%, respectively). Cases of veno-occlusive disease were reported for up to 2 years after randomization. Veno-occlusive disease occurred more frequently in the inotuzumab ozogamicin group than in the standard-therapy group (in 11% [15 patients] vs. 1% [1 patient]). In the inotuzumab ozogamicin group, veno-occlusive disease developed during or shortly after treatment was administered in 5 patients (2 of these 5 patients

Figure 2. Duration of Remission, Progression-free Survival, and Overall Survival.

Panel A shows the probability of remaining in remission among patients who achieved complete remission or complete remission with incomplete hematologic recovery (as determined by investigator's assessment). The median duration of remission was 4.6 months (95% CI, 3.9 to 5.4) in the inotuzumab ozogamicin group and 3.1 months (95% CI, 1.4 to 4.9) in the standard-therapy group; the hazard ratio is for disease progression or death. Panel B shows the probability of progression-free survival in the two groups. The median progression-free survival was 5.0 months (95% CI, 3.7 to 5.6) in the inotuzumab ozogamicin group and 1.8 months (95% CI, 1.5 to 2.2) in the standard-therapy group; the hazard ratio is for disease progression, starting new induction therapy or stem-cell transplantation without achieving complete remission, or death. Panel C shows the probability of overall survival in the two groups. The median overall survival was 7.7 months (95% CI, 6.0 to 9.2) in the inotuzumab ozogamicin group and 6.7 months (95% CI, 4.9 to 8.3) in the standard-therapy group; the hazard ratio is for death. The analysis of duration of remission was performed in the remission-analysis population; the survival analyses were performed in the intention-to-treat population. Medians were estimated with the Kaplan–Meier method. P values were determined by means of the log-rank test with adjustment for stratification. Hazard ratios and corresponding confidence intervals were estimated by means of a Cox proportional-hazard regression analysis with adjustment for stratification. The duration of follow-up was different for each outcome.



had received a stem-cell transplant before the trial). Of the 48 patients in the inotuzumab ozogamicin group who underwent stem-cell transplantation after the trial, 10 had veno-occlusive disease after transplantation, and 3 of these 10 patients had also received a transplant before the trial. Seven of these 10 patients received defibrotide; 2 of these 7 patients had resolved disease, 4 had ongoing disease, and 1 died. Of the 20 patients in the standard-therapy group who proceeded to stem-cell transplantation after treatment, 1 had veno-occlusive disease after transplantation; no cases of veno-occlusive disease occurred during the administration of standard therapy. The median time to the development of veno-occlusive disease after transplantation in the inotuzumab ozogamicin group was 16 days (range, 3 to 39). In a multivariate analysis of baseline factors associated with the development of veno-occlusive disease after transplantation, use of a dual-alkylator conditioning regimen (in 8 patients) versus a single-alkylator conditioning

Table 3. Serious Adverse Events That Occurred during Treatment.*

Serious Adverse Event	Inotuzumab Ozogamicin Group (N=139)		Standard-Therapy Group (N=120)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)			
Any event	67 (48)	64 (46)	55 (46)	52 (43)
Febrile neutropenia	16 (12)	15 (11)	22 (18)	21 (18)
Veno-occlusive disease	15 (11)	13 (9)	1 (1)	1 (1)
Sepsis	3 (2)	3 (2)	6 (5)	6 (5)
Pyrexia	4 (3)	2 (1)	3 (2)	1 (1)
Disease progression	5 (4)	5 (4)	2 (2)	2 (2)
Pneumonia	5 (4)	5 (4)	1 (1)	0
Neutropenic sepsis	3 (2)	3 (2)	3 (2)	3 (2)
Respiratory failure	1 (1)	1 (1)	4 (3)	4 (3)
Abdominal pain	3 (2)	2 (1)	1 (1)	1 (1)
Septic shock	2 (1)	2 (1)	1 (1)	1 (1)
Escherichia sepsis	1 (1)	1 (1)	2 (2)	2 (2)
Multiorgan failure	1 (1)	1 (1)	2 (2)	2 (2)
Hyperbilirubinemia	0	0	3 (2)	2 (2)
Hypotension	0	0	3 (2)	2 (2)
Stomatitis	2 (1)	2 (1)	1 (1)	1 (1)
Bacteremia	2 (1)	2 (1)	1 (1)	1 (1)
Clostridium difficile colitis	2 (1)	2 (1)	1 (1)	1 (1)
Nausea	2 (1)	2 (1)	0	0
Influenza	2 (1)	2 (1)	0	0
Asthenia	2 (1)	2 (1)	0	0
Pancytopenia	0	0	2 (2)	2 (2)
Tumor lysis syndrome	2 (1)	1 (1)	0	0
Acute renal failure	2 (1)	1 (1)	0	0
Klebsiella infection	0	0	2 (2)	2 (2)
Fungal pneumonia	0	0	2 (2)	2 (2)

* Data are for the safety population; the data cutoff date was October 2, 2014. Serious adverse events of any cause that occurred in more than one patient in either treatment group during any treatment cycle are listed in descending order of total frequency across groups. Serious adverse events were defined as serious events that occurred between the first dose and 42 days after the last dose, all serious treatment-related adverse events that occurred after the last dose, and all serious cases of veno-occlusive liver disease or the sinusoidal obstruction syndrome (of any cause) that occurred within 2 years after randomization.

regimen (in 33 patients) was the only significant covariate (P=0.04) (Table S2 in the Supplementary Appendix).

A total of 17 grade 5 adverse events occurred during treatment in the inotuzumab ozogamicin group, and 11 occurred during treatment in the standard-therapy group; of those events, 4 in the inotuzumab ozogamicin group and 2 in the standard-therapy group were fatal and were deemed by the investigators to be treatment-related. Two treatment-related deaths due to veno-occlusive disease occurred in the inotuzumab ozogamicin group, both after post-trial transplantation.

DISCUSSION

In this phase 3 trial, treatment with inotuzumab ozogamicin was associated with a significantly higher rate of remission than was standard intensive chemotherapy in adults with relapsed or refractory B-cell ALL. Among patients who had complete remission, the percentage who had bone marrow blast results below the threshold for minimal residual disease was 2.8 times as high in the inotuzumab ozogamicin group as in the standard-therapy group (P<0.001), and more patients in the inotuzumab ozogamicin group proceeded to stem-cell transplantation after treatment (P<0.001). Progression-free survival was significantly longer in the inotuzumab ozogamicin group than in the standard-therapy group, and evidence for improved long-term survival with inotuzumab ozogamicin was seen, as well. Remission rates were significantly higher with inotuzumab ozogamicin than with standard therapy among patients with both higher (≥90%) and lower (<90%) levels of CD22 expression. The only patients among whom remission rates did not differ significantly between the two treatment groups were those with Ph-positive or t(4;11)-positive ALL. Overall, the safety profile of inotuzumab ozogamicin was consistent with that reported previously[30]; veno-occlusive disease was a major nonhematologic adverse event.

The remission rate associated with single-agent inotuzumab ozogamicin that was observed in this trial was higher than a previously reported rate of 58%,[30] possibly because the patients involved in the previous study were treated later in the disease course. The remission rate was also significantly higher than a previously reported rate with conventional chemotherapy. Newer targeted therapies have also been associated with remission rates that are higher than those reported with conventional chemotherapy.[23] For example, 69% of patients with ALL who were selected for treatment of early and refractory relapses achieved complete remission or complete remission with incomplete hematologic recovery (median duration of remission, 9 months) while receiving blinatumomab (a bispecific anti-CD19 and anti-CD3 monoclonal antibody).[33,34] Remission rates associated with blinatumomab treatment were relatively higher among patients with lower disease burden.[33] In contrast, the rates of complete remission or complete remission with incomplete hematologic recovery associated with inotuzumab ozogamicin were similar among patients with high disease burden and those with low disease burden, as assessed by the percentage of bone marrow blasts at baseline (Fig. 1B). Among children and young adults with relapsed or refractory ALL, chimeric antigen receptor–modified T-cell therapy targeting CD19 has been associated with a rate of complete remission of approximately 60 to 90%, and, among patients with complete remission, the percentage with bone marrow blast results below the threshold for minimal residual disease has been shown to be 70 to 100%.[35-37]

The observation that progression-free survival was significantly longer and the rate of 2-year overall survival was higher with inotuzumab ozogamicin than with standard therapy is consistent with the observed significantly higher remission rate. Although the results also provide evidence for longer overall survival, the second primary objective — to show significantly longer overall survival with inotuzumab ozogamicin than with standard therapy, at a prespecified two-sided boundary of P=0.0208 — was not met. However, it was noted that the data for overall survival appeared to depart from the proportional-hazards assumption, as reflected by an apparent heterogeneity in the curve for standard therapy (Fig. 2C). Because of this, an exploratory post hoc analysis of restricted mean survival time was performed,[32] which showed longer mean overall survival with inotuzumab ozogamicin than with standard therapy (P=0.005). On the basis of the apparent separation of the overall survival curves after approximately 14 months, it may be speculated that the survival benefit occurs at later time points. Separate subgroup analyses of overall survival according to patient and disease characteristics (e.g., age, salvage-treatment phase, transplantation status, and cytogenetic features) to delineate reasons underlying this apparent heterogeneity in the data for overall survival are not reported here. The post hoc analysis presented here must be considered exploratory.

Hematologic cytopenias were the most common adverse events associated with inotuzumab ozogamicin treatment. Fewer patients in the inotuzumab ozogamicin group than in the standard-

therapy group received platelet transfusions, and among those who did receive transfusions, those in the inotuzumab ozogamicin group received them for fewer days. Febrile neutropenia was less common with inotuzumab ozogamicin than with standard therapy; however, hepatic adverse events, including hyperbilirubinemia and veno-occlusive disease, were much more common with inotuzumab ozogamicin. The conditioning regimen may contribute to the risk of veno-occlusive disease, given that use of a dual-alkylator versus a single-alkylator conditioning regimen was a significant covariate. This finding is consistent with results from a previous study showing that among inotuzumab ozogamicin–treated patients undergoing stem-cell transplantation, the incidence of veno-occlusive disease was higher among those who received a dual-alkylator conditioning regimen (5 of 13 patients) than among those who received a single-alkylator conditioning regimen (1 of 21 patients).[30] In a previous study involving patients with relapsed or refractory non-Hodgkin's lymphoma, veno-occlusive disease developed in only 1 of 79 patients who received single-agent inotuzumab ozogamicin.[38] The study excluded patients who had undergone a previous allogeneic stem-cell transplantation; this suggests that inotuzumab ozogamicin therapy outside the context of stem-cell transplantation is associated with a low risk of veno-occlusive disease.

A significantly higher percentage of patients in the remission-analysis population were able to proceed to transplantation after treatment with inotuzumab ozogamicin than after standard treatment (41% vs. 11%, P<0.001). Because stem-cell transplantation is considered to be the only curative treatment option, the capacity of inotuzumab ozogamicin treatment to increase the number of patients who can proceed to transplantation after salvage therapy is encouraging.

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