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Allogeneic – Adult

Outcomes of Allogeneic Stem Cell Transplantation after Inotuzumab Ozogamicin Treatment for Relapsed or Refractory Acute Lymphoblastic Leukemia

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A B S T R A C T

Attaining complete remission of acute lymphoblastic leukemia (ALL) before hematopoietic stem cell transplantation (HSCT) correlates with better post-transplant outcomes. Inotuzumab ozogamicin (InO), an anti-CD22 antibody conjugated to calicheamicin, has shown significantly higher rates of remission, minimal residual disease negativity, and HSCT versus standard chemotherapy in treating relapsed/refractory (R/R) ALL. We investigated the role of previous transplant and proceeding directly to HSCT after remission as factors in determining post-transplant survival in the setting of InO treatment for R/R ALL. The analyzed population comprised InO-treated patients who proceeded to allogeneic HSCT in 2 clinical trials (phase 1/2: NCT01363297 and phase 3: NCT01564784). Overall survival (OS) was defined as time from HSCT to death (any cause). Of 236 InO-treated patients, 101 (43%) proceeded to allogeneic HSCT and were included in this analysis. Most received InO as first salvage (62%); 85% had no previous HSCT. Median (95% confidence interval [CI]) post-transplant OS was 9.2 months (5.1, not evaluable) with 2-year survival probability (95% CI) of 41% (32% to 51%). In first-HSCT patients (n = 86), median (95% CI) post-transplant OS was 11.8 months (5.9, not evaluable) with 2-year survival probability (95% CI) of 46% (35% to 56%); some patients relapsed and needed additional treatment before HSCT (n = 28). Those who went directly to first HSCT upon remission with no additional salvage/induction treatment (n = 73) fared best: median post-transplant OS was not reached with a 2-year survival probability (95% CI) of 51% (39% to 62%). In patients with R/R ALL, InO followed by allogeneic HSCT provided an optimal long-term survival benefit among those with no previous HSCT who went directly to transplant after remission.

INTRODUCTION

Using currently available therapies, >90% of adults with newly diagnosed acute lymphoblastic leukemia (ALL) achieve complete remission (CR) [1]. However, 40% to 50% of these patients will relapse [2,3], and their prognosis remains poor [2,4,5]. Standard chemotherapies for adult patients with ALL at first relapse provide CR rates of 31% to 46%, with 5-year overall

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survival (OS) rates of <20% [3,6-9]. In the salvage setting, CR rates of 18% to 25% have been reported, with median OS of 3 to 4 months [7,10,11].

The only established curative option for relapsed ALL is allogeneic hematopoietic stem cell transplantation (HSCT). Bridging patients safely to HSCT is the primary goal of postrelapse ALL treatment, but HSCT is associated with considerable treatment-related morbidity and mortality. Furthermore, CR is required for optimal disease control post-HSCT; however, most patients with relapsed ALL do not attain CR with salvage chemotherapy and are not eligible for transplant. Improved salvage therapies are required to provide higher CR rates that could bridge patients to transplant and improve long-term outcomes.

Inotuzumab ozogamicin (InO) is a humanized anti-CD22 monoclonal antibody conjugated to the cytotoxic antibiotic, calicheamicin [12,13]. A phase 1/2 study (NCT01363297) of adults with relapsed or refractory (R/R) $CD22^+$ ALL showed that InO was well tolerated and demonstrated high single-agent activity and minimal residual disease (MRD) negativity rates [14]. INotuzumab Ozogamicin trial to inVestigAte Tolerability and Efficacy (INO-VATE) (NCT01564784) was a randomized, phase 3 study in patients with R/R B cell precursor ALL that compared single-agent InO with standard intensive chemotherapy (SC; consisting of fludarabine, cytarabine, and granulocyte colony-stimulating factor; cytarabine plus mitoxantrone; or high-dose cytarabine) at first or second salvage treatment [15]. Patients in the InO group had a significantly higher ($P < .001$) rate of CR/CR with incomplete hematologic recovery (CRi; 80.7% versus 29.4%) and, among those achieving CR/CRi, a higher percentage of MRD-negative patients (78.4% versus 28.1%) than those receiving SC [15]. Of note, approximately 4 times as many InO-treated patients proceeded to follow-up HSCT after study therapy than SC-treated patients (41.3% versus 11.0%) [15]. Based on these results, in August 2017, InO was approved by the US Food and Drug Administration for R/R B cell precursor ALL in adults [16].

Using pooled data from INO-VATE and the earlier phase 1/2 "Study 1010," we analyzed outcomes for a larger subset of patients who received HSCT after InO treatment. Our objectives were to (1) assess post-HSCT outcomes for patients with ALL proceeding to allogeneic HSCT after InO or SC treatment in the salvage setting, (2) identify predictors of post-HSCT outcomes, and (3) describe any unique drug-related toxicity potentially exacerbated by subsequent transplant—post-HSCT veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS).

METHODS

Study Design

Methods for both studies from which we pooled data were previously published [14,15]. Briefly, Study 1010 enrolled 72 adult patients with R/R, $CD22^+$ ALL, including Philadelphia chromosome $(Ph)^+$ patients for whom standard tyrosine kinase inhibitor treatment had failed and who were receiving first salvage therapy or greater. The study consisted of an InO dose escalation phase to determine the recommended phase 2 dose, followed by a dose expansion phase. In phase 2, patients undergoing second salvage therapy or greater received 0.8 mg/m^2 InO on day 1 and 0.5 mg/m^2 on days 8 and 15 of each 21-day cycle. Patients with suitable donors could undergo allogeneic HSCT at investigator discretion following InO treatment [14].

In INO-VATE, adult patients with R/R, $CD22^+$, Ph^+ or Ph^- ALL, scheduled to receive first/second salvage treatment, were randomly assigned to either SC or InO [15] (0.8 mg/m^2 InO on day 1; 0.5 mg/m^2 on days 8 and 15 of each 21-day cycle). Patients achieving CR were then dose reduced to 1.5 g/m^2/cycle and could undergo HSCT at investigator discretion.

Patients

The study population consisted of all patients from the 2 studies who proceeded to allogeneic HSCT. For these patients, treatment with InO was recommended to be limited to 2 cycles of induction or the fewest number of cycles required to achieve CR/CRi (if not achieved after 2 cycles). To balance risk of relapse against potential risk of toxicity, ~5 to 6 weeks was recommended (per protocol) between last dose of InO and HSCT.

Procedures

Procedures for the 2 studies included in this analysis have been published previously [14,15]. MRD analysis was performed at least once in patients with previous assessment of CR/CRi. Bone marrow aspirates (taken at screening; days 16 to 28 of cycles 1, 2, and 3, then every 1 to 2 cycles as clinically indicated; and end of treatment) were analyzed by a central laboratory using multiparametric flow cytometry, with antibody combinations designed to maximize discrimination between normal and abnormal cells of B cell lineage and similar maturational stage. The threshold for MRD was specified as 0.01%; therefore, MRD status was considered negative if the lowest MRD value by end of treatment was $<1 \times 10^{-4}$ blasts/nucleated cells (mononuclear cells specified for Study 1010) [14,15].

Identification of VOD/SOS was based on the modified Seattle criteria requiring 2 of 3 of the following clinical criteria in the absence of other explanations (or development of bilirubin elevation, weight gain, or hepatomegaly plus histologic abnormalities on liver biopsy) [17].

- Total serum bilirubin level >34 μmol/L (>2.0 mg/dL)
- Increase in liver size from baseline or development of right upper quadrant pain of liver origin
- Sudden weight gain >2.5% (within a 72-hour period) because of fluid accumulation in the period after treatment infusion or HSCT conditioning/preparative therapy, or development of ascites not present at baseline, following such exposures

Severity of VOD/SOS was defined as mild (clinically apparent, required no treatment, and resolved completely), moderate (signs and symptoms requiring treatment such as diuretics or pain medications but resolved completely), or severe (required treatment but did not resolve before study day 100 or before death) [17]. An independent, external, and blinded adjudication board also reviewed all significant hepatic events, including any possible cases of VOD/SOS.

Outcomes

The following time-to-event outcomes are reported relative to time of post-treatment HSCT, after administration of InO or SC: (1) post-transplant nonrelapse mortality (NRM)—time to death without relapse or disease progression; (2) post-transplant relapse—time to relapse or disease progression; (3) post-transplant progression-free survival (PFS)—time to earliest date of death or progressive disease (objective progression or relapse from CR/CRi); and (4) post-transplant survival (OS)—time to date of death from any cause or last date the patient was known to be alive (without confirmation of death).

Statistical Analyses

Probabilities of PFS and OS were estimated using Kaplan-Meier methods. Hazard ratios (HRs) were calculated using the Cox proportional hazards model inclusive of all patient-related or disease-related parameters with a potential impact on post-transplant outcomes (Appendix p2). *P* values for tests comparing InO with SC were calculated using a 1-sided log-rank test. Post-transplant NRM was analyzed using a competing risk model with post-transplant relapse as the competing risk and vice versa. Subdistribution HRs for post-transplant NRM were calculated, and 2-sided *P* values were obtained based on Gray's test. Univariate and multivariate analyses based on the Cox regression model were used to evaluate potential risk factors for time-to-event outcomes. Appendix p2 lists baseline characteristics and disease/transplant-related characteristics included in the models for evaluation. "Baseline" refers to time of study entry and randomization, before InO dosing.

Data Sharing

Upon request and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the United States/European Union or (2) in programs that have been terminated (ie, development for all indications is discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions,

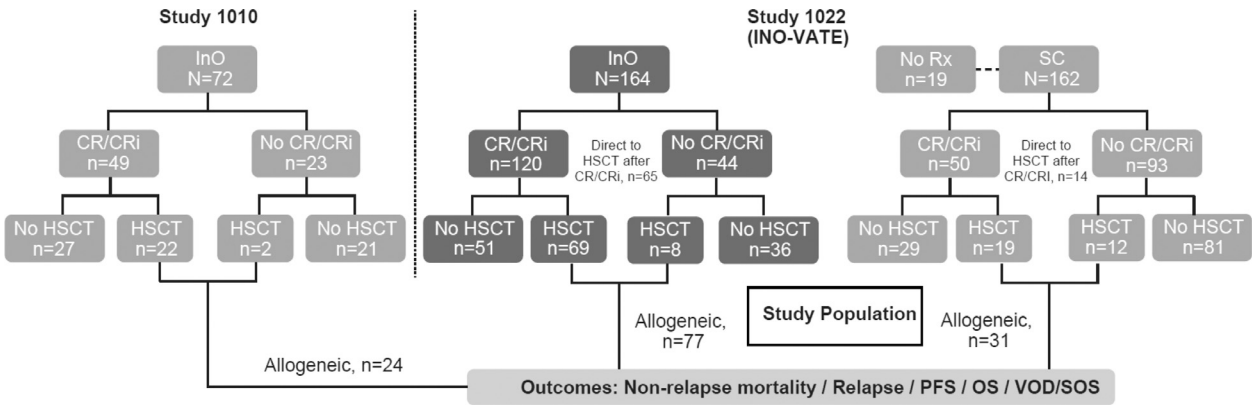

Figure 1. Trial profile.

and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

RESULTS

This pooled analysis included 101 InO-treated patients and 31 SC-treated patients with R/R ALL (Figure 1). Most patient and disease characteristics at baseline were similar between groups (Table 1). Overall, 62% of InO patients and 77% of SC patients were in salvage 1. Baseline cytogenetics were similar between groups. Patients in the InO group were more likely than those in the SC group to have elevated bilirubin and aspartate aminotransferase or alanine aminotransferase and reduced platelets at last measure before transplant.

Also, 15% versus 19% of InO- and SC-assigned patients had previous HSCT (mostly matched HSCT per checkbox on the case report form; level of matching unspecified), with peripheral blood as the most common cell source. Conditioning regimens used for follow-up HSCT were mainly myeloablative and predominantly involved total-body irradiation. Dual alkylators (including cyclophosphamide with busulfan or thiotepa, busulfan or melphalan with thiotepa, and melphalan with carmustine or ranimustine) were used in 13% of patients assigned to InO and 19% of patients assigned to SC; thiotepa was part of the regimen in 8% and 13% of patients, respectively (Appendix p4). InO-treated patients were more likely than SC-treated patients to have achieved CR/CRi at last assessment before HSCT (82.2% versus 67.7%) and to have achieved MRD negativity (74.3% versus 25.8%). Mean time from study arm randomization until HSCT was 110.3 days in the InO arm and 130.5 days in the SC arm. Among InO-treated patients, mean time from last InO dose to HSCT was 47.2 days (range, 9 to 167 days). For InO-treated patients who did not achieve CR/CRi before proceeding to HSCT (n = 16), average time from last response assessment to HSCT was 35 days (versus 28 days for the pooled InO group; n = 101). Appendix p5 lists variables significantly associated with post-transplant survival in this analysis population (n = 132).

Table 2 summarizes post-transplant efficacy outcomes. Potential differences in post-transplant relapse and NRM were observed for InO versus SC. The cumulative incidence rate for relapse at month 24 was 28.6% versus 45.7%, $P = .16$ (subdistribution HR, 0.65; 95% confidence interval [CI], 0.34 to 1.24; $P = .18$). The cumulative incidence rate for NRM at month 24 was 39.3% versus 31.0%, $P = .47$ (subdistribution HR, 1.67; 95% CI, 0.80 to 3.48; $P = .18$). Neither difference was statistically significant. Of note, the cumulative incidence rate of NRM at 100 days was significantly higher in the InO versus SC arm (21.78% versus 6.45%, $P = .01$), but between-arm differences generally decreased over time. Appendix p6 shows cumulative incidence plots of post-transplant relapse with NRM as a competing risk and of post-transplant NRM.

Post-transplant PFS and OS varied over time with evidence of increased mortality early but decreased mortality later in the InO-treated patients post-HSCT compared with SC (Figure 2). At 12 months post-transplant, OS probability was 45.1% for InO-treated patients and 64.8% for SC. By 24 months post-transplant, a higher post-transplant OS was observed for InO-treated patients (41.4% versus 34.1%), as shown in Figure 2 and Table 2. Among subgroups of InO-treated patients, post-transplant OS at 24 months was higher for those receiving their first allogeneic HSCT (45.7%) and those receiving their first allogeneic HSCT who had achieved CR/CRi before transplant (51.1%; Table 2 and Figure 3).

Post-transplant survival probability was similar at 6 months for InO-treated patients who had one transplant (n = 86) or more than one transplant (n = 15; 80.2% versus 80.0%). However, patients with 1 transplant had >3-fold greater survival probability at 12 months (55.8% versus 14.7%) and 24 months (45.7% versus 14.7%). We observed that NRM was lower in patients without a previous HSCT, and the relapse rate appeared lower in patients who achieved CR/CRi before proceeding directly to first transplant (Appendix p7). Median survival time for patients with 1 transplant was approximately double that for patients with >1 transplant (16.5 versus 8.4 months).

Among patients in the InO arm, 71 patients (versus 5 in the SC arm) achieved MRD negativity. For InO-treated, MRD-negative patients in this cohort, median post-transplant OS was 17.8 months (95% CI, 6.7 to not evaluable [NE]) compared with 5.0 months (95% CI, 3.4 to 9.2) for MRD-positive patients (n = 30). Similarly, post-transplant PFS was 10.8 months (95% CI, 3.7 to NE) for MRD-negative patients in the InO arm versus 3.4 months (95% CI, 1.9 to 6.9) for MRD-positive patients.

We used exploratory stepwise Cox multivariate analysis to identify factors potentially associated with post-transplant OS, PFS, relapse, and NRM in patients treated with InO (n = 71; Table 3). Factors associated with worse OS ($P < .05$) were older age as a continuous variable, previous HSCT, high baseline lactate dehydrogenase (LDH) (≥970 IU/L), high pretransplant bilirubin, failure to achieve MRD negativity, and use of thiotepa as conditioning for HSCT. High baseline LDH was significantly associated with high baseline absolute circulating blasts ($\geq 1 \times 10^9$/L) in the InO arm ($P = .0007$) but not with high

Table 1
Patient-, Disease-, and Transplantation-Related Characteristics at Time of Study Entry

Characteristic	InO Group (n = 101)	SC Group (n = 31)
Age		
Median (range), years	37.0 (20-71)	38.0 (19-60)
Age ≥55 years	24 (23.8)	5 (16.1)
Male	56 (55.4)	15 (48.4)
Race		
White	73 (72.3)	26 (83.9)
Black	1 (1.0)	0
Asian	19 (18.8)	3 (9.7)
Other	8 (7.9)	2 (6.5)
ECOG performance status		
0	40 (39.6)	16 (51.6)
1	46 (45.5)	12 (38.7)
2	14 (13.9)	3 (9.7)
3	1 (1.0)	0
Salvage status		
Salvage 1	63 (62.4)	24 (77.4)
Salvage 2	30 (29.7)	7 (22.6)
Salvage ≥3	7 (6.9)	0
Missing	1 (1.0)	0
Baseline WBC count, $\times 10^3/mm^3$		
Median (range)	3.5 (0.0-47.4)	4.6 (0.9-20.5)
Peripheral blast count, per μL*		
Median (range)	0.0 (0.0-42660)	0.0 (0.0-11890)
Missing	1 (1.0)	0
Bone marrow blasts <50%	30 (29.7)	10 (32.3)
Baseline LDH		
<970 IU/L	86 (85.1)	29 (93.5)
≥970 IU/L	13 (12.9)	2 (6.5)
Missing	2 (2.0)	0
$CD22^+$ leukemic blasts		
<90%	16 (15.8)	7 (22.6)
≥90%	78 (77.2)	13 (41.9)
Missing	7 (6.9)	11 (35.5)
Baseline cytogenetics		
Normal	35 (34.7)	9 (29.0)
Ph^+	11 (10.9)	4 (12.9)
$t(4;11)^+$	2 (2.0)	2 (6.5)
Other abnormalities	44 (43.6)	11 (35.5)
Duration of first remission		
<12 months	44 (43.6)	17 (54.8)
≥12 months	46 (45.5)	14 (45.2)
Missing	11 (10.9)	0
Previous stem cell transplant	15 (14.9)	6 (19.4)
Last bilirubin level before transplant ≥ULN	16 (15.8)	1 (3.2)
Last AST or ALT level before transplant >1.5 × ULN	19 (18.8)	2 (6.5)
Last platelet level before transplant $<100 \times 10^9/L$	59 (58.4)	6 (19.4)
Total-body irradiation	63 (62.4)	16 (51.6)
Use of thiotepa	8 (7.9)	4 (12.9)
Use of dual alkylators	13 (12.9)	6 (19.4)
Achieved CR/CRi at last assessment before SCT	83 (82.2)	21 (67.7)
Type of conditioning therapy		
Myeloablative	61 (60.4)	21 (67.7)
Reduced intensity	34 (33.7)	9 (29.0)
Unknown	6 (5.9)	1 (3.2)
Donor type		
Matched related	25 (24.8)	11 (35.5)
Matched unrelated	45 (44.6)	11 (35.5)
Mismatched related	8 (7.9)	3 (9.7)
Mismatched unrelated	20 (19.8)	5 (16.1)
Unknown unrelated	3 (3.0)	0
Unknown	0	1 (3.2)
Best MRD status		
Positive	21 (20.8)	18 (58.1)
Negative	75 (74.3)	8 (25.8)
Missing	5 (5.0)	5 (16.1)
Graft type		
Bone marrow	13 (12.9)	5 (16.1)
Peripheral blood	63 (62.4)	20 (64.5)
Cord blood	11 (10.9)	5 (16.1)
Missing	14 (13.9)	1 (3.2)

Values are presented as n (%) unless otherwise specified.
ECOG indicates Eastern Cooperative Oncology Group; AST, aspartate aminotransferase; ALT, alanine aminotransferase; SCT, stem cell transplantation.
*Determined by local laboratory.

baseline bone marrow blasts (P = .0663). Factors associated with risk of treatment failure (defined as inverse of PFS, P < .05) were older age, high pretransplant bilirubin, failure to achieve MRD negativity, high baseline absolute circulating blasts (continuous variable), low pretransplantation platelets, male sex, and nonwhite race (mostly Asian [Table 1]; there were some differences in regional use of conditioning regimens [data not shown], but we do not know whether these differences explain inferior outcomes). Table 3 lists factors associated with risk of relapse/NRM. We found no significant associations between type of conditioning regimen (myeloablative versus reduced intensity) and any post-HSCT outcomes.

Nineteen patients (18.8%) in the InO group developed VOD after HSCT (1 additional patient in Study 1010 developed VOD before HSCT); 5 of these (26.3%) were fatal. Among InO-treated patients who developed VOD, 7 received busulfan, 6 received dual alkylators (including 4 who received a thiotepa-containing conditioning regimen), and 3 received cyclophosphamide with total-body irradiation (counted separately from the dual alkylator group). After 1 cycle of InO, 1 (of 14; 7.1%) patient developed VOD, and 7 (of 35; 20.0%), 6 (of 31; 19.4%), and 5 (of 21; 23.8%) patients developed VOD following 2, 3, and 4 to 6 cycles, respectively. Twelve of the post-HSCT VOD cases were grade 3/4 post-HSCT, with 9 patients receiving defibrotide (5/9 [56%] recovered) and 3 who did not receive defibrotide (none survived). Median time from last InO dose to follow-up HSCT was similar between those who experienced VOD (40.0 days; range, 17 to 135 days) and those who did not (36.0 days; range, 9 to 167 days). Median time from last InO dose to VOD was 57.5 days (range, 8 to 144 days), and median time from follow-up SCT to VOD was 15.0 days (range, 3 to 57 days). No late cases of VOD were seen. Detailed analyses of VOD from INO-VATE have been previously published [18].

Table 2
Post-HSCT Efficacy Outcome Probabilities, Including for Overall Survival by Treatment Subgroups

Post-HSCT Outcome	100 Days, % (95% CI)	12 Months, % (95% CI)	24 Months, % (95% CI)	HR (CI)*	*P* Value†
Relapse,‡ all patients					
InO (n = 101)	10.9 (5.8-17.9)	21.8 (14.3-30.3)	28.6 (19.9-37.9)	0.65 (0.34-1.24)	.18
SC (n = 31)	3.2 (0.2-14.4)	29.5 (13.3-47.7)	45.7 (23.6-65.4)		
NRM,‡ all patients					
InO (n = 101)	21.8 (14.3-30.3)	37.7 (28.2-47.1)	39.3 (29.5-48.9)	1.67 (0.80-3.48)	.18
SC (n = 31)	6.45 (1.1-18.9)	20.1 (7.9-36.3)	31.0 (13.3-50.8)		
PFS, all patients					
InO (n = 101)	65.6 (53.7-75.1)	41.2 (29.4-52.5)	33.8 (21.9-46.1)	1.02 (0.39-2.71)	.52
SC (n = 31)	72.7 (37.1-90.3)	34.1 (9.1-61.6)	NE		
OS, all patients					
InO (n = 101)	73.2 (63.4-80.7)	45.1 (35.2-54.5)	41.4 (31.5-51.0)	1.26 (0.66-2.41)	.78
SC (n = 31)	93.5 (76.6-98.3)	64.8 (44.1-79.4)	34.1 (15.3-54.0)		
OS, no previous HSCT					
InO (n = 86)	75.6 (65.1-83.3)	50.0 (39.0-60.0)	45.7 (34.7-56.0)	1.11 (0.54-2.28)	.63
SC (n = 25)	96.0 (74.8-99.4)	61.7 (39.0-78.0)	28.0 (10.6-48.7)		
OS, CR/CRi directly to HSCT and no previous HSCT					
InO (n = 73)	75.3 (63.8-83.7)	56.1 (44.0-66.6)	51.1 (38.9-62.1)	1.03 (0.40-2.63)	.52
SC (n = 12)	100 (NE-NE)	64.8 (31.0-85.2)	27.8 (6.7-54.5)		

*For relapse and NRM: proportional hazards model, subdistribution HR (95% CI). For PFS and OS: stratified HR (97.5% CI). Stratification factors provided in Methods.
†For relapse and NRM: 2-sided *P* value of Gray's test for equality of cumulative distribution functions between treatment arms. For PFS and OS: 1-sided stratified log-rank *P* value. Stratification factors provided in Methods.
‡Cumulative incidence.

There were 58 deaths in the InO group (57.4%) and 17 in the SC group (54.8%), with 39 and 8 deaths in each group, respectively, categorized as NRM. At 100 days, deaths attributed as NRM numbered 22 (21.8%) in the InO arm (6 from VOD) and 2 (6.1%) in the SC arm. Causes of death for NRM within the first 100 days and after 100 days are shown in Table 4. Appendix p8 provides a complete and detailed listing of the causes of death noted by study investigators in the total patient population for the follow-up period.

The risk of death was lower with InO versus SC for patients who were MRD negative by end of treatment (n = 71) than with InO versus SC for MRD-positive patients (n = 30): HR = 0.244 (95% CI, 0.114 to 0.524) among MRD-negative patients and HR = 1.279 (95% CI, 0.532 to 3.078) among MRD-positive patients.

Among patients who did not achieve CR/CRi and underwent follow-up HSCT, 7 of 8 in the InO arm died (3 of ALL, 2 of infection, 1 of respiratory disorder/failure, and 1 of nonstudy treatment-related toxicity); 2 of 5 in the SC arm died (infection). Median time to death for these few patients was 5.4 months (95% CI, 1.2 to 6.7) in the InO arm and 8.2 months (95% CI, 0.5 to NE) in the SC arm.

DISCUSSION

In this pooled analysis of post-transplant outcomes among adults with R/R B cell precursor ALL, patients receiving InO were about one third less likely to experience relapse than those who received SC. Although the InO group was more likely to experience NRM than the SC group, the ability to bridge more than double the percentage of patients (versus SC) to HSCT led to improved OS for patients with R/R ALL. The Kaplan-Meier curves (Figure 2) and time-to-event data (Table 2) suggest improved outcome probabilities with InO (versus SC) in the longer term (PFS at 24 months [33.8% versus NE] and OS at 24 months [41.4% versus 34.1%]). These data apply to post-transplantation outcomes; any comparison of OS from time of salvage therapy must also consider the notably higher percentage of patients able to proceed to HSCT in the InO group, along with the poor prognosis of patients not eligible for postsalvage transplantation. However, any differences observed between patients treated with InO versus SC in this post hoc analysis must be interpreted with caution because of the small numbers involved.

In the InO group, the longest OS was achieved by patients with no previous transplant who achieved CR/CRi as best response and proceeded directly to HSCT (without intervening or additional treatment). Potential factors associated with poor OS (based on multivariate analysis) included high baseline LDH levels (≥970 IU/L), previous HSCT, high last pretransplant bilirubin levels (≥ upper limit of normal [ULN]), inability to achieve MRD negativity, and older age. Baseline LDH level previously has been identified as prognostic for survival in patients with ALL in first salvage [19]. In Cox regression analysis, number of cycles of salvage therapy was not associated with survival outcome.

MRD negativity can affect outcomes in R/R ALL, in which it has been associated with improved overall/event-free survival in patients receiving first salvage [20]. Similar outcomes were observed in patients who received HSCT beyond first remission but were MRD negative at the time versus those who underwent transplant after achieving first MRD-negative remission [21]. Another study found that MRD-negative status improved OS in InO-treated patients undergoing HSCT at any relapse [22]. We also found that among those who underwent follow-up HSCT, patients who were MRD negative after InO treatment had longer survival than those who were not. Given that more patients in the INO-VATE study achieved MRD negativity with InO treatment than with SC, our subgroup analysis in patients treated with InO

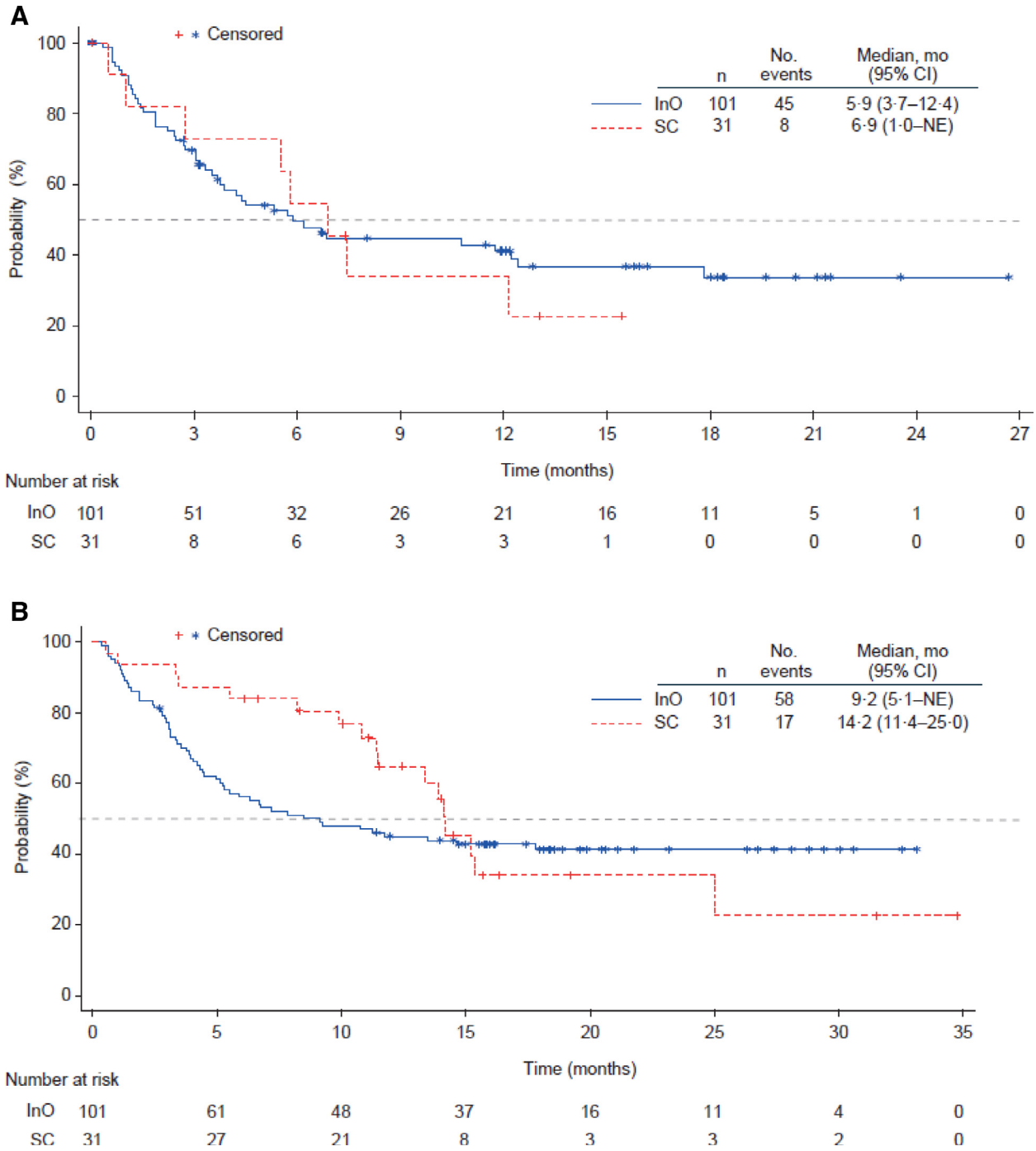

Figure 2. (A) Kaplan-Meier plots of post-transplant progression-free survival and (B) post-transplant overall survival for patients treated with InO and SC.

points to MRD negativity as an important factor associated with survival, one that should be considered when choosing treatment for patients intending to proceed to HSCT.

Multivariate analysis also identified several factors significantly associated with multiple outcomes (OS, PFS, relapse, NRM; Table 3). Those associated with 3 or more outcomes were age, baseline LDH levels (<970/≥970 IU/L), last pretransplant bilirubin levels (≥ULN/<ULN), and best MRD status (+/−). Several studies have identified age as a prognostic factor for survival in patients with R/R ALL [6,7,19]. To our knowledge, baseline bilirubin levels have not been associated with survival outcomes in ALL, but elevated bilirubin levels have been associated with use of InO [2,22], and pre-HSCT bilirubin levels ≥ULN were associated with an increased risk of VOD among patients receiving InO in the INO-VATE study [18].

Notably, among factors predictive of highest risk of NRM (but not of OS, PFS, or relapse) was use of dual alkylators in conditioning regimens. This has been associated with increased incidence of VOD, as reported in a single-institution retrospective study investigating the feasibility of allogeneic HSCT in patients with ALL following treatment with InO salvage therapy [22]. In that study, 1-year OS was 42% for patients who were MRD negative at

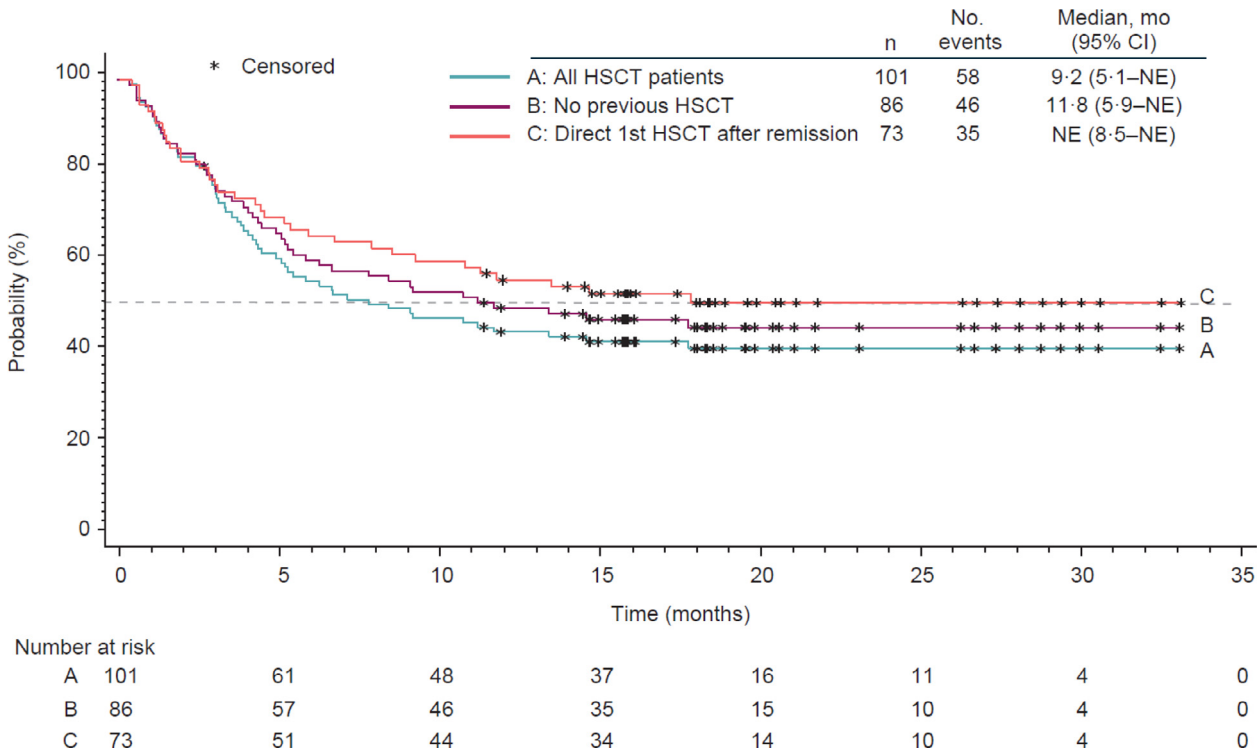

Figure 3. Kaplan-Meier plot of post-transplant survival for subgroups of patients who received InO (intent-to-treat [ITT] population) and proceeded to allogeneic follow-up HSCT. (A) All InO-treated patients in Studies 1010 and 1022 who had post-treatment allogeneic HSCT. (B) Subset of these InO-treated patients who did not have previous HSCT. (C) Subset of these InO-treated patients who had no previous HSCT and proceeded to HSCT in CR/CRi.

transplantation. However, fatal hepatic VOD/SOS occurred in 5 patients (19%), 4 of whom received HSCT preparative regimens containing dual alkylators [21]. A recent analysis of hepatic adverse events in InO-treated patients in the INO-VATE study (including most patients in the present analysis) reported a 6.6-fold increase in frequency of VOD among patients treated with 2 (versus 1) alkylating agents [18]. The authors suggest that careful selection and further investigation of conditioning regimens (such as reduced-intensity conditioning regimens) or avoiding the use of dual alkylators may mitigate risk of VOD, which in the present analysis was the cause of death in 5 (5%) patients in the InO group. In our cohort, only 13% of InO-treated patients received dual alkylating agents (Appendix p2). The safety of alternative conditioning regimens warrants further study in larger numbers of InO-treated patients.

As reported in the primary analysis from INO-VATE [15], VOD occurred more frequently with InO (15/139 [11%]) than SC (1/120 [1%]). Among patients in the InO group, VOD was more frequent in those who received more than 2 cycles of InO; given that additional cycles may increase risk of post-transplant VOD [18], patients in remission and MRD negative should proceed to HSCT after 2 cycles of InO. The approved recommended dose of InO is to give patients no more than 2 courses of treatment before proceeding to HSCT for those patients achieving a remission and MRD negativity. ALL patients undergoing curative therapy should have tissue typing at diagnosis to enable efficient donor identification and coordination of HSCT within the 2-month time frame required for 2 cycles of InO. Patients should be monitored for hepatotoxicity and VOD before and even more closely after HSCT. However, some patients with significant hepatic dysfunction in the past or at relapse may be unsuitable for InO salvage [18].

Aside from the high rate of HSCT already seen among InO-treated patients, who comprised our analysis population, this post hoc exploratory study has several limitations that must be considered before drawing any clinical conclusions. Although several factors appeared to be associated with worse post-transplant outcomes (eg, Asian/nonwhite race; male sex), these correlations could result from other patient or disease characteristics not considered or controlled for in this analysis. Also, MRD status was recorded only up to end of treatment on study but not after subsequent therapy. These analyses are also limited by the set of factors included in univariate and multivariate analyses, which did not, for example, include cytogenetics [23,24]. Although our findings were similar between the 2 trials, a further limitation is lack of an SC treatment arm in Study 1010.

Nonetheless, even though these data do show an apparent additive clinical benefit when patients without previous transplant are treated with InO and proceed directly to first HSCT after achieving remission, the findings reported here should be interpreted with caution given the post hoc nature of this subgroup analysis and modest sample size. A prospective study is under way to assess our findings further.

The present analyses show that in patients with R/R ALL, administration of InO followed by allogeneic HSCT provided the best long-term survival benefit among patients with no previous HSCT who went directly to HSCT after attaining remission. These findings support use of InO salvage therapy as a bridge to potentially curative transplantation in

Table 3
Factors Potentially Associated with Post-Transplant Outcomes (Overall Survival, Progression-Free Survival, Relapse, and Nonrelapse Mortality) for Patients in the InO Group (n = 71) by Multivariate Analysis

	Overall Survival			Progression-Free Survival			Relapse			Nonrelapse Mortality		
Factor	Patients, n	HR (95% CI)	*P* Value	Patients, n	HR (95% CI)	*P* Value	Patients, n	HR (95% CI)	*P* Value	Patients, n	HR (95% CI)	*P* Value
Age (continuous)	71	1.04 (1.02-1.06)	.0007	71	1.09 (1.05-1.12)	<.0001		—	*	71	1.07 (1.03-1.10)	<.0001
Previous HSCT (yes, no)	11, 60	4.31 (1.79-10.4)	.0012		—	*		—	*		—	*
Baseline LDH (<970 IU/L, ≥970 IU/L)	63, 8	0.128 (0.051-0.319)	<.0001		—	*	63, 8	0.002 (<0.001-0.041)	<.0001	63, 8	0.171 (0.047-0.622)	.0074
Last pretransplant bilirubin (≥ULN, <ULN)	12, 59	5.10 (2.28-11.4)	<.0001	12, 59	5.98 (1.90-18.8)	.0022	12, 59	488 (16.6->9999)	.0003		—	*
Best MRD status (positive, negative)†	15, 56	3.34 (1.62-6.86)	.0011	15, 56	34.2 (9.48-123)	<.0001		—	*	15, 56	4.93 (1.65-14.7)	.0043
Use of thiotepa (yes, no)	8, 63	2.97 (1.19-7.45)	.0203		—	*		—	*		—	*
Sex (female, male)		—	*	31, 40	0.180 (0.071-0.460)	.0003		—	*		—	*
Race (other, white)		—	*	17, 54	2.88 (1.13-7.36)	.0275	17, 54	0.112 (0.021-0.597)	.0104		—	*
Baseline absolute circulating blasts ($<1 \times 10^9$/L, $\geq 1 \times 10^9$/L)		—	*	55, 16	0.149 (0.057-0.385)	<.0001		—	*		—	*
Last pretransplant platelet value ($<100 \times 10^9$/L, $\geq 100 \times 10^9$/L)		—	*	40, 31	9.54 (3.60-25.3)	<.0001		—	*	40, 31	4.14 (1.50-11.4)	.0062
Baseline hemoglobin (<10 g/dL, ≥10 g/dL)		—	*		—	*	24, 47	24.6 (4.09-149)	.0005		—	*
Baseline platelets ($<100 \times 10^9$/L, $\geq 100 \times 10^9$/L)		—	*		—	*	41, 30	0.04 (0.005-0.334)	.003		—	*
Baseline % bone marrow blasts (continuous)		—	*		—	*	71	1.04 (1.01-1.06)	.0063		—	*
Duration of first remission (<12 months, ≥12 months)		—	*		—	*	33, 38	45.3 (7.13-288)	<.0001		—	*
Salvage status (≥2, 1)		—	*		—	*	20, 51	0.120 (0.023-0.627)	.012		—	*
CR/CRi at last pre-HSCT assessment (yes, no)		—	*		—	*	62, 9	0.084 (0.016-0.429)	.0029		—	*
Duration of first remission (continuous)		—	*		—	*		—	*	71	1.05 (1.02-1.08)	.0002
Response to most recent regimen before study entry (other, CR)		—	*		—	*		—	*	18, 53	2.83 (1.02-7.88)	.0458
Dual alkylators (yes, no)		—	*		—	*		—	*	12, 59	8.18 (2.37-28.2)	.0009
Received follow-up induction, consolidation, or maintenance treatment after InO before HSCT (yes, no)		—	*		—	*		—	*	12, 59	0.051 (0.009-0.274)	.0005

HR >1.0 means that the first paired variable is a risk factor for worse outcome; <1.0 means that the second paired variable is a risk factor for worse outcome.

*Excluded from final model.

†MRD negativity was considered achieved if the lowest value of MRD from the first date of CR/CRi to end of treatment was $<1 \times 10^{-4}$ blasts/nucleated cells.

Table 4
Post-Transplant Nonrelapse Mortality within the First 100 Days and after 100 Days

	NRM at ≤100 Days		NRM at >100 Days	
Characteristic	InO	SC	InO	SC
Deaths, n (%)*	22 (21.8)	2 (6.5)	17 (16.8)	6 (19.4)
Causes of death, n (%)†				
VOD	6 (27.3)	0	0	0
Hepatic failure/SOS	1 (4.5)	0	0	0
VOD	5 (22.7)	0	0	0
Multiorgan failure with ongoing VOD	1 (4.5)	0	0	0
Infection (eg, sepsis related)	6 (27.3)	1 (50.0)	5 (29.4)	1 (16.7)
GVHD‡	2 (9.1)	0	2 (11.8)	1 (16.7)
GVHD/infection§	0	0	1 (5.9)	0
Cardiac disorders	3 (13.6)	0	0	0
Respiratory disorders/failures	1 (4.5)	0	3 (17.6)	1 (16.7)
General disorders (multiorgan/multisystem failure)	1 (4.5)	0	2 (11.8)	0
ALL treatment toxicity (nonstudy drugs)‖	3 (13.6)	1 (50.0)	2 (11.8)	1 (16.7)
Leukemia relapse¶	0	0	0	1 (16.7)
Other	1 (4.5)	0	1 (5.9)	1 (16.7)
Unknown	1 (4.5)	0	2 (11.8)	0

GVHD indicates graft-versus-host disease.
* Percentage is calculated based on number of patients (InO, n = 101; SC, n = 31).
† Percentage is calculated based on the number of deaths. Note that more than 1 cause of death per patient could be indicated by the investigator.
‡ GVHD site was not required as part of the event recording.
§ *Klebsiella pneumoniae* and liver GVHD.
‖ Includes complications related to transplant or follow-up/salvage therapy.
¶ Assessed by investigator as "other" cause of death with a mechanism of death listed as "refractory acute lymphoblastic leukemia to multiple agents."

this difficult-to-treat population. Consistent with previous observations and expert clinical recommendations [25], a priority for InO treatment should be to minimize risk of hepatotoxicity following InO administration by limiting exposure to the minimum number of cycles needed to achieve best response, as well as exploring lower doses of InO, avoiding use of dual alkylators, and monitoring patients closely.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi: 10.1016/j.bbmt.2019.04.020.

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