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Inotuzumab Ozogamicin Versus Standard Care for Acute Lymphoblastic Leukemia

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Abstract

Background—Inotuzumab ozogamicin, an anti-CD22 antibody conjugated to calicheamicin, is active in acute lymphoblastic leukemia.

Methods—In this phase 3 trial, adults with relapsed/refractory acute lymphoblastic leukemia were randomized to inotuzumab ozogamicin or standard intensive chemotherapy. Primary endpoints were complete remission and overall survival.

Results—Primary intent-to-treat (ITT) analysis of complete remission included the first 218 (inotuzumab ozogamicin, n=109; standard, n=109) of 326 patients randomized. Complete remission rate was significantly better with inotuzumab ozogamicin (80.7% [95% CI, 72%–88%] vs 29.4% [21%–39%]; $P<0.001$), as was minimal residual disease (MRD)-negativity among responders (78.4% [68%–87%] vs 28.1% [14%–47%]; $P<0.001$); remission duration was longer (median, 4.6 [3.9–5.4] vs 3.1 [1.4–4.9] months; hazard ratio=0.55 [0.31–0.96], $P=0.034$). More

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patients proceeded to transplant with inotuzumab ozogamicin (41%) versus standard (11%; *P*<0.001). In the ITT survival analysis (n=326), progression-free survival was significantly longer with inotuzumab ozogamicin vs standard (HR, 0.45 [97.5% CI, 0.34–0.61]; *P*<0.001; median, 5.0 [95% CI, 3.7–5.6] vs 1.8 [1.5–2.2] months). The overall survival HR was 0.77 (97.5% CI, 0.58–1.03); *P*=0.04; median was 7.7 (95% CI, 6.0–9.2) vs 6.7 (4.9–8.3) months. 2-year overall survival rate was 23% (95% CI, 16%–30%) vs 10% (5%–16%). In the safety population, the most frequent nonhematologic inotuzumab ozogamicin treatment-emergent grade ≥3 adverse events were liver-related. Any grade veno-occlusive liver disease occurred in 15 (11%) patients receiving inotuzumab ozogamicin.

Conclusion—Patients receiving inotuzumab ozogamicin versus standard care achieved higher response, MRD-negativity rates, and prolonged progression-free survival and overall survival. Veno-occlusive disease was a major non-hematologic toxicity.

Keywords

acute lymphoblastic leukemia; phase 3; clinical study; efficacy; inotuzumab ozogamicin; safety

Introduction

An estimated 2650 adults in the United States were newly diagnosed with acute lymphocytic leukemia (ALL) in 2015; the prognosis of these patients remains poor.[1] Current therapies for adults with newly diagnosed B-cell ALL result in complete remission (CR) rates of 60% to 90%.[2–9] However, many of these patients will relapse and only about 30% to 50% will achieve long-term disease-free survival lasting ≥3 years.[5–9] Current standard chemotherapy regimens in adult relapsed/refractory B-cell ALL are associated with CR rates of 31% to 44% in first salvage of early relapses and 18% to 25% in second salvage.[10–13] Because CR typically is a prerequisite for subsequent allogeneic stem cell transplant, few (5%–30%) of these patients are eligible for bridging to transplant,[10–12,14] which is considered to be the main goal of postrelapse treatment as the only potentially curative treatment option.[10,11]

The cell surface glycoprotein CD22 is expressed in most (>90%) patients with B-cell ALL, is not shed into the extracellular matrix,[15–20] and has emerged as an attractive therapeutic target in B-cell malignancies.[21–23] Inotuzumab ozogamicin (CMC-544) is a humanized anti-CD22 monoclonal antibody conjugated to calicheamicin, a cytotoxic antibiotic.[24–26] Upon binding to CD22, the CD22-conjugate complex is rapidly internalized and calicheamicin is released to bind to the minor groove of DNA and induce double-strand cleavage with subsequent apoptosis.[24,26–29] A previous phase 2 study of single-dose InO administered on either a weekly or monthly schedule for the treatment of patients with relapsed/refractory B-cell ALL demonstrated antitumor activity.[30] Herein, we present results of the ongoing global, phase 3 INO-VATE ALL study, assessing the clinical activity and safety of single-agent inotuzumab ozogamicin compared with standard intensive chemotherapy in adults with relapsed/refractory B-cell ALL given as the first or second salvage treatment.

Methods

Study Design and Patients

In this open-label, 2-arm, randomized phase 3 trial (NCT01564784), eligible patients were aged ≥18 years with relapsed or refractory (≥5% bone marrow blasts based on local morphologic analysis) CD22-positive, Philadelphia chromosome (Ph)–positive or Ph-negative ALL, who were due to receive their first or second salvage treatment. See Supplementary Appendix for additional eligibility criteria. Patients were randomized (1:1) to inotuzumab ozogamicin or investigator's choice of standard therapies; no crossover between arms was allowed. Stratification factors at randomization were duration of first remission (<12 or ≥12 months), salvage treatment phase (1 or 2), and age (<55 or ≥55 years). Responders could undergo stem cell transplant at the investigator's discretion.

The protocol was approved by the Independent Ethics Committee and/or Institutional Review Board at each study center. Informed consent was obtained in accordance with the Declaration of Helsinki. The study was designed through a collaboration of the sponsor and lead investigators. The sponsor held the data included in this manuscript. Generated data tables were freely accessible to all authors, who together with sponsor representatives, were responsible for analyses. All authors vouch for data/analysis accuracy and adherence to the protocol, which is available at NEJM.org, and contributed to drafting and critically reviewing the manuscript, approving the final draft, and the decision to publish it. Editorial support for this manuscript was provided by Johna Van Stelten, PhD, and Simon Slater, PhD, of Complete Healthcare Communications, LLC, who developed the first draft under direction from the authors, and was funded by Pfizer Inc.

Treatments

Patients in the inotuzumab ozogamicin arm received a starting dose of 1.8 mg/m^2 intravenously per cycle (0.8 mg/m^2 on day 1; 0.5 mg/m^2 on days 8 and 15 of each cycle [cycle 1, 21 days; subsequent cycles, 28 days; ≤6 cycles]). Once complete remission (CR) or CR with incomplete hematologic recovery (CRi) was achieved, the day 1 dose was reduced to 0.5 mg/m^2 for the duration of the study. Patients in the standard therapy arm received (per investigator's choice) either FLAG (cytarabine 2.0 g/m^2/d on days 1–6; fludarabine 30 mg/m^2/d on days 2–6; granulocyte-colony stimulating factor 5 μg/kg/d [or per institutional standard] during a 28-day cycle [≤4 cycles]), cytarabine plus mitoxantrone (cytarabine 200 mg/m^2/d on days 1–7; mitoxantrone [Mitox] 12 mg/m^2/d on days 1–3 during a 15- to 20-day cycle [≤4 cycles; dose reduction to ≥8 mg/m^2 allowed based on age, comorbidities and prior anthracycline use]), or high-dose cytarabine (HIDAC; 3 g/m^2 every 12 hours [≤12 doses; 1.5 g/m^2 recommended for patients aged ≥55 years]). These 3 regimens are commonly used for the treatment of relapsed and refractory ALL and were chosen for the comparator arm to provide investigators latitude to tailor the regimen to the patient's condition, treatment history, and standard practice. Dose schedule modifications are detailed in the Supplementary Appendix.

Outcomes

This study has 2 primary endpoints (see *Statistical Analysis* section): (1) CR/CRi and (2) overall survival. Secondary endpoints included safety, remission duration, progression-free survival, stem cell transplant rate, and MRD rate among responders.

For all patients, marrow aspirate (or biopsies if clinically indicated) and disease assessments were performed at screening; days 16 to 28 of cycles 1, 2, and 3, then every 1 to 2 cycles; at the end-of-treatment visit; during planned follow-up visits; and as clinically indicated. CR and disease progression status were assessed using modified Cheson criteria[31] (Supplementary Appendix); CRi was defined as for CR except with absolute neutrophil count <1000/μL and/or platelets <100,000/μL. MRD-negativity was assessed as <0.01% marrow blasts and was analyzed by a central laboratory using multicolor, multiparameter flow cytometry. Definitions of duration of remission among patients with CR/CRi, progression-free survival, and overall survival are provided in the Supplementary Appendix.

Treatment-emergent adverse events (from all causes) were defined as any event occurring between the first dose and ≤42 days after last dose, all treatment-related adverse events occurring after last dose, and all veno-occlusive liver disease/sinusoidal obstruction syndrome events (any cause) occurring within 2 years after randomization. Veno-occlusive disease/sinusoidal obstruction syndrome was assessed and diagnosed by the investigators and evaluated according to previously defined clinical criteria (Supplementary Appendix).

Statistical Analysis

The sample size was calculated to adequately assess differences in CR/CRi and overall survival independently by splitting the 1-sided alpha of 0.025 evenly between the 2 primary endpoints. With 218 patients and 1-sided alpha of 0.0125, the study had ≥88.5% power to detect a difference in CR/CRi probabilities of 61% in the inotuzumab ozogamicin arm versus 37% in the standard care arm; with 248 overall survival events and 1-sided alpha of 0.0125, the study had 80% power to detect a difference in overall survival (median of 6.45 months in the inotuzumab ozogamicin arm and 4.30 months in the standard arm; hazard ratio [HR], 0.67). All reported *P* values are 2-sided.

Results

Patients and Study Treatment

A total of 279 patients (inotuzumab ozogamicin, n=141; standard, n=138) from 18 countries were randomized between August 27, 2012 and a data cutoff date of October 2, 2014 (Fig. S1), among whom 259 received ≥1 dose of study treatment and were included in the safety population (inotuzumab ozogamicin, n=139; standard, n=120). The remaining 20 patients were randomized but not treated by the cutoff date. An additional 47 patients were then randomized after this cut-off date for a total of 326 patients to obtain further survival data. The prespecified requirement for ≥248 events to trigger the final overall survival analysis was achieved on March 8, 2016 when 252 events were observed. Therefore, survival data as of March 8, 2016 are presented for 326 patients included in the ITT population. Data based on an unlocked trial database.

Among the safety population, a total of 369 treatment cycles were initiated with inotuzumab ozogamicin versus 152 with standard therapy (FLAG, n=106; cytarabine + mitoxantrone, n=29; HIDAC, n=17). Patients in the inotuzumab ozogamicin arm received a median (range) of 3 (1–6) treatment cycles versus 1 (1–4) cycle in the standard arm. Compared with inotuzumab ozogamicin, few patients received ≥2 cycles of standard therapy, as was expected (73% vs 22%).

Dose reductions were more common over the duration of study treatment with inotuzumab ozogamicin versus standard therapies (12% vs 3%), whereas dose interruptions were less common (3% vs 15%). Compared with standard therapy, more patients receiving inotuzumab ozogamicin discontinued treatment due to achieving a complete response (35% vs 15%), whereas fewer patients discontinued inotuzumab ozogamicin because of resistant disease (10% vs 40%; Fig. S1). Currently, no patients remain on active study treatment.

Efficacy

The final CR/CRi primary analysis was prespecified to include the first 218 patients randomized in the intention-to-treat population (ITT218: inotuzumab ozogamicin, n=109 and standard, n=109) and was assessed by an independent, blinded, central endpoint adjudication committee (CR/CRi in subsequently randomized patients was not adjudicated). The demographics and baseline characteristics of the ITT218 population were well-balanced across treatment arms (Table 1). In the ITT218 population, the CR/CRi rate was significantly higher with inotuzumab ozogamicin versus standard therapy (80.7% [95% CI, 72%–88%] vs 29.4% [21%–39%]; $P<0.001$). Thirteen patients randomized to standard therapy in the ITT218 population refused to start treatment; CR/CRi rate with the standard care arm would have been skewed by their inclusion in the denominator. In an “as-treated” analysis excluding these 13 patients (inotuzumab ozogamicin, n=109; standard, n=96), the CR/CRi rate was again significantly higher with inotuzumab ozogamicin (80.7% [95% CI, 72%–88%] vs 33.3% [24%–44%]; $P<0.001$). In a subgroup analysis of the ITT218 population defined by randomization stratification factors and baseline patient characteristics, CR/CRi rate per endpoint adjucation committee was significantly higher ($P\leq0.004$) with inotuzumab ozogamicin for all factors examined, except baseline Ph+ or t(4;11) karyotype (Fig. 1). In both arms, most patients achieving a CR/CRi did so at the end of cycle 1 (inotuzumab ozogamicin, n=64/88 [73%]; standard, n=29/32 [91%]). Among patients with CR/CRi, the MRD-negativity rate was significantly higher with inotuzumab ozogamicin versus standard therapy (78.4% [95% CI, 68%–87%] vs 28.1% [14%–47%]; $P<0.001$; Table 2).

Among patients in the ITT218 cohort with CR/CRi (per investigator’s assessment: inotuzumab ozogamicin, n=85; standard, n=31), with or without follow-up stem cell transplant, the median (95% CI) remission duration was 4.6 (3.9–5.4) months with inotuzumab ozogamicin versus 3.1 (1.4–4.9) with standard therapy (overall HR [95% CI], 0.55 [0.31–0.96]; $P=0.03$; Fig. 2A). Remission duration by MRD status is shown in Fig. S2. Significantly more patients proceeded to stem cell transplant directly after treatment with inotuzumab ozogamicin versus standard therapy (41% [n=45/109] vs 11% [n=12/109]; $P<0.001$); more patients received myeloablative conditioning (inotuzumab ozogamicin, 71% [n=32/45] vs standard therapy, 75% [n=9/12]) versus reduced intensity conditioning (29%

[n=13/45] vs 17% [n=2/12]). More patients achieving CR/CRi (per investigator's assessment) proceeded directly to stem cell transplant after inotuzumab ozogamicin versus standard therapy (48% [n=41/85] vs 32% [n=10/31]; *P*=0.12); the remission duration for these patients was 5.5 (95% CI, 4.9–8.0) months for inotuzumab ozogamicin versus 5.7 (0.8–not reached) months for standard therapy.

In the ITT survival analysis (inotuzumab ozogamicin, n=164; standard, n=162), progression-free survival was significantly longer with inotuzumab ozogamicin vs standard care (HR, 0.45 [97.5% CI, 0.34–0.61]; *P*<0.001; Fig. 2B), with median progression-free survival 5.0 [95% CI, 3.7–5.6] vs 1.8 [95% CI, 1.5–2.2] months. The overall survival hazard ratio was 0.77 (97.5% CI, 0.58–1.03; *P*=0.04; Fig. 2C) Median overall survival for inotuzumab ozogamicin was 7.7 [95% CI, 6.0–9.2] vs 6.7 [4.9–8.3] months for standard care; 2-year overall survival rate, 23% [95% CI, 16%–30%] vs 10% [5%–16%]; Fig. 2C). The primary objective to demonstrate significantly improved final overall survival with inotuzumab ozogamicin vs standard care was not met at prespecified boundary of *P*=0.0208. However, overall survival data appeared to depart from the proportional hazards assumption; therefore, an exploratory posthoc restricted mean survival time analysis was applied[32] (truncation time, 37.7 months) to more precisely define the clinical benefit of inotuzumab ozogamicin. This analysis demonstrated a longer mean overall survival with inotuzumab ozogamicin vs standard care (mean [SE] 13.9 [1.10] vs 9.9 [0.85] months; *P*=0.005).

Safety

Among the safety population (data cutoff: October 2, 2014), the most common all-cause and treatment-related hematologic treatment emergent adverse events in both arms were cytopenias (Table S1). The incidence of grade ≥3 thrombocytopenia was lower with inotuzumab ozogamicin versus standard therapy (37% vs 59%); fewer patients received platelet transfusions with inotuzumab ozogamicin versus standard therapy (64% vs 95%; median [range] days of transfusion, 5 [1–51] vs 7 [1–26]). Grade ≥3 febrile neutropenia occurred in 24% of patients treated with inotuzumab ozogamicin and 49% of patients treated with standard therapy. Common nonhematologic treatment emergent adverse events (all grade; grade ≥3) with inotuzumab ozogamicin included nausea (32%; 2%), headache (28%; 1%), and pyrexia (27%; 4%); most common nonhematologic treatment emergent adverse events (all grade; grade ≥3) with standard therapy were nausea (47%; 0%), pyrexia (43%; 5%), and diarrhea (40%; 1%). Overall, the number of patients experiencing serious adverse events was similar with inotuzumab ozogamicin and standard therapy (48% vs 46%) during a median of 3 versus 1 treatment cycle, respectively; febrile neutropenia was the most frequently reported serious adverse event in both arms (inotuzumab ozogamicin, 12%; standard, 18%; Table 3).

Liver toxicities were more common with inotuzumab ozogamicin versus standard therapy (Table S1) for the total duration of treatment cycles initiated (inotuzumab ozogamicin, 369 cycles; standard care, 152 cycles); the most frequent any grade liver-related treatment emergent adverse events were increased aspartate aminotransferase (inotuzumab ozogamicin, 20%; standard, 10%), hyperbilirubinemia (15%; 10%), and increased alanine aminotransferase (14%; 11%). All cases of veno-occlusive disease were reported for up to 2

years from randomization. Veno-occlusive disease occurred more frequently with inotuzumab ozogamicin compared with standard therapy (11% [n=15] vs 1% [n=1]). In the inotuzumab ozogamicin arm, 5 patients developed veno-occlusive disease during or shortly after study treatment (2 of these 5 patients received prestudy stem cell transplant). Of 48 patients in the inotuzumab ozogamicin arm who proceeded to transplant, 10 developed veno-occlusive disease after transplant (3 with prestudy transplant), 7 of whom had received defibrotide (2 cases resolved, 4 ongoing, and 1 fatal). Of 20 patients in the standard therapy arm who proceeded to transplant, 1 developed veno-occlusive disease after transplant; no cases of veno-occlusive disease occurred during standard therapy. The median (range) time to develop veno-occlusive disease after transplant in the inotuzumab ozogamicin arm was 16 (3–39) days. In a multivariate analysis of baseline factors associated with post-transplant veno-occlusive disease, alkylator conditioning regimen (dual [n=8] vs single [n=33]) was the only significant covariate (P=0.04; Table S2).

A total of 17 and 11 grade 5 treatment emergent adverse events occurred with inotuzumab ozogamicin and standard therapy, respectively, including 4 and 2 fatal adverse events deemed to be treatment-related. Two treatment-related deaths due to veno-occlusive disease occurred with inotuzumab ozogamicin (both after poststudy transplant).

Discussion

In this phase 3 trial, inotuzumab ozogamicin demonstrated a significantly higher remission rate compared with standard intensive chemotherapy in adults with relapsed/refractory B-cell ALL; more responders achieved MRD-negativity (2.8-fold increase; P<0.001); and more patients proceeded to stem cell transplant (P<0.001). Compared with standard care, inotuzumab ozogamicin also provided significantly prolonged progression-free survival and evidence for improved long-term survival. Of note, remission rates were significantly improved with inotuzumab ozogamicin versus standard care in patients with both higher (≥90%) and lower (<90%) CD22 expression levels. The only patients for whom remission rates were not significantly different between arms were those with Ph+ or t(4;11) ALL. Overall, the safety profile of inotuzumab ozogamicin is consistent with that reported previously;[30] veno-occlusive disease was a major non-hematologic toxicity. The remission rate observed in this study is higher than reported previously for single-agent inotuzumab ozogamicin (58%),[30] possibly due to patients being treated later in the disease course in the prior study. The remission rate is also significantly higher than reported previously for conventional chemotherapy. Newer targeted therapies have also demonstrated higher remission rates than reported with conventional chemotherapy.[33] For example, 69% of patients with ALL selected for early and refractory relapses achieved CR/CRi (median remission duration, 9 months) while receiving blinatumomab (a bispecific anti-CD19/CD3 monoclonal antibody).[34,35] Remission rates associated with blinatumomab were relatively higher among patients with lower disease burden.[34] In contrast, observed CR/CRi rates associated with inotuzumab ozogamicin were similar for patients with high versus low disease burden as assessed by baseline marrow blasts (Fig. 1B). Chimeric antigen receptor–modified T-cells targeting CD19 are also associated with high CR (~60%–90%) and MRD negativity rates (70%–100% of responders) among pediatric and young adult patients with relapsed/refractory ALL.[36–38]

The observation that progression-free survival was significantly longer and the 2-year overall survival rate was higher with inotuzumab ozogamicin versus standard care is consistent with the observed significantly higher response rate. Although the results also provide evidence for longer overall survival, the second primary objective of demonstrating a significant improvement in final overall survival with inotuzumab ozogamicin vs standard care was not met at the prespecified 2-sided *P*-value boundary of 0.0208. However, it was noted that overall survival data appeared to depart from the proportional hazards assumption, as reflected by an apparent heterogeneity in the curve for standard care (see Fig. 2C). Given this, an exploratory posthoc restricted mean survival time analysis was performed,[32] which demonstrated prolonged mean overall survival with inotuzumab ozogamicin versus standard care (*P*=0.005). Based on the apparent separation of the overall survival curves after ~14 months, it may be speculated that the survival benefit occurs at later time points. Separate subgroup analyses of overall survival by patient and disease characteristics (eg, age, salvage status, transplant status, cytogenetics) are planned to delineate reasons underlying this apparent heterogeneity in the overall survival data.

Hematologic cytopenias were the most common toxicities associated with inotuzumab treatment. Fewer patients in the inotuzumab ozogamicin arm received platelet transfusions; those who did, received fewer days of transfusion. Febrile neutropenia was less common with inotuzumab ozogamicin; however, hepatic toxicities, including hyperbilirubinemia and veno-occlusive disease, were much more common. The conditioning regimen may make a contribution to the risk of veno-occlusive disease given that dual versus single alkylator conditioning was a significant covariate. Consistent with this, a previous study reported a higher incidence of veno-occlusive disease in inotuzumab ozogamicin-treated patients undergoing stem cell transplant after receiving a dual alkylator conditioning regimen (n=5/13) compared with a single alkylator regimen (n=1/21).[30] In a previous study of patients with relapsed/refractory non-Hodgkin lymphoma, only 1 of 79 receiving single-agent inotuzumab ozogamicin developed veno-occlusive disease.[39] The study excluded patients with prior allogeneic stem cell transplant, suggesting that inotuzumab ozogamicin therapy outside the context of stem cell transplant carries a low risk of veno-occlusive disease.

A significantly greater proportion of patients in the ITT218 population were able to proceed to transplant after inotuzumab ozogamicin compared with standard treatment (41% vs 11%; *P*<0.001). Given that stem cell transplant is considered the only curative treatment option, the ability of inotuzumab ozogamicin treatment to increase the number of patients able to bridge to transplant after salvage therapy is encouraging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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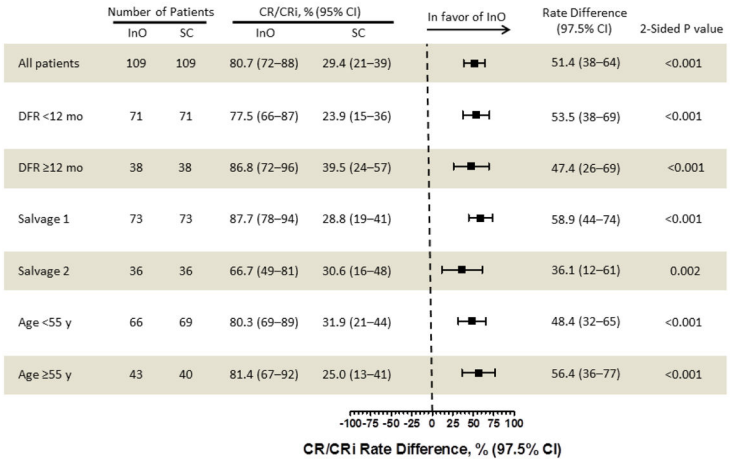
A



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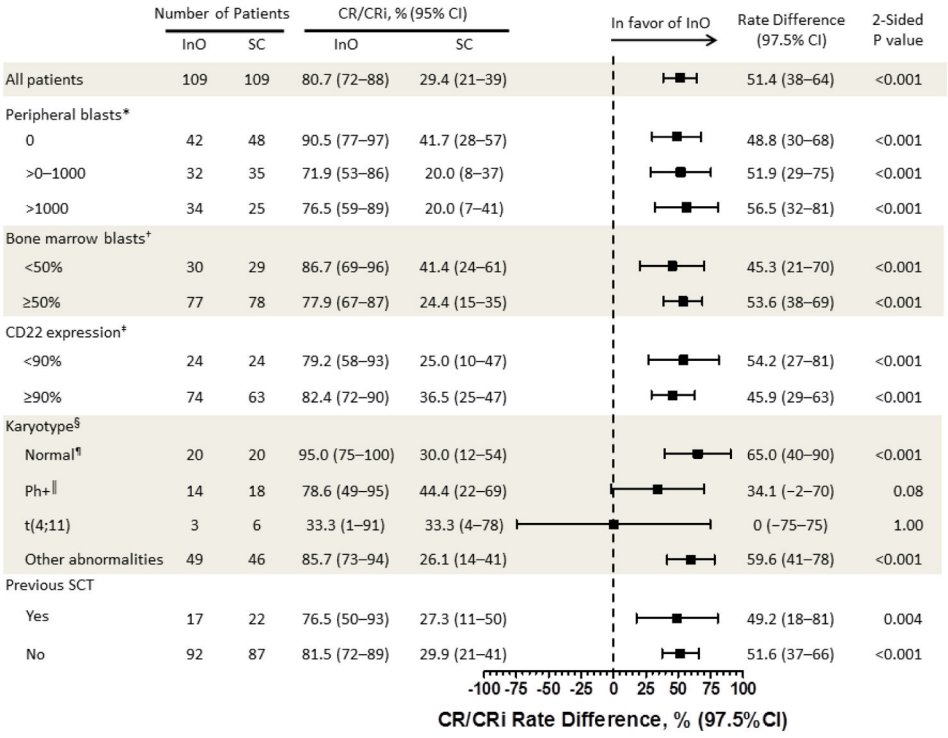
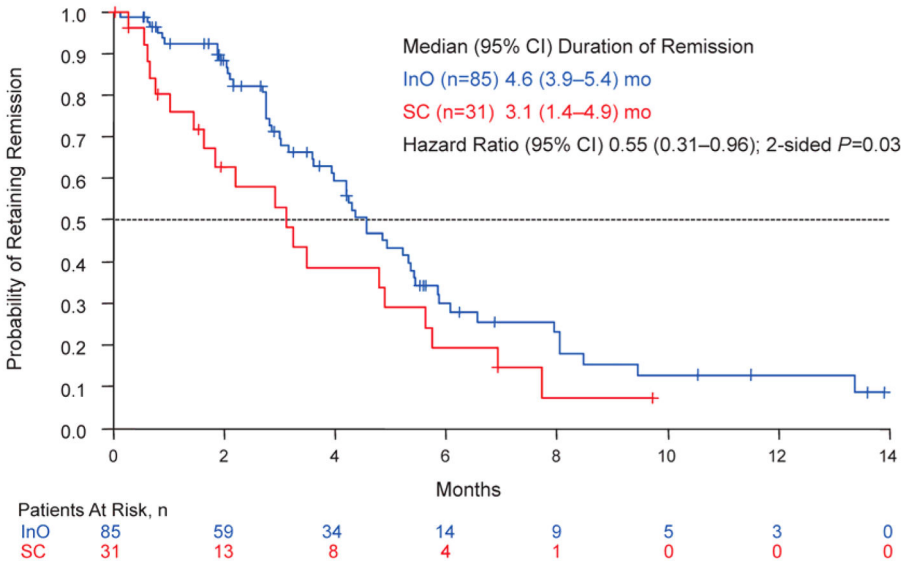


Figure 1. Remission (CR/CRi) by Randomization Stratification Factors (A) and Baseline Patient Characteristics (B)

CR=complete remission; CRi=complete remission with incomplete hematologic recovery; DFR=duration of first remission; InO=inotuzumab ozogamicin; SC=standard of care. Analysis of CR/CRi was based on an ITT218 population (InO, n=109; SC, n=109). *P* values are 2-sided and based on chi-square or Fisher's exact tests (if any cell count is <5). *Data

missing for 1 patient in each InO and SC arm; [†]Data missing for 2 patients in each InO and SC arm [‡]By central laboratory analysis (data missing for 11 and 22 patients receiving InO and SC, respectively); [§]By local laboratory analysis; [¶]The assessment of CR/CRi in patients with normal karyotype required a minimum of 20 analyzed chromosomes; [‖]By central/local laboratory analysis or medical history.

A.



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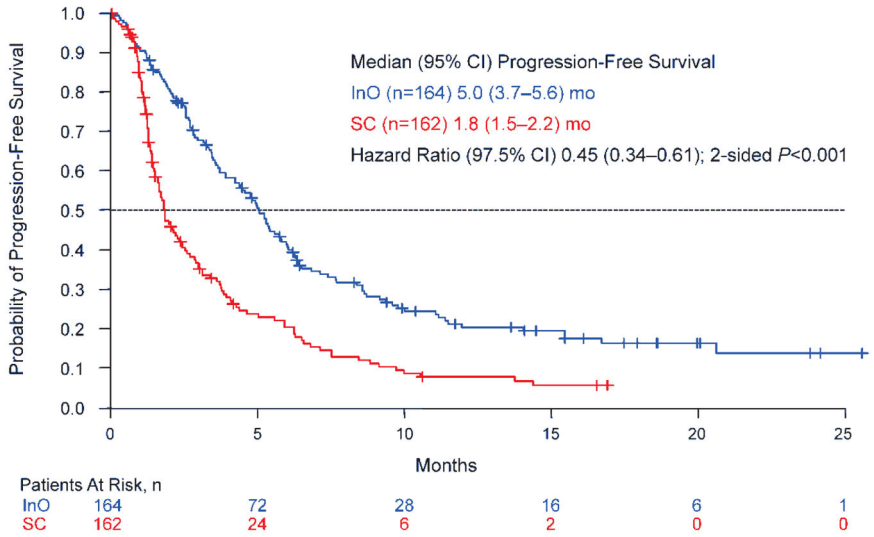

C.

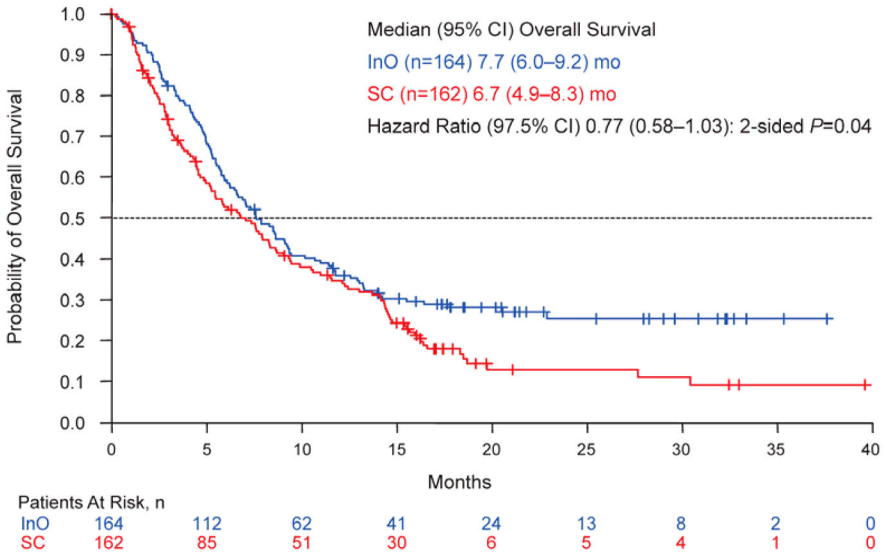

Figure 2. Duration of Remission Among Patients with CR/CRi (A), Progression-Free Survival (B), and Overall Survival (C)

Medians were estimated using the Kaplan-Meier method, *P* values are from stratified log-rank test, and hazard ratio (HR) and corresponding CI were estimated using stratified Cox proportional hazard regression. OS and PFS data represent all 326 patients included in the ITT population (InO, n=164; SC, n=162), and duration of remission is based on the patients with best response of CR/CRi (investigator assessed). Note: because no disease assessments were evaluated by the endpoint adjudication committee after the end of treatment, analysis of DoR was based on the investigator's assessments. CR=complete remission; CRi=complete remission with incomplete hematologic recovery; InO= inotuzumab ozogamicin; DoR=duration of remission; PFS=progression-free survival; OS=overall survival; SC=standard of care. Data represent the ITT218 population (InO, n=109; SC, n=109).

Table 1

Patient Characteristics*

Characteristic	InO (n=109)	SC (n=109)
Median (range) age, y	47 (18–78)	47 (18–79)
<55 y, n (%)	66 (61)	69 (63)
≥55y, n (%)	43 (39)	40 (37)
Men, n (%)	61 (56)	73 (67)
Race, n (%)		
White	76 (70)	79 (73)
Asian	17 (16)	17 (16)
Other	15 (14)	11 (10)
Black	1 (1)	2 (2)
ECOG performance status,† n (%)		
0	43 (39)	45 (41)
1	50 (46)	53 (49)
2	15 (14)	10 (9)
Salvage status,† n (%)		
1	73 (67)	69 (63)
2	35 (32)	39 (36)
Duration of first remission at baseline, n (%)		
<12 mo	62 (57)	71 (65)
≥12 mo	47 (43)	38 (35)
Prestudy SCT, n (%)	17 (16)	22 (20)
Number of prior induction therapies, n (%)		
1	75 (69)	69 (63)
2	33 (30)	39 (36)
3	1 (1)	1 (1)
Response to most recent prior induction therapy, n (%)		
Complete	78 (72)	74 (68)
Partial	9 (8)	7 (6)
Resistant disease	17 (16)	18 (17)
PD/SD	4 (4)	10 (9)
Median (range) WBC count, $10^3/\mu L$	3.5 (0–47.4)	3.8 (0.1–51.0)
Median (range) peripheral blast count,‡ $10^3/\mu L$	0.2 (0–42.7)	0.04 (0–31.5)
No circulating peripheral blasts, n (%)	42 (39)	48 (44)
Bone marrow blasts, n (%)		
<50%	30 (28)	29 (27)
≥50%	77 (71)	78 (72)
Missing	2 (2)	2 (2)
CD22 expression on ALL blasts,§ n (%)		
<90%	24 (22)	24 (22)

Characteristic	InO (n=109)	SC (n=109)
≥90%	74 (68)	63 (58)
Missing	11 (10)	22 (20)
Karyotype,[¶] n (%)		
Normal[//]	27 (25)	23 (21)
Ph+	14 (13)	18 (17)
t(4;11)	3 (3)	6 (6)
Other abnormalities	49 (45)	46 (42)
Unknown/missing	16 (15)	16 (15)

BM=bone marrow; ECOG=Eastern Cooperative Oncology Group; InO=inotuzumab ozogamicin; PD=progressive disease; Ph+=Philadelphia chromosome positive; SCT=stem cell transplantation; SD=stable disease; SC=standard of care; WBC=white blood cell.

[*] ITT218 population.

[†] Data missing for 1 patient in each arm.

[‡] Peripheral blast count = (peripheral blasts × 0.01) × (WBC × 1000).

[§] By central laboratory analysis.

[¶] By local and central laboratory analysis.

[//] 20 patients in the InO arm and 20 patients in the SC arm had normal karyotype assessed based on a minimum of 20 metaphases.

Table 2

Treatment Response*

	InO	SC	Rate Difference, % (97.5% CI)	*P* Value†
N	109	109		
CR/CRi, n (%) [95% CI]	88 (80.7) [72–88]	32 (29.4) [21–39]	51.4 (38–64)	<0.001
CR	39 (35.8) [27–46]	19 (17.4) [11–26]	18.3 (5–32)	0.002
CRi	49 (45.0) [35–55]	13 (11.9) [7–20]	33.0 (20–46)	<0.001
MRD negativity among responders, n (%) [95% CI]				
CR/CRi	69/88 (78.4) [68–87]	9/32 (28.1) [14–47]	50.3 (30–71)	<0.001
CR	35/39 (89.7) [76–97]	6/19 (31.6) [13–57]	58.2 (32–84)	<0.001
CRi	34/49 (69.4) [55–82]	3/13 (23.1) [5–54]	46.3 (16–76)	0.004

CR=complete remission; CRi=complete remission with incomplete hematologic recovery; InO=inotuzumab ozogamicin; ITT=intent-to-treat population; MRD=minimal residual disease; SC=standard of care.

*Data represent the ITT218 population.

†2-Sided *P* values for between-arm differences were assessed based on the chi-square or the Fisher's exact test (if cell count <5); CIs for rates were computed using the Clopper-Pearson method and CIs for rate differences were asymptotic.

Table 3

Treatment-Emergent SAEs*

	InO (n=139)		SC (n=120)	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Any SAE, n (%)	67 (48)	64 (46)	55 (46)	52 (43)
Febrile neutropenia	16 (12)	15 (11)	22 (18)	21 (18)
VOD	15 (11)	13 (9)	1 (1)	1 (1)
Sepsis	3 (2)	3 (2)	6 (5)	6 (5)
Pyrexia	4 (3)	2 (1)	3 (3)	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 (3)	3 (3)
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 (3)	2 (2)
Hypotension	0	0	3 (3)	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)

ALP=alkaline phosphatase; InO=inotuzumab ozogamicin; SAE=serious adverse event; SC=standard of care; VOD=veno-occlusive disease.

*Data represent the safety population (data cutoff date of October 2, 2014); all causality SAEs occurring in >1 patient in either arm (any treatment cycle) in descending order of total frequency across arms. VOD events (any causality) were captured for up to 2 years after randomization.