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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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Running head: Safety and efficacy of InO before HSCT in R/R ALL

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Data accessibility: 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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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 versus chemotherapy prior to HSCT. It is unknown if a lower InO dose would reduce risk of post-HSCT SOS or if it would impact 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 4 study (NCT03677596) had 2 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 10 patients (9.8%); all were 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), respectively. The CR/CRi rates were 50.0%, 83.3%, 71.9%, and 68.4% in the respective subgroups.

The study found that a starting dose of 1.2mg/m^2/cycle demonstrated consistent efficacy and safety to 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 (OS) 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 in the US, the European Union, and many countries globally for R/R ALL.[4, 5] The approved starting dose is 1.8 mg/m^2/cycle in 3 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 3 clinical trial, patients receiving InO versus standard of care had a higher rate of CR/CRi (80.7% [95% CI, 72-88%] vs 29.4% [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 and whether this would impact efficacy.

This phase 4 study (NCT03677596) was a post-marketing requirement of the US Food and Drug Administration and investigates 2 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) for 2 dose levels of InO in adults with R/R ALL who are eligible for HSCT and who have a higher risk of post-HSCT SOS.

METHODS

Study design and interventions

This open-label, phase 4 study (NCT03677596) was conducted between July 1, 2019, and September 21, 2022, in 33 sites across 8 countries. The study had 2 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 at 1.2 mg/m^2/cycle administered over 3 divided doses (0.6 mg/m^2 on Day 1, 0.3 mg/m^2 on Days 8 and 15), and after CR/CRi was achieved the dose was reduced to 0.9 mg/m^2 administered over 3 divided doses (0.3 mg/m^2 on Days 1, 8, and 15). A Simon's 2-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 over 3 divided doses on Days 1, 8, and 15) or 1.2 mg/m^2/cycle (administered over 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 was 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, 2 cycles of InO were recommended, with the option of a third cycle for patients who did not achieve CR/CRi and MRD negativity after 2 cycles. Per study protocol, patients who did not achieve CR/CRi within 3 cycles in the 1.8 mg/m^2/cycle arm or within 4 cycles in the 1.2 mg/m^2/cycle arm were discontinued from treatment.

Participants

Eligible patients were adults aged 18-75 years with R/R precursor CD22-positive B-cell ALL with M2 or M3 marrow (≥5% blasts), Eastern Cooperative Oncology Group (ECOG) performance status 0-2, were eligible for HSCT, and had ≥1 risk factor for developing SOS (aged ≥55 years; due to receive second salvage or greater, received prior HSCT; and/or ongoing or prior hepatic disease—including prior history of hepatitis or drug-induced liver injury, as well as hepatic steatosis, nonalcoholic steatohepatitis, baseline elevations of bilirubin > upper limit of normal [ULN] and ≤1.5 x ULN). Patients with Ph+ ALL must have experienced failure of at least 1 second- or third-generation tyrosine kinase inhibitor and standard multi-agent induction chemotherapy.

Full inclusion and exclusion criteria are provided in **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, OS, duration of remission (DoR), event-free survival (EFS; 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 occurs 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 supplementary materials.

RESULTS

Participant 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), 42 in the 1.2 mg/m^2/cycle (randomized), and 38 in the 1.8 mg/m^2/cycle (randomized).

Patient demographics and baseline characteristics are shown in **Table 1**. 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 normal karyotype, 33 (32.4%) had abnormal karyotype, and 7 (21.2%) were Philadelphia chromosome–positive (Ph+). Forty-six participants (45.1%) received 1 line of salvage therapy and 56 (54.9%) received ≥2 salvage lines. Twenty-nine participants (28.4%) had prior HSCT. Median peripheral blood blasts count was 0.52 × 10^9/L (range: 0-95 × 10^9/L). Seventy participants (68.6%) had bone marrow blasts ≥50%. 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%), salvage ≥2 (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, 8 (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, 8 patients (72.7%) reached MRD negativity, and 7 (63.6%) subsequently progressed or died during the study. The median DoR was 5.2 months (95% CI: 1.9 months, NE).

In the randomized part of the study, the CR/CRi rate was 83.3% (35/42 patients; CR n=24; 57.1%) for 1.2 mg/m^2/cycle, 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) at 1.2 mg/m^2/cycle (run-in and randomized). The median DoR was 5.5 months (95% CI: 4.7, 13.4 months) for the 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 DoR 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 DoR was 6.8 months (95% CI, 4.7, 10.6 months).

Rate of SOS

In total, SOS (during study treatment, post HSCT, and overall) was reported in 10 patients (9.8%). All of these (100%) were post-HSCT SOS. Of 8 patients who had a transplant both before and after InO, 2 (25%) developed SOS. Of the 35 transplanted patients who did not have a transplant prior to InO, 8 (23%) developed SOS. (**Table 3**). Of the 10 patients experiencing SOS, 3 had received dual alkylator conditioning.

In the 1.2 mg/m^2/cycle (run-in), SOS was reported in 2 patients (9.1%): 1 was grade 2 and was not resolved at the time of the patient's death (cause: sepsis), and 1 was grade 5 and led to a fatal outcome. In the 1.2 mg/m^2/cycle (randomized), SOS was reported in 6 patients (14.3%): 1 case was grade 4, 1 case was grade 3, 3 cases were grade 2, and 1 case was grade unknown. The patient with unknown grade SOS had concomitant graft-versus-host disease and hepatosplenic candidiasis, which led to a fatal outcome. In the 1.8 mg/m^2/cycle (randomized), SOS was reported in 2 patients (5.3%): both cases were grade 3. **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).

In patients who proceeded to HSCT, post-HSCT SOS rates were 20.0%, 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), respectively (**Table 4**).

Defibrotide was used in a total of 4 patients (1 in 1.2 mg/m^2/cycle run-in, 2 in 1.2 mg/m^2/cycle randomized, and 1 in 1.8 mg/m^2/cycle randomized).

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 EFS was 2.9 months (95% CI: 1.7, 5.8 months) in the 1.2 mg/m^2/cycle (run-in) group. In the randomized part of the study, the median EFS 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/m^2/cycle and 1.8 mg/m^2/cycle groups, respectively (**Figure 3**). The median EFS was 5.3 months (95% CI: 3.4, 7.2 months) in 1.2 mg/m^2/cycle (run-in and randomized).

The median OS was 4.5 months (95% CI: 3.2, 8.6 months), 9.6 months (95% CI: 6.4 months, NE), 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/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.

Post-HSCT 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 1.2 mg/m^2/cycle (run-in), 50.0% in 1.2 mg/m^2/cycle (randomized), 48.4% in 1.2 mg/m^2/cycle (run-in and randomized), 48.4% in 1.2 mg/m^2/cycle (run-in and randomized), and 31.6% in 1.8 mg/m^2/cycle (randomized).

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/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 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/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), respectively (**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 transplant <2 months after last InO dose versus 10.0%, 19.0%, 16.0%, and 8.3% of patients who received transplant ≥2 months after last InO dose 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.

The cumulative incidence rate of post-HSCT relapse at 18 months was 11.1% (95% CI: 0.4%, 41.7%) for 1.2 mg/m^2/cycle (run-in), 20.5% (95% CI: 6.0%, 41.0%) for 1.2 mg/m^2/cycle (randomized), 17.6% (95% CI: 6.2%, 33.8%) for 1.2 mg/m^2/cycle (run-in and randomized), and 26.7% (95% CI: 5.2%, 55.3%) for 1.8 mg/m^2/cycle (randomized).

Post-HSCT mortality was defined as death by 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 post InO 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**).

Of those that proceeded to HSCT, 1 patient (10%), 3 patients (14.3%), 4 patients (12.9%), and 2 patients (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 (run-in) groups, respectively, had post-HSCT relapse-related death.

Five (50.0%) participants in the 1.2 mg/m^2/cycle (run-in) had post-HSCT non-relapse mortality (NRM). The reason for the deaths included AEs not related to study treatment in 2

participants, clinical sepsis in 1 participant, toxoplasmosis in 1 participant and study treatment toxicity (SOS) in 1 participant. Five (23.8%) participants in the 1.2 mg/m^2/cycle (randomized) had post-HSCT NRM, including AEs not related to study treatment in 3 participants and unknown cause in 2 participants. Four (33.3%) participants in 1.8 mg/m^2/cycle (randomized) had post-HSCT NRM including septic shock in 1 participant and AEs not related to study treatment in 3 participants.

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 NRM; no associations were statistically significant.

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 (TEAE), and 64 (62.7%) experienced a treatment-emergent serious adverse event (TESAE).

Across all treatment groups, the most frequently reported all-grade TEAEs (≥20%) were hematological AEs: 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/m^2/cycle (run-in), 1.2 mg/m^2/cycle (randomized), and 1.8 mg/m^2/cycle (randomized) groups, respectively. Four (18.2%), 16 (38.1%), and 10 patients (26.3%) experienced neutropenia in the 1.2 mg/m^2/cycle (run-in), 1.2 mg/m^2/cycle (randomized), and 1.8 mg/m^2/cycle (randomized) groups, respectively.

The most frequently reported all-grade AEs of 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 9 (41%), 17 (40%), and 9 patients (24%) in the 1.2 mg/m^2/cycle (run-in), 1.2 mg/m^2/cycle (randomized), and 1.8 mg/m^2/cycle (randomized) groups, respectively.

Two participants experienced AEs reported as drug-induced liver injury (DILI). One patient in the 1.2 mg/m^2/cycle (randomized) experienced grade 2 DILI 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/m^2/cycle (randomized) experienced grade 2 DILI on Study Day 77 and recovered on Study Day 83. The investigator considered the DILI event to be unrelated to InO. In the 1.2 mg/m^2/cycle (run-in and randomized), blood bilirubin increased in 2 patients who had a shift from grade 0 at baseline to grade 3 post baseline. Increased aspartate aminotransferase (AST) and increased alanine aminotransferase (ALT) were common TEAEs across all groups. Five (22.7%), 5 (11.9%), and 3 patients (7.9%) in the 1.2 mg/m^2/cycle (run-in), 1.2 mg/m^2/cycle (randomized), and 1.8 mg/m^2/cycle (randomized) groups, respectively, experienced increased ALT. Increased AST occurred in 4 (18.2%), 3 (7.1%), and 8 patients (21.1%) in the 1.2 mg/m^2/cycle (run-in), 1.2 mg/m^2/cycle (randomized), and 1.8 mg/m^2/cycle (randomized) groups, respectively. Four (18.2%), 3 (7.1%), and 8 patients (21.1%) had hemorrhage in the 1.2 mg/m^2/cycle (run-in), 1.2 mg/m^2/cycle (randomized), and 1.8 mg/m^2/cycle (randomized) groups, respectively.

In the 1.2 mg/m^2/cycle (run-in) group, 2 patients (9.1%) discontinued treatment and 2 patients (9.1%) had an interruption of the study drug due to a TEAE. In the 1.2 mg/m^2/cycle (randomized) group, 3 patients (7.1%) discontinued treatment and 7 (16.7%) had a study drug interruption due to a TEAE. In the 1.8 mg/m^2/cycle (randomized) group, 9 patients (23.7%) discontinued treatment and 10 (26.3%) had a study drug interruption due to a TEAE. There were no dose reductions due to AEs.

A total of 66 patients (64.7%) died across all treatment groups. The most common cause of death was AE not related to 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, 8 (36.4%), 3 (7.1%), and 4 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 (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 compared to those receiving 1.8 mg/m^2/cycle.

Immunogenicity

Of the 101 participants tested for anti-drug antibody (ADA), 6 patients (5.9%) were positive at pre-dose, and none of them had treatment-boosted ADA. Two patients (2.0%) had treatment-induced ADA. The overall ADA incidence was 2.0%.

Neutralizing antibody was not detected in any of the 8 patients whose sera tested positive for anti-InO antibodies.

DISCUSSION

This study evaluated the safety and efficacy of 2 dose levels of InO in adults with R/R ALL who are eligible for HSCT and who have a higher risk of post-HSCT SOS. Overall, efficacy appeared to be similar across the 2 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/m^2/cycle) was similar to that of the currently approved dosage (1.8 mg/m^2/cycle).

Exposure response analysis demonstrated that there was a statistically significant relationship between InO exposure and achieving CR/CRi (unpublished data) which is consistent what is previously published.[9] Participants with higher InO exposure are more likely to achieve CR/CRi. In addition, the phase 3 INO-VATE study demonstrated statistically

significant and clinically meaningful improvement in CR/CRi for InO at 1.8 mg/m^2/cycle compared to control observed for all patients.[7, 8]

The number of patients achieving remission was also similar to that observed in the INO-VATE phase 3 clinical trial. In the randomized part of this study, 71.9% of patients in the 1.2 mg/m^2/cycle group, and 68.4% 1.8 mg/m^2/cycle group achieved remission, compared with 73.8% in the INO-VATE trial.[7] It is worth noting that patients in the INOVATE 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 INOVATE study had prior HSCT. [7]

While some differences were observed between dose levels, such as higher rates of discontinuations and interruptions at the 1.8 mg/m^2/cycle dose level, no substantial differences were observed in survival, DoR, and EFS between the 2 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 DoR was 6.5 months in the 1.2 mg/m^2/cycle group, and 6.8 months in the 1.8 mg/m^2/cycle group, compared with 5.4 months in the INO-VATE trial. Similarly, in the randomized part of this study, the median EFS was 6.4 months in the 1.2 mg/m^2/cycle group and 6.3 months in 1.8 mg/m^2/cycle group, compared with 5.0 months in the INO-VATE trial.[7]

Overall, VOD rates were not reduced at the lower dose of 1.2 mg/m^2/cycle compared with 1.8 mg/m^2/cycle.Ten incidences of SOS occurred, and all were following HSCT. Rates of post-HSCT SOS were higher in both 1.2 mg/m^2/cycle groups compared with the 1.8 mg/m^2/cycle group. SOS rates post HSCT were 20%, 28.6%, and 16.7% in the 1.2 mg/m^2/cycle (run-in), 1.2 mg/m^2/cycle (randomized), and 1.8 mg/m^2/cycle (randomized) groups, respectively. However, this should be interpreted with caution given the small sample sizes of patients in each group who received HSCT post InO (n=10, n=21, n=12 in the 1.2 mg/m^2/cycle run-in, 1.2 mg/m^2/cycle randomized, and 1.8 mg/m^2/cycle randomized groups, respectively). This also applies to any inferences about the impact of differences within subgroups, such as the lower rate of MAC in the 1.8 mg/m^2 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/m^2, with the first 3 adults and children receiving doses of 1.3 mg/m^2) 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 reported 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 to be at higher risk of SOS, with 28.4% of patients with prior HSCT and 54.9% of patients being Salvage 2 or higher, particularly when compared to the patients in the INO-VATE study. These data suggest clinicians may be enacting practices other than dose reduction that reduce 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 the INO-VATE trial found an association between number of treatment cycles with InO and increased risk of post-HSCT SOS, suggesting number of treatment cycles could potentially contribute to risk of post-HSCT SOS.[7]

The relationship between InO exposure and SOS has previously been reported using 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 1-2 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 compared to those receiving 1.8 mg/m^2/cycle in this study. The observed InO exposures from patients receiving 1.8 mg/m^2/cycle in this study were similar to those from patients receiving 1.8 mg/m^2/cycle in INO-VATE trial.

CONCLUSIONS

The results of the study suggest that the efficacy of InO is consistent across both dose groups. Efficacy in the lower dose treatment group (1.2mg/m^2/cycle) was similar to that of the currently approved dosage (in 1.8mg/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.

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TABLES

Table 1. Demographic and baseline characteristics.

	Starting dose of InO and trial phase				
	1.2 mg/m^2/cycle (run-in) N=22	**1.2 mg/m^2/cycle (randomized) N=42**	**1.2 mg/m^2/cycle (run-in + randomized) N=64**	**1.8 mg/m^2/cycle (randomized) N=38**	**Total N=102**
Age, median (range), y	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 performance status, 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 status, n (%)					

Ph+	2 (20.0)	4 (28.6)	6 (25.0)	1 (11.1)	7 (21.2)
Peripheral blood blasts (x10^9/L), median (range)	21445 (5890–37000)	170.0 (0–56000)	260.0 (0–56000)	1245 (0–95000)	520.0 (0–95000)
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)

CD22, cluster of differentiation-22; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HSCT, hematopoietic stem cell transplant; InO, inotuzumab ozogamicin; Ph, Philadelphia.

Table 2. Remission and survival outcomes (ITT population).

	Starting dose of InO and trial phase			
	1.2 mg/m^2/cycle (run-in) N=22	1.2 mg/m^2/cycle (randomized) N=42	1.2 mg/m^2/cycle (run-in + randomized) N=64	1.8 mg/m^2/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 (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 (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 (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 (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.

CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; DoR, duration of remission; HSCT, hematopoietic stem cell transplant; InO, inotuzumab ozogamicin; ITT, intent to treat; MRD, minimal residual disease; NR, not reached; OS, overall survival; EFS, event-free survival.

Table 3. Sinusoidal obstruction syndrome.

	Starting dose of InO and trial phase				
	1.2 mg/m^2/cycle (run-in) N=22	**1.2 mg/m^2/cycle (randomized) N=42**	**1.2 mg/m^2/cycle (run-in + randomized) N=64**	**1.8 mg/m^2/cycle (randomized) N=38**	**Total N=102**
Number of participants with prior HSCT, n (%)	6 (27.3)	12 (28.6)	18 (28.1)	11 (28.9)	29 (28.4)
Number of 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	0	0	0	0	0
Following post-study HSCT	2	6	8	2	10
With prior HSCT	1	1	2	0	2
Without prior HSCT	1	5	6	2	8
Time to SOS post HSCT (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)

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

Table 4. Post-HSCT outcomes.

	Starting dose of InO and trial phase			
Number of patients who received follow-up HSCT, n	**1.2 mg/m^2/cycle (run-in) n=10**	**1.2 mg/m^2/cycle (randomized) n=21**	**1.2 mg/m^2/cycle (run-in + randomized) n=31**	**1.8 mg/m^2/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)
Number of patients with post-HSCT relapse-related mortality adjusting for competing risks, n (%)	1 (10)	3 (14.3)	4 (12.9)	1 (8.3)
Number of patients with post-HSCT NRM adjusting for competing risks, n (%)	5 (50.0)	5 (23.8)	10 (32.3)	4 (33.3)

HSCT, hematopoietic stem cell transplant; InO, inotuzumab ozogamicin; NRM, nonrelapse-related mortality.

Table 5. Summary of treatment-emergent adverse events.

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

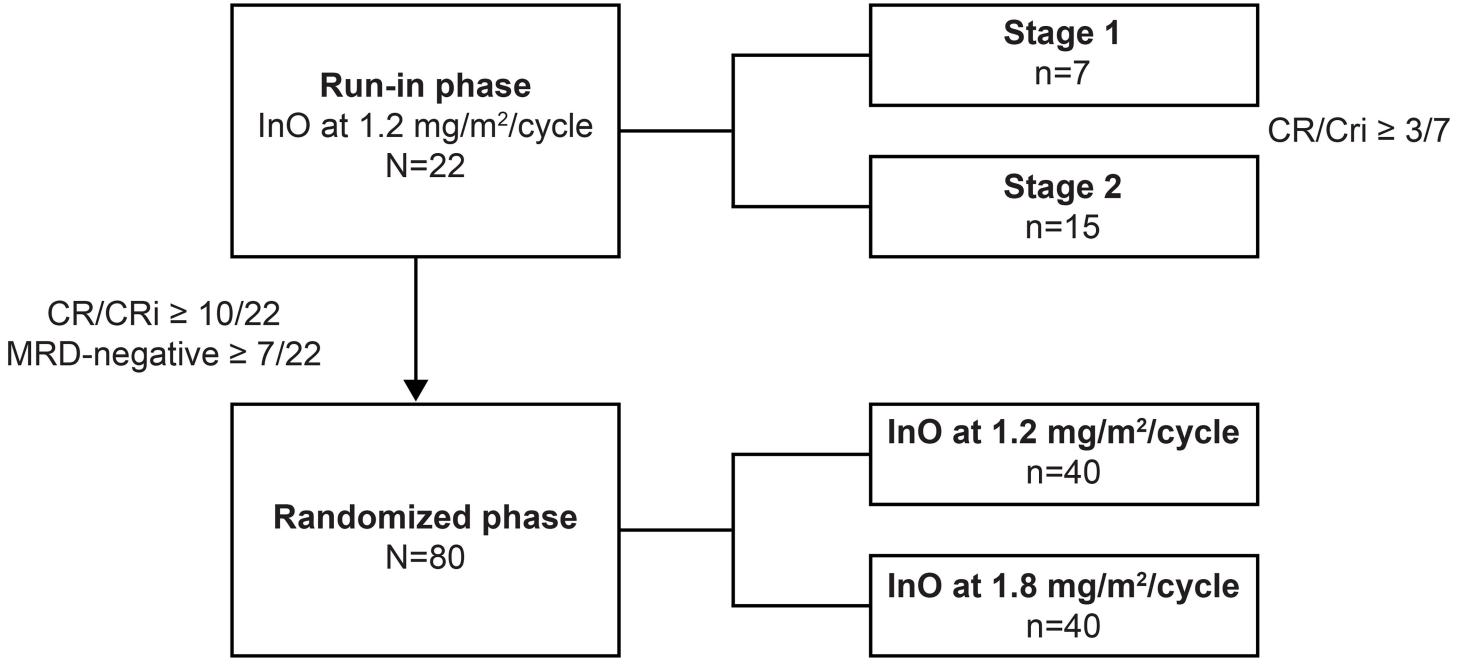
InO, inotuzumab ozogamicin.

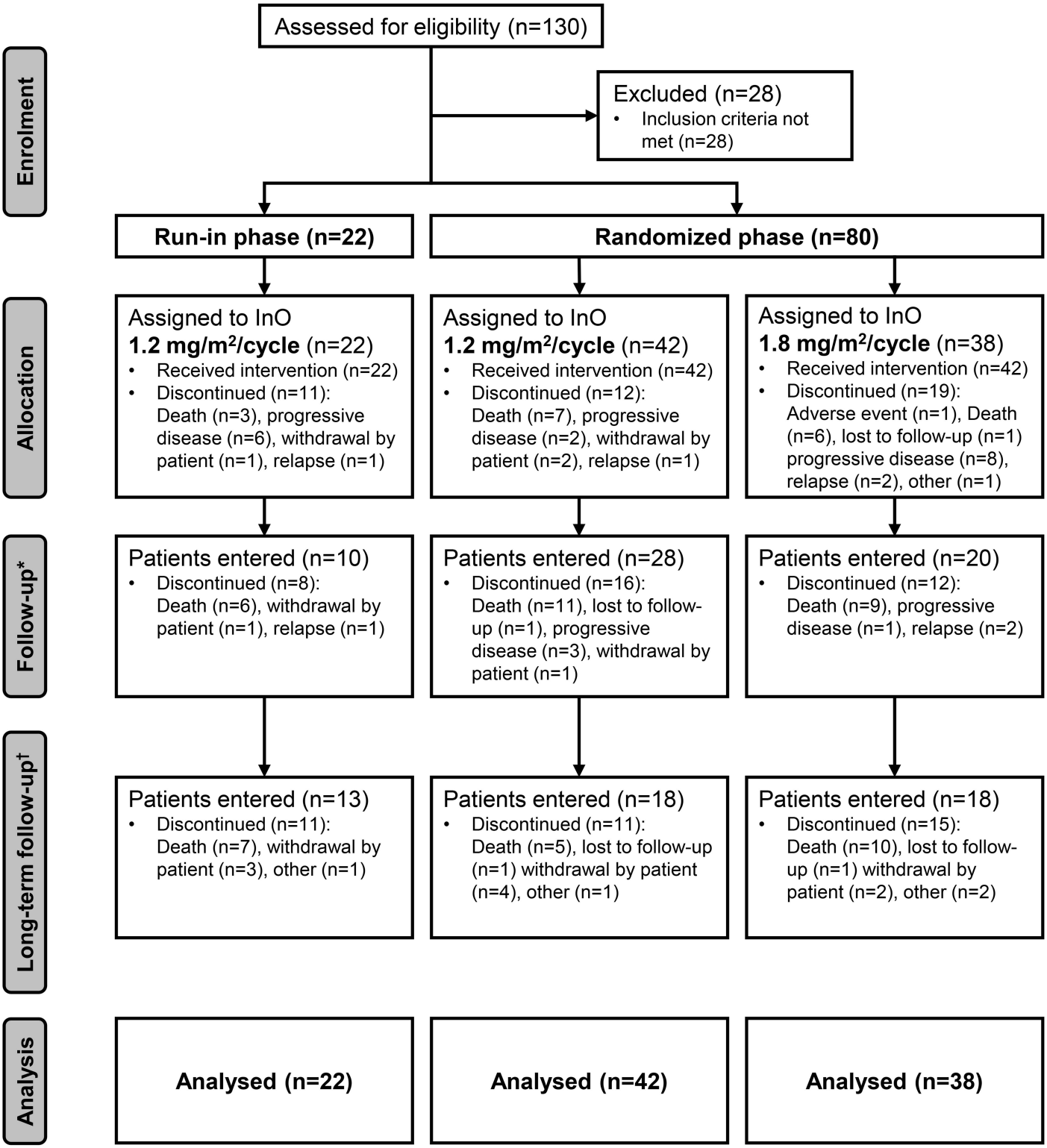
FIGURES LEGENDS

Figure 1. Study design.

Figure 2. Study Flow Chart.

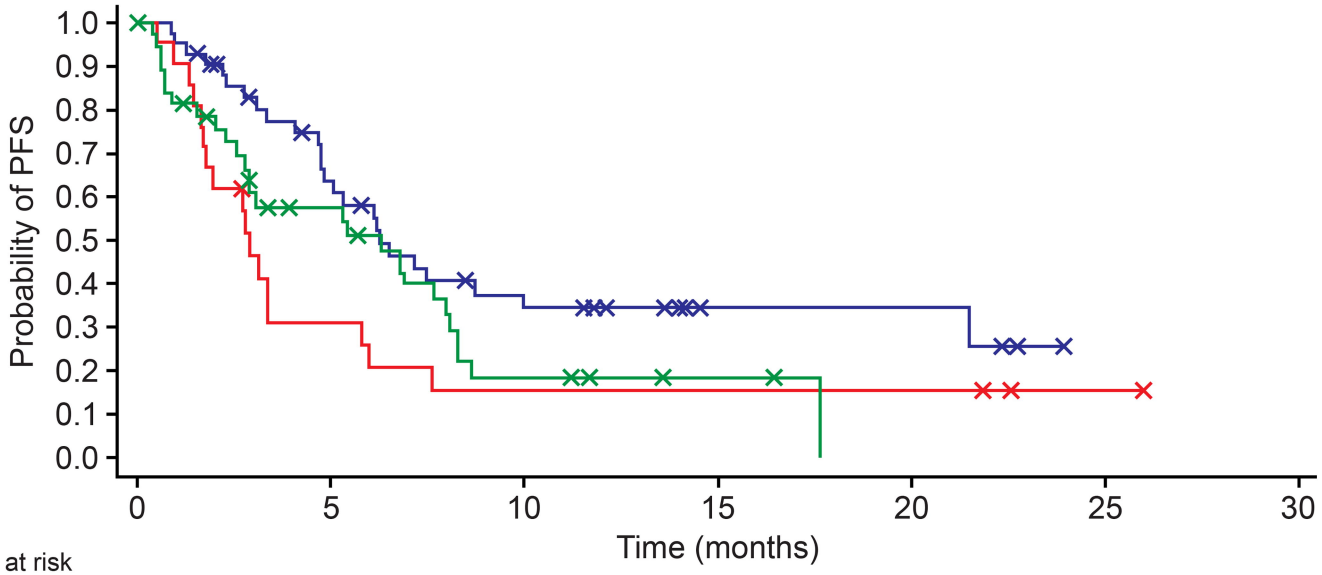
Figure 3. Kaplan-Meier plots of survival outcomes. (A) progression-free survival and (B) overall survival.


Run-in phase
InO at 1.2 mg/m2/cycle
N=22
Stage 1
n=7
CR/Cri ≥ 3/7
Stage 2
n=15
CR/CRi ≥ 10/22
MRD-negative ≥ 7/22
Randomized phase
N=80
InO at 1.2 mg/m2/cycle
n=40
InO at 1.8 mg/m2/cycle
n=40



*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.

A

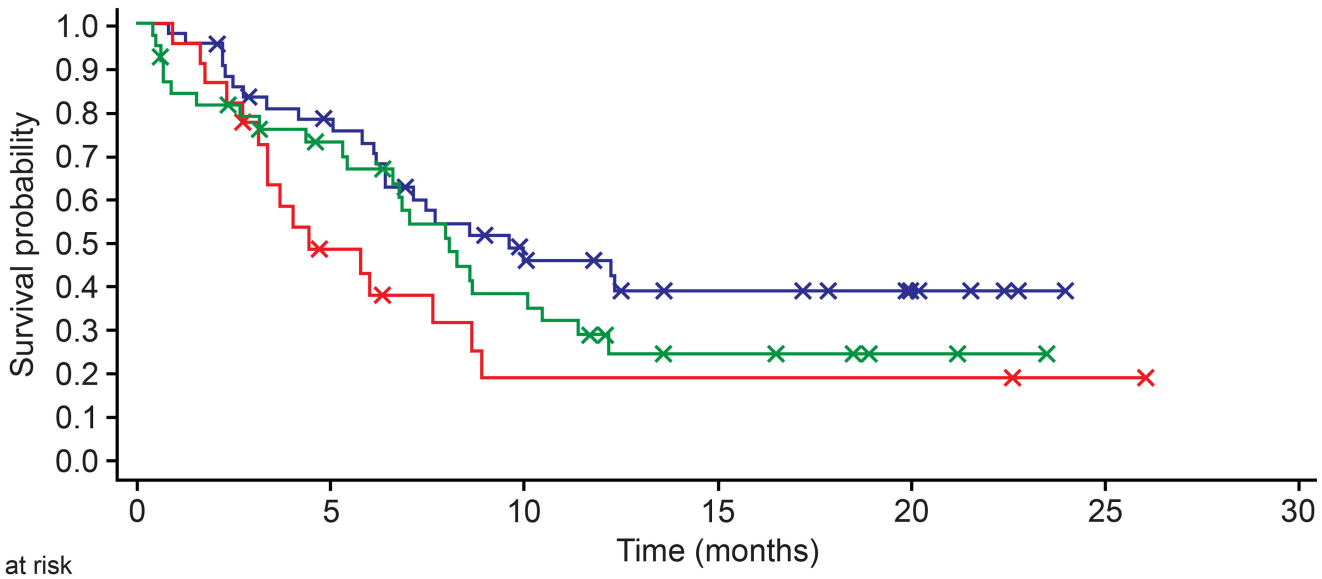


No. at risk

A:	22	6	3	3	3	1	0
B:	42	23	11	4	4	0	0
C:	38	17	5	2	0	0	0

A: 1.2 mg/m^2/cycle (Run-in) (Median=2.9 Months) B: 1.2 mg/m^2/cycle (Randomized) (Median=6.3 Months)
C: 1.8 mg/m^2/cycle (Randomized) (Median=6.3 Months)

B



No. at risk

A:	22	9	3	3	3	2	0
B:	42	30	15	9	5	0	0
C:	38	24	12	5	2	0	0

A: 1.2 mg/m^2/cycle (Run-in) (Median=4.5 Months) B: 1.2 mg/m^2/cycle (Randomized) (Median=9.6 Months)
C: 1.8 mg/m^2/cycle (Randomized) (Median=8.1 Months)

SUPPLEMENTARY MATERIALS

Additional methods

Safety endpoints were assessed during treatment and post HSCT and included adverse events (AEs; graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 3.0) and laboratory abnormalities.

Bone marrow aspirates and disease assessments were performed at screening, once at Days 16-28 of cycles 1 and 2, or until CR/CRi and MRD negativity were achieved, then after every 1-2 cycles as clinically indicated, and at the end of treatment. Bone marrow aspirates were analyzed at the study site. Disease assessments were determined using information from bone marrow evaluations, laboratory assessments (e.g., hematology), and clinical and radiological information (e.g., extramedullary disease).

CR was defined as <5% blasts in bone marrow and absence of peripheral blood leukemic blasts, full recovery of peripheral blood counts (platelets ≥100 x 10^9/L and absolute neutrophil counts [ANC] ≥1 x 10^9/L), and resolution of any extramedullary disease. CRi was defined as <5% blasts in the bone marrow and absence of peripheral blood leukemic blasts, incomplete recovery of peripheral blood counts (platelets <100 x 10^9/L and/or ANC <1 x 10^9/L), and resolution of any extramedullary disease. For determination of MRD, bone marrow aspirates were analyzed at a central laboratory (Navigate, Carlsbad, CA, USA) by flow cytometry for cell surface markers associated with B-cell ALL. MRD negativity (in patients who achieved CR/CRi) was defined as minimum MRD percentage <0.01% between the date of CR/CRi and end of treatment test.[6, 8]

Blood samples were collected for pharmacokinetics of InO and unconjugated calicheamicin at protocol-specified time points and analyzed by a specific and sensitive LC-MS/MS method. Blood samples for the anti-drug antibody (ADA) assessment were collected at protocol-specified time points and analyzed using a validated, electro-chemiluminescent bridging assay. ADA-positive samples were evaluated for neutralizing antibody (NAb) using a cell-based assay.

Statistical analysis

Twenty-two patients were enrolled in the run-in phase. In order to minimize the expected number of patients enrolled in the event that the lower dose level (1.2 mg/m^2/cycle of InO, dose level 2) proves to be of minimal efficacy benefit, a Simon Two-Stage optimal design was used for the run-in phase. The run-in phase tested the null hypothesis (H0) that the CR/CRi rate is ≤31.2% versus the alternative hypothesis (Ha) that the CR/CRi rate is ≥57% (ie, predicted based on the exposure response model) with a significance level of 0.10 and 80% power.

Seven patients were enrolled in Stage 1. If ≤2 CR/CRi responders were observed in Stage 1, accrual was stopped for further evaluation. Once at least 3 (ie, 42.9%) CR/CRi responders were documented, an additional 15 enrolled patients were evaluated in Stage 2. If ≥10 CR/CRi responders were observed in the total of 22 patients from both stages, it was concluded that the true CR/CRi rate for the lower dose is higher than the historical control (31.2% for Study

B1931022 control arm subgroup of patients with risk factors for VOD post-HSCT).

The expected MRD negativity rate among the patients who achieved CR/CRi was ≥70%. With ≥10 CR/CRi responders expected at the end of Stage 2, the expected number of patients with MRD negativity among the 22 patients in the run-in phase was ≥7. Given a CR/CRi rate of 57%, predicted by the exposure response model, and ≥70% expected MRD negativity rate among CR/CRi responders, 40% was the expected MRD negativity rate among all patients enrolled in the run-in phase. Twenty-two (22) patients also provided 80% power to reject the null hypothesis of the MRD negativity rate ≤20% when the alternative hypothesis of the true MRD negativity rate was ≥40% with significance level of 0.10. There was an 84% probability to observe a minimum of 7 patients who achieved MRD negativity if the true MRD negativity rate was at least 40%.

Once at least 10 CR/CRi responders and at least 7 patients achieving MRD negativity were documented among the 22 patients in the run-in phase, patients enrolled in the randomized phase were then evaluated, with approximately 80 patients randomized (1:1) to the approved dose level of 1.8 mg/m^2/cycle (dose level 1, Arm 1) or the lower dose level of 1.2 mg/m^2/cycle (dose level 2, Arm 2). A sample size of 40 patients per arm provided the estimated VOD rate in each dose level with a maximum standard error of 0.08.

All efficacy and safety endpoints were analyzed descriptively (i.e., the number and percent of patients achieving the endpoint and 2-sided 95% confidence interval [CI]) using SAS version 9.4 (Cary, NC) without formal hypothesis testing across dose levels. Efficacy data were analyzed in the full analysis population, which included all patients enrolled and randomly assigned into the study. Safety data were analyzed in the safety population, which included all enrolled patients who received at least 1 dose of InO, with treatment assignment designated according to actual treatment received. Safety data post HSCT were evaluated in the HSCT safety population, which included all enrolled patients who receive at least 1 dose of InO, with treatment assignment designated according to actual treatment received, and who had undergone HSCT after InO treatment.

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Supplementary Tables and Figures

Supplementary Table S1. Inclusion and exclusion criteria

Inclusion criteria

Participants must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Relapsed or refractory precursor CD22-positive B-cell ALL with M2 or M3 marrow (≥5% blasts) and who are eligible for HSCT.
2. Have 1 or more of the following risk factors for developing SOS:
    a. Due to receive Salvage 2 or greater;
    b. Prior HSCT;
    c. Age ≥55 years;
    d. Ongoing or prior hepatic disease which may include a prior history of hepatitis or drug-induced liver injury, as well as hepatic steatosis, nonalcoholic steatohepatitis, baseline elevations of bilirubin >ULN and ≤1.5 x ULN.
3. Ph+ ALL patients must have failed treatment with at least 1 second- or third-generation tyrosine kinase inhibitor and standard multi-agent induction chemotherapy.
4. Patients in Salvage 1 with late relapse should be deemed poor candidates for reinduction with initial therapy.
5. Patients with lymphoblastic lymphoma and bone marrow involvement ≥5% lymphoblasts by morphologic assessment.
6. Age 18 years to 75 years.
7. ECOG performance status 0-2.
8. Adequate liver function, including total serum bilirubin ≤1.5 x ULN unless the patient has documented Gilbert syndrome, and AST and ALT ≤2.5 x
9. Serum creatinine ≤1.5 x ULN or any serum creatinine level associated with a measured or calculated creatinine clearance of ≥40 mL/min.
10. Male and female patients of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for a minimum of 8 months (females) and 5 months (males) after the last dose of assigned treatment. A patient is of childbearing potential if, in the opinion of the Investigator, he/she is biologically capable of having children and is sexually active. Female subjects of nonchildbearing potential must meet at least 1 of the following criteria:
    a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum FSH level confirming the postmenopausal state;
    b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;
    c. Have medically confirmed ovarian failure.

All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential.

11. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study; patients with mental capacity which requires the presence of a legally authorized representative will be excluded from the study.
12. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

Exclusion criteria

Participants with any of the following characteristics/conditions were not included in the study:

1. Isolated extramedullary relapse (ie, testicular or central nervous system).
2. Burkitt's or mixed phenotype acute leukemia based on the WHO 2008 criteria.6
3. Active CNS leukemia, as defined by unequivocal morphologic evidence of lymphoblasts in the CSF, use of CNS-directed local treatment for active disease within the prior 28 days, symptomatic CNS leukemia (ie, cranial nerve palsies or other significant neurologic dysfunction) within 28 days. Prophylactic intrathecal medication is not a reason for exclusion.
4. Prior chemotherapy within 2 weeks before randomization with the following exceptions:
    a. To reduce the circulating lymphoblast count or palliation: ie, steroids, hydroxyurea or vincristine;
    b. For ALL maintenance: mercaptopurine, methotrexate, vincristine, thioguanine, and/or tyrosine kinase inhibitors.

Patients must have recovered from acute nonhematologic toxicity (to ≤Grade 1) of all previous therapy prior to enrollment.

5. Prior monoclonal antibodies within 6 weeks of randomization, with the exception of rituximab which must be discontinued at least 2 weeks prior to randomization.
6. Prior inotuzumab ozogamicin treatment or other anti-CD22 immunotherapy ≤6 months before randomization.
7. Prior allogeneic HSCT ≤90 days before randomization. Patients must have completed immunosuppression therapy for treatment of GvHD prior to enrollment. At randomization, patients must not have ≥Grade 2 acute GvHD, or extensive chronic GvHD.
8. Peripheral absolute lymphoblast count ≥10,000/μL (treatment with hydroxyurea and/or steroids/vincristine is permitted within 2 weeks of randomization to reduce the WBC count).
9. Known systemic vasculitides (eg, Wegener's granulomatosis, polyarteritis nodosa, systemic lupus erythematosus), primary or secondary immunodeficiency (such as HIV infection or severe inflammatory disease).
10. Active hepatitis B infection as evidenced by hepatitis B surface antigen, active hepatitis C infection (must be anti-hepatitis C antibody negative or hepatitis C ribonucleic acid negative), or known seropositivity for HIV. HIV testing may need to be performed in accordance with local regulations or local practice.
11. Major surgery within ≤4 weeks before randomization.
12. Unstable or severe uncontrolled medical condition (eg, unstable cardiac function or unstable pulmonary condition).
13. Concurrent active malignancy other than nonmelanoma skin cancer, carcinoma in situ of the cervix, or localized prostate cancer that has been definitely treated with radiation or surgery. Patients with previous malignancies are eligible provided that they have been disease free for ≥2 years.
14. Patients with active heart disease or the presence of NYHA stage III or IV congestive heart failure.
15. QTcF >470 msec (based on the average of 3 consecutive ECGs).
16. Myocardial infarction ≤6 months before randomization.
17. History of clinically significant ventricular arrhythmia, or unexplained syncope not believed to be vasovagal in nature, or chronic bradycardic states such as sinoatrial block or higher degrees of AV block unless a permanent pacemaker has been implanted.
18. Uncontrolled electrolyte disorders that can compound the effects of a QTc prolonging drug (eg, hypokalemia, hypocalcemia, hypomagnesemia).
19. Prior confirmed or ongoing SOS, or other serious or current ongoing liver disease such as cirrhosis or nodular regenerative hyperplasia.
20. Total serum bilirubin >1.5 x ULN unless the patient has documented Gilbert syndrome, and AST and ALT ≥2.5 x
21. Administration of live vaccine ≤6 weeks before randomization.
22. Evidence of uncontrolled current serious active infection (including sepsis, bacteremia, fungemia) or patients with a recent history (within 4 months) of deep tissue infections such as fasciitis or osteomyelitis.
23. Patients who have had a severe allergic reaction or anaphylactic reaction to any humanized monoclonal antibodies.
24. Pregnant female subjects; breastfeeding female subjects; fertile male subjects and female subjects of childbearing potential who are unwilling or unable to use highly effective contraception as outlined in this protocol for the duration of the study and for a minimum of 8 months (females) and 5 months (males) after the last dose of investigational product.

25. Investigative site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the Investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.
26. Participation in other studies involving investigational drug(s) within 2 weeks prior to study entry and/or during study participation (up through the end of treatment visit).
27. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study.

ALL=acute lymphoblastic leukemia; ALT=alanine aminotransferase; AST=aspartate aminotransferase; AV=atrioventricular; CNS=central nervous system; CSF=cerebrospinal fluid; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; FSH=follicle-stimulating hormone; GvHD=graft vs host disease; HSCT=hematopoietic stem cell transplantation; NYHA=New York Heart Association; Ph+=Philadelphia chromosome–positive; SOS=sinusoidal obstruction syndrome; ULN=upper limit of normal; WBC=white blood cell.

Supplementary Table S2. Association of baseline characteristics at time of HSCT with post-HSCT SOS. Treatment group: Total (N=43) univariate analysis

	Subsets N	Estimate	SE	Odds ratio	95% CI	p-value
Age (<55 years, ≥55 years)	35, 8	0.89	1.14	2.423	0.261, 22.493	0.436
Salvage status (1, ≥2)	17, 26	-1.20	0.86	0.300	0.055, 1.633	0.164
Prior HSCT (Yes, No)	8, 35	0.12	0.91	1.125	0.189, 6.699	0.897
Prior history of liver disease/hepatitis (Yes, No)	16,27	-1.08	0.87	0.339	0.062, 1.850	0.212
Number of treatment cycles received (continuous)	43	-0.17	0.47	0.843	0.335, 2.123	0.717
Dual alkylator conditioning (Yes, No)	8, 35	0.12	0.91	1.125	0.189, 6.699	0.897
Last bilirubin prior to follow-up HSCT (<ULN, ≥ULN)	40, 3	11.52	318.03	>999.999	<0.001, >999.999	0.971
Time from InO to transplant (days) (continuous)	43	-0.00	0.01	0.996	0.977, 1.016	0.711
Cumulative dose (mg) (continuous)	43	-0.15	0.38	0.857	0.408, 1.801	0.685
Region (Asia, EU/NA)	24, 19	0.22	0.73	1.250	0.297, 5.269	0.761

EU=European Union; HSCT=hematopoietic stem cell transplantation; InO=inotuzumab ozogamicin; NA=North America; SOS=sinusoidal obstruction syndrome; ULN=upper limit of normal.

Supplementary Table S3. Summary of rate of follow-up HSCT.

Number of patients who received follow-up HSCT, n	Starting dose of InO and trial phase				
	1.2 mg/m^2/cycle (run-in) n=10	1.2 mg/m^2/cycle (randomized) n=21	1.2 mg/m^2/cycle (run-in + randomized) n=31	1.8 mg/m^2/cycle (randomized) n=12	Total n=43
Number of participants received HSCT post InO treatment directly without new induction therapy	10 (100.0)	21 (100.0)	31 (100.0)	11 (91.7)	42 (97.7)
Time of transplant relative to last InO dose					
<2 months after last dose of InO	9 (90.0)	17 (81.0)	26 (83.9)	11 (91.7)	37 (86.0)
≥2 months after last dose of InO	1 (10.0)	4 (19.0)	5 (16.1)	1 (8.3)	6 (14.0)
Type of transplant					
Allogeneic	9 (90.0)	21 (100.0)	30 (96.8)	12 (100)	42 (97.7)
Unknown	1 (10.0)	0	1 (3.2)	0	1 (2.3)
Hla compatibility					
Hla-haploidentical	1 (10.0)	3 (14.3)	4 (12.9)	0	4 (9.3)
Hla-matched	7 (70.0)	15 (71.4)	22 (71.0)	11 (91.7)	33 (76.7)
Hla-unmatched	0	2 (9.5)	2 (6.5)	0	2 (4.7)
Unknown	2 (20.0)	1 (4.8)	3 (9.7)	1 (8.3)	4 (9.3)
Stem cell source					
Bone marrow	1 (10.0)	0	1 (3.2)	2 (16.7)	3 (7.0)
Cord blood	0	1 (4.8)	1 (3.2)	0	1 (2.3)
Peripheral blood	8 (80.0)	19 (90.5)	27 (87.1)	9 (75.0)	36 (83.7)
Unknown	1 (10.0)	1 (4.8)	2 (6.5)	1 (8.3)	3 (7.0)
Type of conditioning					
Myeloablative	7 (70.0)	13 (61.9)	20 (64.5)	5 (41.7)	25 (58.1)
Reduced intensity	3 (30.0)	6 (28.6)	9 (29.0)	6 (50.0)	15 (34.9)
Unknown	0	2 (9.5)	2 (6.5)	1 (8.3)	3 (7.0)

Disease risk at transplant					
Disease in remission	8 (80.0)	17 (81.0)	25 (80.6)	10 (83.3)	35 (81.4)
Disease not in remission	2 (20.0)	4 (19.0)	6 (19.4)	2 (16.7)	8 (18.6)

HSCT, hematopoietic stem cell transplant; Hla, human leukocyte antigen; InO, inotuzumab ozogamicin.

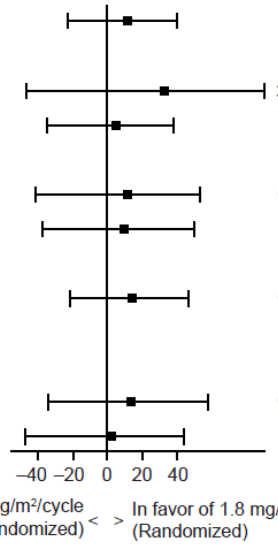
Supplementary Table S4. Association of baseline characteristics at time of HSCT with NRM. Treatment group: Total (N=43) univariate analysis.

	Subsets N	Estimate	SE	Odds ratio	95% CI	p-value
Age (<55 years, ≥55 years)	35,8	1.04	1.10	2.832	0.329, 24.353	0.343
Salvage status (1, ≥2)	17, 26	0.56	0.53	1.748	0.624, 4.895	0.288
Prior HSCT (Yes, No)	8, 35	0.96	0.51	2.621	0.964, 7.128	0.059
Prior history of liver disease/hepatitis (Yes, No)	16, 27	0.64	0.52	1.901	0.691, 5.233	0.213
Number of treatment cycles received (continuous)	43	-0.17	0.47	0.843	0.335, 2.123	0.717
Dual alkylator conditioning (Yes, No)	8, 35	-0.39	0.77	0.678	0.149, 3.081	0.615
Last bilirubin prior to follow-up HSCT (<ULN, ≥ULN)	40, 3	-0.12	1.15	0.884	0.093, 8.368	0.914
Time from InO to transplant (days) (continuous)	43	-0.00	0.01	0.996	0.977, 1.016	0.711
Cumulative dose (mg) (continuous)	43	-0.15	0.38	0.857	0.408, 1.801	0.685
Region (Asia, EU/NA)	24, 19	1.22	0.65	3.380	0.947, 12.063	0.061

EU, European Union, HSCT, hematopoietic stem cell transplant; InO, inotuzumab ozogamicin; NA, not applicable; ULN, upper limit of normal.

Supplementary Figure S1. Forest plot of SOS rate by SOS risk factors - HSCT safety analysis set

Subgroup	Arm 2 (n)	Arm 1 (n)	VOD rate Arm 2	VOD rate Arm 1	Rate diff	[95% CI]	P value
All Participants	21 (6)	12 (2)	28.6	16.7	11.9	[–22.3, 40.1]	0.6776
Prior HSCT							
Yes	3 (1)	3 (0)	33.3	0.0	33.3	[–46.2, 90.6]	1.0000
No	18 (5)	9 (2)	27.8	22.2	5.6	[–34.7, 37.9]	1.0000
Salvage Treatment							
Salvage 1	8 (1)	5 (0)	12.5	0.0	12.5	[–41.1, 53.7]	1.0000
Salvage ≥2	13 (5)	7 (2)	38.5	28.6	9.9	[–37.9, 50.1]	1.0000
Age							
<55 Years	16 (5)	12 (2)	31.3	16.7	14.6	[–21.4, 47.3]	0.6618
≥55 Years	5 (1)	0	20.0	0	NA	[NA, NA]	NA
Ongoing or Prior Heptic Disease							
Yes	7 (1)	6 (0)	14.3	0.0	14.3	[–34.2, 57.9]	1.0000
No	14 (5)	6 (2)	35.7	33.3	2.4	[–47.3, 44.0]	1.0000



Note: n is number of participants with VOD. Arm 2 is 1.2 mg/m²/cycle (randomized) and Arm 1 is 1.8 mg/m²/cycle (randomized).
P values calculated using the exact method.
HSCT=hematopoietic stem cell transplant; SOS=sinusoidal obstruction syndrome; VOD=veno-occlusive disease.