Efficacy and safety of currently approved and lower starting doses of inotuzumab ozogamicin in adult patients with relapsed or refractory acute lymphoblastic leukemia: a phase IV study

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Abstract

Inotuzumab ozogamicin (InO) is approved for treatment of relapsed/refractory acute lymphoblastic leukemia (R/R ALL). Previous studies reported higher rates of post–hematopoietic stem cell transplant (HSCT) hepatic sinusoidal obstruction syndrome (SOS) in patients receiving InO than in those receiving chemotherapy prior to HSCT. It is unknown whether a lower InO dose would reduce the risk of post-HSCT SOS or affect efficacy. This study evaluated efficacy and safety of the currently approved InO starting dose and a lower dose in adults with R/R ALL who were eligible for HSCT and were identified as being at higher risk of post-HSCT SOS. This open-label, phase IV study (NCT03677596) had two phases: in the run-in phase patients received InO at 1.2 mg/m^2/cycle (N=22); in the randomized phase patients received InO starting at dose levels of 1.8 mg/m^2/cycle (N=38) or 1.2 mg/m^2/cycle (N=42). Primary endpoints were rate of SOS and rate of hematologic remission. Overall, SOS was reported in ten patients (9.8%) and in all cases was post-HSCT SOS. In patients who proceeded to HSCT, post-HSCT SOS rates were 20%, 28.6%, 25.8%, and 16.7% in 1.2 mg/m^2/cycle (run-in), 1.2 mg/m^2/cycle (randomized), 1.2 mg/m^2/cycle (run-in and randomized), and 1.8 mg/m^2/cycle (randomized) InO dosing subgroups, respectively. The rates of complete remission with or without complete hematologic recovery were 50.0%, 83.3%, 71.9%, and 68.4% in the respective subgroups. The study found that a starting dose of the 1.2 mg/m^2/cycle demonstrated efficacy and safety consistent with those of the recommended 1.8 mg/m^2/cycle dose in adults with R/R ALL who were eligible for HSCT and had a higher risk of post-HSCT SOS.

Introduction

Acute lymphoblastic leukemia (ALL) is a rare cancer that affects the bone marrow, blood, and/or extramedullary sites. Whereas standard therapies for ALL result in disease remission in around 90% of newly diagnosed adult patients, many experience disease relapse, and cure rates are less than 40%.[1,2] The prognosis for adults with relapsed/refractory (R/R) ALL is poor, with 20-40% overall survival at 5 years.[1,3] Currently, the main curative treatment for adults with R/R ALL is allogeneic hematopoietic stem cell transplantation (HSCT). This treatment is typically only offered once hematologic remission has been established.

Inotuzumab ozogamicin (InO) is an antibody-drug conjugate approved for R/R ALL in the USA, the European Union, and many countries globally.[4,5] The approved starting dose is 1.8 mg/m^2/cycle in three divided doses for the first cycle. For subsequent cycles the recommended dose is 1.5 mg/m^2/cycle after achieving complete remission (CR)/CR with incomplete hematologic recovery (CRi), or 1.8 mg/m^2/cycle in patients who do not achieve CR/CRi. As a monotherapy, doses as low as 1.2 mg/m^2/cycle have been studied in ALL.[6] In the INO-VATE phase III clinical trial, patients receiving InO were compared with those given standard of care; those receiving InO had a higher rate of CR/CRi (80.7%, 95% confidence interval [95% CI]: 72-88% *vs*. 29.4%, 95% CI: 21-39%;

P<0.001) and were more likely to proceed to HSCT (41% *vs*. 11%; *P*<0.001).[7,8] Patients who received InO, compared with patients who received chemotherapy, were also more likely to experience post-HSCT hepatic sinusoidal obstruction syndrome (SOS; also known as veno-occlusive disease), with a reported incidence of 14.0% (N=23/164) *versus* 2.1% (N=3/143), respectively.[7] It is not known whether a lower dose of InO would improve safety and reduce the likelihood of post-HSCT SOS or whether this would affect efficacy.

This phase IV study (NCT03677596) was a post-marketing requirement of the US Food and Drug Administration (FDA) and investigated two dose levels of InO in adults with R/R ALL. The primary objective of this study was to evaluate the rates of hepatic SOS and hematologic remission (CR/CRi) achieved with two dose levels of InO in adults with R/R ALL who were eligible for HSCT and who had a higher risk of post-HSCT SOS.

Methods

Study design and interventions

This open-label, phase IV study (NCT03677596) was conducted between July 1, 2019 and September 21, 2022 in 33 sites across eight countries. The study had two phases: a run-in phase and a randomized phase (Figure 1). The study protocol was approved by institutional review boards or independent ethics committees at each trial center, and the study was conducted according to the principles of the Declaration of Helsinki. All participants provided written informed consent. The study was not designed to show non-inferiority to the standard dose of InO, rather, to explore whether a lower dose of InO might result in a reduced SOS rate while maintaining efficacy.

In the run-in phase patients received InO 1.2 mg/m^2/cycle administered as three divided doses (0.6 mg/m^2 on day 1, 0.3 mg/m^2 on days 8 and 15), and after CR/CRi had been achieved the dose was reduced to 0.9 mg/m^2 administered as three divided doses (0.3 mg/m^2 on days 1, 8, and 15). A Simon's two-stage optimal design was used in the run-in phase. If acceptable efficacy was observed (CR/CRi and minimal residual disease [MRD] negativity in a minimum of 3 patients) the study entered into stage 2. An interim analysis was then conducted at the end of the run-in phase, and the trial proceeded to the randomized phase.

In the randomized phase, 80 patients were stratified on the basis of age (<55 *vs*. ≥55 years),[8] salvage status (salvage 1 *vs*. ≥2), and prior HSCT (yes *vs*. no) and randomly assigned (1:1) to InO treatment starting at dose levels of 1.8 mg/m^2/cycle (administered as 3 divided doses on days 1, 8, and 15) or 1.2 mg/m^2/cycle (administered as 3 divided doses as outlined for the run-in phase). The cycle length for InO treatment (both treatment arms) was 21-28 days with InO administered on days 1, 8, and 15. After CR/CRi had been achieved, the dose of InO was reduced to 1.5 mg/m^2/cycle for patients randomly assigned to 1.8 mg/m^2/cycle and reduced to 0.9 mg/m^2/cycle for patients randomly assigned to 1.2 mg/m^2/cycle.

For patients who proceeded to HSCT, two cycles of InO were recommended, with the option of a third cycle for patients who did not achieve CR/CRi and MRD negativity after two cycles. Per study protocol, treatment was discontinued in patients who did not achieve CR/CRi within three cycles in the 1.8 mg/m^2/cycle arm or within four cycles in the 1.2 mg/m^2/cycle arm.

Participants

Eligible patients were adults aged 18-75 years with R/R precursor CD22$^+$ B-cell ALL with M2 or M3 marrow (≥5% blasts), Eastern Cooperative Oncology Group performance status 0-2, eligible for HSCT, who had ≥1 risk factor for developing SOS (aged ≥55 years; due to receive second salvage or greater, had received prior HSCT; and/or had ongoing or prior hepatic disease - including a prior history

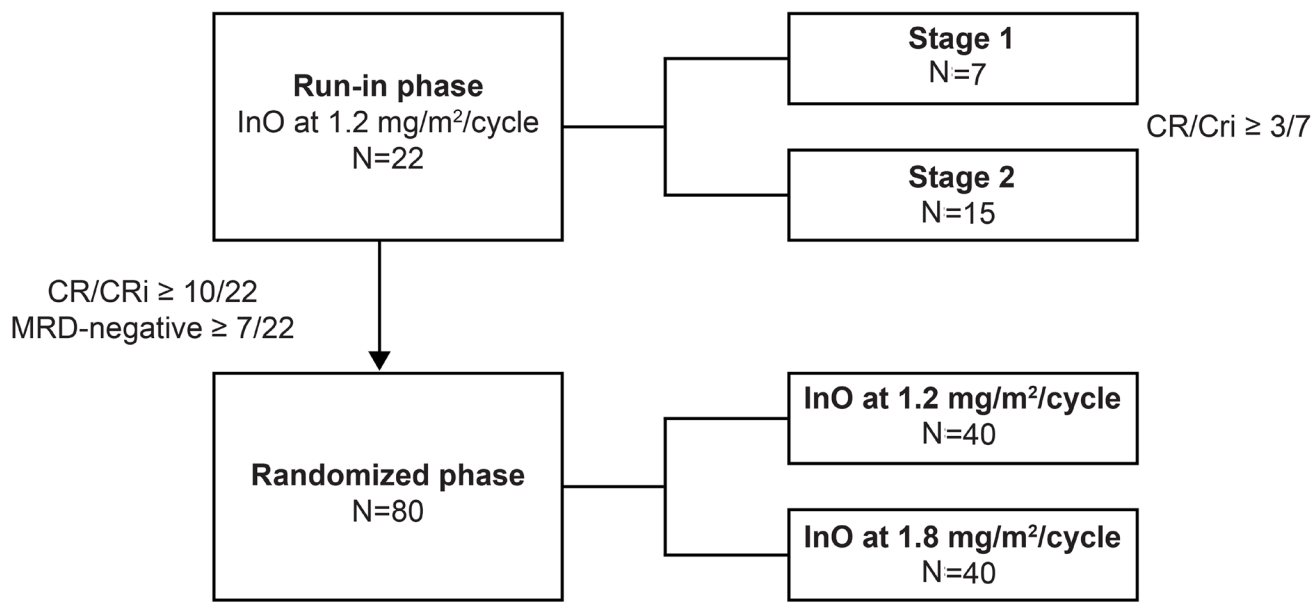


Figure 1. Study design. CR: complete remission; CRi: complete remission with incomplete hematologic recovery; MRD: minimal residual disease; InO: inotuzumab ozogamicin.

of hepatitis or drug-induced liver injury, as well as hepatic steatosis, non-alcoholic steatohepatitis, baseline elevation of bilirubin > upper limit of normal and ≤1.5 x upper limit of normal). Patients with Philadelphia chromosome-positive ALL had to have experienced failure of at least one second- or third-generation tyrosine kinase inhibitor and standard multi-agent induction chemotherapy.
Full inclusion and exclusion criteria are provided in *Online Supplementary Table S1*.

Endpoints and assessments

The primary endpoints of the study were the rates of SOS and hematologic remission (CR/CRi). Secondary endpoints included measures of remission and survival such as MRD, overall survival, duration of remission, event-free survival (defined as the time from date of randomization to the date of disease progression, death due to any cause, or starting new induction therapy/post-therapy HSCT without achieving CR/CRi, whichever occurred first [including post-study treatment follow-up disease assessments]). In addition, HSCT-related endpoints included rate of HSCT, post-HSCT relapse, post-HSCT mortality, post-HSCT non-relapse mortality, and post-HSCT relapse-related mortality.
Additional methods and statistical analysis are provided in the *Online Supplementary Material*.

Results

Participants' disposition and disease characteristics

A total of 102 patients were enrolled into the study and received treatment (Figure 2): 22 patients were enrolled in the 1.2 mg/m^2/cycle (run-in) group, 42 in the 1.2 mg/m^2/cycle (randomized) group, and 38 in the 1.8 mg/m^2/cycle (randomized) group.
The patients' demographics and baseline characteristics are shown in Table 1. The median age was 40.5 years (range, 18-75). The majority of patients were male (54.9%) and White (74.5%). Thirty-six participants (35.3%) had a normal karyotype, 33 (32.4%) had an abnormal karyotype, and seven (21.2%) were Philadelphia chromosome-positive. Forty-six participants (45.1%) received one line of salvage therapy and 56 (54.9%) received two or more lines of salvage treatment. Twenty-nine participants (28.4%) had previously undergone HSCT. The median peripheral blood blast count was 0.52×10^9/L (range, 0-95×10^9/L). Seventy participants (68.6%) had ≥50% bone marrow blasts. Median baseline central CD22 expression (leukemic blast positivity) at screening was 96.57% (range, 15-100%). At baseline, risk factors for post-HSCT SOS included prior HSCT (N=29; 28.4%), ≥2 lines of salvage treatment (N=56; 54.9%), age ≥55 years (N=24; 23.5%), and prior or ongoing hepatic disease (N=35; 34.3%). In patients who proceeded to HSCT, eight (18.6%) received dual alkylator conditioning.

Hematologic remission

Remission and survival outcomes are shown in Table 2. In the run-in phase the CR/CRi rate was 50.0% (11/22 patients; CR N=5; 22.7%). Of the 11 patients who entered CR/CRi, eight patients (72.7%) reached MRD negativity, and seven (63.6%) subsequently progressed or died during the study. The median duration of remission was 5.2 months (95% CI: 1.9 months - not estimable).
In the randomized part of the study, the CR/CRi rate was 83.3% (35/42 patients; CR N=24; 57.1%) in the 1.2 mg/m^2/cycle group, with 71.4% reaching MRD negativity. In the 1.8 mg/m^2/cycle group, the CR/CRi rate was 68.4% (26/38 patients; CR N=13; 34.2%) with 69.2% reaching MRD negativity. The CR/CRi rate was 71.9% (46/64 patients) in the patients given 1.2 mg/m^2/cycle (run-in and randomized). The median duration of remission was 5.5 months (95% CI: 4.7-13.4 months) for the patients given 1.2 mg/m^2/cycle (run-in and randomized).
Of the 35 patients who achieved CR/CRi in the 1.2 mg/m^2/cycle (randomized) group, the median duration of remission was 6.5 months (95% CI: 4.6-20.9 months). Of the 26 patients who achieved CR/CRi in the 1.8 mg/m^2/cycle (randomized) group, the median duration of remission was 6.8 months (95% CI: 4.7-10.6 months).

Rate of sinusoidal obstruction syndrome

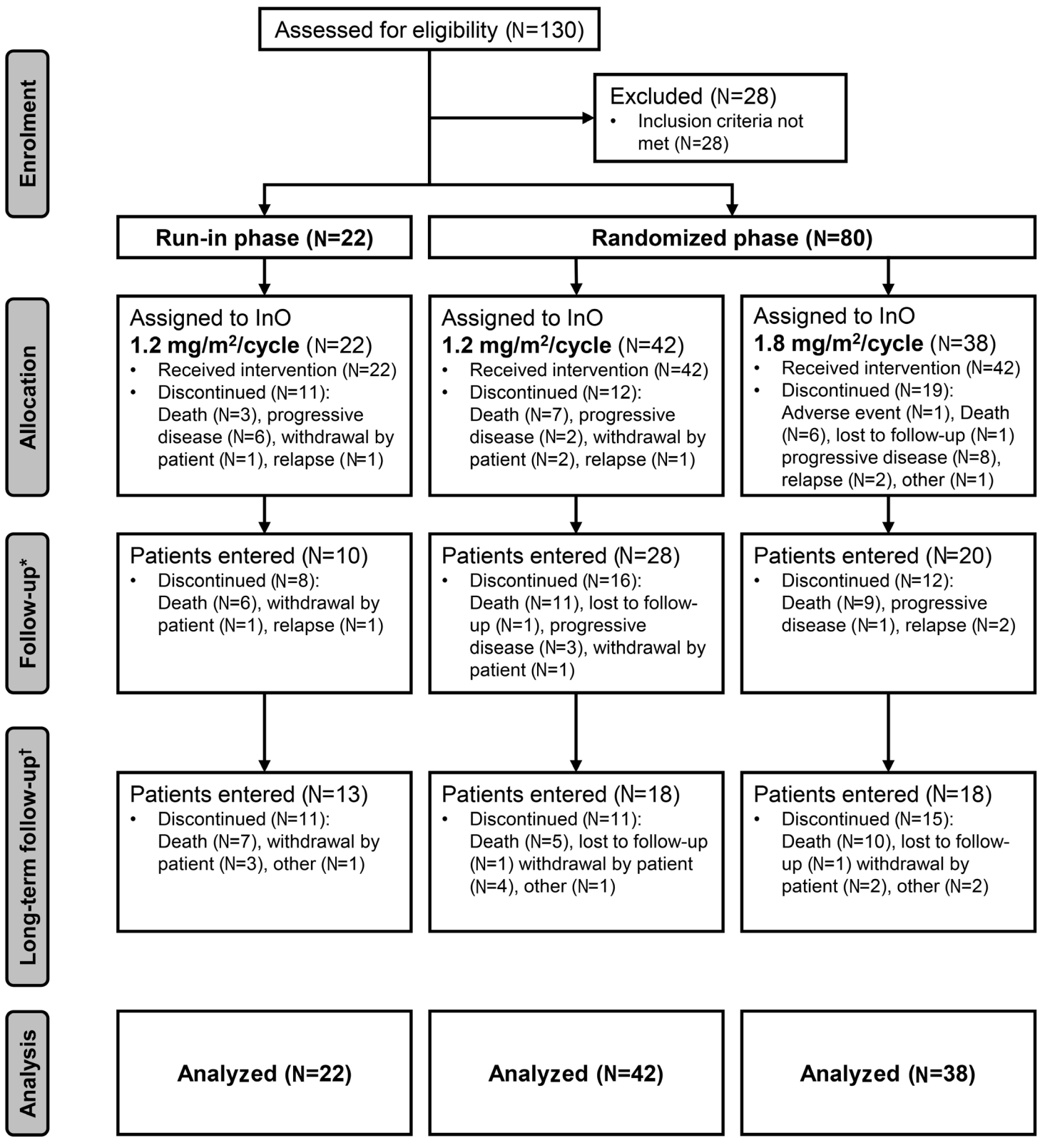
In total, SOS (during study treatment, after HSCT, and overall) was reported in ten patients (9.8%). In all cases (100%) the SOS occurred after HSCT. Of eight patients who had a transplant both before and after InO, two (25%) developed SOS. Of the 35 transplanted patients who did not have a transplant prior to InO, eight (23%) developed SOS (Table 3). Of the ten patients experiencing SOS, three had received dual alkylator conditioning.
In the 1.2 mg/m^2/cycle (run-in) group, SOS was reported in two patients (9.1%): one case was grade 2 and was not resolved at the time of the patient's death (cause: sepsis), and one case was grade 5 and led to a fatal outcome. In the 1.2 mg/m^2/cycle (randomized) group, SOS was reported in six patients (14.3%): one case was grade 4, one case was grade 3, three cases were grade 2, and the grade was unknown in one case. The patient with SOS of unknown grade had concomitant graft-*versus*-host disease and hepatosplenic candidiasis, which led to a fatal outcome. In the 1.8 mg/m^2/cycle (randomized) group, SOS was reported in two patients (5.3%): both cases were grade 3. *Online Supplementary Figure S1* shows SOS rate by SOS risk factors. The median time to post-HSCT SOS across all treatment groups was 0.79 months (range, 0.4-3.8 months).
In patients who proceeded to HSCT, post-HSCT SOS rates were 20.0%, 28.6%, 25.8%, and 16.7% in the 1.2 mg/m^2/cycle (run-in), 1.2 mg/m^2/cycle (randomized), 1.2 mg/m^2/cycle (run-in and randomized), and 1.8 mg/m^2/cycle (randomized) groups, respectively (Table 4).
Defibrotide was used in a total of four patients (1 in the 1.2

mg/m²/cycle run-in group, 2 in the 1.2 mg/m²/cycle randomized group, and 1 in the 1.8 mg/m²/cycle randomized group). *Online Supplementary Table S2* summarizes the association of baseline characteristics, time from last dose of InO to HSCT, and cumulative dose of InO with post-HSCT SOS; no associations were statistically significant.

Survival outcomes

The median event-free survival was 2.9 months (95% CI: 1.7-5.8 months) in the 1.2 mg/m²/cycle (run-in) group. In the randomized part of the study, the median event-free survival was 6.4 months (95% CI: 4.8-16.0 months) and 6.3 months (95% CI: 2.8-8.0 months) in the 1.2 mg/m²/cycle and 1.8 mg/m²/cycle groups, respectively (Figure 3). The median event-free survival was 5.3 months (95% CI: 3.4-7.2 months) in the patients given 1.2 mg/m²/cycle (run-in and randomized).

The median overall survival was 4.5 months (95% CI: 3.2-8.6 months), 9.6 months (95% CI: 6.4 months - not estimable), 7.6 months (95% CI: 5.8-10.0 months), and 8.1 months (95% CI: 5.4-10.4 months) in the 1.2 mg/m²/cycle (run-in), 1.2 mg/m²/cycle (randomized), 1.2 mg/m²/cycle (run-in and randomized) and 1.8 mg/m²/cycle (randomized) groups, respectively.



*Includes patients who completed treatment but did not progress.
†Includes patients who discontinued treatment due to disease progression or patients who completed treatment and follow-up.

Figure 2. Study flow chart. InO: inotuzumab ozogamicin.

Table 1. Demographic and baseline characteristics.

Characteristic	Starting dose of InO and trial phase				
	1.2 mg/m²/cycle (run-in) N=22	1.2 mg/m²/cycle (randomized) N=42	1.2 mg/m²/cycle (run-in + randomized) N=64	1.8 mg/m²/cycle (randomized) N=38	Total N=102
Age in years, median (range)	44.5 (20-67)	41.5 (18-75)	43.0 (18-75)	37.5 (19–69)	40.5 (18-75)
Male, N (%)	12 (54.5)	24 (57.1)	36 (56.3)	20 (52.6)	56 (54.9)
Race, N (%)					
White	17 (77.3)	34 (81.0)	51 (79.7)	25 (65.8)	76 (74.5)
Asian	5 (22.7)	6 (14.3)	11 (17.2)	11 (28.9)	22 (21.6)
ECOG PS, N (%)					
0	9 (40.9)	19 (45.2)	28 (43.8)	20 (52.6)	48 (47.1)
1	13 (59.1)	20 (47.6)	33 (51.6)	13 (34.2)	46 (45.1)
2	0	3 (7.1)	3 (4.7)	5 (13.2)	8 (7.8)
Prior HSCT, N (%)	6 (27.3)	12 (28.6)	18 (28.1)	11 (28.9)	29 (28.4)
Salvage ≥2, N (%)	15 (68.2)	23 (54.8)	38 (59.4)	18 (47.4)	56 (54.9)
Karyotype, N (%)					
Abnormal	10 (45.5)	14 (33.3)	24 (37.5)	9 (23.7)	33 (32.4)
Normal	4 (18.2)	14 (33.3)	18 (28.1)	18 (47.4)	36 (35.3)
Ph chromosome positive, N (%)	2 (20.0)	4 (28.6)	6 (25.0)	1 (11.1)	7 (21.2)
Peripheral blood blasts, x10⁹/L, median (range)	21.45 (6-37)	0.17 (0-56)	0.26 (0-56)	1.25 (0-95)	0.52 (0-95)
Bone marrow blasts ≥50%, N (%)	12 (54.5)	32 (76.2)	44 (68.8)	26 (68.4)	70 (68.6)
Baseline central CD22 expression, %, median (range)	N=19 97.96 (21-100)	N=33 95.08 (15-100)	N=52 97.00 (15-100)	N=30 95.26 (37-100)	N=82 96.57 (15-100)

InO: inotuzumab ozogamicin; ECOG PS: Eastern Cooperative Oncology Group performance status; HSCT: hematopoietic stem cell transplant; Ph: Philadelphia; CD22: cluster of differentiation-22.

Post-transplant outcomes

The follow-up HSCT rate (patients who received HSCT after their disease entered CR/CRi following InO treatment) was 42.2% in total: 45.5% in the 1.2 mg/m²/cycle (run-in), 50.0% in the 1.2 mg/m²/cycle (randomized), 48.4% in the 1.2 mg/m²/cycle (run-in and randomized), 48.4% in the 1.2 mg/m²/cycle (run-in and randomized), and 31.6% in the 1.8 mg/m²/cycle (randomized) groups.

Of the total 43 patients who received follow-up HSCT, myeloablative conditioning was administered to 70.0%, 62.0%, 64.5%, and 41.7% of patients; reduced intensity conditioning was administered to 30%, 28.6%, 29.0%, and 50.0% of patients; and conditioning was unknown in 0.0%, 9.5%, and 8.3% of patients in the 1.2 mg/m²/cycle (run-in), 1.2 mg/m²/cycle (randomized), 1.2 mg/m²/cycle (run-in and randomized), and 1.8 mg/m²/cycle (randomized) groups, respectively (*Online Supplementary Table S3*). HLA-matched (related/unrelated) was the most common donor type across all treatment groups, representing 70.0%, 71.4%, 71.0%, and 91.6% of donors in the 1.2 mg/m²/cycle (run-in), 1.2 mg/m²/cycle (randomized), 1.2 mg/m²/cycle (run-in and randomized), and 1.8 mg/m²/cycle (randomized) groups, respectively (*Online Supplementary Table S3*).

Time of transplant relative to last InO dose was <2 months for most patients across all dosing groups; 90.0%, 81.0%, 84.0%, and 91.7% of patients received their transplant <2 months after their last InO dose whereas 10.0%, 19.0%, 16.0%, and 8.3% of patients received their transplant ≥2 months after their last InO dose in the 1.2 mg/m²/cycle (run-in), 1.2 mg/m²/cycle (randomized), 1.2 mg/m²/cycle (run-in and randomized), and 1.8 mg/m²/cycle (randomized) groups, respectively.

The cumulative incidence rate of post-HSCT relapse at 18 months was 11.1% (95% CI: 0.4-41.7%) for the 1.2 mg/m²/cycle (run-in) group, 20.5% (95% CI: 6.0-41.0%) for the 1.2 mg/m²/cycle (randomized) group, 17.6% (95% CI: 6.2-33.8%) for the 1.2 mg/m²/cycle (run-in and randomized) group, and 26.7% (95% CI: 5.2-55.3%) for 1.8 mg/m²/cycle (randomized) group.

Post-HSCT mortality was defined as death from any cause from the date of first HSCT following InO treatment. The post-HSCT mortality rate was 60.0%, 38.1%, 45.2%, and 50.0% in patients who received HSCT after InO treatment in the 1.2 mg/m²/cycle (run-in), 1.2 mg/m²/cycle (randomized), 1.2 mg/m²/cycle (run-in and randomized), and 1.8 mg/m²/cycle (randomized) groups, respectively (Table 4).

Of those who proceeded to HSCT, one patient (10%), three patients (14.3%), four patients (12.9%), and two patients

(16.7%) in the 1.2 mg/m²/cycle (run-in), 1.2 mg/m²/cycle (randomized), 1.2 mg/m²/cycle (run-in and randomized), and 1.8 mg/m²/cycle (run-in) groups, respectively, had post-HSCT relapse-related death.

With regard to non-relapse mortality, five (50.0%) participants in the 1.2 mg/m²/cycle (run-in) group died following HSCT of causes other than relapse. The reasons for the deaths included adverse events not related to study treatment in two participants, clinical sepsis in one participant, toxoplasmosis in one participant and study treatment toxicity (SOS) in one participant. Five (23.8%) participants in the 1.2 mg/m²/cycle (randomized) group died of non-relapse causes following HSCT: in three cases from adverse events not related to the study treatment and in two cases from unknown causes. Four (33.3%) participants in the 1.8 mg/m²/cycle (randomized) group died following HSCT of causes other than relapse: one died of septic shock and three from adverse events not related to the study treatment.

Online Supplementary Table S4 summarizes the association of baseline characteristics, time from last dose of InO to HSCT, and cumulative dose of InO with post-HSCT non-relapse mortality; no associations were statistically significant.

Table 2. Remission and survival outcomes (intention-to-treat population).

Outcomes	Starting dose of InO and trial phase			
	1.2 mg/m²/cycle (run-in) N=22	1.2 mg/m²/cycle (randomized) N=42	1.2 mg/m²/cycle (run-in + randomized) N=64	1.8 mg/m²/cycle (randomized) N=38
CR/CRi, N (%)	11 (50.0)	35 (83.3)	46 (71.9)	26 (68.4)
CR	5 (22.7)	24 (57.1)	29 (45.3)	13 (34.2)
CRi	6 (27.3)	11 (26.2)	17 (26.6)	13 (34.2)
MRD negativity,[a] N (%)	8 (72.7)	25 (71.4)	33 (71.7)	18 (69.2)
Time to remission in months,[b] median (range)	0.76 (0.6-0.9)	0.95 (0.0-2.8)	0.90 (0.0-2.8)	0.90 (0.7-2.5)
DoR in months,[b] median (95% CI)	5.2 (1.1-NR)	6.5 (4.6-20.9)	5.5 (4.7-13.4)	6.8 (4.7-10.6)
EFS in months, median (95% CI)	2.9 (1.7-5.8)	6.4 (4.8-16.0)	5.3 (3.4-7.2)	6.3 (2.8-8.0)
6-month probability, % (95% CI)	25.8 (9.5-45.9)	59.1 (42.0-72.6)	48.0 (34.8-60.1)	50.9 (33.1-66.2)
12-month probability, % (95% CI)	15.5 (3.9-34.3)	36.2 (21.1-51.5)	29.3 (18.1-41.5)	18.2 (6.8-34.0)
18-month probability % (95% CI)	15.5 (3.9-34.3)	32.1 (17.4-47.9)	26.9 (15.9-39.2)	12.1 (2.8-28.8)
24-month probability % (95% CI)	15.5 (3.9-34.3)	NE (NE)	23.5 (12.7-36.3)	NE (NE)
OS in months, median (95% CI)	4.5 (3.2-8.6)	9.6 (6.4-NE)	7.6 (5.8-10.0)	8.1 (5.4-10.4)
6-month probability, % (95% CI)	42.9 (21.8-62.6)	72.8 (56.2-83.9)	62.6 (49.2-73.4)	66.7 (48.7-79.6)
12-month probability, % (95% CI)	18.8 (5.0-39.4)	45.6 (29.4-60.5)	36.8 (24.4-49.2)	28.6 (14.4-44.5)
24-month probability, % (95% CI)	18.8 (5.0-39.4)	37.0 (21.8-52.2)	31.0 (19.3-43.3)	22.2 (9.9-37.6)
Proceeded to HSCT, N (%)	10 (45.5)	21 (50.0)	31 (48.4)	12 (31.6)

[a]Minimum MRD <0.01%; percentage based on number of patients who achieved CR/CRi; assessed based on flow cytometry at Navigate (Carlsbad, CA, USA). [b]In patients who achieved CR/CRi. InO: inotuzumab ozogamicin; CR: complete remission; CRi: complete remission with incomplete hematologic recovery; MRD: minimal residual disease; DoR: duration of remission; NE: not estimable; NR: not reached; 95% CI: 95% confidence interval; EFS: event-free survival; OS: overall survival; HSCT: hematopoietic stem cell transplant.

Table 3. Sinusoidal obstruction syndrome.

Participants and SOS	Starting dose of InO and trial phase				
	1.2 mg/m²/cycle (run-in) N=22	1.2 mg/m²/cycle (randomized) N=42	1.2 mg/m²/cycle (run-in + randomized) N=64	1.8 mg/m²/cycle (randomized) N=38	Total N=102
Participants with prior HSCT, N (%)	6 (27.3)	12 (28.6)	18 (28.1)	11 (28.9)	29 (28.4)
Participants without prior HSCT, N (%)	16 (72.7)	30 (71.4)	46 (71.9)	27 (71.1)	73 (71.6)
Participants reporting SOS, N (%)	2 (9.1)	6 (14.3)	8 (12.5)	2 (5.3)	10 (9.8)
During treatment or follow-up without HSCT, N	0	0	0	0	0
Following post-study HSCT, N	2	6	8	2	10
With prior HSCT, N	1	1	2	0	2
Without prior HSCT, N	1	5	6	2	8
Time to SOS post HSCT in months, median (range)	0.71 (0.5-1.0)	0.67 (0.4-3.8)	0.67 (0.4-3.8)	0.79 (0.7-0.9)	0.79 (0.4-3.8)

InO: inotuzumab ozogamicin; SOS: sinusoidal obstruction syndrome; HSCT: hematopoietic stem cell transplant.

Table 4. Post-transplant outcomes.

Patients who received follow-up HSCT	Starting dose of InO and trial phase			
	1.2 mg/m²/cycle (run-in) N=10	1.2 mg/m²/cycle (randomized) N=21	1.2 mg/m²/cycle (run-in + randomized) N=31	1.8 mg/m²/cycle (randomized) N=12
Patients who reported post-HSCT SOS, N (%)	2 (20)	6 (28.6)	8 (25.9)	2 (16.7)
Patients who died post HSCT, N (%)	6 (60.0)	8 (38.1)	14 (45.2)	5 (41.7)
Probability of being alive at:				
6 months (95% CI)	0.333 (0.078-0.623)	0.702 (0.453-0.854)	0.589 (0.391-0.742)	0.667 (0.337-0.860)
12 months (95% CI)	0.333 (0.078-0.623)	0.602 (0.359-0.777)	0.520 (0.328-0.682)	0.583 (0.270-0.801)
18 months (95%, CI)	0.333 (0.078-0.623)	0.602 (0.359-0.777)	0.520 (0.328-0.682)	0.486 (0.192-0.730)
24 months (95%, CI)	NE (NE)	NE (NE)	NE (NE)	NE (NE)
Patients with post-HSCT relapse-related mortality adjusting for competing risks, N (%)	1 (10)	3 (14.3)	4 (12.9)	1 (8.3)
Patients with post-HSCT NRM adjusting for competing risks, N (%)	5 (50.0)	5 (23.8)	10 (32.3)	4 (33.3)

InO: inotuzumab ozogamicin; HSCT: hematopoietic stem cell transplant; SOS: sinusoidal obstruction syndrome; 95% CI: 95% confidence interval; NE: not estimable; NRM: non-relapse-related mortality.

Safety outcomes

A summary of treatment-emergent adverse effects can be found in Table 5. Most patients, 95 (93.1%) of the total evaluable, experienced ≥1 treatment-emergent adverse event and 64 (62.7%) experienced a treatment-emergent serious adverse event.

Across all treatment groups, the most frequently reported all-grade treatment-emergent adverse events (≥20%) were hematologic: thrombocytopenia (N=32; 31.4%) and neutropenia (N=30; 29.4%). Five (22.7%), 14 (33.3%), and 13 patients (34.2%) experienced thrombocytopenia in the 1.2 mg/m²/cycle (run-in), 1.2 mg/m²/cycle (randomized), and 1.8 mg/m²/cycle (randomized) groups, respectively. Four (18.2%), 16 (38.1%), and ten patients (26.3%) experienced neutropenia in the 1.2 mg/m²/cycle (run-in), 1.2 mg/m²/cycle (randomized), and 1.8 mg/m²/cycle (randomized) groups, respectively.

The most frequently reported all-grade adverse events according to system organ class across all treatment groups were blood and lymphatic system disorders, reported in 56 patients (54.9%), and infections and infestations, reported in 47 patients (46.1%).

Grade ≥3 infections and infestations were reported in nine (41%), 17 (40%), and nine patients (24%) in the 1.2 mg/m²/cycle (run-in), 1.2 mg/m²/cycle (randomized), and 1.8 mg/m²/cycle (randomized) groups, respectively.

Two participants experienced adverse events reported as drug-induced liver injury. One patient in the 1.2 mg/m²/cycle (randomized) group experienced grade 2 drug-induced liver injury on study day 99 which was resolved on study day 105 and was considered related to InO by the investigator. One patient in the 1.8 mg/m²/cycle (randomized) group experienced grade 2 drug-induced liver injury on study day 77 and recovered on study day 83. The investigator considered this event to be unrelated to InO. In the 1.2 mg/m²/cycle (run-in and randomized) group, blood bilirubin increased in two patients who had a shift from grade 0 at baseline to grade 3 after baseline. Increased levels of aspartate aminotransferase and alanine aminotransferase were common treatment-emergent adverse events across all groups. Five (22.7%), five (11.9%), and three patients (7.9%) in the 1.2 mg/m²/cycle (run-in), 1.2 mg/m²/cycle (randomized), and 1.8 mg/m²/cycle (randomized) groups, respectively, experienced increased alanine aminotransferase. Increased aspartate aminotransferase occurred in four (18.2%), three (7.1%), and eight patients (21.1%) in the 1.2 mg/m²/cycle (run-in), 1.2 mg/m²/cycle (randomized), and 1.8 mg/m²/cycle (randomized) groups, respectively. Four (18.2%), three (7.1%), and eight patients (21.1%) had hemorrhage in the 1.2 mg/m²/cycle (run-in), 1.2 mg/m²/cycle (randomized), and 1.8 mg/m²/cycle (randomized) groups, respectively.

In the 1.2 mg/m²/cycle (run-in) group, two patients (9.1%) discontinued treatment and two patients (9.1%) had an interruption of the study drug due to a treatment-emergent adverse event. In the 1.2 mg/m²/cycle (randomized) group, three patients (7.1%) discontinued treatment and seven (16.7%) had a study drug interruption due to a treatment-emergent adverse event. In the 1.8 mg/m²/cycle (randomized) group, nine patients (23.7%) discontinued treatment and ten (26.3%) had a study drug interruption due to a treatment-emergent adverse event. There were no dose reductions due to adverse events.

A total of 66 patients (64.7%) died across all treatment groups. The most common cause of death was an adverse event not related to the study treatment (N=30; 29.4%), followed by disease progression (N=21; 20.6%). One patient died as a result of SOS, and another of SOS with concomitant hepatic graft-*versus*-host disease and hepatosplenic candidiasis.

Overall, eight (36.4%), three (7.1%), and four patients (10.5%)

were hospitalized in the 1.2 mg/m^2/cycle (run-in), 1.2 mg/m^2/cycle (randomized), and 1.8 mg/m^2/cycle (run-in) groups, respectively; the median duration of hospitalization in days was 46 (range, 10-110), 82 (range, 16-90), and 15 (range, 7-23) in the respective groups.

Pharmacokinetics

Following multiple doses of InO (cycle 3, day 1), the mean peak serum concentrations in the 1.2 mg/m^2/cycle (run-in), 1.2 mg/m^2/cycle (randomized), 1.2 mg/m^2/cycle (run-in and randomized), and 1.8 mg/m^2/cycle (randomized) groups were 122 ng/mL, 140 ng/mL, 135 ng/mL, and 351 ng/mL, respectively. The InO exposures in patients receiving 1.2 mg/m^2/cycle were consistently lower than those in the patients receiving 1.8 mg/m^2/cycle.

Immunogenicity

Of the 101 participants tested for anti-drug antibody, six patients (5.9%) were positive at pre-dose, and none of them had treatment-boosted anti-drug antibody. Two patients (2.0%) had treatment-induced anti-drug antibody. The overall incidence of anti-drug antibody was 2.0%.

Neutralizing antibody was not detected in any of the eight patients whose sera tested positive for anti-InO antibodies.

Discussion

This study evaluated the safety and efficacy of two dose levels of InO in adults with R/R ALL who were eligible for HSCT and who had a higher risk of post-HSCT SOS. Overall,

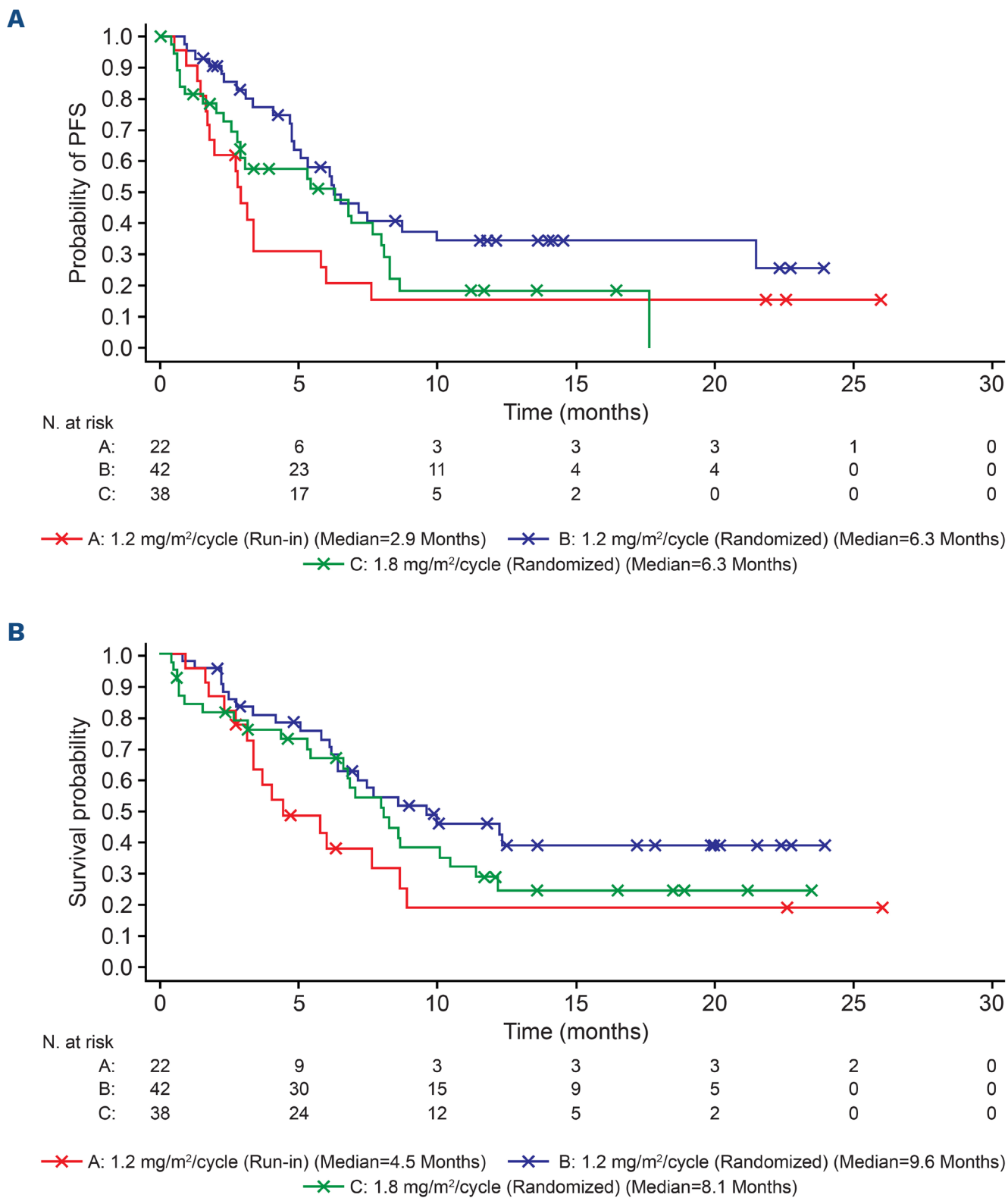


Figure 3. Kaplan-Meier plots of survival outcomes. (A) Progression-free survival. (B) Overall survival. PFS: progression-free survival.

Table 5. Summary of treatment-emergent adverse events.

Adverse events	Starting dose of InO and trial phase				
	1.2 mg/m²/cycle (run-in) N=22	1.2 mg/m²/cycle (randomized) N=42	1.2 mg/m²/cycle (run-in + randomized) N=64	1.8 mg/m²/cycle (randomized) N=38	Total N=102
Participants evaluable for AE, N	22	42	64	38	102
AE, N	117	239	356	203	559
Participants with AE, N (%)	21 (95.5)	39 (92.9)	60 (93.8)	35 (92.1)	95 (93.1)
Participants with serious AE, N (%)	15 (68.2)	28 (66.7)	43 (67.2)	21 (55.3)	64 (62.7)
Participants with maximum grade 3 or 4 AE, N (%)	9 (40.9)	21 (50.0)	30 (46.9)	18 (47.4)	48 (47.1)
Participants with maximum grade 5 AE, N (%)	7 (31.8)	12 (28.6)	19 (29.7)	10 (26.3)	29 (28.4)
Participants with AE leading to treatment discontinuation, N (%)	2 (9.1)	3 (7.1)	5 (7.8)	9 (23.7)	14 (13.7)
Participants with AE leading to study drug reduction, N (%)	0	0	0	0	0
Participants with AE leading to study drug interruption, N (%)	2 (9.1)	7 (16.7)	9 (14.1)	10 (26.3)	19 (18.6)

InO: inotuzumab ozogamicin; AE: adverse events

efficacy appeared to be similar across the two dose levels, with the majority of patients achieving remission (CR or CRi) and the majority of those in remission achieving MRD negativity. Efficacy endpoints in the lower-dose treatment group (1.2 mg/m²/cycle) were similar to those of the currently approved dosage (1.8 mg/m²/cycle).

Exposure response analysis demonstrated that there was a statistically significant relationship between InO exposure and achieving CR/CRi (*unpublished data*) which is consistent with what has been previously published.[9] Participants with higher InO exposure were more likely to achieve CR/CRi. In addition, the phase III INO-VATE study demonstrated a statistically significant and clinically meaningful improvement in CR/CRi for InO at 1.8 mg/m²/cycle compared with control observed for all patients.[7,8]

The number of patients achieving remission was also similar to that observed in the INO-VATE phase III clinical trial. In the randomized part of this study, 71.9% of patients in the 1.2 mg/m²/cycle group, and 68.4% in the 1.8 mg/m²/cycle group achieved remission, compared with 73.8% in the INO-VATE trial.[7] It is worth noting that patients in the INO-VATE study were less heavily pretreated; approximately two-thirds of patients were at salvage 1 with the remaining at salvage 2. Additionally, fewer patients in the INO-VATE study had previously undergone HSCT.[7]

While some differences were observed between dose levels, such as higher rates of treatment discontinuations and interruptions at the 1.8 mg/m²/cycle dose level, no substantial differences were observed in survival, duration of remission, and event-free survival between patients receiving the two dose levels. Secondary efficacy endpoints were again similar to those observed in the INO-VATE trial. Of the randomized patients who achieved remission, the median duration of remission was 6.5 months in the 1.2 mg/m²/cycle group and 6.8 months in the 1.8 mg/m²/cycle group, compared with 5.4 months in the INO-VATE trial. Similarly, in the randomized part of this study, the median event-free survival was 6.4 months in the 1.2 mg/m²/cycle group and 6.3 months in the 1.8 mg/m²/cycle group, compared with 5.0 months in the INO-VATE trial.[7]

Overall, SOS rates were not reduced at the lower dose of 1.2 mg/m²/cycle compared with 1.8 mg/m²/cycle. Ten cases of SOS occurred, and all were following HSCT. Rates of post-HSCT SOS were higher in both 1.2 mg/m²/cycle groups than in the 1.8 mg/m²/cycle group. SOS rates after HSCT were 20%, 28.6%, and 16.7% in the 1.2 mg/m²/cycle (run-in), 1.2 mg/m²/cycle (randomized), and 1.8 mg/m²/cycle (randomized) groups, respectively. However, this should be interpreted with caution given the small numbers of patients in each group who received HSCT after InO (N=10, N=21, N=12 in the 1.2 mg/m²/cycle run-in, 1.2 mg/m²/cycle randomized, and 1.8 mg/m²/cycle randomized groups, respectively). This also applies to any inferences about the impact of differences within subgroups, such as the lower rate of myeloablative conditioning in the 1.8 mg/m² group. In the INO-VATE clinical trial, the rate of post-HSCT SOS in adult patients with R/R ALL previously treated with InO was 22.8%.[7] The literature reports similar rates of post-HSCT SOS in patients with ALL treated with InO. A previous study of 26 patients (adults and children) with advanced ALL who received allogeneic HSCT after treatment with InO (doses of 1.8 mg/m², with the first 3 adults and children receiving doses of 1.3 mg/m²) reported post-HSCT SOS in 19% of patients.[7,10] Other studies investigating patients with R/R ALL receiving HSCT after InO have reported post-HSCT SOS rates of 8-19%.[11-14]

Overall, the rates of post-HSCT SOS in the current study were similar to those previously reported in patients with

ALL receiving InO prior to HSCT.[7] However, the patients in this study were selected for being at higher risk of SOS, particularly when compared to the patients in the INO-VATE study, with 28.4% of patients in this study having had a prior HSCT and 54.9% of patients being at salvage 2 or higher. These data suggest that clinicians may be enacting practices other than dose reduction that lower the risk of SOS after InO, such as limiting the number of cycles prior to HSCT, or administering ursodeoxycholic acid concomitantly prior to transplant.[15,16]

It is worth noting that rates of those who proceeded to HSCT were higher in this study than previously reported with blinatumomab (42.2% *vs*. 24%). It is also notable that the INO-VATE trial found an association between number of treatment cycles with InO and increased risk of post-HSCT SOS, suggesting that the number of treatment cycles could potentially contribute to the risk of post-HSCT SOS.[7] The relationship between InO exposure and SOS has previously been reported based on data from 234 patients.[9] The analyses demonstrated that InO exposure was significantly correlated with hepatic event adjudication board-reported SOS. However, InO exposure did not have a statistically significant positive relationship with investigator-reported SOS.[9] Exposure-response analysis using data from this study demonstrated there were no statistically significant relationships between InO exposure and investigator-reported SOS (*data not shown*), consistent with previous findings.

This study indicates that the current FDA-approved higher dose of 1.8 mg/m^2/cycle[4] provides a favorable balance of safety and efficacy as compared to the lower dose of 1.2 mg/m^2/cycle in adult patients with R/R ALL. Reducing the InO starting dose is not recommended. Instead, other measures should be considered to reduce the risk of SOS, for example, limiting InO exposure to one or two cycles before HSCT.[15]

This analysis is limited by the relatively small sample size, particularly when considering the number of patients who proceeded to HSCT. Nevertheless, post-HSCT SOS rates were similar to those reported in the literature, and this study addresses the limited evidence regarding SOS risk with reduced doses of InO. No new safety signals were identified. A correlation analysis between the expression of CD22 and response rates was not performed in this study. Lastly, the observed InO concentrations in patients receiving 1.2 mg/m^2/cycle were consistently lower than those in patients receiving 1.8 mg/m^2/cycle in this study. The observed InO exposures in patients receiving 1.8 mg/m^2/cycle in this study were similar to those in patients receiving 1.8 mg/m^2/cycle in the INO-VATE trial.

In conclusion, the results of this study suggest that the efficacy of InO is consistent across both dose groups. Efficacy in the lower dose treatment group (1.2 mg/m^2/cycle) was similar to that of the currently approved dosage (1.8 mg/m^2/cycle). Rates of post-HSCT SOS in this study were similar across doses and similar to rates reported in previous studies in patients with ALL who received InO prior to HSCT. Overall, these results add to the limited literature on the safety and efficacy of lower doses of InO in patients with ALL prior to HSCT; however, this study provides insufficient evidence to conclude that dose reduction improves safety.

Disclosures

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Contributions

MO, RC, EZ, EV, FZ, YC, AN, FD, PM, and FA authored the manuscript. FZ was also the statistician for the manuscript.

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Data-sharing statement

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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