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A Non-Interventional Post-Authorization Safety Study (PASS) of Inotuzumab Ozogamicin to Characterize Complications Post-Hematopoietic Stem Cell Transplantation (HSCT) Following Inotuzumab Ozogamicin Treatment in Adult and Pediatric Patients with B-Cell Precursor Acute Lymphoblastic Leukemia (ALL)

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1 Abstract

Title: A Non-Interventional Post-Authorization Safety Study (PASS) of Inotuzumab Ozogamicin to Characterize Complications Post-Hematopoietic Stem Cell Transplantation (HSCT) Following Inotuzumab Ozogamicin Treatment in Adult and Pediatric Patients with B-Cell Precursor Acute Lymphoblastic Leukemia (ALL).

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Keywords: Inotuzumab ozogamicin; post-HSCT toxicities; veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS); transplant-related mortality (TRM) or non-relapse mortality; non-transplant related mortality (NTRM).

Rationale and background:
Inotuzumab ozogamicin is an antibody-drug conjugate (ADC) composed of a cluster of differentiation 22 (CD22) -directed monoclonal antibody that is covalently linked to N-acetyl-gamma-calicheamicin dimethylhydrazide. In the United States (US), inotuzumab ozogamicin was approved by the Food and Drug Administration (FDA) on 17 August 2017 for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

In clinical trials, inotuzumab ozogamicin has been associated with severe, life-threatening, and potentially fatal adverse events, including hepatotoxicity and hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS). In pivotal study B1931022, inotuzumab ozogamicin was associated with the occurrence of VOD/SOS, particularly following HSCT. Among the 79 patients treated with inotuzumab ozogamicin who proceeded to a subsequent HSCT, 18/79 patients (23%) developed VOD/SOS post-HSCT, compared to 3/34 patients (9%) in the treating physicians' choice of chemotherapy arm.

The following post-marketing requirement (PMR 3259-1) was agreed with the US FDA:

> *"Characterize toxicity after HSCT in adult and pediatric patients who receive inotuzumab ozogamicin. Include hepatic VOD, TRM (non-relapse mortality), and NTRM. Conduct an analysis of registry data (for example the CIBMTR registry) to evaluate safety at least through day 180 after transplantation. The number of available patients in the database will determine the sample size. Include details of all prior therapies. The minimum duration of the study is to be no less than five years."*

This non-interventional study is being conducted to fulfill this post-marketing requirement (PMR) and is designated as a post-authorization safety study (PASS).

Research question and objectives:

Research question: What are the toxicities after HSCT in adult and pediatric patients who receive inotuzumab ozogamicin?

Objectives: Based on collected data obtained from the Center for International Blood and Marrow Transplant Research® (CIBMTR®) Research Database, the following were evaluated in adult and pediatric patients with B-cell ALL who received inotuzumab ozogamicin and proceeded to HSCT:

- Patient-, disease- and HSCT-related characteristics, including details of all prior anti-cancer therapies;
- Timing of inotuzumab ozogamicin treatment prior to HSCT;
- Transplant-related mortality (TRM) or non-relapse mortality; non-transplant related mortality (NTRM); relapse; and overall survival (OS);
- Post-HSCT adverse events of interest, including hepatic VOD/SOS;
- Cause of death (COD).

Study design:

This secondary data collection non-interventional PASS uses de-identified healthcare data from the CIBMTR database. This retrospective study will evaluate safety outcomes post-HSCT in patients with B-cell precursor ALL who have been treated with inotuzumab ozogamicin prior to HSCT. The study will utilize all relevant data available in the CIBMTR database from US transplant centers for a 5-year period following the approval of inotuzumab ozogamicin in the US (i.e., 18 August 2017 – 17 August 2022).

Setting:

The data source is the CIBMTR Research Database. CIBMTR is a collaboration between the National Marrow Donor Program (NMDP)/Be The Match and the Medical College of Wisconsin (MCW). CIBMTR facilitates critical observational and interventional research through scientific and statistical expertise, a large network of transplant centers, and a unique and extensive clinical outcomes database. CIBMTR is also mandated by the U.S. Health Resources and Services Administration (HRSA) to collect data from all patients undergoing allogeneic HSCT in the US.

The CIBMTR receives data for approximately 24,000 new HSCT recipients annually, as well as follow-up data on previously reported patients. In 2014-2016, a total of 2,506 US patients with B-cell ALL (1,984 adults [age ≥ 18 years] and 522 pediatric patients [age < 18 at the time of HSCT]), who underwent their first allogeneic HSCT, and provided consent to CIBMTR for research.

The CIBMTR collects data on two levels, using a Transplant Essential Data (TED) form and a Comprehensive Report Form (CRF). The TED data set is an internationally accepted standard data set that contains a limited number of key variables for all consecutive HSCT recipients. The

CRF captures additional patient-, disease-, and treatment-related data in a subset of patients. (i.e., the CRF does not include data from all patients in the registry).

Subjects and study size, including dropouts:

The study population included all adult and pediatric US patients with B-cell ALL treated with inotuzumab ozogamicin who proceeded to HSCT and whose data were available in the CIBMTR database. Data from pediatric patients was included in accordance with the agreement reached during negotiation of the PMR with the FDA.

Data from all available adult (age ≥ 18) and pediatric (age < 18 years at the time of HSCT) US patients with B-cell ALL in the CIBMTR database who were treated with inotuzumab ozogamicin and who underwent allogeneic HSCT during the accrual period were included in the present analysis.

Statistical methods:

There was no hypothesis testing in this study. All statistical analyses were descriptive. Data from all patients who proceeded to HSCT was obtained using routine CIBMTR data collection forms, as well as an additional form to specifically collect inotuzumab ozogamicin exposure data.

Data is presented for adult and pediatric patients, separately and combined.

Patients who received a prior allogeneic HSCT for B-cell ALL are presented separately from those patients who underwent their first allogeneic HSCT for B-cell ALL, because the underlying disease, risk for relapse and post-HSCT complications are different for patients with a prior allogeneic HSCT for B-cell ALL than for patients undergoing their first allogeneic HSCT for B-cell ALL.

Results: This is the third interim descriptive report containing data from 18 August 2017 – 17 August 2020 (3 years). The study is ongoing and will continue until 17 August 2022 (i.e., for a total of 5 years).

Overall patients included in analyses

A total of 3140 B-cell ALL patients underwent an allogeneic HSCT transplant in the US between 18 August 2017 – 17 August 2020. Out of those 3,140 patients, 282 patients were excluded from this study as they had not consented to research, 67 patients were excluded from embargoed centers, and 1,354 patients were excluded as they belonged to centers not participating in the study. Of the remaining 1,437 patients, 184 received at least one dose of inotuzumab ozogamicin.

Therefore, between 18 August 2017 and 17 August 2020, 184 patients (152 adult and 32 pediatric) were accrued and included in the study. The data lock date for this interim report, when data collection forms were last evaluated, was 11 November 2020.

Of the 184 patients included in this study, 163 patients underwent their first allogeneic HSCT for B-cell ALL (136 adult and 27 pediatric) and 21 patients (16 adult and 5 pediatric) had received a prior allogeneic HSCT for B-cell ALL before receiving inotuzumab ozogamicin.

The 21 patients who had a prior allogeneic HSCT for B-cell ALL before receiving inotuzumab ozogamicin are described separately since the underlying disease, risk for relapse and post-HSCT complications are different for patients with a prior HSCT than for patients undergoing their first allogeneic HSCT for B-cell ALL.

Patients who underwent their first allogeneic HSCT for B-cell ALL

In total, 163 patients (136 adults and 27 pediatric patients with a median age of 35 years) underwent their first allogeneic HSCT for B-cell ALL after treatment with inotuzumab ozogamicin.

Prior to transplant, 15 patients had 1 line of therapy; 30 patients had 2 lines of therapy; 24 patients had 3 lines of therapy; and 86 patients had four or more lines of therapy. Data were not available for 8 patients.

As of the data lock date, post-HSCT follow-up information was available for 158 / 163 (97%) patients:

- 100 / 158 patients (63%) did not experience post-HSCT relapse; of these:
  - 30 / 100 patients (30%; 26 adult and 4 pediatric) died in remission, with a median time from transplant to transplant-related mortality (TRM) of 2.18 months; their causes of death (COD) were:
    - VOD/SOS – 8 patients (27%; 6 adult, 2 pediatric)
    - GVHD – 7 patients (23%; 7 adult, 0 pediatric)
    - Interstitial pneumonitis – 3 patients (10%; 2 adult, 1 pediatric)
    - Hemorrhage – 3 patients (10%; 3 adult, 0 pediatric)
    - Organ failure – 3 patients (10%; 3 adult, 0 pediatric)
    - Infection – 2 patients (7%; 2 adult, 0 pediatric)
    - Septic shock – 2 patients (7%; 2 adult, 0 pediatric)
    - Thrombotic microangiopathy – 1 (3%) pediatric patient
    - Graft failure – 1 (3%) adult patient
- 56 / 158 patients (35%) experienced post-HSCT relapse; of these:
  - 34 / 56 patients (61%; 29 adult, 5 pediatric) died after post-HSCT relapse of ALL, with a median time from transplant to NTRM of 6.64 months;
- 2 / 158 patients (1%) have unknown post-HSCT relapse. The involved transplant centers have been notified and these data will be updated.
- 24 / 158 patients (15%; 17 adult, 7 pediatric) experienced post-transplant VOD/SOS; of these:
  - 10 cases were mild (42%; 7 adult, 3 pediatric)
  - 14 cases were severe (58%; 10 adult, 4 pediatric)
  - 2 cases (8%; 1 adult, 1 pediatric) did not receive liver toxicity prophylaxis

- 14 cases (58%; 10 adult, 4 pediatric) died after reporting VOD
  - 8 out of the 14 cases (57%) reported VOD as COD
    - 1 out of the 8 patients (13%) with reported VOD as COD had not received liver toxicity prophylaxis
  - Other CODs were:
    - GVHD (2 cases [14%], died 0.2 and 1.8 months after VOD),
    - Recurrence of B-Cell ALL (2 cases [14%], died 0.3 and 2.9 months after VOD),
    - Septic shock (1 case [7%], died 0.5 months after VOD), and
    - Interstitial pneumonitis (1 case [7%], died 0.1 months after VOD).

- 17 / 158 patients (11%) did not receive liver toxicity prophylaxis
- 108 / 158 patients (68%) received liver toxicity prophylaxis with ursodiol alone
- 22 / 158 patients (14%) received liver toxicity prophylaxis with ursodiol and defibrotide
- 8 / 158 patients (5%) received liver toxicity prophylaxis with ursodiol and other drugs (not specified)
- 2 / 158 patients (1%) received liver toxicity prophylaxis with defibrotide alone
- 1 / 158 patient (1%) did not have any reported liver toxicity prophylaxis

For the remaining 5 / 163 (3%) patients (all adults) for whom post-HSCT follow-up information was not available as of the data lock point, follow-up data will be provided in subsequent reports.

The summary table below shows the incidence of VOD/SOS, post-transplant VOD/SOS mortality, 6-month and 12-month OS, 6-month and 12-month NRM, 6-month and 12-month relapse in adult patients without a prior HSCT in this ongoing non-interventional study.

Adults without a prior HSCT, summary of VOD/SOS, overall survival, non-relapse mortality and relapse

	Day 100 incidence of VOD/SOS	Post-transplant VOD/SOS mortality [a]	6-mo OS	12-mo OS	6-mo NRM	12-mo NRM	6-mo relapse	12-mo relapse
All adult patients n=131[b]	13%	41%	76%	55%	16%	21%	25%	36%
Adult R/R n= 91 [c]	18%	38%	71%	50%	18%	23%	25%	37%

HSCT: hematopoietic stem cell transplantation; mo: months; OS: overall survival; NRM: non-relapse mortality; R/R: relapsed/refractory; VOD/SOS: veno-occlusive disease/sinusoidal obstruction syndrome.
[a] Caution must be exercised in assessing unadjusted mortality rates. There were n= 17 adult patients who experienced post-transplant VOD/SOS and n= 16 adult patients with R/R ALL who experienced post-transplant VOD/SOS.
[b] Follow-up information available for 131/ 136 adult patients.
[c] Follow-up information available for 91 / 95 adult R/R patients

Patients undergoing second, or greater HSCT for B-cell ALL

As of the data lock date, post-HSCT follow-up information was available for 21 / 21 (100%) patients:

Among the 21 patients (16 adult, 5 pediatric) who had a prior allogeneic HSCT for B-cell ALL before receiving inotuzumab ozogamicin, 9 patients (43%) had ≥ 3 comorbidities prior to HSCT, and 7 patients (33%) had mild hepatic disease prior to HSCT. All 21 patients underwent HSCT for relapsed or refractory disease, and 4 of the 21 patients (19%) had a history of proven invasive fungal infection. Seven (7) patients (33%) received a bone marrow product, 1 patient (5%) received a cord blood product, and the remaining 13 patients (62%) received peripheral blood stem cells. Thirteen (13) patients (62%) received their product from an unrelated donor, 3 patients (14%) had an HLA-identical sibling donor, and the remaining 5 patients (24%) had another related donor (though not a human leukocyte antigen [HLA]-identical sibling). The median time from ALL diagnosis to transplant was 36 months, and the median time from ALL diagnosis to first dose of inotuzumab ozogamicin was 33 months.

Five (5) of the 21 patients (24%) with prior allogeneic HSCT experienced VOD/SOS after the second allogeneic HSCT. All 5 patients experienced severe VOD/SOS, and 2 patients (40%) died after reporting VOD/SOS at 0.5 months and 1.1 months after VOD.

Discussion:

Overall, interim data collected between August 2017 and August 2020 in the CIBMTR Research Database appear to be consistent with the results observed in completed Phase 3 Study B1931022.

In Phase 3 Study B1931022, which examined the safety and efficacy of inotuzumab ozogamicin in adult patients with relapsed or refractory ALL who received either 1 or 2 prior lines of therapy, the VOD incidence was 19% among adult patients undergoing a first HSCT for relapsed or refractory B-cell ALL. Based on data collected between August 2017 and August 2020 in the CIBMTR Research Database, the VOD incidence rate was 18% in adult patients with relapsed or refractory ALL who received a median of 4 prior lines of therapy. Although there are only data from n=27 pediatric patients undergoing a first transplant collected between August 2017 and August 2020 in the CIBMTR Research Database, the incidence of VOD post-HSCT is 26%.

In adult patients (n=131), the 12-month overall survival was 55% and 12-month NRM was 21%. Given the relatively small number of pediatric patients accrued for this interim report, these time-to-event endpoints were not calculated. A comprehensive analysis of the association between patient baseline characteristics, pre-HSCT exposure to inotuzumab ozogamicin, patient characteristics at the time of HSCT and the occurrence of post-transplant VOD/SOS will require a larger sample size.

In conclusion, interim data collected between August 2017 and August 2020 in the CIBMTR Research Database suggest that the safety data obtained from the use of inotuzumab

ozogamicin in the real-world post-transplant setting appear to be consistent with the data observed in Phase 3 Study B1931022.

2 List of abbreviations

Abbreviation	Definition
ABT	antibody-based therapy
ADC	antibody-drug conjugate
AE	adverse event
ALL	acute lymphoblastic leukemia
ANC	absolute neutrophil count
AST/ALT	ratio between aspartate transaminase and alanine transaminase
BM	bone marrow
BMI	Body Mass Index
BOOP	bronchiolitis obliterans organizing pneumonia
CD22	cluster of differentiation 22
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CMV	cytomegalovirus
CNS	central nervous system
COD	cause of death
COP/BOOP	cryptogenic organizing pneumonia/bronchiolitis obliterans organizing pneumonia
CR	complete remission
CR1, CR2….	first complete remission, second complete remission….
CRF	Comprehensive Report Form
Cri	complete remission with incomplete hematologic recovery
CSA	cyclosporine
EU	European Union
FDA	Food and Drug Administration
Form 2000	Recipient Baseline Data
Form 2011	ALL Pre-HSCT Data
Form 2100	Post-HSCT Data
Form 2111	ALL Post-HSCT Data
Form 2400	Pre-Transplant Essential Data
Form 2402	Pre-Transplant Essential Data: Disease Classification
Form 2450	Post-Transplant Essential Data
Form 2541	Inotuzumab Ozogamicin Supplemental Data
Form 2553	VOD/SOS Supplemental Data
Form 2900	Recipient Death Data
GVHD	graft-versus-host disease
HCT-CI	Hematopoietic Cell Transplantation Comorbidity Index
HLA	human leukocyte antigen
HRSA	Health Resources and Services Administration
HSCT	hematopoietic stem cell transplantation
HTN	hypertension
IPN	interstitial pneumonitis
IRB	Institutional Review Board
IV	intravenous
MAC	myeloablative conditioning
MCW	Medical College of Wisconsin
MMF	mycophenolate mofetil
MRD	minimal residual disease
MTX	methotrexate
N/A	not applicable

Abbreviation	Definition
NE	not evaluable
NMA	nonmyeloablative
NMDP	National Marrow Donor Program
NRM	non-transplant related mortality
OS	overall survival
PAS	post-authorization study
PASS	post-authorization safety study
PB	peripheral blood
PIF	primary induction failure
PMR	post-marketing requirement
PT-Cy	post-transplant cyclophosphamide
PTSD	post-traumatic stress disorder
REL1	first relapse
R/R	relapsed or refractory
RIC	reduced-intensity conditioning
SAP	statistical analysis plan
SIRS	systemic inflammatory response syndrome
SOS	sinusoidal obstruction syndrome
Tac	tacrolimus
TBI	total body irradiation
TCD	T-cell depletion
TED	transplant essential data
TKI	tyrosine-kinase inhibitor (includes dasatinib, imatinib, nilotinib, ponatinib)
TMA	thrombotic microangiopathy
TRM	transplant-related mortality
UCB	umbilical cord blood
US	United States
VOD	veno-occlusive disease

3 Investigators

Table 1 Principal investigators

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4 Other responsible parties

Not applicable.

5 Milestones

Table 2 Study milestones

Milestone	Planned date	Actual date
Draft protocol submission to the FDA	End November 2017	28 November 2017
Final protocol submission to the FDA	28 February 2018	22 January 2018
Registration in EU PAS register	28 March 2018	14 March 2018
Start of data collection	18 August 2018	18 August 2018
Interim study report #1 (18 Aug 2017 - 17 Aug 2018)	28 February 2019	20 February 2019
Interim report 2 (18 Aug 2017 - 17 Aug 2019)	28 February 2020	20 February 2020
Interim report 3 (18 Aug 2017 - 17 Aug 2020)	28 February 2021	
Interim report 4 (18 Aug 2017 - 17 Aug 2021)	28 February 2022	
End of data collection	17 August 2022	
Final study report (18 Aug 2017 - 17 Aug 2022)	28 February 2023	

6 Rationale and background

Inotuzumab ozogamicin is an antibody-drug conjugate (ADC) composed of a CD22-directed monoclonal antibody that is covalently linked to N-acetyl-gamma-calicheamicin dimethylhydrazide.

In the United States (US), inotuzumab ozogamicin was approved by the Food and Drug Administration (FDA), on 17 August 2017, for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

ALL is a heterogeneous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs [1]. ALL represents approximately 20% of leukemias among adults and 80% of acute leukemias in children [1]. The age-adjusted incidence rate (2008-2012) of ALL in the US was 1.7 per 100,000 individuals per year, with males having a slightly higher overall rate than females (1.9/100,000 versus 1.5/100,000)[2]. The median age of diagnosis for ALL is 14 years, with approximately 58% of patients diagnosed before the age of 20 years. By contrast, approximately 26% of cases are diagnosed after 45 years of age, and approximately 11% of patients are diagnosed after 65 years of age[2]. The B-cell subtype accounts for approximately 75% of ALL cases in adults and approximately 88% in children[3,4]. B-cell ALL is a frequently fatal disease in adults. While the cure rates and survival outcomes for B-cell ALL have improved during the last several decades, most of the improvements have occurred in younger patients, primarily among children[5].

Inotuzumab ozogamicin has been associated with severe, life-threatening, and sometimes fatal adverse events (AEs), including hepatotoxicity and hepatic veno-occlusive disease / sinusoidal obstruction syndrome (VOD/SOS). In Phase 3 Study B1931022, VOD/SOS occurred during inotuzumab treatment and, more frequently, after subsequent treatment with hematopoietic stem cell transplantation (HSCT). Inotuzumab ozogamicin showed a statistically significant improvement in complete remission/complete remission with incomplete hematologic recovery (CR/CRi) compared to treating physicians' choice of 3 chemotherapy regimens (80.7% vs 29.4%). While HSCT after treatment with inotuzumab ozogamicin appeared to be associated with improved long-term survival, post-HSCT toxicity, especially VOD/SOS and TRM

(transplant-related mortality or non-relapse mortality), was higher in patients treated with inotuzumab ozogamicin than with treating physicians' choice of chemotherapy. Specifically, among the 79 patients treated with inotuzumab ozogamicin who proceeded to a subsequent HSCT, 18/79 patients (23%) developed VOD/SOS post-HSCT compared to 3/34 patients (9%) in the treating physicians' choice of chemotherapy arm. In addition, the cumulative post-HSCT TRM (non-relapse mortality) was 31/79 (39%) in the inotuzumab ozogamicin arm compared to 8/35 (23%) in the control arm.

The current non-interventional study is designated as a post-authorization safety study (PASS) and is a post-marketing requirement (PMR 3259-1) by the FDA. The PMR wording which was agreed with the FDA is as follows:

> *"Characterize toxicity after HSCT in adult and pediatric patients who receive inotuzumab ozogamicin. Include hepatic VOD, TRM (non-relapse mortality), and NTRM. Conduct an analysis of registry data (for example the CIBMTR registry) to evaluate safety at least through day 180 after transplantation. The number of available patients in the database will determine the sample size. Include details of all prior therapies. The minimum duration of the study is to be no less than five years."*

7 Research question and objectives

7.1 Research question

What are the toxicities after HSCT in adult and pediatric patients who receive inotuzumab ozogamicin?

7.2 Objectives

Based on data obtained from the Center for International Blood and Marrow Transplant Research® (CIBMTR®) Research Database, the objectives were to evaluate the following in adult and pediatric patients with B-cell ALL who received inotuzumab ozogamicin and proceeded to HSCT:

- Patient-, disease- and HSCT-related characteristics, including details of all prior anti-cancer therapies;
- Timing of inotuzumab ozogamicin treatment prior to HSCT;
- TRM (non-relapse mortality), NTRM, relapse, and OS;
- Post-HSCT adverse events of interest, including hepatic VOD/SOS;
- Cause of death (COD).

The term "adverse events" used in the study objectives and throughout this report generally refers to the safety events of interest in this study. Section 10.5 refers to the requirements of individual case reporting of adverse events.

8 Amendments and updates

There have been no amendments to the Study B1931028 protocol since the original version was submitted to the FDA on 22 January 2018.

9 Research methods

9.1 Study design

This secondary data collection non-interventional PASS uses de-identified healthcare data from the CIBMTR database. This retrospective study will evaluate safety outcomes post-HSCT in patients with B-cell precursor ALL who have been treated with inotuzumab ozogamicin prior to HSCT. The study will utilize all relevant data available in the CIBMTR database from US transplant centers for a 5-year period following the approval of inotuzumab ozogamicin in the US (i.e., 18 August 2017 – 17 August 2022).

The protocol is included in Appendix 1: Protocol.

9.2 Setting

The study population included all adult and pediatric patients in the US with B-cell ALL in the CIBMTR database at the CRF level of data collection treated with inotuzumab ozogamicin who proceeded to HSCT. Data in pediatric patients were included in accordance with the agreement reached during negotiation of the PMR with the FDA.

9.3 Subjects

9.3.1 Inclusion Criteria

Patients met each of the following inclusion criteria:

- A record of B-cell precursor ALL diagnosis for adult and pediatric patients
- At least 1 dose of inotuzumab ozogamicin prior to proceeding to HSCT.
- Received HSCT from a US transplant center participating in the study.

9.3.2 Exclusion Criteria

Patients were excluded from the study if they met 1 of the following criteria:

- Treated at a transplant center not participating in the study
- Treated at a transplant center embargoed from contributing to research studies because center did not meet the CIBMTR's data quality standards
- Had not given consent to participate in the CIBMTR Research Database

9.4 Variables

Definition of exposures, outcomes, and other variables including measured risk factors, co-morbidities, co-medications, etc. with operational definitions and measurement; potential confounding variables and effect modifiers are included in the Statistical Analysis Plan (SAP) (see Appendix 2: Statistical Analysis Plan).

9.4.1 Demographic

- Patient characteristics (including age, race, weight, body mass index, body surface area, height, sex)

9.4.2 Baseline

- Co-morbid conditions (i.e., HSCT co-morbidity score, and specific comorbidities like arrhythmia, cardiac, cerebrovascular disease, mild and moderate/severe hepatic disease)
- Pre-HSCT therapy (lines of therapy prior to transplant, lines of therapy prior to inotuzumab ozogamicin)
- Baseline organ function of recipient prior to HSCT conditioning regimen (aspartate transaminase levels, total serum bilirubin levels)
- Baseline hematologic function prior to HSCT conditioning regimen (platelets, neutrophils, hemoglobin levels)
- Laboratory values at diagnosis of ALL (white blood cells, blasts in blood, blasts in bone marrow)
- Laboratory values prior to transplant (white blood cells, blasts in blood, blasts in bone marrow)
- Karnofsky/Lansky performance score prior to transplant
- Disease assessment at diagnosis
- HSCT data (prior autologous HSCT, time from diagnosis to HSCT)
- Graft-versus-host disease (GVHD) prophylaxis
- Pre-HSCT conditioning regimen (including use of dual alkylators, use of busulfan, use of thiotepa)
- Product type (bone marrow, peripheral blood stem cell, or cord blood for index HSCT)
- Donor type
- Number of treatment regimen(s) prior to receiving inotuzumab ozogamicin
  Pre-HSCT therapy (central nervous system prophylaxis, lines of therapy prior to transplant, purpose of therapy prior to inotuzumab ozogamicin, radiation therapy prior to inotuzumab ozogamicin, regimens for different purposes of therapy prior to inotuzumab ozogamicin)

9.4.3 Exposure

- Inotuzumab ozogamicin data (number of cycles, regimen containing inotuzumab ozogamicin, response to inotuzumab ozogamicin, minimal residual disease rate and methods of testing, time from last dose of inotuzumab ozogamicin to HSCT, inotuzumab ozogamicin doses)
- Treatments received at time of HSCT (liver toxicity prophylaxis, antibacterial infection prophylaxis, antiviral infection prophylaxis, antifungal infection prophylaxis, anti-pneumocystis infection prophylaxis)
- Post-HSCT therapies (systemic therapy given for reasons other than relapse, persistent or minimal residual disease; systemic therapy given for relapse, persistent or minimal residual disease; radiation therapy given for reasons other than relapse, persistent or minimal residual disease)

9.4.4 Outcomes

- Post-HSCT infections, up to day 100 (viral, bacterial, fungal)
- Systemic inflammatory response syndrome (SIRS) development, up to day 100
- Septic shock, up to day 100
- Acute GVHD, up to day 100 (maximum grade, time to date of acute GVHD)
- Chronic GVHD, up to 1 year (time to date of chronic GVHD)
- VOD/SOS data (time to VOD/SOS, grade of VOD/SOS, treatment for VOD/SOS, post-VOD/SOS survival)
- Secondary malignancy (time to secondary malignancy)
- Pulmonary adverse events, within 100 days post-HSCT (IPN/idiopathic pneumonia syndrome, bronchiolitis obliterans, COP/BOOP, diffuse alveolar hemorrhage)
- Cardiovascular adverse events, within 100 days post-HSCT (arrhythmia, congestive heart failure, coronary artery disease, myocardial infarction or unstable angina, hypertension requiring therapy, thrombotic microangiopathy [TMA])
- Acute renal failure requiring dialysis, within 100 days post-HSCT
- Avascular necrosis, within 100 days post-HSCT
- Endocrine dysfunction, within 100 days post-HSCT (diabetes or hyperglycemia requiring chronic treatment, growth hormone deficiency or short stature, hypothyroidism requiring replacement therapy, pancreatitis, depression requiring therapy, anxiety requiring therapy, CNS hemorrhage and stroke, post-traumatic stress disorder [PTSD] requiring therapy)
- Post-HSCT clinical status (best response to HSCT, granulopoiesis/neutrophil recovery, megakaryopoiesis/platelet recovery, engraftment syndrome within 100 days post-HSCT, time to engraftment syndrome within 100 days post-HSCT, recipient weight (most recent post-HSCT), recipient height (most recent post-HSCT), Karnofsky/Lansky performance status (post-HSCT), total inpatient days in first 100 days post-HSCT, time from HSCT to date of last contact)

9.5 Data sources/measurement

This non-interventional PASS used data from the CIBMTR Research Database.

The CIBMTR® is a research collaboration between the National Marrow Donor Program® (NMDP)/Be The Match® and the Medical College of Wisconsin. The CIBMTR facilitates critical research through medical, scientific, and statistical expertise; a network of more than 330 centers worldwide; a database with clinical data for more than 575,000 patients; and a biospecimen repository[6].

The CIBMTR holds the contract for the Stem Cell Therapeutic Outcomes Database (SCTOD), awarded by the Health Resources and Services Administration of the U.S. Department of Health and Human Services. As the contract holder, the CIBMTR is charged with collecting data on all allogeneic (related and unrelated) HSCTs performed in the United States. All US transplant centers are required to report data to the CIBMTR; participation of non-U.S. centers is voluntary.

The CIBMTR receives data for approximately 24,000 new HSCT recipients annually as well as follow-up data on previously reported patients. In 2014-2016, a total of 2,506 (1984 adult [age ≥ 18] and 522 pediatric [age < 18 at time of transplantation]) B-cell ALL patients in the US who underwent their first allogeneic HSCT and who provided consent to CIBMTR for research.

The CIBMTR collects data on two levels, using a Transplant Essential Data (TED) form and a Comprehensive Report Form (CRF). CIBMTR collects TED data, an internationally accepted standard data set, on all patients receiving an allogeneic transplant within the US. Also, using a regularly reviewed, weighted algorithm, CIBMTR selects some patients for more detailed CRF data.

The algorithm randomly selects an epidemiologic sample of recipients for whom a CRF is to be requested. The algorithm includes, but is not limited to, type of HSCT, age of the recipient, disease, etc. It gives higher weights to patients receiving HSCT for rare indications, to very young and very old patients, and novel treatment approaches. It aims to provide representative, adequately sized subsets of patients for studies requiring detailed data. The algorithm is periodically reviewed to assess the burden of data submission for centers.

The CRF captures additional patient, disease and treatment-related data for a subset of patients. (i.e., the CRF does not include data from all patients in the registry). Approximately 75% of CIBMTR centers provide CRF data; this accounts for more than 25% of cases submitted to CIBMTR annually.

TED- and CRF-level data are collected pre-transplant, 100 days post-transplant, six months post-transplant, annually until year 6 post-transplant, and biannually thereafter until death or lost to follow-up.

Data (TED- and CRF-level) from all consenting US patients in the CIBMTR database treated with inotuzumab ozogamicin during the accrual period are included in the analysis. These patients were placed on the CRF data track, so data necessary for the study would be collected.

Data for the PASS regarding post-HSCT adverse events of interest in patients treated with inotuzumab ozogamicin were collected from the CIBMTR database using the standard and supplemental forms shown in Appendix 3: CIBMTR Data Collection Forms.

Table 3 Data collection forms for post-HSCT adverse events of interest in patients with B-Cell precursor ALL who received inotuzumab ozogamicin prior to HSCT

Variable	Data Source (CIBMTR form number and title)
Infection up to day 100	2100 Post-HSCT Follow-up Data,
GVHD	2450 Post-Transplant Essential Data
VOD up to day 100	2100 Post-HSCT Follow-up Data,
	2450 Post-Transplant Essential Data,
	2553 VOD/SOS Supplemental Data,
Secondary Malignancy	2100 Post-HSCT Follow-up Data,
	2450 Post-Transplant Essential Data
Pulmonary adverse events	
IPN/Idiopathic pneumonia syndrome	2100 Post-HSCT Follow-up Data,
Bronchiolitis obliterans	2450 Post-Transplant Essential Data
COP/BOOP	
Diffuse alveolar hemorrhage	
Cardiovascular disease	
Arrhythmia	2100 Post-HSCT Follow-up Data,
Congestive heart failure	2450 Post-Transplant Essential Data
Coronary artery disease	
Myocardial infarction/unstable angina	
Hypertension requiring therapy	
Thrombotic microangiopathy	
Renal adverse events	
Acute renal failure requiring dialysis	2100 Post-HSCT Follow-up Data,
	2450 Post-Transplant Essential Data
Musculoskeletal dysfunction	
Avascular necrosis	2100 Post-HSCT Follow-up Data,
	2450 Post-Transplant Essential Data
Endocrine dysfunction	
Diabetes/hyperglycemia requiring chronic treatment	2100 Post-HSCT Follow-up Data,
Growth hormone deficiency/short stature	2450 Post-Transplant Essential Data
Hypothyroidism requiring replacement therapy	
Pancreatitis	
Neurologic/psychiatric	
Depression requiring therapy	2100 Post-HSCT Follow-up Data,
Anxiety requiring therapy	2450 Post-Transplant Essential Data
Central nervous system hemorrhage and stroke	
Post-traumatic stress disorder requiring therapy	

Note: Forms are available online; see Appendix 3: CIBMTR Data Collection Forms

9.6 Bias

Selection bias was minimal as all patients who consent for research from participating US transplant centers are eligible for the study and the rate of non-consenting patients is low (8%). Selection bias is possible in any registry study; however, the CIBMTR Research Database was designed specifically to collect data prospectively on real-world effectiveness with long-term follow-up. CIBMTR tracks outcomes that treating physicians can measure objectively, rather than subjectively.

9.7 Study size

The CIBMTR invited 203 US transplant centers to participate in this study. Patients were eligible if they consented for research and received inotuzumab ozogamicin prior to HSCT for B-cell ALL from a participating US center.

9.8 Data transformation

Detailed methodology for data transformations are documented in the SAP, which is dated, filed and maintained by the Sponsor (see Appendix 2: Statistical Analysis Plan).

Data analyses in adult and pediatric patients with B-cell ALL who proceeded to HSCT:

- Patient-, disease- and HSCT-related characteristics, including details of all prior anti-cancer therapies;
- Timing of inotuzumab ozogamicin treatment prior to HSCT;
- TRM or non-relapse mortality; NTRM; relapse; and OS;
- Post-HSCT adverse events of interest, including hepatic VOD/SOS;
- COD.

Data are presented for adults, pediatric patients, and adults and pediatrics combined.

The study baseline time point is the date of the current HSCT i.e., a pediatric patient was defined as a patient who was < 18 years at the time of HSCT, regardless of whether they became > 18 years of age during the 5-year follow-up. There was no minimum age requirement for this study.

9.9 Statistical methods

9.9.1 Main summary measures – Definitions

The following are the main summary measures that were collected and presented for all study participants. The definitions are provided below.

9.9.1.1 Transplant-related mortality (TRM)

TRM (which can also be referred to as non-relapse mortality) is time from HSCT to death within the first 28 days post-HSCT, or death from any cause without prior relapse/progression post-HSCT. In the absence of confirmation of death, TRM was censored at the date that the patient was last known to be alive. The duration (in months) of TRM was calculated as follows: [date of event/ competing event/ last known to be alive − date of transplant + 1]/30.4375.

9.9.1.2 Non-transplant related mortality (NTRM)

NTRM is time from HSCT to death after the first 28 days from any cause with prior relapse/progression post-HSCT. In the absence of confirmation of death, NTRM was censored at the date that the patient was last known to be alive. The duration (in months) of NTRM was calculated as follows: [date of event/ competing event/ last known to be alive − date of transplant + 1]/30.4375.

9.9.1.3 Post-transplant relapse

Post-transplant relapse of ALL is time from HSCT to first relapse post-HSCT without death post-relapse, or with death after the first 28 days post-HSCT. In the absence of confirmation of relapse/death, relapse was censored at the date that the patient was last known to be alive. The duration (in months) of relapse was calculated as follows: [date of event/ competing event/ last known to be alive − date of transplant + 1]/30.4375.

9.9.1.4 Post-transplant overall survival (OS)

Post-transplant OS is the time from HSCT to death due to any cause. In the absence of confirmation of death, post-transplant OS was censored at the date that the patient was last known to be alive. The duration (months) of post-transplant OS was calculated as follows: [date of death/ last known to be alive − date of transplant + 1]/30.4375.

9.9.1.5 Post-inotuzumab ozogamicin survival

Post-inotuzumab ozogamicin survival is the time from the first dose (i.e., cycle 1 day 1 [C1D1]) of inotuzumab ozogamicin to death due to any cause. In the absence of confirmation of death, post-inotuzumab ozogamicin survival was censored at the date that the patient was last known to be alive. The duration (months) of post-inotuzumab ozogamicin survival was calculated as follows: [date of death/ last known to be alive − date of C1D1 + 1]/30.4375.

9.9.1.6 Post-HSCT follow-up

Post-HSCT follow-up is the time from HSCT to date of last contact. The duration (months) of post-HSCT follow-up was calculated as follows: [date of last contact − date of HSCT + 1]/30. 4375.

9.9.1.7 Subgroups

Exploratory subgroup analysis was conducted separately for the following patient cohorts:

- Adult patients (≥18 years);
- Pediatric patients (<18 years);
- All patients who had relapsed or refractory B-cell ALL prior to HSCT;
    - Adult patients (≥18 years) who had relapsed or refractory B-cell ALL prior to HSCT;
    - Pediatric patients (<18 years) who had relapsed or refractory B-cell ALL prior to HSCT.
- All patients who were in first complete remission B-cell ALL prior to HSCT;
    - Adult patients (≥18 years);
    - Pediatric patients (<18 years).

9.9.1.8 Lines of therapy

Lines of therapy given prior to an event, either conditioning regimen or inotuzumab ozogamicin, were measured in the following categories:

- No therapy given prior to event
- One line of therapy given prior to event
- Two lines of therapy given prior to event
- Three lines of therapy given prior to event
- Four or more lines of therapy given prior to event

9.9.2 Main statistical methods

All analyses were based on descriptive statistics (i.e., no hypothesis testing is planned). Unadjusted P values were provided, but no definite conclusions were made based on P values, and no adjustments for multiple comparisons were applied.

9.9.2.1 Time-to-event endpoints

Time-to-event endpoints (e.g., post-transplant OS and post-inotuzumab ozogamicin survival) were summarized using the Kaplan-Meier method. Median event times were summarized, with confidence intervals (CI) calculated using the method described by Brookmeyer and Crowley[7].

9.9.2.2 Competing-risks analyses

TRM, NTRM, and post-transplant relapse were summarized using competing-risks analyses. Competing-risks analyses evaluated the hazard of events in the presence of potentially competing events. The cumulative incidence of events was summarized with the CI calculated based on the cumulative incidence function using the SAS macro by Lin et al[8], which is based on the method described by Kalbfleisch JD and Prentice RL (1980)[9].

9.9.2.3 Categorical variables

Categorical variables were summarized using counts and percentages.

9.9.2.4 Continuous variables

Continuous variables were summarized using descriptive statistics (median, minimum, maximum and number of patients).

9.9.3 Missing values

Missing dates (except for death dates) were handled by the following conventions for partial dates following Pfizer standard which was used for the submissions for the approval of inotuzumab ozogamicin:

- If the day of the month was missing for any date used in a calculation, the 1st of the month was used to replace the missing date unless the calculation results in a negative time duration (e.g., date of onset cannot be prior to day 1 date). In this case, the date resulting in 0 time duration was used;
- If the day of the month and the month was missing for any date used in a calculation, the 1st of January was used to replace the missing data;

- If these conventions produced a date that results in a negative time to event, then the time to event was reset to one day.

Missing death dates were handled by the following conventions:

- If the entire date was missing, it was not imputed, and the time to event was censored at the date that the patient was last known to be alive;
- If the day of the month was missing, the maximum of the full (non-imputed) day after the date of last contact and the 1st of the month was used to replace the missing date;
- If the day of the month and the month was missing, the maximum of the full (non-imputed) day after the date of last contact and the 1st of January was used to replace the missing date.

For time-to-event endpoints, patients who had not yet experienced the event of interest were censored.

There are no plans for imputation of missing values for other variables; all missing values were excluded from analyses.

9.9.4 Sensitivity analyses

Not applicable.

9.9.5 Amendments to the statistical analysis plan

The original SAP dated 15 January 2018 was amended three times (versions 2, 3 and 4).

Major changes from the original SAP to SAP version 2.0 (dated 06 July 2018) were:

- The definitions of transplant-related mortality (TRM) and non-transplant related mortality (NTRM) were revised to allow deaths within the first 28 days post-transplant to be considered as an event for TRM (non-relapse mortality);
- An alternative method to estimate the cumulative incidence rate of NTRM, with its CI, was added.

Major changes from SAP version 2.0 to SAP version 3.0 (dated 30 October 2019) were:

- The full analysis set was used only for analyses of pre- and at-HSCT variables.
- The post-transplant evaluable set was introduced to allow the analyses of time-to-event endpoints and post-HSCT variables only being based on patients with post-transplant follow-up.
- The competing risk for TRM was changed from NTRM to post-transplant relapse.
- The definition of post-transplant relapse was revised to allow its competing risk to include any death within 28 days post-transplant.
- Subgroup analyses for patients by number of prior HSCTs (0, ≥ 1) and for patients undergoing allogeneic HSCT were removed. Separate analyses were conducted for patients undergoing first, second, third (if applicable) allogeneic HSCT for B-cell ALL, and patients undergoing autologous HSCT for B-cell ALL (if applicable).

- The subgroup analysis for patients who had relapsed or refractory B-cell ALL prior to receiving inotuzumab ozogamicin was changed to patients who had relapsed or refractory B-cell ALL prior to HSCT.
- A subgroup analysis for patients who were in first complete remission of B-cell ALL prior to HSCT was added.

The major change from SAP version 3.0 to SAP version 4.0 (dated 21 July 2020) was the addition of Section 8.2.13 for Additional Exploratory Analyses.

9.10 Quality control

US centers report to the CIBMTR longitudinal clinical outcomes data on all allogeneic transplants. CIBMTR ensures accuracy via monitoring for consecutive reporting, verification, validation, and computerized record checks. In addition, CIBMTR audits each transplant center every four years. These validations and verifications produce high-quality data.

9.11 Protection of human subjects

9.11.1 Patient information and consent

CIBMTR complies with all laws that protect research participants and their personal data.

Patients and/or legal guardian(s) provide informed consent for research participation.

Protected health information is collected and maintained in CIBMTR's capacity as a Public Health Authority under the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule.

Only data from patients who have consented are used in this study.

CIBMTR does not include patient identifiers in reports, publications, or in any other disclosures.

9.11.2 Institutional Review Board (IRB)

The NMDP/Be The Match central IRB, which is fully accredited by the Association for the Accreditation of Human Research Protection Programs, reviews and approves all human subject research conducted by the CIBMTR.

CIBMTR rules requiring the registration of all consecutive HSCT recipients ensure the inclusion of women, minorities, and children, so the CIBMTR Research Database includes women and minorities in the same proportion as found in the general HSCT population. Children are included in most CIBMTR studies; their inclusion is dependent on the study focus.

9.11.3 Ethical conduct

The CIBMTR is committed to the ethical conduct of research. All Coordinating Center personnel maintain Collaborative IRB Training Initiative (CITI) certification.

The study is being conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices (e.g., FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, Good

Pharmacoepidemiology Practices [GPP] issued by the International Society for Pharmacoepidemiology [ISPE], the International Society for Pharmacoeconomics and Outcomes Research [ISPOR] guidance, and Pharmaceutical Research and Manufacturers Association [PhRMA] guidelines)

10 Results

Note: The data presented in this interim study report are preliminary and were obtained from the Coordinating Center of the CIBMTR. The analysis has not been reviewed or approved by the Statistical or Scientific Committees of the CIBMTR. The data may not be published without prior approval of the CIBMTR.

10.1 Participants

A total of 3140 B-cell ALL patients underwent an allogeneic HSCT transplant in the US between 18 August 2017 – 17 August 2020. Out of those 3,140 patients, 282 patients were excluded from this study as they had not consented to research, 67 patients were excluded from embargoed centers, and 1,354 patients were excluded as they belonged to centers not participating in the study. Of the remaining 1,437 patients, 184 received at least one dose of inotuzumab ozogamicin.

Table 4. Disposition of participants

Selection criteria	Number of patients excluded	Number of patients remaining in the study cohort
AlloHSCT for B-cell ALL in US between 18 Aug. 2017 – 17 Aug. 2020		3140
Patient consented for research	282	2858
Excluded patients from embargoed centers [a]	67	2791
Excluded patients from centers not participating in study	1354	1437
Patient indicated inotuzumab ozogamicin had been given	1253	184

[a] Embargoed centers are those with data that do not meet CIBMTR's quality standards

Therefore, between 18 August 2017 and 17 August 2020, 184 patients (152 adult and 32 pediatric) were accrued and included in the study. The data lock date for this interim report, when data collection forms were last evaluated, was 11 November 2020.

Of the 184 patients included in this study, 163 patients underwent their first allogeneic HSCT for B-cell ALL (136 adult and 27 pediatric) and 21 patients (16 adult and 5 pediatric) had received a prior allogeneic HSCT for B-cell ALL before receiving inotuzumab ozogamicin.

The 21 patients who had a prior allogeneic HSCT for B-cell ALL before receiving inotuzumab ozogamicin are described separately since the underlying disease, risk for relapse and post-HSCT complications are different for patients with a prior HSCT than for patients undergoing their first allogeneic HSCT for B-cell ALL.

10.1.1 Patients who underwent their first allogeneic HSCT for B-cell ALL

In total, 163 patients (136 adults and 27 pediatric patients with a median age of 35 years) underwent their first allogeneic HSCT for B-cell ALL after treatment with inotuzumab ozogamicin.

Prior to transplant, 15 patients had 1 line of therapy; 30 patients had 2 lines of therapy; 24 patients had 3 lines of therapy; and 86 patients had four or more lines of therapy. Data were not available for 8 patients.

As of the data lock date, post-HSCT follow-up information was available for 158 / 163 (97%) patients:

- 100 / 158 patients (63%) did not experience post-HSCT relapse; of these:
  - 30 / 100 patients (30%; 26 adult and 4 pediatric) died in remission, with a median time from transplant to transplant-related mortality (TRM) of 2.18 months; their causes of death (COD) were:
    - VOD/SOS – 8 patients (27%; 6 adult, 2 pediatric)
    - GVHD – 7 patients (23%; 7 adult, 0 pediatric)
    - Interstitial pneumonitis – 3 patients (10%; 2 adult, 1 pediatric)
    - Hemorrhage – 3 patients (10%; 3 adult, 0 pediatric)
    - Organ failure – 3 patients (10%; 3 adult, 0 pediatric)
    - Infection – 2 patients (7%; 2 adult, 0 pediatric)
    - Septic shock – 2 patients (7%; 2 adult, 0 pediatric)
    - Thrombotic microangiopathy – 1 (3%) pediatric patient
    - Graft failure – 1 (3%) adult patient
- 56 / 158 patients (35%) experienced post-HSCT relapse; of these:
  - 34 / 56 patients (61%; 29 adult, 5 pediatric) died after post-HSCT relapse of ALL, with a median time from transplant to NTRM of 6.64 months;
- 2 / 158 patients (1%) have unknown post-HSCT relapse. The involved transplant centers have been notified and these data will be updated.
- 24 / 158 patients (15%; 17 adult, 7 pediatric) experienced post-transplant VOD/SOS; of these:
  - 10 cases were mild (42%; 7 adult, 3 pediatric)
  - 14 cases were severe (58%; 10 adult, 4 pediatric)
  - 2 cases (8%; 1 adult, 1 pediatric) did not receive liver toxicity prophylaxis
  - 14 cases (58%; 10 adult, 4 pediatric) died after reporting VOD
    - 8 out of the 14 cases (57%) reported VOD as COD
      - 1 out of the 8 patients (13%) with reported VOD as COD had not received liver toxicity prophylaxis
    - Other CODs were:
      - GVHD (2 cases [14%], died 0.2 and 1.8 months after VOD),
      - Recurrence of B-Cell ALL (2 cases [14%], died 0.3 and 2.9 months after VOD),
      - Septic shock (1 case [7%], died 0.5 months after VOD), and

    - Interstitial pneumonitis (1 case [7%], died 0.1 months after VOD).
- 17 / 158 patients (11%) did not receive liver toxicity prophylaxis
- 108 / 158 patients (68%) received liver toxicity prophylaxis with ursodiol alone
- 22 / 158 patients (14%) received liver toxicity prophylaxis with ursodiol and defibrotide
- 8 / 158 patients (5%) received liver toxicity prophylaxis with ursodiol and other drugs (not specified)
- 2 / 158 patients (1%) received liver toxicity prophylaxis with defibrotide alone
- 1 / 158 patient (1%) did not have any reported liver toxicity prophylaxis

For the remaining 5 / 163 (3%) patients (all adults) for whom post-HSCT follow-up information was not available as of the data lock point, follow-up data will be provided in subsequent reports.

10.1.2 Patients undergoing second, or greater, HSCT for B-cell ALL

As of the data lock date, post-HSCT follow-up information was available for 21 / 21 (100%) patients:

Among the 21 patients (16 adult, 5 pediatric) who had a prior allogeneic HSCT for B-cell ALL before receiving inotuzumab ozogamicin, 9 patients (43%) had ≥ 3 comorbidities prior to HSCT, and 7 patients (33%) had mild hepatic disease prior to HSCT. All 21 patients underwent HSCT for relapsed or refractory disease, and 4 of the 21 patients (19%) had a history of proven invasive fungal infection. Seven (7) patients (33%) received a bone marrow product, 1 patient (5%) received a cord blood product, and the remaining 13 patients (62%) received peripheral blood stem cells. Thirteen (13) patients (62%) received their product from an unrelated donor, 3 patients (14%) had an HLA-identical sibling donor, and the remaining 5 patients (24%) had another related donor (though not a human leukocyte antigen [HLA]-identical sibling). The median time from ALL diagnosis to transplant was 36 months, and the median time from ALL diagnosis to first dose of inotuzumab ozogamicin was 33 months.

Five (5) of the 21 patients (24%) with prior allogeneic HSCT experienced VOD/SOS after the second allogeneic HSCT. All 5 patients experienced severe VOD/SOS, and 2 patients (40%) died after reporting VOD/SOS at 0.5 months and 1.1 months after VOD.

Follow-up for the remaining patients will be conducted for subsequent reports.

10.2 Descriptive data

10.2.1 Subject evaluation groups

10.2.1.1 Form completeness

The 163 patients who underwent their first allogeneic HSCT for B-cell ALL after inotuzumab ozogamicin treatment were requested to complete data collection forms necessary for the study. Table 5 below summarizes the descriptive data collected for these 163 patients.

Table 5 Forms completed

Form	Pediatric patients No. (%)	Adult patients No. (%)	All patients No. (%)
No. patients	27	136	163
Form 2000 Recipient Baseline Data	24 (89)	118 (87)	142 (87)
Form 2011 ALL Pre-HSCT Data	24 (89)	131 (96)	155 (95)
Form 2541 Inotuzumab Ozogamicin Supplemental Data	27	134 (99)	161 (99)
Follow-up reported [a]	27	131	158
Form 2100 Post-HSCT Data	26 (96)	129 (95)	155 (95)
Form 2111 ALL Post-HSCT Data	27	132 (97)	159 (98)
Form 2450 Post-Transplant Essential Data [b]	2 (7)	4 (3)	6 (4)

[a] Since some patients completed multiple follow-up forms; therefore, the number of follow-up forms (forms 2100, 2111, 2450) does not add up to the number of patients who reported follow-up. A patient needed a complete Form 2100 or 2450 to be considered as having reported follow-up, as survival status and date of last contact are only reported on those follow-up forms.
[b] Patients enrolled in the study are moved to the CRF track, and the CRF follow-up forms (Forms 2100, 2111) are required. These CRF follow-up forms include the data collected on the TED follow-up form (Form 2450), plus additional data. However, any data submitted on the Form 2450 will still be assessed, when applicable.

10.2.1.2 Completeness index

Table 6 summarizes the completeness of follow-up (completeness index) in patients who underwent their first allogeneic HSCT and whose centers submitted post-HSCT follow-up forms. This was measured to quantify the effect of losses to follow-up.

The completeness index was calculated as the ratio of observed time (entry time into study until study end or event [death]) to potential time. Follow-up was determined at last contact date on 1-month, 100-day, 6-month, and 12-month follow-up forms submitted by transplant centers.

Table 6 Completeness index

Time	Pediatric patients	Adult patients	All patients
No. patients with follow-up	27	131	158
1 month	100%	100%	100%
100 days	100%	100%	100%
6 months	100%	98%	98%
12 months	98%	93%	94%

Note: Completeness Index calculated per Clark et al.[10]

10.2.2 Demographic, baseline characteristics, and comorbid conditions

Table 7 summarizes the demographic characteristics, baseline characteristics, and comorbid conditions in patients who received inotuzumab ozogamicin prior to first allogeneic HSCT for ALL. Among all 163 patients, the median age was 35 years (range: < 1-75 years).

Table 7. Demographic, baseline characteristics, and comorbid conditions of participants

Characteristic	Pediatric patients (< 18 y)	Adult patients (≥ 18 y)	All patients
No. of patients	**27**	**136**	**163**
No. of centers	10	41	46
Age, years, no. (%)			
< 1	1 (4)	0	1 (1)
1-9	14 (52)	0	14 (9)
10-17	12 (44)	0	12 (7)
18-29	0	37 (27)	37 (23)
30-39	0	27 (20)	27 (17)
40-49	0	32 (24)	32 (20)
50-59	0	17 (13)	17 (10)
60+	0	23 (17)	23 (14)
Median	9	40.5	35
Range	(<1-17)	(18-75)	(<1-75)
Mean	9.1	41.8	36.4
Standard deviation	5.1	15.1	18.5
Race, no. (%)			
White	22 (81)	106 (78)	128 (79)
Black or African-American	0	9 (7)	9 (6)
Asian or Pacific Islander	2 (7)	8 (6)	10 (6)
Others	1 (4)	0	1 (1)
Not reported	2 (7)	13 (10)	15 (9)
Weight, kg			
Median	30	83	80
Range	(8-89)	(32-203)	(8-203)
Mean	37	89	80
Standard deviation	24	28	34
Body mass index, kg/m^2, no. (%)			
N/A; BMI does not apply to pediatric patients	27	0	27 (17)
Underweight	0	3 (2)	3 (2)
Healthy weight	0	25 (18)	25 (15)
Overweight	0	46 (34)	46 (28)
Obese	0	62 (46)	62 (38)
Median	18.1	29.1	28
Range	(14.6-35.8)	(12.2-62.5)	(12.2-62.5)
Mean	20.4	30.5	28.9
Standard deviation	5.8	8.2	8.7

Characteristic	Pediatric patients (< 18 y)	Adult patients (≥ 18 y)	All patients
No. of patients	**27**	**136**	**163**
Body surface area, m^2			
Median	1	2	1.9
Range	(0.4-2)	(1.2-3.2)	(0.4-3.2)
Mean	1.1	2	1.9
Standard deviation	0.5	0.4	0.5
Height, cm			
Median	128	170	168
Range	(67-172)	(130-189)	(67-189)
Mean	128.1	169.9	163
Standard deviation	29.9	10.7	21.9
Sex, no. (%)			
Male	13 (48)	75 (55)	88 (54)
Female	14 (52)	61 (45)	75 (46)
Sorror HCT-CI, no. (%) [a]			
0	14 (52)	19 (14)	33 (20)
1-2	8 (30)	46 (34)	54 (33)
3-4	4 (15)	56 (41)	60 (37)
5	1 (4)	12 (9)	13 (8)
6	0	1 (1)	1 (1)
7	0	1 (1)	1 (1)
Not reported	0	1 (1)	1 (1)
Arrhythmia, no. (%) [b]			
Yes	1 (4)	8 (6)	9 (6)
No	26 (96)	127 (93)	153 (94)
Not reported	0	1 (1)	1 (1)
Cardiac disease, no. (%) [c]			
Yes	1 (4)	6 (4)	7 (4)
No	26 (96)	129 (95)	155 (95)
Not reported	0	1 (1)	1 (1)
Cerebrovascular disease, no. (%) [d]			
Yes	0	2 (1)	2 (1)
No	27	133 (98)	160 (98)
Not reported	0	1 (1)	1 (1)
Hepatic disease, no. (%)			
Moderate/severe [e], not mild	2 (7)	6 (4)	8 (5)
Mild [f], not moderate/severe	3 (11)	35 (26)	38 (23)
No hepatic disease	22 (81)	94 (69)	116 (71)
Not reported	0	1 (1)	1 (1)

Characteristic	Pediatric patients (< 18 y)	Adult patients (≥ 18 y)	All patients
No. of patients	**27**	**136**	**163**
Lines of therapy prior to transplant, no. (%) [g]			
N/A; CIBMTR Form 2011 not yet received	3 (11)	5 (4)	8 (5)
First line	4 (15)	12 (9)	16 (10)
Salvage 1	4 (15)	26 (19)	30 (18)
Salvage 2	1 (4)	24 (18)	25 (15)
Salvage > 2	15 (56)	69 (51)	84 (52)
Number evaluable	24	131	155
Median	4	4	4
Range	(1-14)	(1-10)	(1-14)
Mean	5.4	3.7	41
Standard deviation	4	1.9	2.4
Lines of therapy prior to inotuzumab ozogamicin, no. (%)			
N/A; CIBMTR Form 2011 not yet received	3 (11)	5 (4)	8 (5)
No treatment given	5 (19)	17 (13)	22 (13)
First line	3 (11)	30 (22)	33 (20)
Salvage 1	1 (4)	25 (18)	26 (16)
Salvage 2	3 (11)	31 (23)	34 (21)
Salvage > 2	12 (44)	24 (18)	36 (22)
Not reported	0	4 (3)	4 (2)
Number evaluable	24	127	151
Median	3.5	2	2
Range	(0-13)	(0-9)	(0-13)
Mean	4	2.3	2.6
Standard deviation	3.7	1.7	2.2
Aspartate transaminase (AST), prior to transplant, no. (%), units/L			
N/A: CIBMTR Form 2000 not yet received	3 (11)	18 (13)	21 (13)
Normal	8 (30)	76 (56)	84 (52)
Abnormal	16 (59)	42 (31)	58 (36)
Number evaluable	24	118	142
Median	1.2	0.8	0.9
Range	(0.3-3.6)	(0.3-3.3)	(0.3-3.6)
Mean	1.3	0.9	1
Standard deviation	0.7	0.5	0.6
Total serum bilirubin, prior to transplant, mg/dL, no. (%)			
N/A: CIBMTR Form 2000 not yet received	3 (11)	18 (13)	21 (13)
Normal	22 (81)	109 (80)	131 (80)
Abnormal	2 (7)	9 (7)	11 (7)
Number evaluable	24	118	142
Median	0.3	0.4	0.4
Range	(0-1.1)	(0.2-3.6)	(0-3.6)
Mean	0.4	0.5	0.5
Standard deviation	0.3	0.4	0.4

Characteristic	Pediatric patients (< 18 y)	Adult patients (≥ 18 y)	All patients
No. of patients	**27**	**136**	**163**
Platelets, prior to transplant, × 10^9/L			
N/A; CIBMTR Form 2000 not received prior to Jan 2020	1 (4)	2 (1)	3 (2)
Number evaluable	26	134	160
Median	128	106	115.5
Range	(9-310)	(11-582)	(9-582)
Mean	136.1	123.2	125.3
Standard deviation	83	74.2	75.5
Neutrophils, prior to transplant, %, no. (%)			
N/A; CIBMTR Form 2000 not yet received	3 (11)	18 (13)	21 (13)
Not reported	0	1 (1)	1 (1)
Number evaluable	24	117	141
Median	51	54	54
Range	(20-86)	(7-90)	(7-90)
Mean	51.5	53.5	53.1
Standard deviation	16.2	17.5	17.2
Hemoglobin, prior to transplant, g/dL, no. (%)			
N/A; CIBMTR Form 2000 not yet received	3 (11)	18 (13)	21 (13)
Not reported	0	1 (1)	1 (1)
Number evaluable	24	117	141
Median	11.3	12.4	12.2
Range	(8.7-15.3)	(6.4-17.2)	(6.4-17.2)
Mean	11.6	12.3	12.2
Standard deviation	1.7	2.1	2.1
White blood cells. at diagnosis of ALL, × 10^9/L , no. (%)			
N/A; CIBMTR Form 2000 not yet received	3 (11)	18 (13)	21 (13)
Not reported	6 (22)	9 (7)	15 (9)
Number evaluable	18	109	127
Median	9.8	9.9	9.9
Range	(0.5-525)	(0.5-368)	(0.5-525)
Mean	79.4	51.1	55.1
Standard deviation	141.8	86.9	96.4
Blasts in blood, at diagnosis of ALL, no. (%)			
N/A; CIBMTR Form 2011 not yet received	3 (11)	5 (4)	8 (5)
< 1%	0	14 (10)	14 (9)
≥ 1%	11 (41)	92 (68)	103 (63)
Not reported	13 (48)	25 (18)	38 (23)
Number evaluable	11	106	117
Median	70	45	51
Range	(1-98)	(0-98)	(0-98)
Mean	55.6	47	47.8
Standard deviation	37.3	35.3	35.4

Characteristic	Pediatric patients (< 18 y)	Adult patients (≥ 18 y)	All patients
No. of patients	**27**	**136**	**163**
Blasts in bone marrow, at diagnosis of ALL, no. (%)			
N/A; CIBMTR Form 2011 not yet received	3 (11)	5 (4)	8 (5)
< 50%	1 (4)	13 (10)	14 (9)
≥ 50%	11 (41)	90 (66)	101 (62)
Not reported	12 (44)	28 (21)	40 (25)
Number evaluable	13	105	118
Median	90	88	89
Range	(1-98)	(0-100)	(0-100)
Mean	77.5	77.2	77.2
Standard deviation	32.5	25.4	26.1
White blood cells, at last evaluation prior to transplant, $\times 10^9$/L, no. (%)			
N/A; CIBMTR Form 2011 not yet received	3 (11)	5 (4)	8 (5)
Not reported	0	10 (7)	10 (6)
Number evaluable	24	121	145
Median	3.3	3.7	3.7
Range	(0.5-11.8)	(0.4-13)	(0.4-13)
Mean	3.6	4	4
Standard deviation	2.5	2	2.1
Blasts in blood prior to transplant, no. (%)			
N/A; CIBMTR Form 2011 not yet received	3 (11)	5 (4)	8 (5)
< 1%	11 (41)	106 (78)	117 (72)
≥ 1%	1 (4)	5 (4)	6 (4)
Not reported	12 (44)	20 (15)	32 (20)
Number evaluable	12	111	123
Median	0	0	0
Range	(0-4)	(0-3)	(0-4)
Mean	0.33	0.09	0.11
Standard deviation	1.15	0.44	0.55
Blasts in bone marrow prior to transplant, no. (%)			
N/A; CIBMTR Form 2011 not yet received	3 (11)	5 (4)	8 (5)
< 5%	15 (56)	109 (80)	124 (76)
≥ 5%	1 (4)	2 (1)	3 (2)
Not reported	8 (30)	20 (15)	28 (17)
Number evaluable	16	111	127
Median	0	1	1
Range	(0-94)	(0-7)	(0-94)
Mean	6.31	1.28	1.91
Standard deviation	23.4	1.36	8.34

Characteristic	Pediatric patients (< 18 y)	Adult patients (≥ 18 y)	All patients
No. of patients	**27**	**136**	**163**
Performance score prior to transplant, no. (%)			
Karnofsky score			
90-100	4 (15)	71 (52)	75 (46)
10-80	0	62 (46)	62 (38)
Not reported	0	3 (2)	3 (2)
Lansky score			
90-100	19 (70)	0	19 (12)
10-80	4 (15)	0	4 (2)
History of proven invasive fungal infection, no. (%)			
Yes	4 (15)	8 (6)	12 (7)
No	23 (85)	128 (94)	151 (93)
Disease status prior to transplant, no. (%)			
1st complete remission	6 (22)	41 (30)	47 (29)
2nd complete remission	9 (33)	63 (46)	72 (44)
≥ 3rd complete remission	12 (44)	17 (13)	29 (18)
1st relapse	0	8 (6)	8 (5)
≥ 3rd relapse	0	3 (2)	3 (2)
Primary induction failure	0	4 (3)	4 (2)
Prior autologous HCT, no. (%)			
Yes	0	5 (4)	5 (3)
No	27	131 (96)	158 (97)
Time from diagnosis to HSCT, no. (%), months			
3-5	2 (7)	16 (12)	18 (11)
6-11	6 (22)	32 (24)	38 (23)
≥ 12	19 (70)	88 (65)	107 (66)
Median	42.18	19.17	20.9
Range	(5.06-91.83)	(3.35-256.62)	(3.35-256.62)
Mean	42.07	31.76	33.46
Standard deviation	31.52	37.3	36.52
Time from diagnosis to first dose of inotuzumab ozogamicin, no. (%), months			
N/A; CIBMTR Form 2541 not yet received	0	2 (1)	2 (1)
< 3	1 (4)	21 (15)	22 (13)
3-5	2 (7)	13 (10)	15 (9)
6-11	4 (15)	22 (16)	26 (16)
≥ 12	19 (70)	76 (56)	95 (58)
Not reported	1 (4)	2 (1)	3 (2)
Number evaluable	26	132	158
Median	40.21	15.61	17.68
Range	(2.43-88.67)	(0.13-253.67)	(0.13-253.67)
Mean	40.45	28	30.05
Standard deviation	30.28	37.04	36.23

Characteristic	Pediatric patients (< 18 y)	Adult patients (≥ 18 y)	All patients
No. of patients	**27**	**136**	**163**
GVHD prophylaxis, no. (%)			
Ex-vivo T-cell depletion	8 (30)	3 (2)	11 (7)
CD34 selection	0	1 (1)	1 (1)
Cyclophosphamide ± others	3 (11)	45 (33)	48 (29)
Tac + MMF ± others (not Cy)	0	17 (13)	17 (10)
Tac + MTX ± others (not Cy, MMF)	0	49 (36)	49 (30)
Tac ± others (not Cy, MMF, MTX)	1 (4)	6 (4)	7 (4)
CsA + MMF ± others (not Cy, Tac)	5 (19)	5 (4)	10 (6)
CsA + MTX ± others (not Cy, Tac, MMF)	8 (30)	10 (7)	18 (11)
CsA ± others (not Cy, Tac, MMF, MTX)	1 (4)	0	1 (1)
Not reported	1 (4)	0	1 (1)
Conditioning regimen intensity, no. (%) [h]			
N/A; CIBMTR Form 2000 not yet received	3 (11)	18 (13)	21 (13)
Myeloablative	23 (85)	65 (48)	88 (54)
RIC/NMA	1 (4)	53 (39)	54 (33)
Dual alkylators used in conditioning regimen, no. (%) [i]			
Yes	9 (33)	11 (8)	20 (12)
No	15 (56)	107 (79)	122 (75)
Not reported	3 (11)	18 (13)	21 (13)
Busulfan used in conditioning regimen, no. (%)			
Yes	1 (4)	15 (11)	16 (10)
No	23 (85)	103 (76)	126 (77)
Not reported	3 (11)	18 (13)	21 (13)
Thiotepa used in conditioning regimen, no. (%)			
Yes	10 (37)	12 (9)	22 (13)
No	14 (52)	106 (78)	120 (74)
Not reported	3 (11)	18 (13)	21 (13)
Product type, no. (%)			
Bone marrow	14 (52)	28 (21)	42 (26)
Peripheral blood stem cells	9 (33)	97 (71)	106 (65)
Umbilical cord blood	4 (15)	11 (8)	15 (9)
Donor type, no. (%)			
HLA-identical sibling	5 (19)	36 (26)	41 (25)
Other related	9 (33)	28 (21)	37 (23)
Unrelated	13 (48)	72 (53)	85 (52)

Note: Median and range values are calculated using only patients with complete data for that variable. For CIBMTR forms, see Appendix 3: CIBMTR Data Collection Forms.
[a] Sorror ML, Maris MB, Storer B, et al. Comparing morbidity and mortality of HLA-matched unrelated donor hematopoietic cell transplantation after nonmyeloablative and myeloablative conditioning: influence of pretransplantation comorbidities. Blood 2004; 104:961-8.
[b] History of atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias requiring treatment
[c] History of coronary artery disease (one or more vessel-coronary artery stenosis requiring medical treatment, stent, or bypass graft), congestive heart failure, myocardial infarction, OR ejection fraction ≤ 50% on the most recent test
[d] History of transient ischemic attack, subarachnoid hemorrhage or cerebrovascular accident
[e] Liver cirrhosis, bilirubin > 1.5 × upper limit of normal, or AST/ALT > 2.5 × upper limit of normal
[f] Chronic hepatitis, bilirubin > upper limit of normal to 1.5 × upper limit of normal, or AST/ALT > upper limit of normal to 2.5 × upper limit of normal at the time of transplant OR any history of hepatitis B or hepatitis C infection

Characteristic	Pediatric patients (< 18 y)	Adult patients (≥ 18 y)	All patients
No. of patients	**27**	**136**	**163**

[g] The lines of therapy prior to a specified event are defined as follows. “No treatment given” means no lines of therapy given prior to specified event; “First line” means 1 line of therapy; “Salvage 1” means 2 lines of therapy; “Salvage 2” means 3 lines of therapy; “Salvage > 2” means 4 (or more) lines of therapy.
[h] Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant 2009;15:1628-33.
[i] Dual alkylators were defined as the conditioning regimen including one of the following pairs of treatments: busulfan + cyclophosphamide; busulfan + melphalan; cyclophosphamide + melphalan; busulfan + thiotepa; or cyclophosphamide + thiotepa.

10.2.3 Summary of treatment

This section provides information on the summary of treatment.

10.2.3.1 Therapies prior to inotuzumab ozogamicin

Table 8 summarizes the therapies patients received prior to inotuzumab ozogamicin treatment, including information on the number of lines of therapy prior to transplant and the purpose of therapy prior to patients receiving inotuzumab ozogamicin.

Table 8 Summary of therapies received prior to inotuzumab ozogamicin

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
Number of patients	**27**	**136**	**163**
No. of treatment regimen(s) prior to receiving inotuzumab ozogamicin			
N/A; CIBMTR Form 2011 not yet received	3 (11)	5 (4)	8 (5)
Yes	19 (70)	110 (81)	129 (79)
1	3	30	33
2	1	25	26
3	3	31	34
4	2	13	15
≥ 5	10	11	21
No	5 (19)	17 (13)	22 (13)
Not reported	0	4 (3)	4 (2)
No. of patients with ≥ 1 treatment prior to inotuzumab ozogamicin	19	110	129
Prior autologous HSCT			
Yes	0	0	0
No	19	110	129
CNS prophylaxis			
Yes	12 (63)	78 (71)	90 (70)
No	7 (37)	32 (29)	39 (30)
Lines of therapy prior to transplant			
2	3 (16)	19 (17)	22 (17)
3	1 (5)	23 (21)	24 (19)
4 or more	15 (79)	68 (62)	83 (64)
Purpose of therapy prior to inotuzumab ozogamicin			
Induction	2 (11)	41 (37)	43 (33)
Consolidation	2 (11)	10 (9)	12 (9)
Maintenance	7 (37)	38 (35)	45 (35)
Treatment for disease relapse [a]	8 (42)	21 (19)	29 (22)
Radiation therapy prior to inotuzumab ozogamicin			
Yes	16 (84)	105 (95)	121 (94)
No	3 (16)	5 (5)	8 (6)
Regimens for first line of therapy, prior to inotuzumab ozogamicin			
None	2 (11)	7 (6)	9 (7)
Chemotherapy	10 (53)	53 (48)	63 (49)
Chemotherapy + ABT	0	20 (18)	20 (16)

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
Number of patients	**27**	**136**	**163**
Chemotherapy + TKI	1 (5)	8 (7)	9 (7)
Chemotherapy + ABT + TKI	0	2 (2)	2 (2)
Chemotherapy / Chemotherapy	3 (16)	2 (2)	5 (4)
Chemotherapy / ABT	0	4 (4)	4 (3)
Chemotherapy + ABT / Chemotherapy + TKI	0	1 (1)	1 (1)
Chemotherapy + ABT / Chemotherapy + ABT	0	1 (1)	1 (1)
Chemotherapy + ABT / Chemotherapy + ABT / ABT	0	1 (1)	1 (1)
Chemotherapy / Chemotherapy + ABT	0	1 (1)	1 (1)
Chemotherapy + ABT / Chemotherapy + ABT / Chemotherapy + ABT / Chemotherapy	0	1 (1)	1 (1)
Chemotherapy + TKI / Chemotherapy + TKI / Chemotherapy + TKI / TKI	0	1 (1)	1 (1)
Chemotherapy / Chemotherapy / Chemotherapy	3 (16)	0	3 (2)
ABT	0	5 (5)	5 (4)
ABT / ABT	0	1 (1)	1 (1)
TKI	0	1 (1)	1 (1)
TKI / Chemotherapy	0	1 (1)	1 (1)
Regimens for consolidation therapy, prior to inotuzumab ozogamicin			
None	5 (26)	70 (64)	75 (58)
Chemotherapy	7 (37)	17 (15)	24 (19)
Chemotherapy + ABT	0	11 (10)	11 (9)
Chemotherapy + TKI	0	4 (4)	4 (3)
Chemotherapy / Chemotherapy	3 (16)	4 (4)	7 (5)
Chemotherapy / ABT / Chemotherapy	0	1 (1)	1 (1)
Chemotherapy / Chemotherapy / Chemotherapy	2 (11)	2 (2)	4 (3)
Chemotherapy / Chemotherapy / Chemotherapy / Chemotherapy	1 (5)	0	1 (1)
Chemotherapy / Chemotherapy / Chemotherapy / Chemotherapy / Chemotherapy / Chemotherapy	1 (5)	0	1 (1)
TKI	0	1 (1)	1 (1)
Regimens for maintenance therapy, prior to inotuzumab ozogamicin			
None	5 (26)	66 (60)	71 (55)
Chemotherapy	7 (37)	29 (26)	36 (28)
Chemotherapy + ABT	1 (5)	2 (2)	3 (2)
Chemotherapy + TKI	0	3 (3)	3 (2)
Chemotherapy / Chemotherapy	2 (11)	2 (2)	4 (3)
Chemotherapy / Chemotherapy / Chemotherapy	2 (11)	2 (2)	4 (3)
Chemotherapy / Chemotherapy / Chemotherapy / Chemotherapy	2 (11)	0	2 (2)
ABT	0	3 (3)	3 (2)
TKI	0	1 (1)	1 (1)
TKI / Chemotherapy + TKI	0	1 (1)	1 (1)
TKI / ABT	0	1 (1)	1 (1)

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
Number of patients	**27**	**136**	**163**
Regimens for therapy, prior to inotuzumab ozogamicin			
None	13 (68)	86 (78)	99 (77)
Chemotherapy	2 (11)	6 (5)	8 (6)
Chemotherapy + ABT	1 (5)	4 (4)	5 (4)
Chemotherapy / Chemotherapy	2 (11)	1 (1)	3 (2)
Chemotherapy + ABT / Chemotherapy	0	2 (2)	2 (2)
Chemotherapy / Chemotherapy / ABT / Chemotherapy	1 (5)	0	1 (1)
Chemotherapy + TKI / TKI / Chemotherapy / TKI	0	1 (1)	1 (1)
ABT	0	6 (5)	6 (5)
ABT + TKI	0	1 (1)	1 (1)
ABT / Chemotherapy	0	1 (1)	1 (1)
ABT / Chemotherapy / Chemotherapy	0	1 (1)	1 (1)
TKI / Chemotherapy + TKI	0	1 (1)	1 (1)

Note: Pluses (+) denote the same line of therapy, while forward slash lines ("/") denote separate lines of therapy. For example, "Chemotherapy + ABT" means that chemo and ABT were given in the same line of therapy. "Chemotherapy / ABT" means that chemo was given in the first line, then ABT was given in a subsequent line of therapy.
[a] Of the n=29 patients who had received therapy to treat disease relapse in the line prior to inotuzumab ozogamicin, the following number of patient(s) received these numbers of lines of therapy prior to inotuzumab ozogamicin: n=1 patient received 1 line, n=4 patients received 2 lines, n=7 patients received 3 lines, n=6 patients received 4 lines, n=4 patients received 5 lines, n=3 patients received 6 lines, and n=4 patients received 7 or more lines prior to inotuzumab ozogamicin.

10.2.3.2 Inotuzumab ozogamicin treatment prior to HSCT

Table 9 summarizes inotuzumab ozogamicin treatment received prior to HSCT.

Table 9 Summary of inotuzumab ozogamicin treatment prior to HSCT

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No (%)
Number of patients	**27**	**136**	**163**
Number of treatment regimen(s) prior to inotuzumab ozogamicin			
N/A; CIBMTR Form 2011 not yet received	3 (11)	5 (4)	8 (5)
0	5 (19)	17 (13)	22 (13)
1	3 (11)	30 (22)	33 (20)
2	1 (4)	25 (18)	26 (16)
3	3 (11)	31 (23)	34 (21)
4	2 (7)	13 (10)	15 (9)
≥ 5	10 (37)	11 (8)	21 (13)
Not reported	0	4 (3)	4 (2)
Number of cycles of inotuzumab ozogamicin			
N/A; CIBMTR Form 2541 not yet received	0	2 (1)	2 (1)
1	15 (56)	49 (36)	64 (39)
2	11 (41)	63 (46)	74 (45)
≥ 3	1 (4)	22 (16)	23 (14)
Regimen containing inotuzumab ozogamicin			
N/A; CIBMTR Form 2011 not yet received	3 (11)	5 (4)	8 (5)
Single agent	12 (44)	67 (49)	79 (48)
Combined with other chemotherapy/systemic therapy	12 (44)	60 (44)	72 (44)
Not reported	0	4 (3)	4 (2)
Response to inotuzumab ozogamicin			
N/A; CIBMTR Form 2541 not yet received	0	2 (1)	2 (1)
CR	22 (81)	89 (65)	111 (68)
CRi [a]	2 (7)	22 (16)	24 (15)
No CR	3 (11)	23 (17)	26 (16)
MRD rate, among responders			
N/A; CIBMTR Form 2541 not yet received	0	2 (1)	2 (1)
Positive	4 (15)	26 (19)	30 (18)
Negative	20 (74)	90 (66)	110 (67)
MRD evaluation not done	1 (4)	7 (5)	8 (5)
Not reported	2 (7)	11 (8)	13 (8)

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No (%)
Number of patients	**27**	**136**	**163**
MRD method of testing			
N/A; CIBMTR Form 2541 not yet received	0	2 (1)	2 (1)
Flow cytometry	18 (67)	92 (68)	110 (67)
Next generation sequencing	3 (11)	2 (1)	5 (3)
Polymerase chain reaction	1 (4)	3 (2)	4 (2)
Not collected	3 (11)	26 (19)	29 (18)
Not reported	2 (7)	11 (8)	13 (8)
MRD testing method and results in responders			
N/A; CIBMTR Form 2541 not yet received	0	2 (1)	2 (1)
Flow cytometry			
Positive	0	4 (3)	4 (2)
Negative	18 (67)	88 (65)	106 (65)
Next generation sequencing			
Positive	1 (4)	2 (1)	3 (2)
Negative	2 (7)	0	2 (1)
Polymerase chain reaction			
Positive	1 (4)	1 (1)	2 (1)
Negative	0	2 (1)	2 (1)
Not collected			
Positive	2 (7)	19 (14)	21 (13)
MRD evaluation not done	1 (4)	7 (5)	8 (5)
Not reported			
Not reported	2 (7)	11 (8)	13 (8)
Time from last dose of inotuzumab ozogamicin to HSCT, months			
N/A; CIBMTR Form 2541 not yet received	0	2 (1)	2 (1)
< 1	3 (11)	18 (13)	21 (13)
1-1.6	17 (63)	35 (26)	52 (32)
1.7-3	3 (11)	37 (27)	40 (25)
> 3	2 (7)	36 (26)	38 (23)
Not reported	2 (7)	8 (6)	10 (6)
Number evaluable	25	126	151
Median	1.3	1.9	1.7
Range	(0.8-5)	(0.4-26.2)	(0.4-26.2)
Mean	1.6	2.9	2.7
Standard deviation	0.9	3.5	3.3

[a] CRi defined as < 5% blasts in bone marrow and the absence of peripheral blood leukemic blasts, incomplete recovery of peripheral blood counts (platelets < 100 × 10^9/L and/or ANC < 1 × 10^9/L) and resolution of any extramedullary disease

Table 10 summarizes inotuzumab ozogamicin doses prior to HSCT among patients whose treatment regimen included only inotuzumab ozogamicin.

Table 10 Summary of inotuzumab ozogamicin doses prior to HSCT among patients whose treatment regimen included only inotuzumab ozogamicin

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
No. patients who received inotuzumab ozogamicin without other agent(s)	**12**	**67**	**79**
No. patients who received 1 cycle of inotuzumab ozogamicin	7	24	31
Inotuzumab ozogamicin combined dose, all cycles, mg/m²			
< 1.8	2 (29)	3 (13)	5 (17)
1.8	5 (71)	17 (71)	22 (71)
> 1.8	0	2 (8)	2 (6)
Not reported	0	2 (8)	2 (6)
Median	1.8	1.8	1.8
Range	(0.9-1.8)	(0.8-3.6)	(0.8-3.6)
Mean	1.6	1.8	1.8
Standard deviation	0.3	0.5	0.5
No. patients who received 2 cycles of inotuzumab ozogamicin	4	29	33
Inotuzumab ozogamicin combined dose, all cycles, mg/m²			
< 3.0	1 (25)	2 (7)	3 (9)
3.0-3.2	0	5 (17)	5 (15)
3.3-3.6	2 (50)	17 (59)	19 (58)
> 3.6	1 (25)	2 (7)	3 (9)
Not reported	0	3 (10)	3 (9)
Median	3.6	3.3	3.3
Range	(2.8-3.8)	(2.8-6.9)	(2.8-6.9)
Mean	3.5	3.5	3.5
Standard deviation	0.4	0.9	0.8
No. patients who received 3 or more cycles of inotuzumab ozogamicin	1	14	15
Inotuzumab ozogamicin combined dose, all cycles, mg/m²			
< 4.9	1	2 (14)	3 (20)
4.9-5.3	0	3 (21)	3 (20)
> 5.3	0	3 (21)	3 (20)
Not reported	0	6 (43)	6 (40)
Median	4.8	5.1	5.1
Range	NE	(4.8-5.4)	(4.8-5.4)
Mean	4.8	5.1	5.1
Standard deviation	NE	0.3	0.3

Note: Outcomes are not evaluable (NE) if sample size is < 20.

Table 11 summarizes inotuzumab ozogamicin doses prior to HSCT among patients whose treatment regimen included other agents.

Table 11 Summary of inotuzumab ozogamicin doses prior to HSCT among patients whose treatment regimen included other agents

	Pediatric patients (< 18 y)	Adults (≥ 18 y)	All patients
No. patients who received inotuzumab ozogamicin with other agent(s)	**12**	**60**	**72**
No. patients who received 1 cycle of inotuzumab ozogamicin	6	22	28
Inotuzumab ozogamicin combined dose, all cycles, mg/m²			
< 1.8	0	14 (64)	14 (50)
1.8	4 (67)	7 (32)	11 (39)
Not reported	2 (33)	1 (5)	3 (11)
Median	1.8	1.3	1.4
Range	(1.8-1.8)	(0.3-1.8)	(0.3-1.8)
Mean	1.8	1.3	1.4
Standard deviation	0	0.5	0.5
No. patients who received 2 cycles of inotuzumab ozogamicin	6	31	37
Inotuzumab ozogamicin combined dose, all cycles, mg/m²			
< 3.0	3 (50)	21 (68)	24 (65)
3.0-3.2	1 (17)	0	1 (3)
3.3-3.6	2 (33)	5 (16)	7 (19)
> 3.6	0	1 (3)	1 (3)
Not reported	0	4 (13)	4 (11)
Median	3.1	1.8	2.1
Range	(2.4-3.6)	(0.9-7.7)	(0.9-7.7)
Mean	3	2.3	2.4
Standard deviation	0.4	1.4	1.3
No. patients who received 3 or more cycles of inotuzumab ozogamicin	0	7	7
Inotuzumab ozogamicin combined dose, all cycles, mg/m²			
< 2.8	0	3 (43)	3 (43)
2.8-4.8	0	1 (14)	1 (14)
4.9-5.3	0	1 (14)	1 (14)
> 5.3	0	1 (14)	1 (14)
Not reported	0	1 (14)	1 (14)
Median	NE	2.7	2.7
Range	NE	(1.8-5.4)	(1.8-5.4)
Mean	NE	3.3	3.3
Standard deviation	NE	1.6	1.6

Note: Outcomes are not evaluable (NE) if sample size is < 20.

10.2.3.3 Treatments at time of HSCT

Table 12 summarizes treatments received at time of HSCT, except for drugs given for conditioning regimen, among patients who received inotuzumab ozogamicin.

Table 12 Summary of treatments received at time of HSCT, except for drugs given for conditioning regimen, among patients who received inotuzumab ozogamicin

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
Number of patients	**27**	**136**	**163**
Liver toxicity prophylaxis			
N/A; CIBMTR Form 2450 or 2100 not yet received	0	5 (4)	5 (3)
No specific therapy used to prevent liver toxicity	6 (22)	11 (8)	17 (10)
Ursodiol	4 (15)	104 (76)	108 (66)
Ursodiol + defibrotide	7 (26)	8 (6)	15 (9)
Ursodiol + defibrotide + others	5 (19)	2 (1)	7 (4)
Ursodiol + others	4 (15)	4 (3)	8 (5)
Defibrotide	1 (4)	1 (1)	2 (1)
Not reported	0	1 (1)	1 (1)
Antibacterial infection prophylaxis			
N/A; CIBMTR Form 2100 not yet received	1 (4)	7 (5)	8 (5)
None	11 (41)	18 (13)	29 (18)
Levofloxacin (IV or oral)	6 (22)	71 (52)	77 (47)
Ciprofloxacin (IV or oral)	1 (4)	19 (14)	20 (12)
Vancomycin (IV)	3 (11)	4 (3)	7 (4)
Levofloxacin (IV or oral) + others	0	4 (3)	4 (2)
Ciprofloxacin (IV or oral) + others	1 (4)	5 (4)	6 (4)
Not reported	4 (15)	8 (6)	12 (7)
Antiviral infection prophylaxis			
N/A; CIBMTR Form 2100 not yet received	1 (4)	7 (5)	8 (5)
None	1 (4)	0	1 (1)
Acyclovir	18 (67)	83 (61)	101 (62)
Valacyclovir	2 (7)	32 (24)	34 (21)
Ganciclovir	0	4 (3)	4 (2)
Valganciclovir	2 (7)	2 (1)	4 (2)
Livermore	0	4 (3)	4 (2)
Cidofovir	1 (4)	0	1 (1)
Foscarnet	2 (7)	3 (2)	5 (3)
Acyclovir + Valacyclovir + Letermovir	0	1 (1)	1 (1)

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
Number of patients	**27**	**136**	**163**
Antifungal infection prophylaxis			
N/A; CIBMTR Form 2100 not yet received	1 (4)	7 (5)	8 (5)
None	0	1 (1)	1 (1)
Fluconazole	13 (48)	59 (43)	72 (44)
Posaconazole	1 (4)	26 (19)	27 (17)
Micafungin	6 (22)	18 (13)	24 (15)
Caspofungin	0	21 (15)	21 (13)
Nystatin	5 (19)	2 (1)	7 (4)
Voriconazole	0	2 (1)	2 (1)
Anidulafungin	1 (4)	0	1 (1)
Anti-pneumocystis infection prophylaxis			
N/A; CIBMTR Form 2100 not yet received	1 (4)	7 (5)	8 (5)
None	1 (4)	16 (12)	17 (10)
Trimethoprim/Sulfamethoxazole	17 (63)	63 (46)	80 (49)
Pentamidine inhaled	1 (4)	12 (9)	13 (8)
Pentamidine IV	7 (26)	28 (21)	35 (21)
Atovaquone	0	3 (2)	3 (2)
Dapsone	0	7 (5)	7 (4)
GVHD prophylaxis			
Ex-vivo T-cell depletion	8 (30)	3 (2)	11 (7)
CD34 selection	0	1 (1)	1 (1)
Cyclophosphamide ± others	3 (11)	45 (33)	48 (29)
Tac + MMF ± others	0	17 (13)	17 (10)
Tac + MTX ± others	0	49 (36)	49 (30)
Tac ± others	1 (4)	6 (4)	7 (4)
CsA + MMF ± others (not Cy, Tac)	5 (19)	5 (4)	10 (6)
CsA + MTX ± others (not Cy, Tac, MMF)	8 (30)	10 (7)	18 (11)
CsA ± others (not Cy, Tac, MMF, MTX)	1 (4)	0	1 (1)
Not reported	1 (4)	0	1 (1)

10.2.3.4 Post-HSCT therapies

Table 13 summarizes post-HSCT therapies following inotuzumab ozogamicin treatment in patients who received inotuzumab ozogamicin prior to first allogeneic HSCT for ALL.

Table 13 Post-HSCT therapies following inotuzumab ozogamicin treatment

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
Number of patients with follow-up	**27**	**131**	**158**
Systemic therapy given for reasons other than relapse, persistent, or MRD			
None	25 (93)	116 (89)	141 (89)
Ponatinib	0	6 (5)	6 (4)
Nilotinib	0	1 (1)	1 (1)
Imatinib	0	1 (1)	1 (1)
Not reported	2 (7)	7 (5)	9 (6)
Systemic therapy given for relapse, persistent or MRD			
None	20 (74)	98 (75)	118 (75)
Inotuzumab	1 (4)	5 (4)	6 (4)
Inotuzumab + chemotherapy	0	1 (1)	1 (1)
Blinatumomab	0	3 (2)	3 (2)
Blinatumomab + chemotherapy	0	2 (2)	2 (1)
Blinatumomab + vincristine	0	1 (1)	1 (1)
Chemotherapy	3 (11)	4 (3)	7 (4)
Ponatinib	0	1 (1)	1 (1)
Ponatinib + chemotherapy	0	1 (1)	1 (1)
Cytarabine	0	1 (1)	1 (1)
Hydrea + vincristine	0	1 (1)	1 (1)
Vincristine	0	1 (1)	1 (1)
Dexamethasone	0	1 (1)	1 (1)
Hydrea + Decadron	0	1 (1)	1 (1)
Others	0	2 (2)	2 (1)
Not reported	3 (11)	8 (6)	11 (7)
Radiation therapy given for reasons other than relapse, persistent, or MRD			
None	27	131	158

10.3 Outcome data

10.3.1 Post-transplant overall survival

Table 14 summarizes post-transplant overall survival within 12 months in patients who received inotuzumab ozogamicin prior to first allogeneic HSCT for ALL.

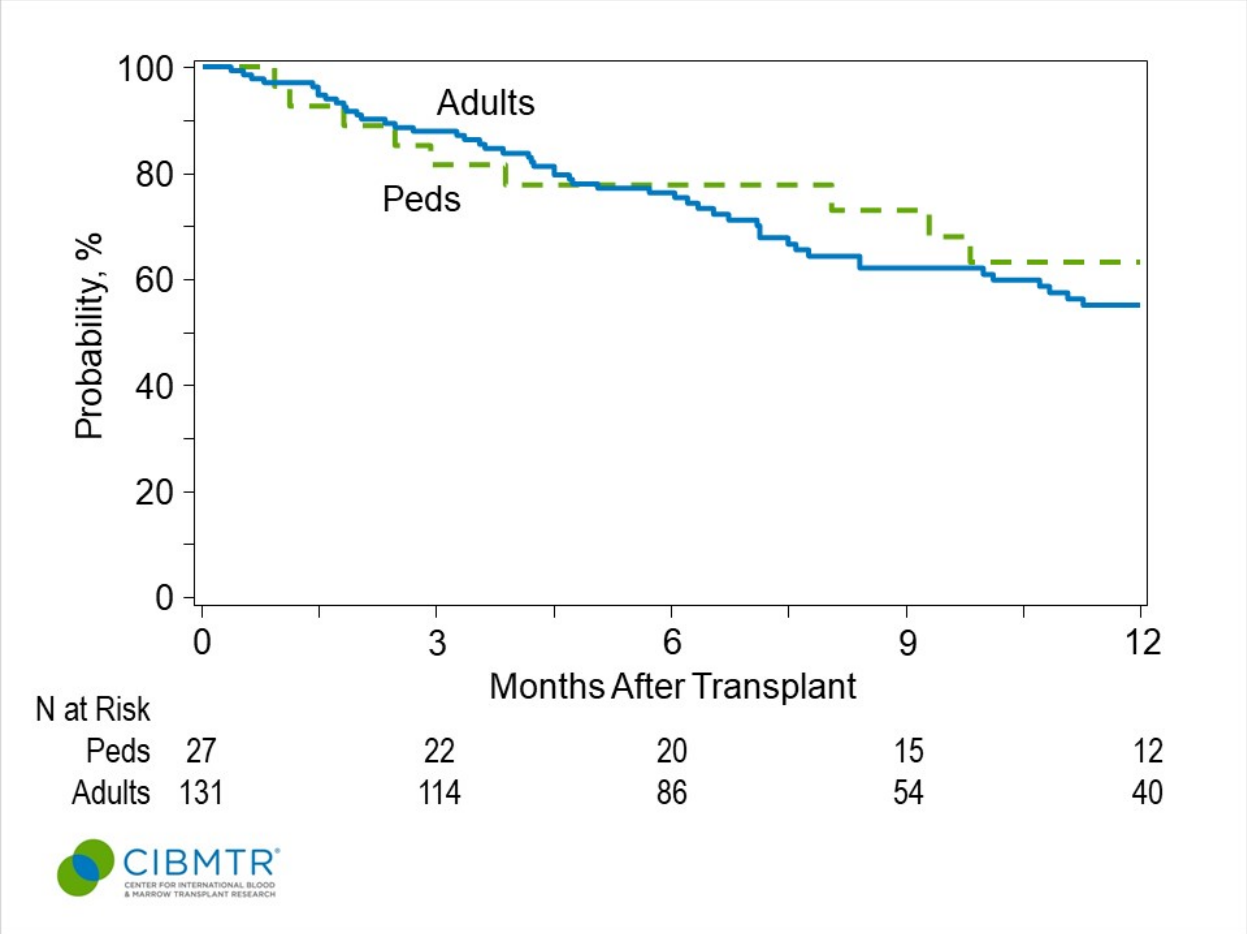
Table 14 Post-transplant overall survival within 12 months

	Pediatric patients (< 18 y)	Adults (≥ 18 y)	All patients
Number of patients with post-transplant follow-up	**27**	**131**	**158**
Post-transplant overall survival (95% CI)			
6 months	78 (61-91)%	76 (68-83)%	77 (69-83)%
12 months	NE	55 (45-65)%	57 (48-65)%
Number of deaths within 12 months	9	49	58
Primary cause of death, no. (%)			
Recurrence of B-cell ALL	5 (56)	20 (41)	25 (43)
GVHD	0	9 (18)	9 (16)
VOD/SOS	2 (22)	7 (14)	9 (16)
Interstitial pneumonitis	1 (11)	2 (4)	3 (5)
Infection	0	3 (6)	3 (5)
Septic shock	0	2 (4)	2 (3)
Thrombotic microangiopathy (TMA)	1 (11)	0	1 (2)
Hemorrhage	0	3 (6)	3 (5)
Organ failure	0	3 (6)	3 (5)
Time from transplant to death, no. (%) months			
< 3	5 (56)	16 (33)	21 (36)
3-5	1 (11)	14 (29)	15 (26)
6-11	3 (33)	19 (39)	22 (38)
Median (95% CI)	2.92 (1.12 - 9.3)	4.5 (3.35 - 6.21)	4.22 (3.25-6.05)
Range	(0.92-9.82)	(0.36-11.27)	(0.36-11.27)
Mean	4.48	4.93	4.86
Standard deviation	3.58	3.13	3.17

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who have not yet completed a follow-up form are not included in the data and estimates shown in this table. Patients with a reported outcome event beyond 12 months post-transplant (or post-inotuzumab ozogamicin) are not shown in this table, as follow-up among survivors in the population is approximately 12 months post-transplant.
Outcomes are not evaluable (NE) if sample size is < 20.
Post-transplant overall survival is time from HSCT to death from any cause. Patients are censored at the last date that the patient was known to be alive. There are no competing risks.

Figure 1 shows post-transplant overall survival within 12 months in patients who received inotuzumab ozogamicin prior to first allogeneic HSCT for ALL.

Figure 1 Post-transplant overall survival within 12 months



10.3.2 Post-transplant overall mortality

Table 15 summarizes post-transplant overall mortality within 12 months in patients who received inotuzumab ozogamicin prior to first allogeneic HSCT for ALL.

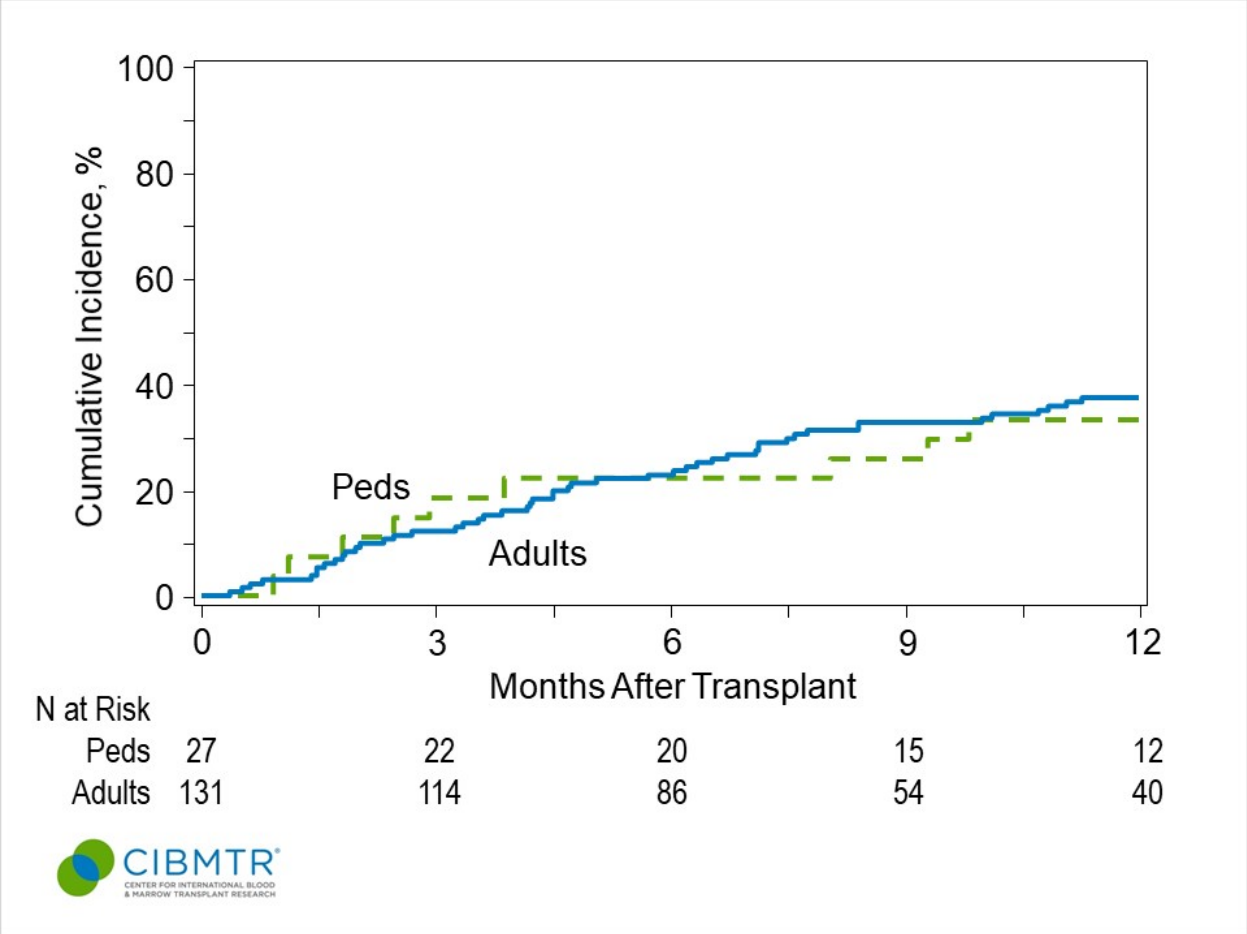
Table 15 Post-transplant overall mortality within 12 months

	Pediatric patients (< 18 y)	Adults (≥ 18 y)	All patients
Number of patients with post-transplant follow-up	**27**	**131**	**158**
Post-transplant overall mortality (95% CI)			
6 months	22 (9-39)%	24 (17-32)%	23 (17-31)%
12 months	NE	45 (35-55)%	43 (35-52)%

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who have not yet completed a follow-up form are not included in the data and estimates shown in this table. Patients with a reported outcome event beyond 12 months post-transplant (or post-inotuzumab ozogamicin) are not shown in this table, as follow-up among survivors in the population is approximately 12 months post-transplant.
Outcomes are not evaluable (NE) if sample size is < 20.
Post-transplant overall mortality is time from HSCT to death from any cause. Patients are censored at the last date that the patient was known to be alive. There are no competing risks.

Figure 2 shows cumulative incidence of post-transplant overall mortality within 12 months in patients who received inotuzumab ozogamicin prior to first allogeneic HSCT for ALL.

Figure 2 Post-transplant overall mortality within 12 months



10.3.3 Post-inotuzumab overall survival

Table 16 summarizes overall survival within 12 months of first dose of inotuzumab ozogamicin in patients who received inotuzumab ozogamicin prior to first allogeneic HSCT for ALL.

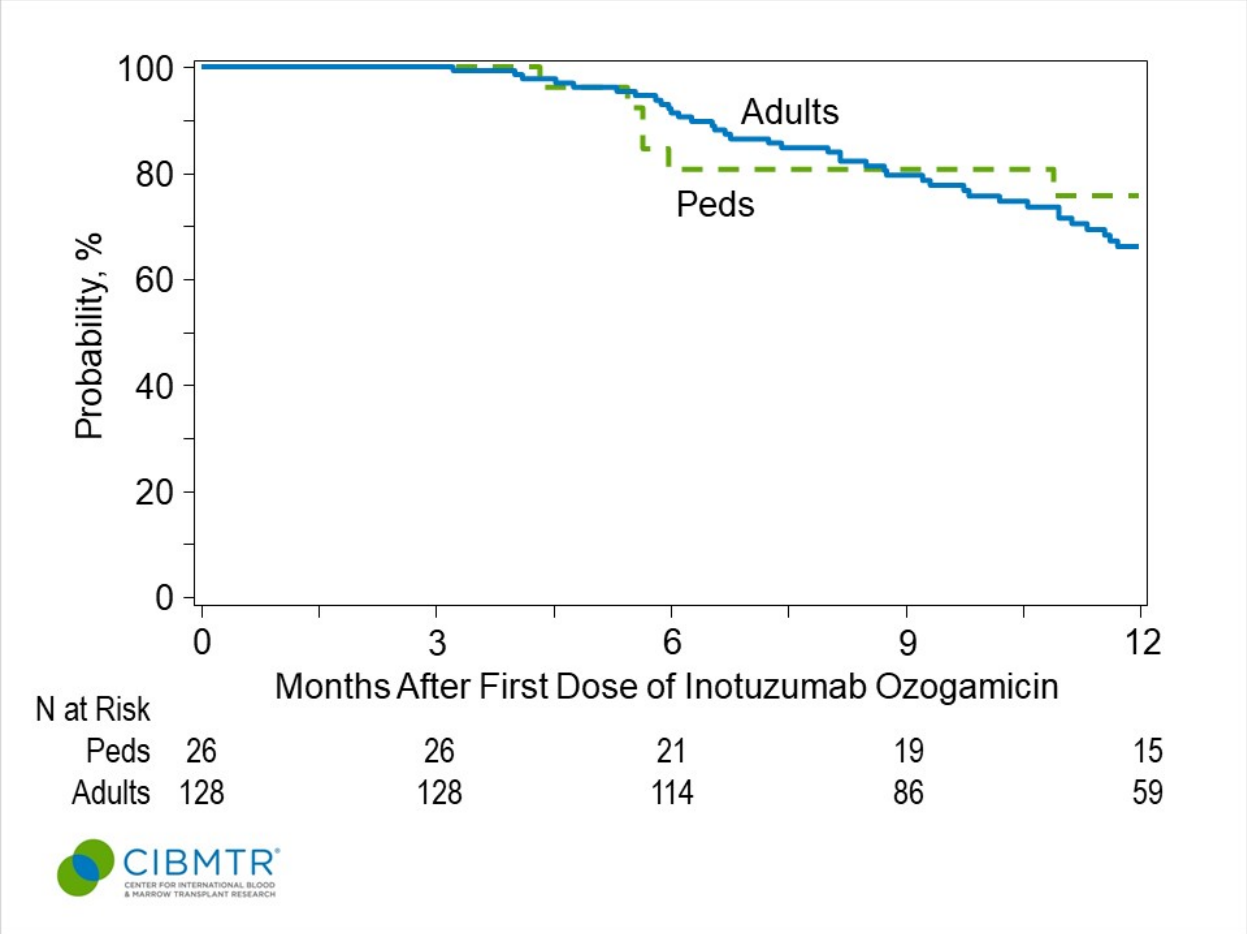
Table 16 Overall survival within 12 months of first dose of inotuzumab ozogamicin

	Pediatric patients (< 18 y)	Adults (≥ 18 y)	All patients
No. patients with follow-up and CIBMTR Form 2541 and date of first dose of inotuzumab ozogamicin provided	**26**	**128**	**154**
Post-inotuzumab ozogamicin overall survival (95% CI)			
6 months	81 (64-93)%	92 (87-96)%	90 (85-94)%
12 months	NE	66 (57-75)%	68 (59-75)%
Number of deaths within 12 months	6	38	44
Primary cause of death, no. (%)			
Recurrence of B-cell ALL	2 (33)	16 (42)	18 (41)
GVHD	0	7 (18)	7 (16)
VOD/SOS	2 (33)	6 (16)	8 (18)
Interstitial pneumonitis	1 (17)	0	1 (2)
Infection	0	3 (6)	3 (5)
Septic shock	0	2 (5)	2 (5)
Thrombotic microangiopathy (TMA)	1 (13)	0	1 (2)
Hemorrhage	0	2 (5)	2 (5)
Organ failure	0	2 (5)	2 (5)
Time from first dose of inotuzumab ozogamicin to death, no. (%), months			
< 3	0	0	0
3-5	5 (83)	10 (26)	15 (34)
6-11	1 (17)	28 (74)	29 (66)
Median (95% CI)	5.65 (4.34 - 10.91)	7.72 (6.28 - 9.23)	7.01 (6.01-8.74)
Range	(4.34-10.91)	(3.22-11.73)	(3.22-11.73)
Mean	6.33	7.83	7.63
Standard deviation	2.31	2.45	2.46

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who have not yet completed a follow-up form are not included in the data and estimates shown in this table. Patients with a reported outcome event beyond 12 months post-transplant (or post-inotuzumab ozogamicin) are not shown in this table, as follow-up among survivors in the population is approximately 12 months post-transplant.
Outcomes are not evaluable (NE) if sample size is < 20.
Post-inotuzumab ozogamicin survival is time from first dose of inotuzumab ozogamicin to death from any cause. Patients are censored at the last date that the patient was known to be alive. There are no competing risks.

Figure 3 shows overall survival within 12 months of first dose of inotuzumab ozogamicin in patients who received inotuzumab ozogamicin prior to first allogeneic HSCT for ALL.

Figure 3 Overall survival within 12 months of first dose of inotuzumab ozogamicin



10.3.4 Transplant-related mortality (post-transplant non-relapse mortality)

Table 17 summarizes transplant-related mortality within 12 months in patients who received inotuzumab ozogamicin prior to first allogeneic HSCT for ALL.

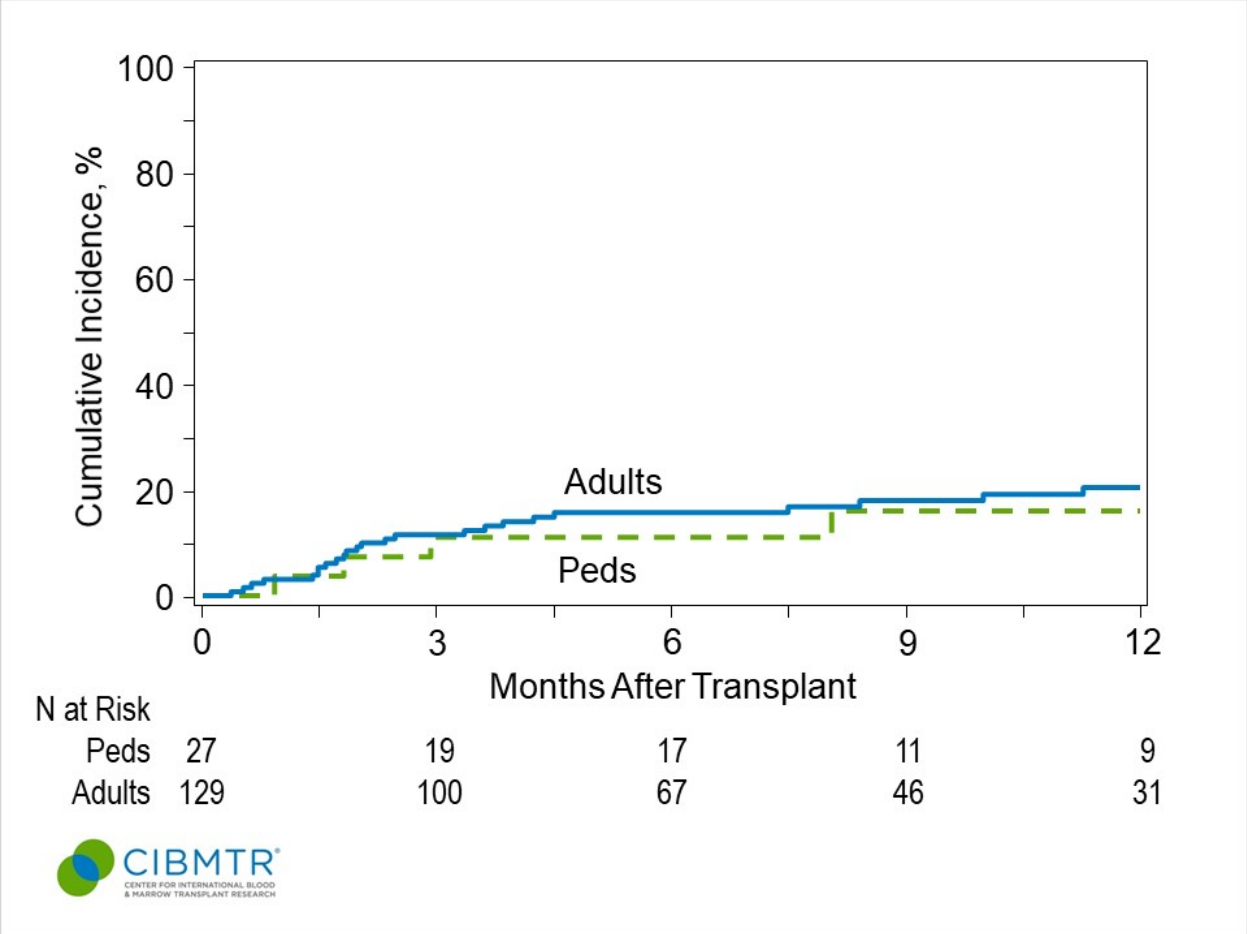
Table 17 Transplant-related mortality within 12 months

	Pediatric patients (< 18 y)	Adults (≥ 18 y)	All patients
No. patients with post-transplant follow-up	**27**	**131**	**158**
Transplant-related mortality (95% CI)			
6 months	NE	16 (10-23)%	15 (10-21)%
12 months	NE	21 (14-29)%	20 (13-27)%
No. patients with TRM within 12 months	4	24	28
No. patients with competing risk (post-transplant relapse)	9	40	49
Primary cause of death, among patients with TRM, no. (%)			
GVHD	0	7 (29)	7 (25)
VOD/SOS	2 (50)	6 (25)	8 (29)
Interstitial pneumonitis	1 (25)	1 (4)	2 (7)
Infection	0	2 (8)	2 (7)
Septic shock	0	2 (8)	2 (7)
Thrombotic microangiopathy (TMA)	1 (25)	0	1 (4)
Hemorrhage	0	3 (13)	3 (11)
Organ failure	0	3 (13)	3 (11)
Time from transplant to TRM, no. (%), months			
< 3	3 (75)	15 (63)	18 (64)
3-5	0	5 (21)	5 (18)
6-11	1 (25)	4 (17)	5 (18)
Median (95% CI)	2.37 (0.92 - 8.05)	2 (1.58 - 3.84)	2 (1.58-3.61)
Range	(0.92-8.05)	(0.36-11.27)	(0.36-11.27)
Mean	3.43	3.3	3.31
Standard deviation	3.19	3.02	2.98

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who have not yet completed a follow-up form are not included in the data and estimates shown in this table. Patients with a reported outcome event beyond 12 months post-transplant (or post-inotuzumab ozogamicin) are not shown in this table, as follow-up among survivors in the population is approximately 12 months post-transplant.
Outcomes are not evaluable (NE) if sample size is < 20.
Transplant-related mortality (post-transplant non-relapse mortality) is time from HSCT to death within the first 28 days post-HSCT, or death from any cause without prior relapse/progression post-HSCT.

Figure 4 shows cumulative incidence of transplant-related mortality within 12 months in patients who received inotuzumab ozogamicin prior to first allogeneic HSCT for ALL.

Figure 4 Transplant-related mortality within 12 months



10.3.5 Non-transplant-related mortality

Table 18 summarizes non-transplanted related mortality within 12 months in patients who received inotuzumab ozogamicin prior to first allogeneic HSCT for ALL.

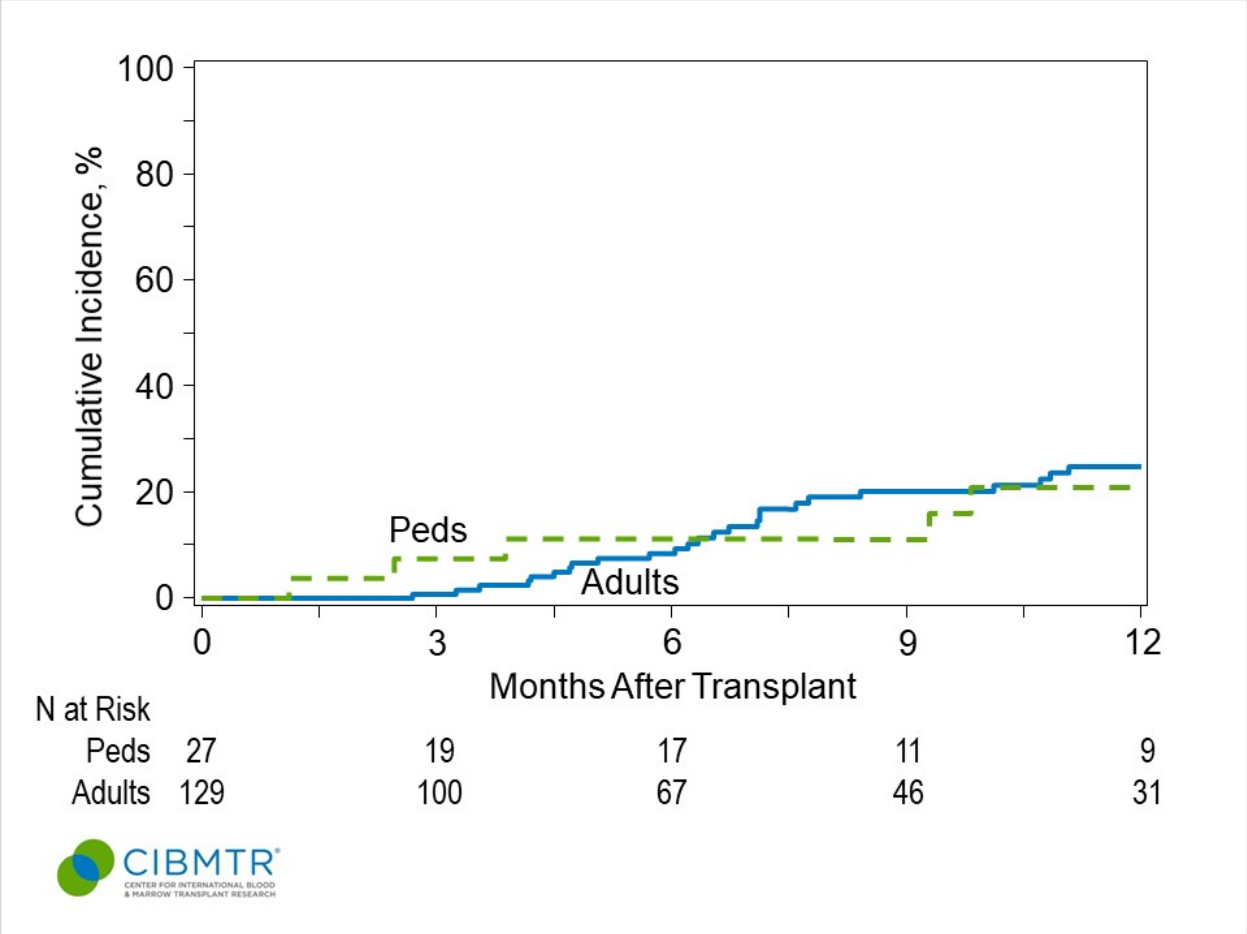
Table 18 Non-transplant-related mortality within 12 months

	Pediatric patients (< 18 y)	Adults (≥ 18 y)	All patients
No. patients with post-transplant follow-up	**27**	**131**	**158**
Non-transplant-related mortality (95% CI)			
6 months	NE	8 (4-14) %	9 (5-14) %
12 months	NE	25 (17-33) %	24 (17-32) %
No. patients with NTRM within 12 months	5	25	30
No. patients with competing risk (transplant-related mortality)	4	24	28
Time from transplant to NTRM, no. (%), months			
< 3	2 (40)	1 (4)	3 (10)
3-5	1 (20)	9 (36)	10 (33)
6-11	2 (40)	15 (60)	17 (57)
Median (95% CI)	3.88 (1.12 - 9.82)	6.34 (4.73 - 7.13)	6.28 (4.70-7.13)
Range	(1.12-9.82)	(2.69-11.07)	(1.12-11.07)
Mean	5.32	6.49	6.3
Standard deviation	4	2.38	2.66

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who have not yet completed a follow-up form are not included in the data and estimates shown in this table. Patients with a reported outcome event beyond 12 months post-transplant (or post-inotuzumab ozogamicin) are not shown in this table, as follow-up among survivors in the population is approximately 12 months post-transplant.
Outcomes are not evaluable (NE) if sample size is < 20.
Non-transplant-related mortality is time from HSCT to death after the first 28 days post-HSCT from any cause after prior relapse/progression post-HSCT.

Figure 5 shows cumulative incidence of non-transplant-related mortality within 12 months in patients who received inotuzumab ozogamicin prior to first allogeneic HSCT for ALL.

Figure 5 Non-transplant-related mortality within 12 months



10.3.6 Post-transplant relapse

Table 19 summarizes post-transplant relapse within 12 months in patients who received inotuzumab ozogamicin prior to first allogeneic HSCT for ALL.

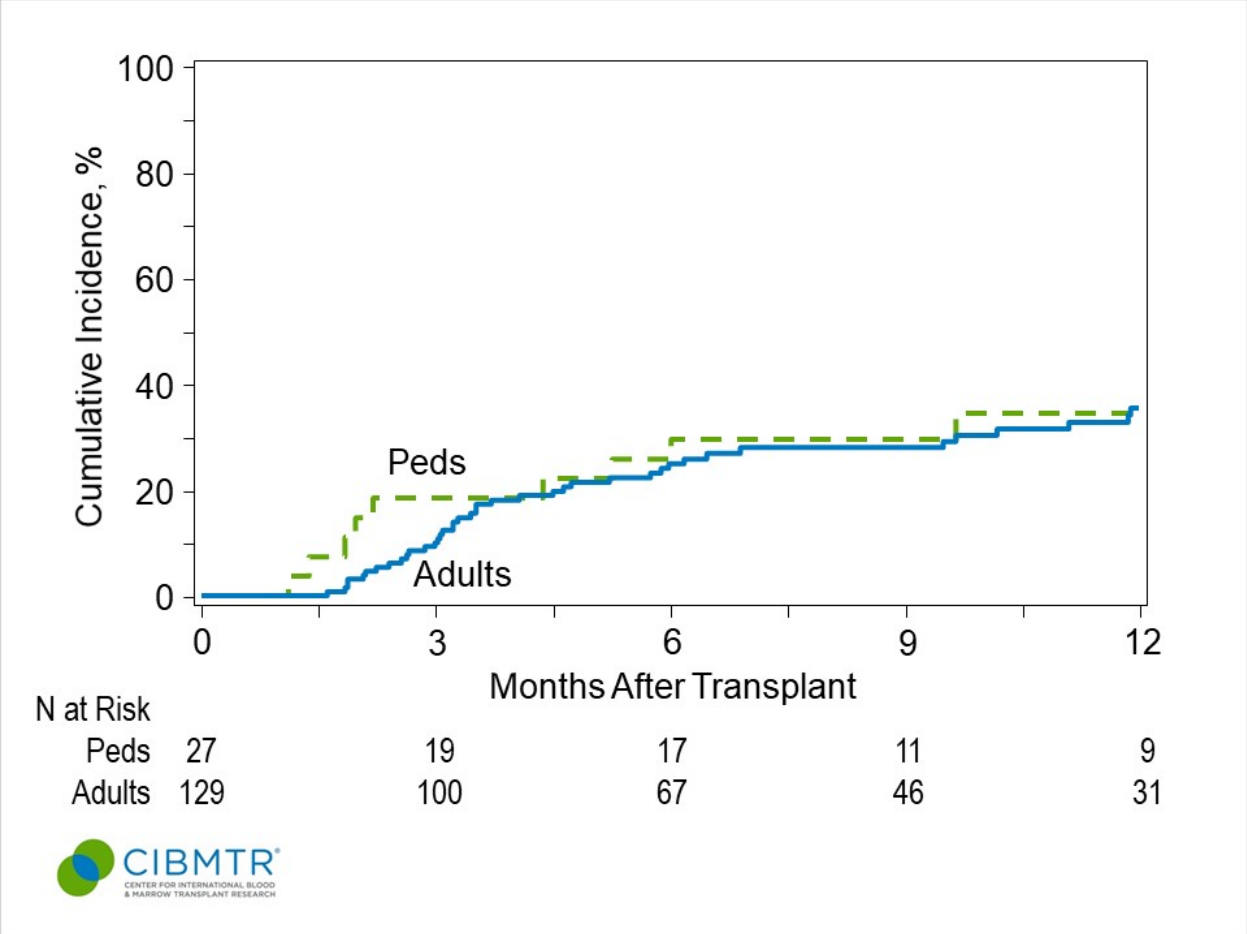
Table 19 Post-transplant relapse within 12 months

	Pediatric patients (< 18 y)	Adults (≥ 18 y)	All patients
No. patients with post-transplant follow-up	**27**	**131**	**158**
Post-transplant relapse (95% CI)			
6 months	NE	25 (18-33) %	25 (18-32) %
12 months	NE	36 (27-45) %	35 (27-44) %
No. patients with post-transplant relapse within 12 months	9	40	49
No. patients with competing risk (transplant-related mortality)	4	24	28
Time from transplant to post-transplant relapse, no. (%), months			
< 3	5 (56)	13 (33)	18 (37)
3-5	2 (22)	18 (45)	20 (41)
6-11	2 (22)	9 (23)	11 (22)
Median (95% CI)	2.2 (1.38 - 6.01)	3.48 (3.02 - 4.73)	6.05 (4.73-7.10)
Range	(1.12-9.66)	(1.61-11.89)	(1.12-11.89)
Mean	3.76	4.68	4.51
Standard deviation	2.84	2.93	2.91

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who have not yet completed a follow-up form are not included in the data and estimates shown in this table. Patients with a reported outcome event beyond 6 months post-transplant (or post-inotuzumab ozogamicin) are not shown in this table, as follow-up among survivors in the population is approximately 6 months post-transplant.
Outcomes are not evaluable (NE) if sample size is < 20.
Post-transplant relapse is time from HSCT to first relapse post-HSCT without death post-relapse, or with death after the first 28 days post-HSCT.

Figure 6 shows cumulative incidence of post-transplant relapse within 12 months in patients who received inotuzumab ozogamicin prior to first allogeneic HSCT for ALL.

Figure 6 Post-transplant relapse within 12 months



10.3.7 100-day post-HSCT adverse events of interest, including hepatic VOD/SOS

Table 20 summarizes 100-day post-HSCT adverse events of interest in patients who received inotuzumab ozogamicin prior to first allogeneic HSCT for ALL.

Table 20 100-day post-HSCT adverse events of interest

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
Number of patients with post-transplant follow-up	**27**	**131**	**158**
Viral infection, up to day 100			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Yes	9 (33)	55 (42)	64 (41)
No	16 (59)	72 (55)	88 (56)
Not reported	1 (4)	2 (2)	3 (2)
Bacterial infection, up to day 100			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Yes	10 (37)	63 (48)	73 (46)
No	15 (56)	62 (47)	77 (49)
Not reported	1 (4)	4 (3)	5 (3)
Fungal infection, up to day 100			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Yes	2 (7)	14 (11)	16 (10)
No	23 (85)	114 (87)	137 (87)
Not reported	1 (4)	1 (1)	2 (1)
SIRS development, up to day 100			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Yes	3 (11)	5 (4)	8 (5)
No	23 (85)	124 (95)	147 (93)
Septic shock, up to day 100			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Yes	3 (11)	15 (11)	18 (11)
No	23 (85)	114 (87)	137 (87)
Maximum grade of acute GVHD, up to day 100[a]			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
None	14 (52)	63 (48)	77 (49)
I	3 (11)	12 (9)	15 (9)
II	4 (15)	33 (25)	37 (23)
III	2 (7)	10 (8)	12 (8)
IV	3 (11)	10 (8)	13 (8)
Not reported	0	1 (1)	1 (1)
Time from HSCT to date of maximum acute GVHD, months			
Number evaluable	12	65	77
Median	0.9	1.2	1.2
Range	(0.4-2.9)	(0.5-3.2)	(0.4-3.2)
Mean	1.1	1.4	1.4
Standard deviation	0.7	0.6	0.6

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
Number of patients with post-transplant follow-up	**27**	**131**	**158**
Chronic GVHD, up to 1 year post-transplant			
Yes	2 (7)	28 (21)	30 (19)
No	25 (93)	100 (76)	125 (79)
Not reported	0	3 (2)	3 (2)
Time from HSCT to chronic GVHD, months			
Number evaluable	2	28	30
Median	NE	7.2	7.2
Range	(3.3-12.4)	(2-13.9)	(2-13.9)
Mean	7.9	7.1	7.2
Standard deviation	6.5	3.5	3.6
VOD/SOS within 100 days post-transplant			
Yes	7 (26)	17 (13)	24 (15)
No	20 (74)	114 (87)	134 (85)
Time from HSCT to VOD/SOS, months			
Number evaluable	7	17	24
Median	0.3	0.4	0.4
Range	(0.2-0.8)	(0.2-2.6)	(0.2-2.6)
Mean	0.5	0.7	0.6
Standard deviation	0.3	0.6	0.6
Secondary malignancy			
Yes [b]	0	2 (2)	2 (1)
No	26 (96)	127 (97)	153 (97)
Not reported	1 (4)	2 (2)	3 (2)
Time from HSCT to secondary malignancy, months			
Number evaluable	0	2	2
Median	NE	NE	NE
Range	NE	(2-4)	(2-4)
Mean	NE	3	3
Standard deviation	NE	1	1
Pulmonary AEs within 100 days post-transplant			
IPN / Idiopathic pneumonia syndrome			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Yes	3 (11)	8 (6)	11 (7)
No	23 (85)	119 (91)	142 (90)
Not reported	0	2 (2)	2 (1)
Bronchiolitis obliterans			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Yes	0	1 (1)	1 (1)
No	26 (96)	128 (98)	154 (97)
COP/BOOP			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Yes	0	0	0
No	26 (96)	129 (98)	155 (98)

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
Number of patients with post-transplant follow-up	**27**	**131**	**158**
Diffuse alveolar hemorrhage			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Yes	0	2 (2)	2 (1)
No	26 (96)	127 (97)	153 (97)
Cardiovascular AEs within 100 days post-transplant			
Arrhythmia			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Yes	0	0	0
No	25 (93)	122 (93)	147 (93)
Not reported	1 (4)	7 (5)	8 (5)
Congestive heart failure			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Yes	0	1 (1)	1 (1)
No	26 (96)	128 (98)	154 (97)
Coronary artery disease			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Yes	0	0	0
No	26 (96)	129 (98)	155 (98)
Myocardial infarction or unstable angina			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Yes	0	1 (1)	1 (1)
No	26 (96)	128 (98)	154 (97)
Hypertension (HTN) requiring therapy			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Yes	5 (19)	9 (7)	14 (9)
No	21 (78)	119 (91)	140 (89)
Not reported	0	1 (1)	1 (1)
TMA			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Yes	1 (4)	3 (2)	4 (3)
No	25 (93)	126 (96)	151 (96)
Renal AEs within 100 days post-transplant			
Acute renal failure requiring dialysis			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Yes	3 (11)	12 (9)	15 (9)
No	23 (85)	117 (89)	140 (89)
Musculoskeletal AEs within 100 days post-transplant			
Avascular necrosis			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Yes	0	1 (1)	1 (1)
No	26 (96)	128 (98)	154 (97)

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
Number of patients with post-transplant follow-up	**27**	**131**	**158**
Endocrine dysfunction within 100 days post-transplant			
Diabetes or hyperglycemia requiring chronic treatment			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Yes	1 (4)	5 (4)	6 (4)
No	25 (93)	124 (95)	149 (94)
Growth hormone deficiency or short stature			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Yes	0	0	0
No	26 (96)	129 (98)	155 (98)
Hypothyroidism requiring replacement therapy			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Yes	0	0	0
No	26 (96)	129 (98)	155 (98)
Pancreatitis			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Yes	0	0	0
No	26 (96)	129 (98)	155 (98)
Depression requiring therapy			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Yes	1 (4)	1 (1)	2 (1)
No	25 (93)	127 (97)	152 (96)
Not reported	0	1 (1)	1 (1)
Anxiety requiring therapy			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Yes	2 (7)	1 (1)	3 (2)
No	24 (89)	126 (96)	150 (95)
Not reported	0	2 (2)	2 (1)
CNS hemorrhage and stroke			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Yes	1 (4)	2 (2)	3 (2)
No	25 (93)	127 (97)	152 (96)
PTSD requiring therapy			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Yes	0	0	0
No	26 (96)	129 (98)	155 (98)

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who have not yet completed a follow-up form are not included in the data and estimates shown in this table.
All events were evaluated up to 100 days post-transplant unless noted otherwise.
[a] Acute GVHD grading follows the Consensus criteria (Przepiorka D, Weisdorf D, Martin P, et al. [1995] 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant 15:825–828.) Acute GVHD was evaluated up to 100 days post-transplant; 2 patients were reported with acute GVHD more than 100 days post-HSCT. These patients were reported as not having acute GVHD in this table.
[b] Secondary malignancies reported for n=2 patients were squamous cell cancer of the skin and acute myeloid leukemia.

10.3.8 Veno-occlusive disease

Table 21 shows a summary of VOD/SOS in patients who received inotuzumab ozogamicin prior to first allogeneic HSCT for ALL.

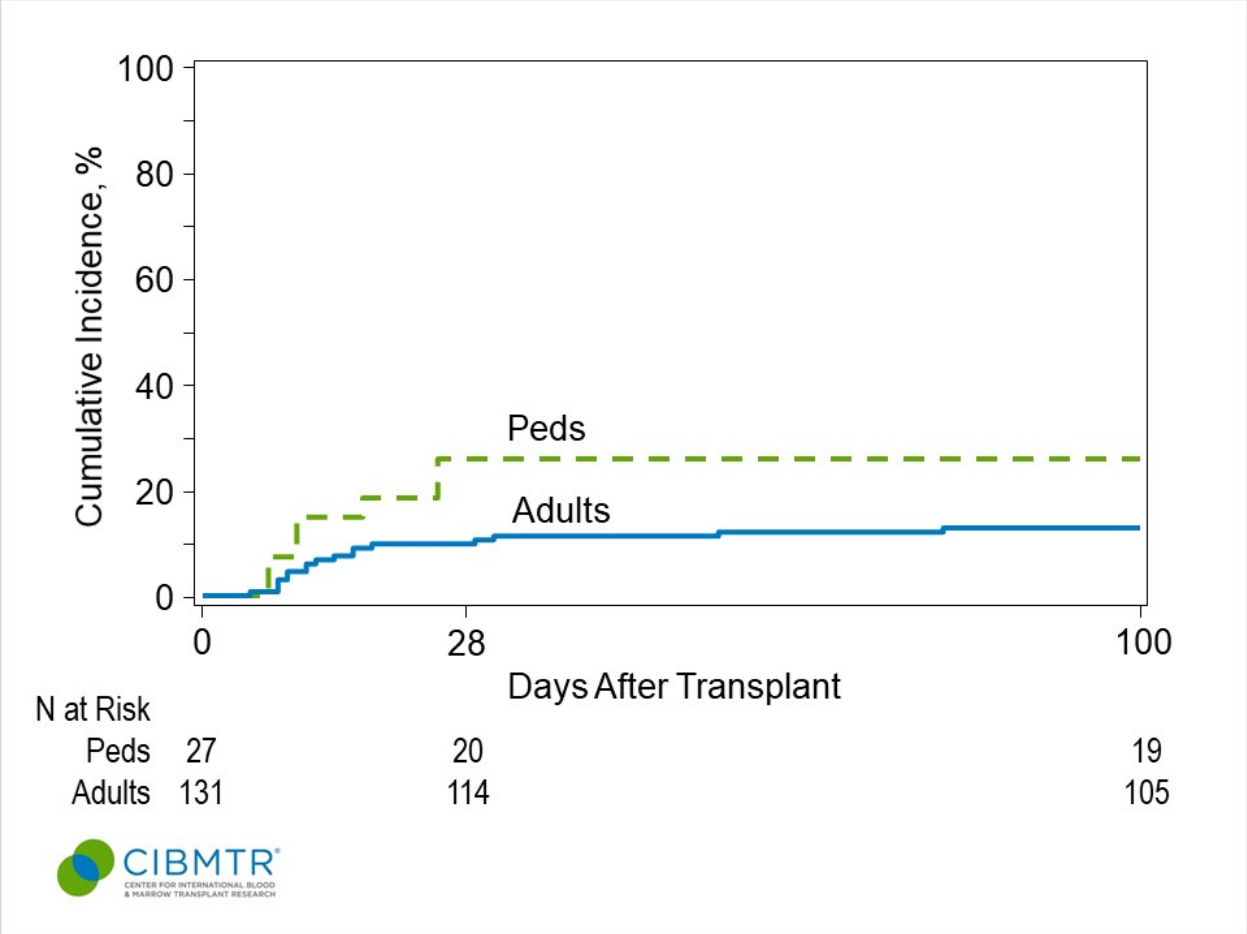
Table 21 Veno-occlusive disease within 100 days

	Pediatric patients (< 18 y)	Adults (≥ 18 y)	All patients
Number of patients with post-transplant follow-up	**27**	**128**	**155**
Veno-occlusive disease			
100 days (95% CI)	26 (11-44)%	13 (8-19)%	15 (10-21)%
Number of patients with veno-occlusive disease	7	17	24
Number of patients with competing risk (death without VOD)	5	39	44
Time from transplant to veno-occlusive disease, no. (%), months			
< 3	7	17	24
Median (95% CI)	0.33 (0.23 - 0.82)	0.39 (0.3 - 0.59)	0.38 (0.30-0.59)
Range	(0.23-0.82)	(0.16-2.6)	(0.16-2.6)
Mean	0.47	0.66	0.6
Standard deviation	0.26	0.64	0.56

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who have not yet completed a follow-up form are not included in the data and estimates shown in this table.
VOD is the occurrence of veno-occlusive disease/sinusoidal obstruction syndrome reported on the CIBMTR Form 2100. VOD is only considered within the first 100 days post-HSCT. Death without VOD is the competing risk.

Figure 7 shows cumulative incidence of veno-occlusive disease within 100 days in patients who received inotuzumab ozogamicin prior to first allogeneic HSCT for ALL.

Figure 7 Veno-occlusive disease within 100 days



10.3.9 VOD with and without defibrotide prophylaxis

Table 22 shows a summary of VOD characteristics up to 100 days post-transplant, with and without defibrotide used as liver toxicity prophylaxis in patients who received inotuzumab ozogamicin prior to first allogeneic HSCT for ALL.

Table 22 VOD characteristics up to 100 days post-transplant, with and without defibrotide used as liver toxicity prophylaxis

	Pediatric patients (< 18 years) No. (%)		Adult patients (≥ 18 years) No. (%)		All patients No. (%)	
	Defibrotide	**No defibrotide**	**Defibrotide**	**No defibrotide**	**Defibrotide**	**No defibrotide**
Number of patients with post-transplant follow-up	**13**	**14**	**11**	**120**	**24**	**134**
Number of patients with post-transplant VOD/SOS	3	4	5	12	8	16
Time to post-transplant VOD/SOS, days						
Median	10	16	16	12	14	12
Range	(10-17)	(7-25)	(8-31)	(5-79)	(8-31)	(5-79)
Mean	12	16	19	20	17	19
Standard deviation	4	10	10	23	9	20
Grade of VOD/SOS						
N/A; no VOD/SOS	10 (77)	10 (71)	6 (55)	108 (90)	16 (67)	118 (88)
Mild VOD/SOS (no other organs involved within 60 days of VOD/SOS diagnosis)	2 (15)	1 (7)	3 (27)	4 (3)	5 (21)	5 (4)
Severe VOD/SOS (multiple organ dysfunction within 60 days of VOD/SOS diagnosis)	1 (8)	3 (21)	2 (18)	8 (7)	3 (13)	11 (8)
Liver toxicity prophylaxis						
None (or no additional)	1 (8)	6 (43)	1 (9)	11 (9)	2 (8)	17 (13)
Ursodiol	0	4 (29)	0	104 (87)	0	108 (81)
Ursodiol + defibrotide	7 (54)	0	8 (73)	0	15 (63)	0
Ursodiol + defibrotide + others	5 (38)	0	2 (18)	0	7 (29)	0
Ursodiol + others	0	4 (29)	0	4 (3)	0	8 (6)
Not reported	0	0	0	1 (1)	0	1 (1)

	Pediatric patients (< 18 years) No. (%)		Adult patients (≥ 18 years) No. (%)		All patients No. (%)	
	Defibrotide	**No defibrotide**	**Defibrotide**	**No defibrotide**	**Defibrotide**	**No defibrotide**
Number of patients with post-transplant follow-up	**13**	**14**	**11**	**120**	**24**	**134**
Treatment for VOD/SOS						
N/A; no VOD/SOS	10 (77)	10 (71)	6 (55)	108 (90)	16 (67)	118 (88)
None	0	1 (7)	1 (9)	2 (2)	1 (4)	2 (2)
Defibrotide	0	1 (7)	1 (9)	1 (1)	1 (4)	2 (2)
Defibrotide + ursodiol	1 (8)	0	0	0	1 (4)	0
Defibrotide + ursodiol + diuretics	0	1 (7)	0	4 (3)	0	5 (4)
Diuretics	0	0	0	1 (1)	0	1 (1)
Defibrotide + ursodiol + methylprednisolone + diuretics + heparin	0	1 (7)	0	1 (1)	0	2 (2)
Defibrotide + ursodiol + methylprednisolone + N-acetylcysteine + rifaximin/lactulose	0	0	0	1 (1)	0	1 (1)
Defibrotide + ursodiol + methylprednisolone + diuretics	0	0	0	1 (1)	0	1 (1)
Defibrotide + diuretics	0	0	0	1 (1)	0	1 (1)
Defibrotide + ursodiol + methylprednisolone + diuretics + N-acetylcysteine + tissue plasminogen activator	0	0	1 (9)	0	1 (4)	0
Not reported	2 (15)	1 (7)	2 (18)	0	4 (17)	1 (1)
Post-VOD/SOS survival						
N/A; no VOD/SOS	10 (77)	10 (71)	6 (55)	108 (90)	16 (67)	118 (88)
Alive	2 (15)	1 (7)	3 (27)	4 (3)	5 (21)	5 (4)
Dead	1 (8)	3 (21)	2 (18)	8 (7)	3 (13)	11 (8)

10.3.10 Post-HSCT clinical status

Table 23 shows a summary of post-HSCT clinical status following inotuzumab ozogamicin treatment in patients who received inotuzumab ozogamicin prior to first allogeneic HSCT for ALL.

Table 23 Post-HSCT clinical status

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
Number of patients with follow-up	**27**	**131**	**158**
Best response to HSCT			
Continued complete remission (CR)[a]	26 (96)	117 (89)	143 (91)
CR	0	9 (7)	9 (6)
Not in CR	1 (4)	4 (3)	5 (3)
Not reported	0	1 (1)	1 (1)
Granulopoiesis / neutrophil recovery[b]			
Yes	26 (96)	127 (97)	153 (97)
No	0	2 (2)	2 (1)
Not reported	1 (4)	2 (2)	3 (2)
Time from HSCT to granulopoiesis/neutrophil recovery, days			
Number evaluable	26	127	153
Median	17	17	17
Range	(10-30)	(9-52)	(9-52)
Mean	18	18	18
Standard deviation	6	7	7
Megakaryopoiesis / platelet recovery[c]			
Yes	21 (78)	108 (82)	129 (82)
No	5 (19)	20 (15)	25 (16)
Not reported	1 (4)	3 (2)	4 (3)
Time from HSCT to megakaryopoiesis/platelet recovery, days			
Number evaluable	21	108	129
Median	31	28	28
Range	(13-49)	(13-97)	(13-97)
Mean	30	31	31
Standard deviation	11	15	15

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
Number of patients with follow-up	**27**	**131**	**158**
Engraftment syndrome within 100 days post-transplant			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Yes	6 (22)	11 (8)	17 (11)
No	20 (74)	118 (90)	138 (87)
Time from HSCT to engraftment syndrome, days			
Number evaluable	6	11	17
Median	12	15	13
Range	(11-13)	(2-42)	(2-42)
Mean	12	16	15
Standard deviation	1	10	8
Weight, most recent post-HSCT, kg			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Not reported	0	4 (3)	4 (3)
Number evaluable	26	125	151
Median	34	75	72
Range	(8-89)	(33-210)	(8-210)
Mean	37	80	72
Standard deviation	21	25	29
Height, most recent post-HSCT, cm			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Not reported	8 (30)	129 (98)	137 (87)
Number evaluable	18	0	18
Median	122	NE	122
Range	(81-158)	NE	(81-158)
Mean	123	NE	123
Standard deviation	24	NE	24
Performance scale and status, post-HSCT			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
Karnofsky			
90-100	3 (11)	57 (44)	60 (38)
10-80	17 (63)	37 (28)	54 (34)
Not reported	6 (22)	35 (27)	41 (26)

Note: Outcomes are not evaluable (NE) if sample size is < 20.

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
Number of patients with follow-up	**27**	**131**	**158**
Total inpatient days in first 100 days post-HSCT [d]			
N/A; CIBMTR Form 2100 not yet received	1 (4)	2 (2)	3 (2)
< 30	5 (19)	64 (49)	69 (44)
30-59	13 (48)	34 (26)	47 (30)
60-100	3 (11)	17 (13)	20 (13)
Not reported	5 (19)	14 (11)	19 (12)
Number evaluable	21	115	136
Median	39	26	29
Range	(21-70)	(6-94)	(6-94)
Mean	41	34	35
Standard deviation	14	21	20
Time from HSCT to date of last contact, months			
< 3	5 (19)	17 (13)	22 (14)
3-5	2 (7)	28 (21)	30 (19)
6-11	8 (30)	46 (35)	54 (34)
≥ 12	12 (44)	40 (31)	52 (33)
Number evaluable	27	131	158
Median	9.82	6.74	7.13
Range	(0.92-28.39)	(0.36-26.18)	(0.36-28.39)
Mean	11.14	8.83	9.22
Standard deviation	8.14	6.05	6.49

[a] Continued complete remission is defined as a patient who underwent transplant during complete remission, and the complete remission is sustained post-transplant. Complete remission is defined as all the following: < 5% blasts in bone marrow, no blasts with Auer rods, no extramedullary disease and no disease progression for at least 4 weeks.

[b] Absolute neutrophil count (ANC) > 500/mm^3 sustained for 3 lab values; evaluated ≤ 100 days post-transplant.

[c] Initial platelet count > 20 × 10^9/L achieved; evaluated ≤ 100 days post-transplant.

[d] The form asks for the number of inpatient days in the first 100 days (day 0 to day 100) post-HSCT.

10.4 Other analyses

10.4.1 Outcome analysis

Post-transplant follow-up information was available for 155 / 163 (95%) patients undergoing their first allogeneic HSCT for B-cell ALL. Of these 155 patients, post-transplant VOD/SOS occurred in 24 patients (15%; 17 adult, 7 pediatric). Fifty-six (56) deaths occurred within the first 12 months post-transplant with TRM occurring in 27 patients within the first 12 months.

Fourteen (58%; 10 adult, 4 pediatric) of the 24 patients (17 adult, 7 pediatric) who developed post-transplant VOD/SOS died within 12 months post-transplant; 6 patients (43%) had a primary cause of death (COD) that was not VOD/SOS (n=2 recurrence of B-Cell ALL, n=2 acute GVHD, n=1 interstitial pneumonitis, n=1 septic shock).

Table 24 shows the incidence of VOD/SOS, post-transplant VOD/SOS mortality, 6-month and 12-month OS, 6-month and 12-month NRM, 6-month and 12-month relapse in adult patients without a prior HSCT in this ongoing non-interventional study.

Table 24 Adults without a prior HSCT, summary of VOD/SOS, overall survival, non-relapse mortality and relapse

	Incidence of VOD/SOS	Post-transplant VOD/SOS mortality [a]	6-mo OS	12-mo OS	6-mo NRM	12-mo NRM	6-mo relapse	12-mo relapse
All adult patients n=131	13%	41%	76%	55%	16%	21%	25%	36%
Adult R/R n=91	18%	38%	71%	50%	18%	23%	25%	37%

[a] Caution must be exercised in assessing unadjusted mortality rates. There were n=17 adult patients who experienced post-transplant VOD/SOS and n=16 adult patients with R/R ALL who experienced post-transplant VOD/SOS.

10.4.2 Subset analysis: adults who underwent first allogeneic HSCT with sufficient follow-up

The following is an interim subset analysis to provide a further evaluation in the outcomes of interest in a subset of the patients included in the broader study population. This subset population includes adults who underwent first allogeneic HSCT and who were either:

- alive at the date of last contact and reported at least 1 year of follow-up, or
- died at any time following their first allogeneic HSCT.

By selecting these patients who either experienced mortality or at least 1 year of follow-up, outcomes could be evaluated at 1 year post-HSCT.

The selection of this subset of patients to be evaluated in this interim analysis are described in Table 25, while their baseline characteristics are described in Table 26. Each outcome of interest is evaluated in a univariate analysis and a multivariate analysis. The outcomes were overall survival (Table 27 and Table 28), non-relapse mortality (Table 29 and Table 30), and VOD/SOS (Table 31 and Table 32).

Note that in Interim Report 3, there was an update made to the variable “lines of therapy prior to inotuzumab ozogamicin,” a variable evaluated in the interim analysis. This would affect n=3 patients in the interim analysis (n=2 would move from “Salvage 1” to “Salvage 2” and n=1 would move from “Salvage 2” to “Salvage 1”). Since “lines of therapy prior to inotuzumab ozogamicin” was not a significant factor in any of the three outcome models evaluated, in either the univariate or multivariate analyses, these analyses were not updated for Interim Report 3.

Table 25 Disposition of adults who underwent first allogeneic HSCT and were eligible for interim subset analysis

Selection criteria	Number of patients excluded	Number of patients remaining in the study cohort
AlloHSCT for B-cell ALL in US during 18 Aug. 2017 – 17 Aug. 2020		3140
Patient consented for research	282	2858
Excluded patients from embargoed centers	67	2791
Excluded patients from centers not participating in study	1354	1437
Patient indicated inotuzumab ozogamicin had been given	1253	184
Patient underwent first allogeneic HSCT	21	163
Adult patient (≥ 18 years old at HSCT)	27	136
Exclude patients who were alive at date of last contact and have < 12 months of follow-up	47	89

Table 26 Baseline characteristics of adults who underwent first allogeneic HSCT and were eligible for interim subset analysis

No. of adult patients eligible for interim subset analysis	**89**
Age, no. (%), years	
Median (range)	44 (18-75)
30-39	18 (20)
40-49	18 (20)
50-59	25 (28)
60-69	12 (13)
≥ 70	16 (18)
Karnofsky performance score prior to transplant, no. (%)	
90-100	48 (54)
10-80	40 (45)
Not reported	1 (1)
Sorror HCT-CI score, no. (%)	
0	12 (13)
1	14 (16)
2	16 (18)
3	27 (30)
4	10 (11)
5	9 (10)
6	1 (1)
History of hepatitis B or C, no. (%)	
Yes	4 (4)
No	85 (96)
Liver disease/hepatitis B or C, no. (%)	
Yes	27 (30)
No	61 (69)
Not reported	1 (1)
Line of therapy prior to transplant, no. (%)	
First line	5 (6)
Relapsed/refractory to therapy	82 (92)
N/A, CIBMTR Form 2011 not yet received	2 (2)
Lines of salvage therapy prior to inotuzumab ozogamicin, no. (%)	
No treatment given	7 (8)
First line	17 (19)
Salvage 1	19 (21)
Salvage ≥ 2	41 (46)
N/A, CIBMTR Form 2011 not yet received	2 (2)
Not reported	3 (3)

No. of adult patients eligible for interim subset analysis	89
Number of cycles, and combined dose, of inotuzumab ozogamicin, no. (%)	
1	32 (36)
Median (range)	1.8 (0.6-3.6)
< 1.8	11 (34)
1.8	16 (50)
> 1.8	2 (6)
Not reported	3 (9)
2	37 (42)
Median (range)	3.0 (1.5-7.7)
< 3.0	17 (46)
3.0-3.2	3 (8)
3.3-3.6	12 (32)
> 3.6	2 (5)
Not reported	3 (8)
3	13 (15)
Median (range)	5.1 (2.1-5.4)
< 2.8	1 (8)
2.8-4.8	1 (8)
4.9-5.3	4 (31)
> 5.3	4 (31)
Not reported	3 (23)
4	6 (7)
Median (range)	4.8 (3.3-4.8)
2.8-4.8	3 (50)
Not reported	3 (50)
N/A, CIBMTR Form 2541 not yet received	1 (1)
Inotuzumab ozogamicin combined dose, all cycles, no. (%)	
Median (range)	2.1 (0.6-7.7)
N/A, CIBMTR Form 2541 not yet received	1 (1)
Time from last dose of inotuzumab ozogamicin to HSCT, months, no. (%)	
Median (range)	2 (0-26)
N/A, CIBMTR Form 2541 not yet received	1 (1)
< 1	14 (16)
1-1.6	20 (22)
1.7-3	28 (31)
> 3	22 (25)
Not reported	4 (4)
Disease status prior to HSCT, no. (%)	
CR1	25 (28)
CR2	44 (49)
Advanced	20 (22)
CR3+	11
REL1	4
REL3+	2
PIF	3

No. of adult patients eligible for interim subset analysis	**89**
Time from diagnosis to 1st CR/CRi, no. (%), months	
Median (range)	3 (0-30)
< 3	35 (39)
3-5	15 (17)
6-11	19 (21)
≥ 12	5 (6)
N/A, CIBMTR Form 2011 not yet received	2 (2)
N/A, not in CR, any time prior to HSCT	2 (2)
Not reported	11 (12)
Time from 1st CR/CRi to HSCT, no. (%), months	
Median (range)	14 (0-226)
< 6	27 (30)
6-11	8 (9)
12-17	7 (8)
18-23	9 (10)
≥ 24	23 (26)
N/A, CIBMTR Form 2011 not yet received	2 (2)
N/A, not in CR, any time prior to HSCT	2 (2)
Not reported	11 (12)
MRD status prior to HSCT, no. (%)	
Positive	23 (26)
Negative	56 (63)
N/A, patient not in CR at HSCT	9 (10)
Not reported	1 (1)
Donor type, no. (%)	
HLA-identical sibling	23 (26)
Other related	16 (18)
Unrelated	50 (56)
Last platelet count, prior to HSCT, $\times 10^9$/L, no. (%)	
< 100	42 (47)
≥ 100	46 (52)
N/A, CIBMTR Form 2000 not yet received	1 (1)
Conditioning regimen intensity, no. (%)	
Myeloablative	45 (51)
RIC/NMA	39 (44)
N/A, CIBMTR Form 2000 not yet received	5 (6)
Busulfan used in conditioning regimen, no. (%)	
Yes	15 (17)
Busulfan dose guided by pharmacokinetics	10
No	69 (78)
N/A, CIBMTR Form 2000 not yet received	5 (6)
Thiotepa used in conditioning regimen, no. (%)	
Yes	8 (9)
No	76 (85)
N/A, CIBMTR Form 2000 not yet received	5 (6)

No. of adult patients eligible for interim subset analysis	**89**
Dual alkylating agents or one alkylating agent, no. (%)	
Two alkylating agents	8 (9)
One alkylating agent	59 (66)
No alkylating agents	16 (18)
N/A, CIBMTR Form 2000 not yet received	5 (6)
Not reported	1 (1)
Combination of alkylating agent(s) with TBI ≥ 12 Gy, no. (%)	
Yes	17 (19)
No	66 (74)
N/A, CIBMTR Form 2000 not yet received	5 (6)
Not reported	1 (1)
Defibrotide use for liver toxicity prophylaxis, no. (%)	
Yes	8 (9)
No	81 (91)
Ursodiol use for liver toxicity prophylaxis, no. (%)	
Yes	82 (92)
No	7 (8)
Graft type, no. (%)	
BM/PB	80 (90)
UCB	9 (10)
Total serum bilirubin, prior to transplant, no. (%)	
Normal	76 (85)
Abnormal	8 (9)
N/A, CIBMTR Form 2000 not yet received	5 (6)
Donor/recipient sex match, no. (%)	
M-M	29 (33)
M-F	27 (30)
F-M	16 (18)
F-F	16 (18)
Not reported	1 (1)
Donor/recipient CMV match, no. (%)	
+/+	35 (39)
+/-	7 (8)
-/+	25 (28)
-/-	17 (19)
Not reported	5 (6)
GVHD prophylaxis, no. (%)	
PT-Cy-based	23 (26)
Tac-based	54 (61)
CsA-based	9 (10)
Ex-vivo TCD or CD34 selection	3 (3)
Sirolimus used in GVHD prophylaxis, no. (%)	
Yes	6 (7)
No	83 (93)
In vivo T-cell depletion, no. (%)	
Yes	22 (25)
No	67 (75)

No. of adult patients eligible for interim subset analysis	**89**
Year of transplant, no. (%)	
2017	8 (9)
2018	47 (53)
2019	33 (37)
2020	1 (1)

Table 27 Univariate analysis of overall survival at 1 year in adults who underwent first allogeneic HSCT and were eligible for interim subset analysis

No. of patients (N=89)	No. patients in each group	Hazard ratio (95% CI)	P value
Patient age at transplant, years	Continuous	1.015 (0.996 - 1.034)	0.1226
Karnofsky performance score prior to transplant (10-80 vs. 90-100)	40 vs. 48	1.167 (0.683 - 1.993)	0.573
Sorror comorbidity score	Continuous	1.156 (0.977 - 1.367)	0.0922
History of hepatitis B or C (yes vs. no)	4 vs. 85	0.331 (0.046 - 2.397)	0.2738
Liver disease / hepatitis B or C (yes vs. no)	27 vs. 61	0.938 (0.524 - 1.679)	0.8304
Line of therapy prior to HSCT (first line vs. relapsed/refractory to therapy)	5 vs. 82	1.327 (0.479 - 3.68)	0.5861
Line of therapy prior to HSCT (N/A Form 2011 not yet received vs. relapsed/refractory to therapy)	2 vs. 82	0.881 (0.122 - 6.385)	0.9005
Lines of salvage therapy prior to inotuzumab ozogamicin (no treatment given vs. salvage ≥ 2)	7 vs. 41	1.301 (0.535 - 3.164)	0.561
Lines of salvage therapy prior to inotuzumab ozogamicin (first line vs. salvage ≥ 2)	17 vs. 41	1.059 (0.51 - 2.197)	0.8777
Lines of salvage therapy prior to inotuzumab ozogamicin (salvage 1 vs. salvage ≥ 2)	19 vs. 41	0.989 (0.489 - 2.002)	0.9753
Lines of salvage therapy prior to inotuzumab ozogamicin (N/A Form 2011 not yet received vs. salvage ≥ 2)	2 vs. 41	0.868 (0.118 - 6.404)	0.8898
Number of cycles of inotuzumab ozogamicin	Continuous	1.003 (0.982 - 1.023)	0.8082
Time from last dose of inotuzumab ozogamicin to HSCT	Continuous	1.069 (0.986 - 1.158)	0.1057
Total dose of inotuzumab ozogamicin	Continuous	1.332 (1.099 - 1.614)	0.0035
Disease status prior to HSCT (advanced vs. CR1)	20 vs. 25	2.259 (1.066 - 4.785)	0.0333
Disease status prior to HSCT (CR2 vs. CR1)	44 vs. 25	1.561 (0.79 - 3.084)	0.1998
Time from diagnosis to CR1, months	Continuous	0.989 (0.94 - 1.041)	0.6729
Time from CR1 to HSCT, months	Continuous	0.995 (0.984 - 1.005)	0.3119
MRD status prior to HSCT (N/A not in CR at HSCT vs. negative)	9 vs. 56	1.248 (0.554 - 2.811)	0.5928
MRD status prior to HSCT (positive vs. negative)	23 vs. 56	0.746 (0.387 - 1.437)	0.3809
Donor type (other related vs. HLA-identical sibling)	16 vs. 23	1.188 (0.562 - 2.512)	0.6522
Donor type (unrelated vs. HLA-identical sibling)	50 vs. 23	0.752 (0.405 - 1.397)	0.3668
Platelet count, × 10^9/L, last evaluation prior to HSCT (< 100 vs. ≥ 100)	42 vs. 46	1.26 (0.738 - 2.15)	0.3964
Platelet count, × 10^9/L, last evaluation prior to HSCT (N/A Form 2000 not yet received vs. ≥ 100)	1 vs. 46	5.603 (0.729 - 43.075)	0.0977
Conditioning regimen intensity (N/A Form 2000 not yet received vs. MAC)	5 vs. 45	4.65 (1.681 - 12.868)	0.0031
Conditioning regimen intensity (RIC/NMA vs. MAC)	39 vs. 45	1.607 (0.919 - 2.81)	0.0963
Busulfan used in conditioning regimen (N/A Form 2000 not yet received vs. no)	5 vs. 69	3.515 (1.329 - 9.297)	0.0113
Busulfan used in conditioning regimen (yes vs. no)	15 vs. 69	0.817 (0.384 - 1.741)	0.6009
Thiotepa used in conditioning regimen (N/A Form 2000 not yet received vs. no)	5 vs. 76	3.72 (1.409 - 9.817)	0.008
Thiotepa used in conditioning regimen (yes vs. no)	8 vs. 76	1.258 (0.499 - 3.17)	0.6269
Dual alkylating agents used in conditioning regimen (N/A Form 2000 not yet received vs. one alkylating agent)	5 vs. 59	4.087 (1.523 - 10.973)	0.0052
Dual alkylating agents used in conditioning regimen (no alkylating agent vs. one alkylating agent)	16 vs. 59	1.216 (0.583 - 2.536)	0.6026
Dual alkylating agents used in conditioning regimen (two alkylating agents vs. one alkylating agent)	8 vs. 59	1.792 (0.752 - 4.271)	0.188

No. of patients (N=89)	No. patients in each group	Hazard ratio (95% CI)	P value
Combination of alkylating agent(s) with TBI ≥ 12 Gy (N/A Form 2000 not yet received vs. no)	5 vs. 66	3.235 (1.222 - 8.565)	0.0181
Combination of alkylating agent(s) with TBI ⩾ 12 Gy (yes vs. no)	17 vs. 66	0.419 (0.178 - 0.985)	0.0462
Graft source (UCB vs. BM/PB)	9 vs. 80	0.768 (0.306 - 1.925)	0.5728
Bilirubin, last evaluation prior to HSCT (N/A Form 2000 not yet received vs. normal)	5 vs. 76	4.566 (1.708 - 12.202)	0.0025
Bilirubin, last evaluation prior to HSCT (abnormal vs. normal)	8 vs. 76	5.808 (2.653 - 12.716)	<.0001
Donor-recipient sex match (N/A UCB vs. not matched)	9 vs. 36	0.612 (0.235 - 1.596)	0.3157
Donor-recipient sex match (matched vs. not matched)	43 vs. 36	0.633 (0.361 - 1.11)	0.1108
Donor-recipient CMV match (N/A UCB vs. not matched)	9 vs. 31	0.885 (0.329 - 2.386)	0.8098
Donor-recipient CMV match (matched vs. not matched)	49 vs. 31	1.263 (0.709 - 2.252)	0.4277
GVHD prophylaxis (CsA-based vs. Tac-based)	9 vs. 54	1.069 (0.416 - 2.749)	0.8902
GVHD prophylaxis (Ex-vivo TCD/CD34 selection vs. Tac-based)	3 vs. 54	0.496 (0.068 - 3.632)	0.4899
GVHD prophylaxis (PT-Cy-based vs. Tac-based)	23 vs. 54	1.751 (0.978 - 3.136)	0.0596
Sirolimus used in GVHD prophylaxis (yes vs. no)	6 vs. 83	1.436 (0.519 - 3.978)	0.4861
In vivo T-cell depletion (yes vs. no)	22 vs. 67	0.767 (0.404 - 1.454)	0.4158
Year of transplant	Continuous	1.286 (0.843 - 1.961)	0.2433

Table 28 Multivariate analysis of overall survival at 1 year in adults who underwent first allogeneic HSCT and were eligible for interim analysis

Covariate	No. evaluable	Hazard ratio (95% CI)	P-value
Total serum bilirubin			
Normal	75	1.00	<0.0001 [a]
Abnormal	8	5.86 (2.62 – 13.08)	<0.0001
Not reported	5	3.61 (1.32 – 9.85)	0.0124
Number of cycles of inotuzumab ozogamicin			
1	32	1.00	0.0437 [b]
2	37	1.09 (0.55 – 2.17)	0.8076
3	13	2.19 (0.96 – 4.97)	0.0617
4	6	3.48 (1.20 – 10.12)	0.0220

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who were alive at date of last contact and reported less than 1 year of post-HSCT follow-up were not included in this analysis.
Overall mortality is time from HSCT to death from any cause post-HSCT. A Cox proportional hazards model has been used to evaluate overall mortality. Data were censored at 1 year post-HSCT.
The following 8 variables were evaluated in the multivariate analysis: dual alkylators used in conditioning regimen (yes vs. no), age (continuous), last bilirubin prior to transplant (≥ ULN vs. < ULN), Karnofsky performance score prior to transplant (90-100 vs. 10-80), sirolimus use in GVHD prophylaxis (yes vs. no), disease status prior to transplant (CR1 vs. not in CR1), cumulative inotuzumab ozogamicin dose (continuous), number of cycles of inotuzumab ozogamicin (continuous).
[a] Wald test with 2 degrees of freedom
[b] Wald test with 3 degrees of freedom

Table 29 Univariate analysis of non-relapse mortality in adults who underwent first allogeneic HSCT and were eligible for interim subset analysis

No. of patients (N=89)	No. patients in each group	Hazard ratio (95% CI)	P-value
Patient age at transplant, years	Continuous	1.039 (1.011 - 1.067)	0.0055
Karnofsky performance score prior to transplant (10-80 vs. 90-100)	40 vs. 48	1.744 (0.791 - 3.847)	0.168
Sorror comorbidity score	Continuous	1.21 (0.949 - 1.542)	0.1241
History of hepatitis B or C (yes vs. no)	4 vs. 85	0.681 (0.092 - 5.05)	0.7073
Liver disease / hepatitis B or C (yes vs. no)	27 vs. 61	0.998 (0.433 - 2.298)	0.9963
Line of therapy prior to HSCT (first line vs. relapsed/refractory to therapy)	5 vs. 82	1.215 (0.287 - 5.145)	0.7915
Line of therapy prior to HSCT (N/A Form 2011 not yet received [a] vs. relapsed/refractory to therapy)	2 vs. 82	n/a	n/a
Lines of salvage therapy prior to inotuzumab ozogamicin (no treatment given vs. salvage ≥ 2)	7 vs. 41	1.117 (0.245 - 5.103)	0.8863
Lines of salvage therapy prior to inotuzumab ozogamicin (first line vs. salvage ≥ 2)	17 vs. 41	2.01 (0.793 - 5.095)	0.1414
Lines of salvage therapy prior to inotuzumab ozogamicin (salvage 1 vs. salvage ≥ 2)	19 vs. 41	1.487 (0.54 - 4.095)	0.4426
Lines of salvage therapy prior to inotuzumab ozogamicin (N/A Form 2011 not yet received [a] vs. salvage ≥ 2)	2 vs. 41	n/a	n/a
Number of cycles of inotuzumab ozogamicin	Continuous	0.99 (0.929 - 1.055)	0.7608
Time from last dose of inotuzumab ozogamicin to HSCT	Continuous	1.089 (1.009 - 1.175)	0.0293
Total dose of inotuzumab ozogamicin	Continuous	1.336 (1.022 - 1.747)	0.0344
Disease status prior to HSCT (advanced vs. CR1)	20 vs. 25	2.113 (0.729 - 6.125)	0.1681
Disease status prior to HSCT (CR2 vs. CR1)	44 vs. 25	1.262 (0.473 - 3.367)	0.6415
Time from diagnosis to CR1, months	Continuous	1.016 (0.959 - 1.077)	0.5905
Time from CR1 to HSCT, months	Continuous	0.997 (0.984 - 1.01)	0.6517
MRD status prior to HSCT (N/A not in CR at HSCT vs. negative)	9 vs. 56	0.77 (0.178 - 3.327)	0.7268
MRD status prior to HSCT (positive vs. negative)	23 vs. 56	0.618 (0.229 - 1.667)	0.3423
Donor type (other related vs. HLA-identical sibling)	16 vs. 23	0.89 (0.26 - 3.042)	0.8525
Donor type (unrelated vs. HLA-identical sibling)	50 vs. 23	0.943 (0.384 - 2.316)	0.8983
Platelet count, last evaluation prior to HSCT, × 10^9/L (< 100 vs. ≥ 100)	42 vs. 46	1.458 (0.673 - 3.158)	0.3388
Platelet count, last evaluation prior to HSCT, × 10^9/L (N/A Form 2000 not yet received [a] vs. ≥ 100)	1 vs. 46	n/a	n/a
Conditioning regimen intensity (N/A Form 2000 not yet received vs. MAC)	5 vs. 45	1.702 (0.21 - 13.808)	0.6187
Conditioning regimen intensity (RIC/NMA vs. MAC)	39 vs. 45	2.135 (0.943 - 4.832)	0.0688
Busulfan used in conditioning regimen (N/A Form 2000 not yet received vs. no)	5 vs. 69	1.037 (0.136 - 7.903)	0.9724
Busulfan used in conditioning regimen (yes vs. no)	15 vs. 69	0.589 (0.176 - 1.97)	0.3901
Thiotepa used in conditioning regimen (N/A Form 2000 not yet received vs. no)	5 vs. 76	1.159 (0.152 - 8.839)	0.8869
Thiotepa used in conditioning regimen (yes vs. no)	8 vs. 76	1.39 (0.416 - 4.649)	0.5926
Dual alkylating agents used in conditioning regimen (N/A Form 2000 not yet received vs. one alkylating agent)	5 vs. 59	1.502 (0.191 - 11.788)	0.699
Dual alkylating agents used in conditioning regimen (no alkylating agent vs. one alkylating agent)	16 vs. 59	2.172 (0.827 - 5.702)	0.1153

No. of patients (N=89)	No. patients in each group	Hazard ratio (95% CI)	P-value
Dual alkylating agents used in conditioning regimen (two alkylating agents vs. one alkylating agent)	8 vs. 59	2.869 (0.942 - 8.736)	0.0635
Combination of alkylating agent(s) with TBI ≥ 12 Gy (N/A Form 2000 not yet received vs. no)	5 vs. 66	0.894 (0.118 - 6.795)	0.9141
Combination of alkylating agent(s) with TBI ⩾ 12 Gy (yes vs. no)	17 vs. 66	0.131 (0.018 - 0.973)	0.047
Graft source (UCB vs. BM/PB)	9 vs. 80	0.338 (0.046 - 2.502)	0.2883
Bilirubin, last evaluation prior to HSCT (N/A Form 2000 not yet received vs. normal)	5 vs. 76	1.57 (0.202 - 12.201)	0.6663
Bilirubin, last evaluation prior to HSCT (abnormal vs. normal)	8 vs. 76	7.328 (2.802 - 19.162)	<.0001
Donor-recipient sex match (N/A UCB vs. not matched)	9 vs. 36	0.247 (0.032 - 1.882)	0.1771
Donor-recipient sex match (matched vs. not matched)	43 vs. 36	0.504 (0.224 - 1.137)	0.0989
Donor-recipient CMV match (N/A UCB vs. not matched)	9 vs. 31	0.35 (0.045 - 2.741)	0.3176
Donor-recipient CMV match (matched vs. not matched)	49 vs. 31	1.06 (0.476 - 2.362)	0.8864
GVHD prophylaxis (CsA-based vs. Tac-based)	9 vs. 54	1.356 (0.392 - 4.692)	0.6301
GVHD prophylaxis (Ex-vivo TCD/CD34 selection [a] vs. Tac-based)	3 vs. 54	n/a	n/a
GVHD prophylaxis (PT-Cy-based vs. Tac-based)	23 vs. 54	1.551 (0.655 - 3.674)	0.3187
Sirolimus used in GVHD prophylaxis (yes vs. no)	6 vs. 83	1.303 (0.308 - 5.514)	0.7194
In vivo T-cell depletion (yes vs. no)	22 vs. 67	1.165 (0.506 - 2.686)	0.7195
Year of transplant	Continuous	1.843 (0.978 - 3.476)	0.0588

[a] There were no events reported for this category.

Table 30 Multivariate analysis of non-relapse mortality at 1 year in adults who underwent first allogeneic HSCT and were eligible for interim subset analysis

Covariate	N Evaluable	Hazard ratio (95% CI)	P-value
Patient age (continuous), years	89	1.04 (1.01 – 1.07)	0.0033 [a]
Total serum bilirubin			
Normal	75	1.00	<0.0001 [b]
Abnormal	8	7.08 (2.88 – 17.37)	<0.0001
Not reported	5	0.69 (0.24 – 1.99)	0.4927
Number of cycles of inotuzumab ozogamicin			
1	32	1.00	0.0002 [c]
2	37	0.91 (0.32 – 2.60)	0.8611
3	13	0.66 (0.18 – 2.42)	0.5278
4	6	5.98 (2.00 – 17.87)	0.0014

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who were alive at date of last contact and reported less than 1 year of post-HSCT follow-up were not included in this analysis.
Transplant-related mortality (post-transplant non-relapse mortality) is time from HSCT to death within the first 28 days post-HSCT, or death from any cause without prior relapse/progression post-HSCT. A Fine and Gray's sub-distribution hazards model was used to account for the competing risk event (post-HSCT relapse). Data were censored at 1 year post-HSCT.
The following 8 variables were evaluated in the multivariate analysis: dual alkylators used in conditioning regimen (yes vs. no), age (continuous), last bilirubin prior to transplant (≥ ULN vs. < ULN), Karnofsky performance score prior to transplant (90-100 vs. 10-80), sirolimus use in GVHD prophylaxis (yes vs. no), disease status prior to transplant (CR1 vs. not in CR1), cumulative inotuzumab ozogamicin dose (continuous), number of cycles of inotuzumab ozogamicin (continuous).
[a] Wald test with 1 degree of freedom
[b] Wald test with 2 degrees of freedom
[c] Wald test with 3 degrees of freedom

Table 31 Univariate analysis of VOD/SOS at 100 days in adults who underwent first allogeneic HSCT and were eligible for interim subset analysis

No. of patients (N=89)	No. patients in each group	Hazard ratio (95% CI)	P-value
Patient age at transplant, years	Continuous	0.984 (0.949 - 1.02)	0.3906
Karnofsky performance score prior to transplant (10-80 vs. 90-100)	40 vs. 48	5.095 (1.419 - 18.298)	0.0126
Sorror comorbidity score	Continuous	1.322 (0.952 - 1.835)	0.0955
History of hepatitis B or C (yes vs. no)	4 vs. 85	3.762 (0.847 - 16.703)	0.0815
Liver disease / hepatitis B or C (yes vs. no)	27 vs. 61	1.5 (0.534 - 4.215)	0.4419
Line of therapy prior to HSCT (first line [a] vs. relapsed/refractory to therapy)	5 vs. 82	n/a	n/a
Line of therapy prior to HSCT (N/A Form 2011 not yet received vs. relapsed/refractory to therapy)	2 vs. 82	3.69 (0.483 - 28.2)	0.2083
Lines of salvage therapy prior to inotuzumab ozogamicin (no treatment given [a] vs. salvage ≥ 2)	7 vs. 41	n/a	n/a
Lines of salvage therapy prior to inotuzumab ozogamicin (first line vs. salvage ≥ 2)	17 vs. 41	0.286 (0.036 - 2.283)	0.2374
Lines of salvage therapy prior to inotuzumab ozogamicin (salvage 1 vs. salvage ≥ 2)	19 vs. 41	1.096 (0.33 - 3.644)	0.8811
Lines of salvage therapy prior to inotuzumab ozogamicin (N/A Form 2011 not yet received vs. salvage ≥ 2)	2 vs. 41	3.134 (0.39 - 25.191)	0.2826
Number of cycles of inotuzumab ozogamicin	Continuous	0.989 (0.909 - 1.075)	0.7883
Time from last dose of inotuzumab ozogamicin to HSCT	Continuous	1.062 (0.967 - 1.166)	0.2069
Total dose of inotuzumab ozogamicin	Continuous	0.971 (0.656 - 1.437)	0.8831
Disease status prior to HSCT (advanced vs. CR1)	20 vs. 25	5.414 (0.605 - 48.445)	0.1309
Disease status prior to HSCT (CR2 vs. CR1)	44 vs. 25	6.137 (0.786 - 47.948)	0.0837
Time from diagnosis to CR1, months	Continuous	0.98 (0.877 - 1.095)	0.7207
Time from CR1 to HSCT, months	Continuous	1.009 (0.999 - 1.018)	0.0692
MRD status prior to HSCT (N/A not in CR at HSCT vs. negative)	9 vs. 56	0.67 (0.085 - 5.287)	0.7038
MRD status prior to HSCT (positive vs. negative)	23 vs. 56	1.129 (0.348 - 3.668)	0.8396
Donor type (other related vs. HLA-identical sibling)	16 vs. 23	0.684 (0.125 - 3.736)	0.6612
Donor type (unrelated vs. HLA-identical sibling)	50 vs. 23	1.098 (0.338 - 3.567)	0.8763
Platelet count, last evaluation prior to HSCT (< 100 vs. ≥ 100)	42 vs. 46	2.005 (0.672 - 5.985)	0.2123
Platelet count, last evaluation prior to HSCT (N/A Form 2000 not yet received vs. ≥ 100)	1 vs. 46	21.131 (2.265 - 197.15)	0.0074
Conditioning regimen intensity (N/A Form 2000 not yet received vs. MAC)	5 vs. 45	1.013 (0.128 - 8.001)	0.9899
Conditioning regimen intensity (RIC/NMA vs. MAC)	39 vs. 45	0.638 (0.214 - 1.903)	0.42
Busulfan used in conditioning regimen (N/A Form 2000 not yet received vs. no)	5 vs. 69	1.147 (0.149 - 8.826)	0.8949
Busulfan used in conditioning regimen (yes vs. no)	15 vs. 69	0.695 (0.156 - 3.108)	0.6343
Thiotepa used in conditioning regimen (N/A Form 2000 not yet received vs. no)	5 vs. 76	1.412 (0.182 - 10.938)	0.7413
Thiotepa used in conditioning regimen (yes vs. no)	8 vs. 76	2.756 (0.769 - 9.881)	0.1197
Dual alkylating agents used in conditioning regimen (N/A Form 2000 not yet received vs. one alkylating agent)	5 vs. 59	1.769 (0.218 - 14.381)	0.5937
Dual alkylating agents used in conditioning regimen (no alkylating agent vs. one alkylating agent)	16 vs. 59	2.363 (0.691 - 8.075)	0.1702

No. of patients (N=89)	No. patients in each group	Hazard ratio (95% CI)	P-value
Dual alkylating agents used in conditioning regimen (two alkylating agents vs. one alkylating agent)	8 vs. 59	3.615 (0.934 - 13.998)	0.0628
Combination of alkylating agent(s) with TBI ≥ 12 Gy (N/A Form 2000 not yet received vs. No)	5 vs. 66	1.214 (0.157 - 9.407)	0.8525
Combination of alkylating agent(s) with TBI ≥ 12 Gy (yes vs. no)	17 vs. 66	1.045 (0.292 - 3.746)	0.946
Defibrotide used in liver toxicity prophylaxis (yes vs. no)	8 vs. 81	2.591 (0.73 - 9.188)	0.1406
Ursodiol used in liver toxicity prophylaxis (yes vs. no)	7 vs. 82	0.872 (0.115 - 6.631)	0.8944
Graft source (UCB [a] vs. BM/PB)	9 vs. 80	n/a	n/a
Bilirubin, last evaluation prior to HSCT (N/A Form 2000 not yet received vs. normal)	5 vs. 76	1.312 (0.171 - 10.096)	0.794
Bilirubin, last evaluation prior to HSCT (abnormal vs. normal)	8 vs. 76	1.987 (0.443 - 8.913)	0.3701
Donor-recipient sex match (N/A UCB [a] vs. not matched)	9 vs. 36	n/a	n/a
Donor-recipient sex match (matched vs. not matched)	43 vs. 36	1.067 (0.37 - 3.075)	0.905
Donor-recipient CMV match (N/A UCB [a] vs. not matched)	9 vs. 31	n/a	n/a
Donor-recipient CMV match (matched vs. not matched)	49 vs. 31	2.895 (0.816 - 10.266)	0.0998
GVHD prophylaxis (CsA-based vs. Tac-based)	9 vs. 54	0.609 (0.078 - 4.759)	0.6366
GVHD prophylaxis (Ex-vivo TCD/CD34 selection [a] vs. Tac-based)	3 vs. 54	n/a	n/a
GVHD prophylaxis (PT-Cy-based vs. Tac-based)	23 vs. 54	0.908 (0.285 - 2.894)	0.8698
Sirolimus used in GVHD prophylaxis (yes vs. no)	6 vs. 83	2.25 (0.507 - 9.982)	0.2859
In vivo T-cell depletion (yes vs. no)	22 vs. 67	1.132 (0.36 - 3.556)	0.8317
Year of transplant	Continuous	1.095 (0.506 - 2.373)	0.8174

[a] There were no events reported for this category.

Table 32 Multivariate analysis of VOD/SOS at 100 days in adults who underwent first allogeneic HSCT and were eligible for interim subset analysis

Covariate	N Evaluable	Odds ratio (95% CI)	P-value
Disease status at HSCT			
1st complete remission (CR1)	62	1.00	0.0741 [a]
Relapsed/refractory B-cell ALL	24	6.71 (0.83 – 54.16)	0.0741

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who were alive at date of last contact and reported less than 1 year of post-HSCT follow-up were not included in this analysis.
VOD is the occurrence of veno-occlusive disease/sinusoidal obstruction syndrome reported on the CIBMTR Form 2100. VOD is only considered within the first 100 days post-HSCT.
Logistic regression was used in this analysis to evaluate VOD within 100 days post-HSCT. There were n=3 patients who were excluded from this analysis due to missing VOD information. There were n=7 patients who died within 100 days without VOD and were considered as having not experienced VOD.
The following 8 variables were evaluated in the multivariate analysis: dual alkylators used in conditioning regimen (yes vs. no), age (continuous), last bilirubin prior to transplant (≥ ULN vs. < ULN), Karnofsky performance score prior to transplant (90-100 vs. 10-80), sirolimus use in GVHD prophylaxis (yes vs. no), disease status prior to transplant (CR1 vs. not in CR1), cumulative inotuzumab ozogamicin dose (continuous), number of cycles of inotuzumab ozogamicin (continuous).
[a] Wald test with 1 degree of freedom

10.5 Adverse events/adverse reactions

The CIBMTR Research Database supports non-interventional observational studies and utilizes a calendar driven reporting of events but is not designed to be a means for detecting and reporting adverse events in an expedited manner. As this is not a clinical trial, the CIBMTR has neither the jurisdiction nor the responsibility of expedited reporting of adverse events to any regulatory authority. Expedited reporting of suspected adverse drug reactions was done by the physician responsible for the treatment of the patient, in accordance with standard routines used at the clinic as specified by regulatory agency.

This study includes unstructured data (e.g., narrative fields in the database) that were converted to structured (i.e., coded) data solely by a computer using automated/algorithmic methods and/or data that already existed as structured data in an electronic database. In these data sources, it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and AEs are not reportable as individual AE reports.

11 Discussion

11.1 Key results

A total of 3140 B-cell ALL patients underwent an allogeneic HSCT transplant in the US between 18 August 2017 – 17 August 2020. Out of those 3,140 patients, 282 patients were excluded from this study as they had not consented to research, 67 patients were excluded from embargoed centers, and 1,354 patients were excluded as they belonged to centers not participating in the study. Of the remaining 1,437 patients, 184 received at least one dose of inotuzumab ozogamicin.

Therefore, between 18 August 2017 and 17 August 2020, 184 patients (152 adult and 32 pediatric) were accrued and included in the study. The data lock date for this interim report, when data collection forms were last evaluated, was 11 November 2020.

Of the 184 patients included in this study, 163 patients underwent their first allogeneic HSCT for B-cell ALL (136 adult and 27 pediatric) and 21 patients (16 adult and 5 pediatric) had received a prior allogeneic HSCT for B-cell ALL before receiving inotuzumab ozogamicin.

The 21 patients who had a prior allogeneic HSCT for B-cell ALL before receiving inotuzumab ozogamicin are described separately since the underlying disease, risk for relapse and post-HSCT complications are different for patients with a prior HSCT than for patients undergoing their first allogeneic HSCT for B-cell ALL.

11.1.1 Patients who underwent their first allogeneic HSCT for B-cell ALL

In total, 163 patients (136 adults and 27 pediatric patients with a median age of 35 years) underwent their first allogeneic HSCT for B-cell ALL after treatment with inotuzumab ozogamicin.

Prior to transplant, 15 patients had 1 line of therapy; 30 patients had 2 lines of therapy; 24 patients had 3 lines of therapy; and 86 patients had four or more lines of therapy. Data were not available for 8 patients.

As of the data lock date, post-HSCT follow-up information was available for 158 / 163 (97%) patients:

- 100 / 158 patients (63%) did not experience post-HSCT relapse; of these:
  - 30 / 100 patients (30%; 26 adult and 4 pediatric) died in remission, with a median time from transplant to transplant-related mortality (TRM) of 2.18 months; their causes of death (COD) were:
    - VOD/SOS – 8 patients (27%; 6 adult, 2 pediatric)
    - GVHD – 7 patients (23%; 7 adult, 0 pediatric)
    - Interstitial pneumonitis – 3 patients (10%; 2 adult, 1 pediatric)
    - Hemorrhage – 3 patients (10%; 3 adult, 0 pediatric)
    - Organ failure – 3 patients (10%; 3 adult, 0 pediatric)
    - Infection – 2 patients (7%; 2 adult, 0 pediatric)
    - Septic shock – 2 patients (7%; 2 adult, 0 pediatric)
    - Thrombotic microangiopathy – 1 (3%) pediatric patient
    - Graft failure – 1 (3%) adult patient
- 56 / 158 patients (35%) experienced post-HSCT relapse; of these:
  - 34 / 56 patients (61%; 29 adult, 5 pediatric) died after post-HSCT relapse of ALL, with a median time from transplant to NTRM of 6.64 months;
- 2 / 158 patients (1%) have unknown post-HSCT relapse. The involved transplant centers have been notified and these data will be updated.
- 24 / 158 patients (15%; 17 adult, 7 pediatric) experienced post-transplant VOD/SOS; of these:
  - 10 cases were mild (42%; 7 adult, 3 pediatric)

    - 14 cases were severe (58%; 10 adult, 4 pediatric)
    - 2 cases (8%; 1 adult, 1 pediatric) did not receive liver toxicity prophylaxis
    - 14 cases (58%; 10 adult, 4 pediatric) died after reporting VOD
        - 8 out of the 14 cases (57%) reported VOD as COD
            - 1 out of the 8 patients (13%) with reported VOD as COD had not received liver toxicity prophylaxis
        - Other CODs were:
            - GVHD (2 cases [14%], died 0.2 and 1.8 months after VOD),
            - Recurrence of B-Cell ALL (2 cases [14%], died 0.3 and 2.9 months after VOD),
            - Septic shock (1 case [7%], died 0.5 months after VOD), and
            - Interstitial pneumonitis (1 case [7%], died 0.1 months after VOD).
- 17 / 158 patients (11%) did not receive liver toxicity prophylaxis
- 108 / 158 patients (68%) received liver toxicity prophylaxis with ursodiol alone
- 22 / 158 patients (14%) received liver toxicity prophylaxis with ursodiol and defibrotide
- 8 / 158 patients (5%) received liver toxicity prophylaxis with ursodiol and other drugs (not specified)
- 2 / 158 patients (1%) received liver toxicity prophylaxis with defibrotide alone
- 1 / 158 patient (1%) did not have any reported liver toxicity prophylaxis

For the remaining 5 / 163 (3%) patients (all adults) for whom post-HSCT follow-up information was not available as of the data lock point, follow-up data will be provided in subsequent reports.

Post-transplant follow-up information was available for 155 / 163 (95%) patients undergoing their first allogeneic HSCT for B-cell ALL. Of these 155 patients, post-transplant VOD/SOS occurred in 24 patients (15%; 17 adult, 7 pediatric). Fifty-six (56) deaths occurred within the first 12 months post-transplant with TRM occurring in 27 patients within the first 12 months.

Fourteen (58%; 10 adult, 4 pediatric) of the 24 patients (17 adult, 7 pediatric) who developed post-transplant VOD/SOS died within 12 months post-transplant; 6 patients (43%) had a primary cause of death (COD) that was not VOD/SOS (n=2 recurrence of B-Cell ALL, n=2 acute GVHD, n=1 interstitial pneumonitis, n=1 septic shock).

11.1.2 Patients undergoing second, or greater, HSCT for B-cell ALL

As of the data lock date, post-HSCT follow-up information was available for 21 / 21 (100%) patients:

Among the 21 patients (16 adult, 5 pediatric) who had a prior allogeneic HSCT for B-cell ALL before receiving inotuzumab ozogamicin, 9 patients (43%) had ≥ 3 comorbidities prior to HSCT, and 7 patients (33%) had mild hepatic disease prior to HSCT. All 21 patients underwent HSCT for relapsed or refractory disease, and 4 of the 21 patients (19%) had a history of proven invasive fungal infection. Seven (7) patients (33%) received a bone marrow product, 1 patient

(5%) received a cord blood product, and the remaining 13 patients (62%) received peripheral blood stem cells. Thirteen (13) patients (62%) received their product from an unrelated donor, 3 patients (14%) had an HLA-identical sibling donor, and the remaining 5 patients (24%) had another related donor (though not a human leukocyte antigen [HLA]-identical sibling). The median time from ALL diagnosis to transplant was 36 months, and the median time from ALL diagnosis to first dose of inotuzumab ozogamicin was 33 months.

Five (5) of the 21 patients (24%) with prior allogeneic HSCT experienced VOD/SOS after the second allogeneic HSCT. All 5 patients experienced severe VOD/SOS, and 2 patients (40%) died after reporting VOD/SOS at 0.5 months and 1.1 months after VOD.

Follow-up for the remaining patients will be conducted for subsequent reports.

11.2 Limitations

CIBMTR is mandated by the U.S. Health Resources and Services Administration (HRSA) to collect data from all patients undergoing allogeneic HSCT in the US and as a result, the CIBMTR Research Database is the largest data source of post-HSCT B-cell ALL in the US. Only data included in the CIBMTR Research Database were analyzed. Not all CIBMTR centers agreed to provide Comprehensive Report Form data, and therefore some US patients who received HSCT after inotuzumab ozogamicin treatment were not available to be included in the study. Also, of those centers who provided CRF level data, not all agreed to provide supplemental information (i.e., the supplemental inotuzumab ozogamicin form); therefore, some US patients who received HSCT after inotuzumab ozogamicin treatment were not included the study.

Due to the design of the study (i.e. no internal comparison group within the CIBMTR Research Database), only descriptive information is provided.

11.3 Interpretation

Overall, interim data collected between August 2017 and August 2020 in the CIBMTR Research Database appear to be consistent with the results observed in completed Phase 3 Study B1931022.

In Phase 3 Study B1931022, which examined the safety and efficacy of inotuzumab ozogamicin in adult patients with relapsed or refractory ALL who received either 1 or 2 prior lines of therapy, the VOD incidence was 19% among adult patients undergoing a first HSCT for relapsed or refractory B-cell ALL. Based on data collected between August 2017 and August 2020 in the CIBMTR Research Database, the VOD incidence rate was 18% in adult patients with relapsed or refractory ALL who received a median of 4 prior lines of therapy. Although there are only data from n=27 pediatric patients undergoing a first transplant collected between August 2017 and August 2020 in the CIBMTR Research Database, the incidence of VOD post-HSCT is 26%.

In adult patients (n=131), the 12-month overall survival was 55% and 12-month NRM was 21%. Given the relatively small number of pediatric patients accrued for this interim report, these time-to-event endpoints were not calculated. A comprehensive analysis of the association

between patient baseline characteristics, pre-HSCT exposure to inotuzumab ozogamicin, patient characteristics at the time of HSCT and the occurrence of post-transplant VOD/SOS will require a larger sample size.

11.4 Generalizability

This study is generalizable to post-HSCT B-cell precursor ALL patients following treatment with inotuzumab ozogamicin in the US. Because supportive treatment for B-cell ALL and post-HSCT adverse events differ from country to country based on country-specific treatment guidelines, the findings from this study may not be generalizable to patients with B-cell ALL outside of the US. Since HSCT also results in adverse events, the findings of this study may not be generalizable to patients with B-cell ALL who are treated with inotuzumab ozogamicin but who do not proceed to HSCT.

12 Other information

Not applicable.

13 Conclusion

In conclusion, interim data collected between August 2017 and August 2020 in the CIBMTR Research Database suggest that the safety data obtained from the use of inotuzumab ozogamicin in the real-world post-transplant setting appear to be consistent with the data observed in Phase 3 Study B1931022.

14 References

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15 List of source tables and figures

Not applicable

16 Supplemental tables

The supplemental tables are included in this report upon request from Pfizer. The purpose of these supplemental tables is to provide results and descriptions of post-transplant outcomes in the population, by the status of the underlying B-cell ALL disease. Each post-transplant outcome is analyzed or described, in the same manner as in Section 10.3, for recipients who underwent transplant with relapsed or refractory B-cell ALL and then for those recipients who underwent transplant with B-cell ALL in first complete remission prior to HSCT.

16.1 Post-transplant overall survival subgroups

Table 33 Post-transplant overall survival within 12 months in patients who had relapsed or refractory B-Cell ALL prior to HSCT

	Pediatric patients (< 18 y)	Adults (≥ 18 y)	All patients
No. patients with relapsed or refractory B-Cell ALL prior to HSCT and with post-transplant follow-up	**21**	**91**	**112**
Post-transplant overall survival (95% CI)			
6 months	NE	71 (61-80)%	71 (63-80)%
12 months	NE	50 (39-61)%	52 (42-62)%
Number of deaths within 12 months	8	39	47
Primary cause of death, no. (%)			
Recurrence of B-cell ALL	5 (63)	16 (41)	21 (45)
GVHD	0	6 (15)	6 (13)
VOD/SOS	2 (25)	7 (18)	9 (19)
Interstitial pneumonitis	1 (13)	1 (3)	2 (4)
Infection	0	2 (5)	2 (4)
Septic shock	0	1 (3)	1 (2)
Hemorrhage	0	3 (8)	3 (6)
Organ failure	0	3 (8)	3 (6)
Time from transplant to death, no. (%) months			
< 3	5 (63)	14 (36)	19 (40)
3-5	1 (13)	11 (28)	12 (26)
6-11	2 (25)	14 (36)	16 (34)
Median (95% CI)	2.69 (1.12 - 9.82)	4.21 (2.69 - 6.21)	3.88 (2.46-5.72)
Range	(0.92-9.82)	(0.62-11.27)	(0.62-11.27)
Mean	4.03	4.77	4.64
Standard deviation	3.55	3.05	3.11

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who have not yet completed a follow-up form are not included in the data and estimates shown in this table. Patients with a reported outcome event beyond 12 months post-transplant (or post-inotuzumab ozogamicin) are not shown in this table, as follow-up among survivors in the population is approximately 12 months post-transplant.
Outcomes are not evaluable (NE) if sample size is < 20.
Post-transplant overall survival is time from HSCT to death from any cause. Patients are censored at the last date that the patient was known to be alive. There are no competing risks.

Figure 8 Post-transplant overall survival within 12 months in patients who had relapsed or refractory B-Cell ALL prior to HSCT

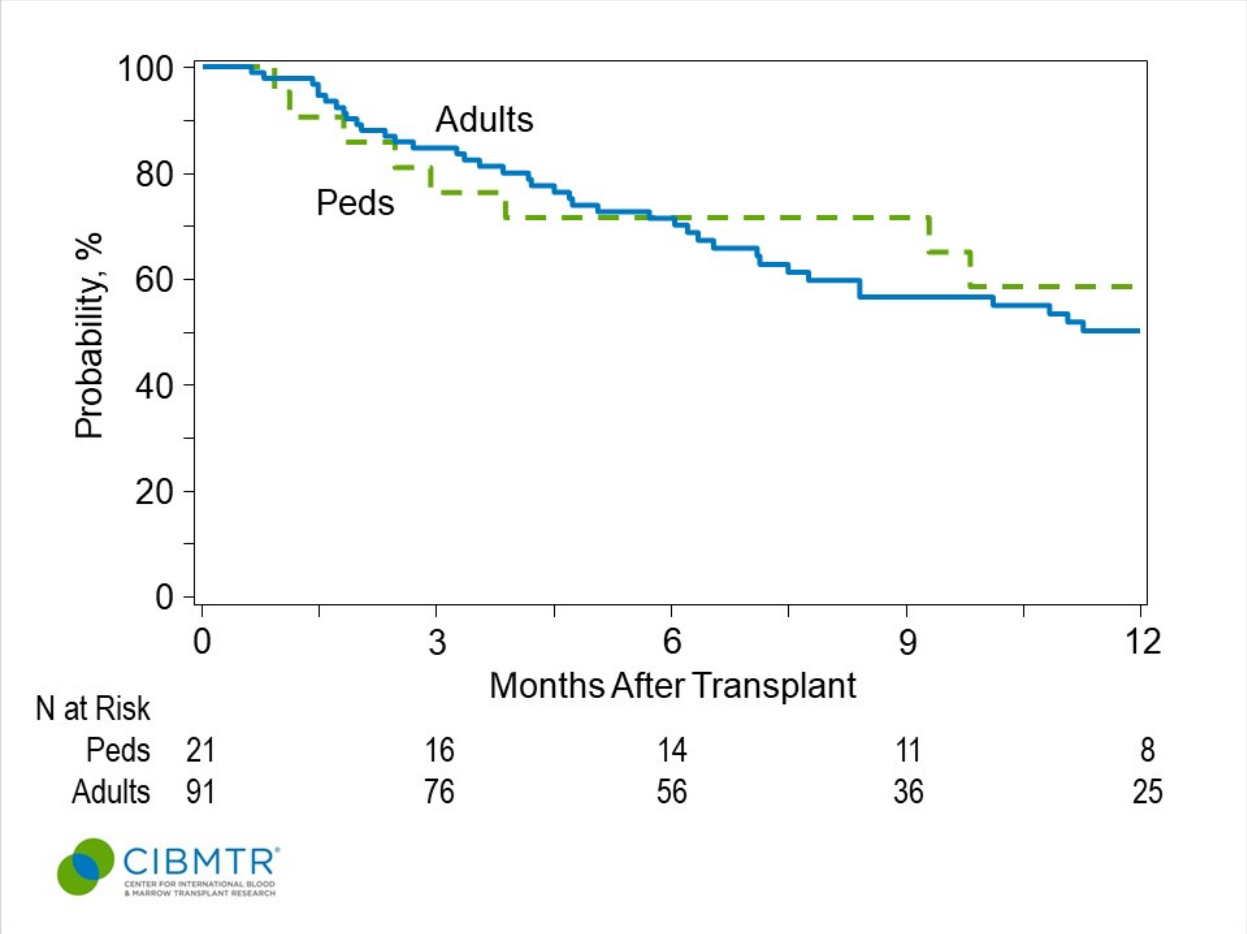
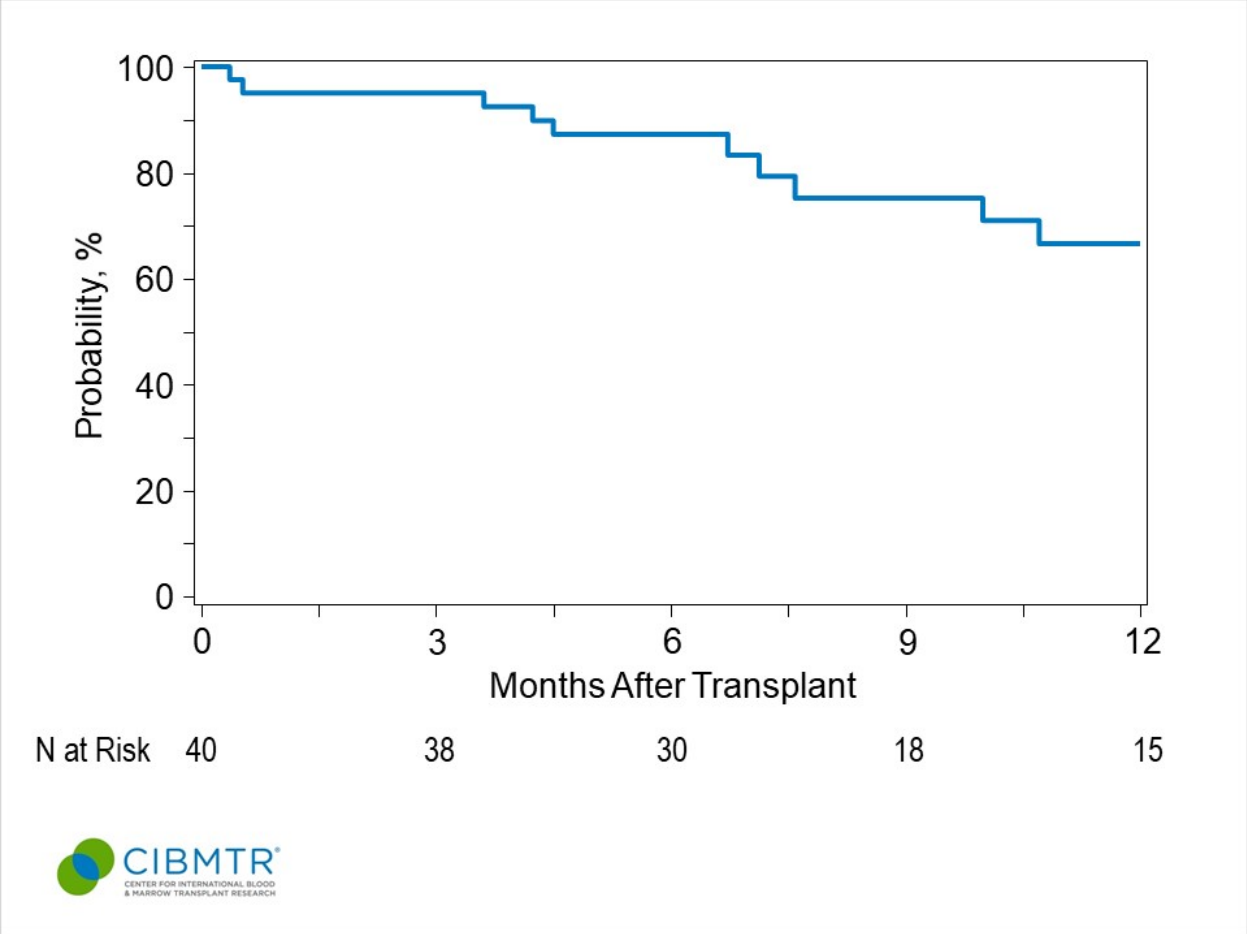


Table 34 Post-transplant overall survival within 12 months in patients in first complete remission prior to HSCT

	Pediatric patients (< 18 y)	Adults (≥ 18 y)	All patients
No. patients in first complete remission prior to HSCT and with post-transplant follow-up	**6**	**40**	**46**
Post-transplant overall survival (95% CI)			
6 months	NE	87 (75-96)%	89 (78-96)%
12 months	NE	NE	NE
Number of deaths within 12 months	1	10	11
Primary cause of death, no. (%)			
Recurrence of B-cell ALL	0	4 (40)	4 (36)
GVHD	0	3 (30)	3 (27)
Interstitial pneumonitis	0	1 (10)	1 (9)
Infection	0	1 (10)	1 (9)
Septic shock	0	1 (10)	1 (9)
Thrombotic microangiopathy (TMA)	1	0	1 (9)
Time from transplant to death, no. (%), months			
< 3	0	2 (20)	2 (18)
3-5	0	3 (30)	3 (27)
6-11	1	5 (50)	6 (55)
Median (95% CI)	8.05	5.62 (0.53 - 9.99)	6.74 (3.61-9.99)
Range	NE	(0.36-10.71)	(0.36-10.71)
Mean	8.05	5.54	5.77
Standard deviation	NE	3.55	3.45

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who have not yet completed a follow-up form are not included in the data and estimates shown in this table. Patients with a reported outcome event beyond 12 months post-transplant (or post-inotuzumab ozogamicin) are not shown in this table, as follow-up among survivors in the population is approximately 12 months post-transplant.
Outcomes are not evaluable (NE) if sample size is < 20.
Post-transplant overall survival is time from HSCT to death from any cause. Patients are censored at the last date that the patient was known to be alive. There are no competing risks.

Figure 9 Post-transplant overall survival within 12 months in adult patients in first complete remission prior to HSCT



16.2 Post-transplant overall mortality subgroups

Table 35 Post-transplant overall mortality within 12 months in patients who had relapsed or refractory B-Cell ALL prior to HSCT

	Pediatric patients (< 18 y)	Adults (≥ 18 y)	All patients
No. patients with relapsed or refractory B-Cell ALL prior to HSCT and with post-transplant follow-up	**21**	**91**	**112**
Post-transplant overall mortality (95% CI)			
6 months	NE	29 (20-39)%	29 (20-37)%
12 months	NE	50 (39-61)%	48 (38-58)%

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who have not yet completed a follow-up form are not included in the data and estimates shown in this table. Patients with a reported outcome event beyond 12 months post-transplant (or post-inotuzumab ozogamicin) are not shown in this table, as follow-up among survivors in the population is approximately 12 months post-transplant.
Outcomes are not evaluable (NE) if sample size is < 20.
Post-transplant overall mortality is time from HSCT to death from any cause. Patients are censored at the last date that the patient was known to be alive. There are no competing risks.

Figure 10 Post-transplant overall mortality within 12 months in patients who had relapsed or refractory B-Cell ALL prior to HSCT

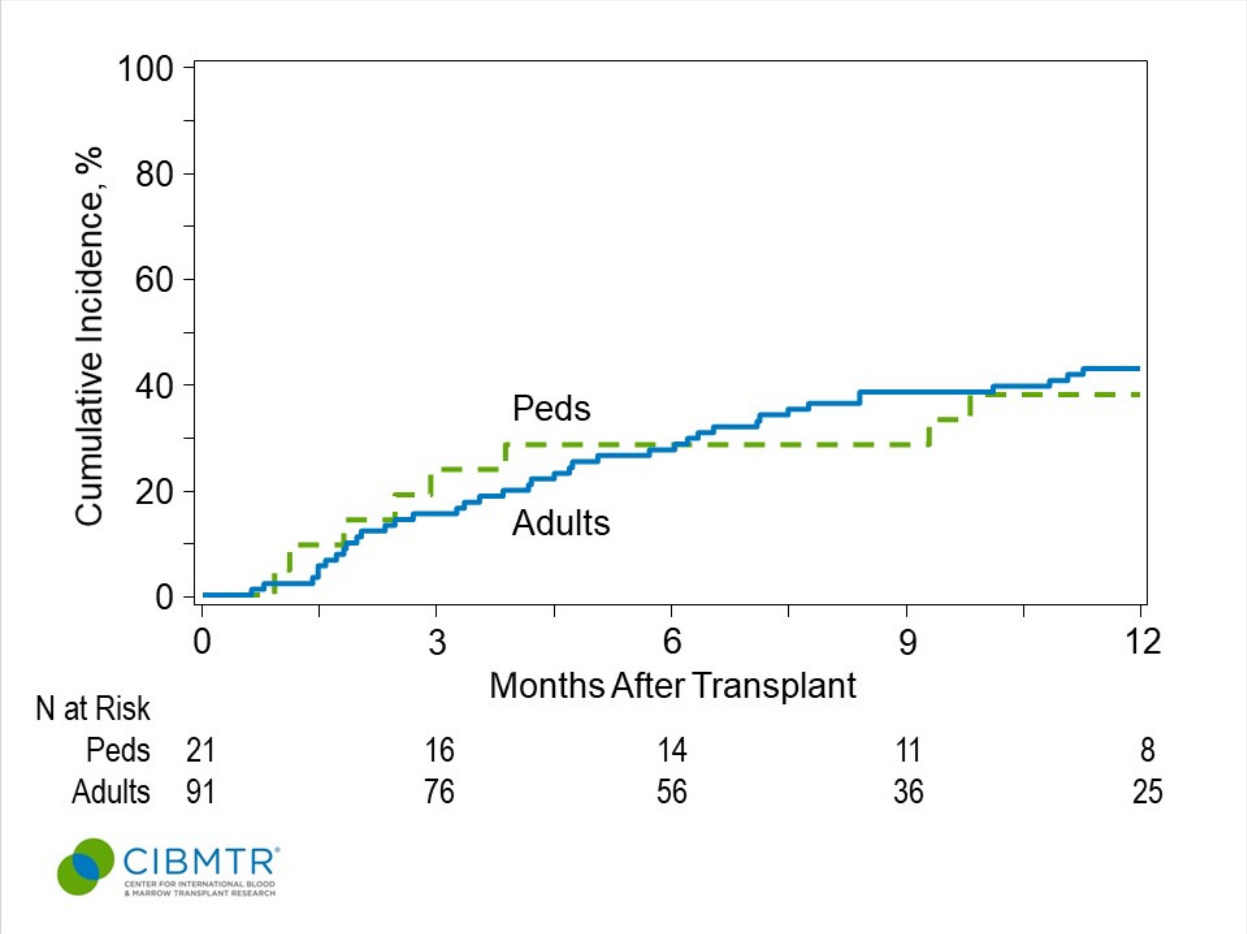
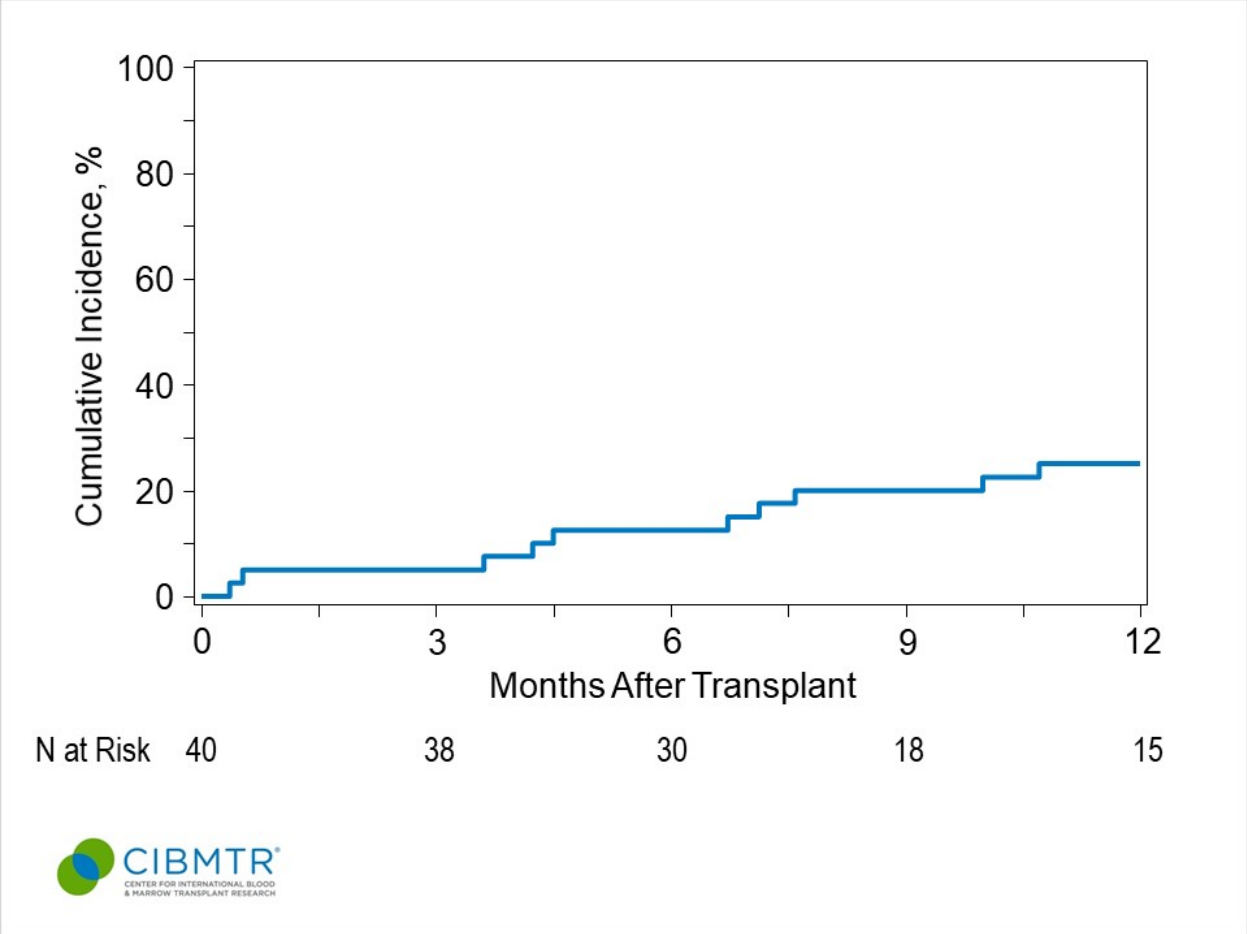


Table 36 Post-transplant overall mortality within 12 months in patients in first complete remission prior to HSCT

	Pediatric patients (< 18 y)	Adults (≥ 18 y)	All patients
No. patients in first complete remission prior to HSCT and with post-transplant follow-up	**6**	**40**	**46**
Post-transplant overall mortality (95% CI)			
6 months	NE	13 (4-25)%	11 (4-22)%
12 months	NE	NE	NE

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who have not yet completed a follow-up form are not included in the data and estimates shown in this table. Patients with a reported outcome event beyond 12 months post-transplant (or post-inotuzumab ozogamicin) are not shown in this table, as follow-up among survivors in the population is approximately 12 months post-transplant.
Outcomes are not evaluable (NE) if sample size is < 20.
Post-transplant overall mortality is time from HSCT to death from any cause. Patients are censored at the last date that the patient was known to be alive. There are no competing risks.

Figure 11 Post-transplant overall mortality within 12 months in adult patients in first complete remission prior to HSCT



16.3 Post-inotuzumab overall survival subgroups

Table 37 Overall survival within 12 months of first dose of inotuzumab ozogamicin in patients who had relapsed or refractory B-Cell ALL prior to HSCT

	Pediatric patients (< 18 y)	Adults (≥ 18 y)	All patients
No. patients with relapsed or refractory B-Cell ALL prior to HSCT, with post-transplant follow-up and CIBMTR Form 2541 and date of first dose of inotuzumab ozogamicin provided	**21**	**88**	**109**
Post-inotuzumab ozogamicin overall survival (95% CI)			
6 months	NE	92 (85-97)%	89 (82-94)%
12 months	NE	60 (48-71)%	63 (53-72)%
Number of deaths within 12 months	5	31	36
Primary cause of death, no. (%)			
Recurrence of B-cell ALL	2 (40)	13 (42)	15 (42)
GVHD	0	5 (16)	5 (14)
VOD/SOS	2 (40)	6 (19)	8 (22)
Interstitial pneumonitis	1 (20)	0	1 (3)
Infection	0	2 (6)	2 (6)
Septic shock	0	1 (3)	1 (3)
Hemorrhage	0	2 (6)	2 (6)
Organ failure	0	2 (6)	2 (6)
Time from first dose of inotuzumab ozogamicin to death, no. (%), months			
< 3	0	0	0
3-5	5	7 (23)	12 (33)
6-11	0	24 (77)	24 (67)
Median (95% CI)	5.65 (4.34 - 5.98)	8.02 (6.28 - 9.33)	6.98 (6.01-8.77)
Range	(4.34-5.98)	(3.22-11.73)	(3.22-11.73)
Mean	5.41	7.9	7.55
Standard deviation	0.63	2.41	2.41

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who have not yet completed a follow-up form are not included in the data and estimates shown in this table. Patients with a reported outcome event beyond 12 months post-transplant (or post-inotuzumab ozogamicin) are not shown in this table, as follow-up among survivors in the population is approximately 12 months post-transplant.
Outcomes are not evaluable (NE) if sample size is < 20.
Post-inotuzumab ozogamicin survival is time from first dose of inotuzumab ozogamicin to death from any cause. Patients are censored at the last date that the patient was known to be alive. There are no competing risks.

Figure 12 Post-inotuzumab ozogamicin overall survival in patients who had relapsed or refractory B-Cell ALL prior to HSCT

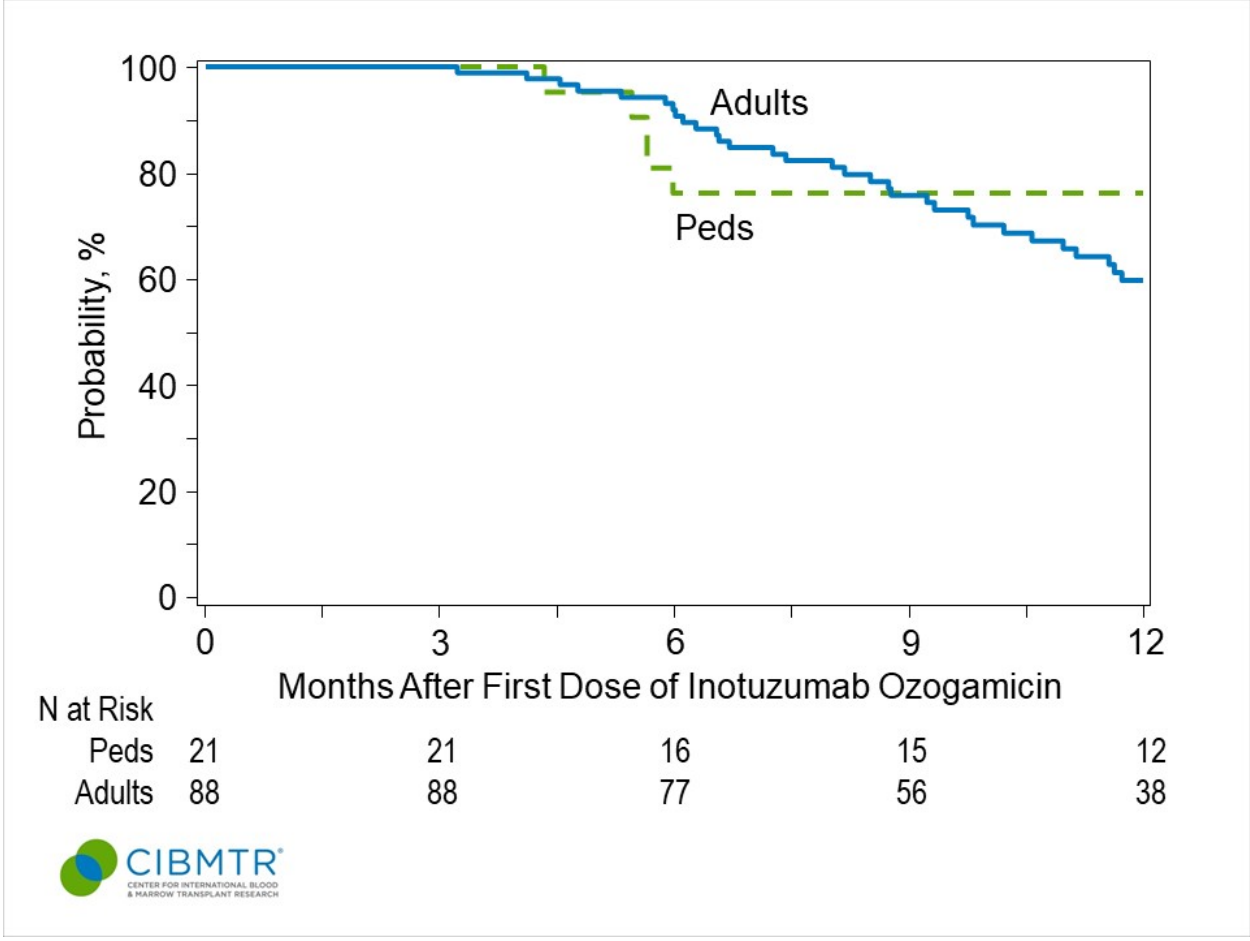
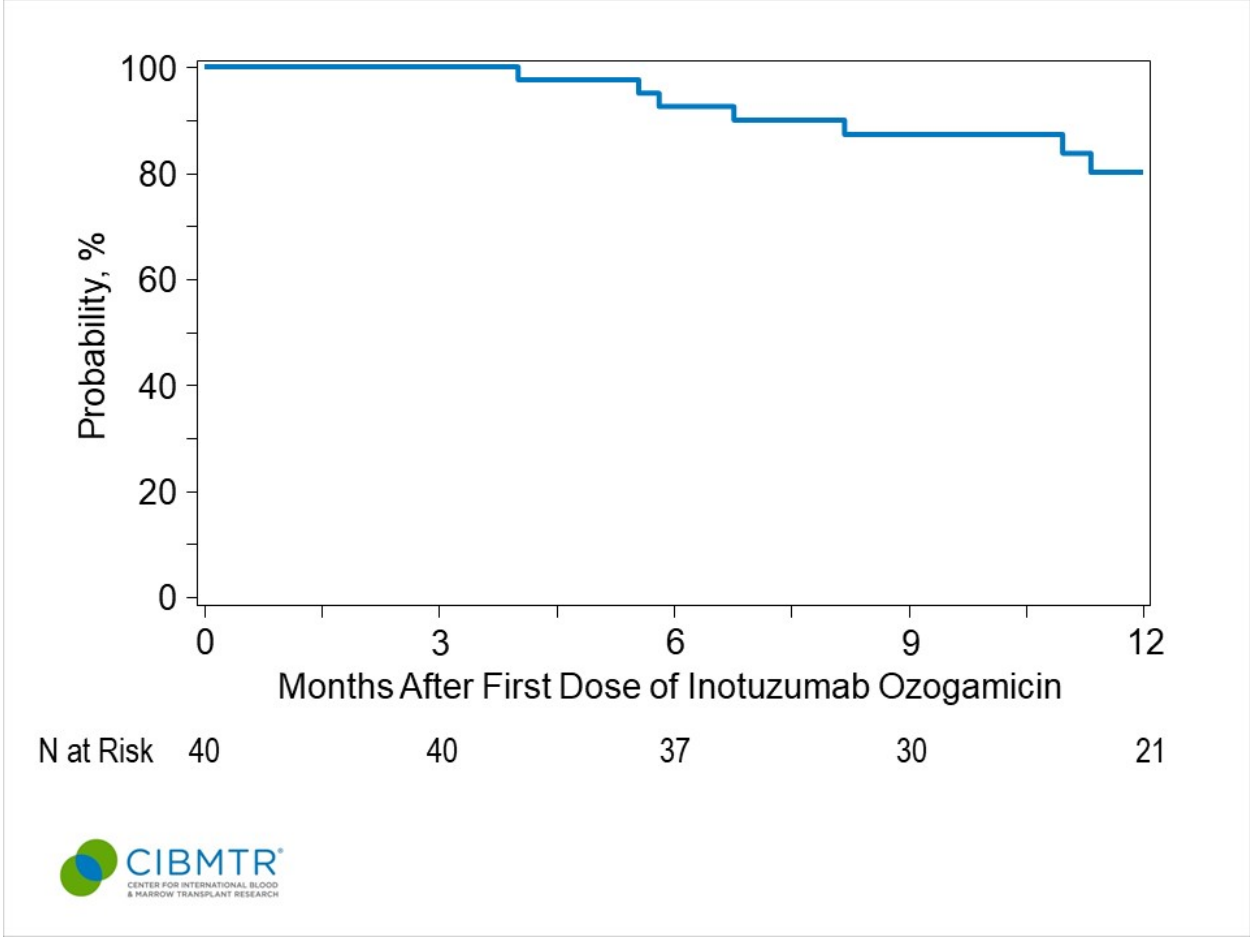


Table 38 Survival within 12 months of first dose of inotuzumab ozogamicin in patients in first complete remission prior to HSCT

	Pediatric patients (< 18 y)	Adults (≥ 18 y)	All patients
No. patients in first complete remission prior to HSCT, with post-transplant follow-up and CIBMTR Form 2541 and date of first dose of inotuzumab ozogamicin provided	**5**	**40**	**45**
Post-inotuzumab ozogamicin overall survival (95% CI)			
6 months	NE	93 (82-99)%	93 (84-99)%
12 months	NE	80 (65-92)%	79 (65-91)%
Number of deaths within 12 months	1	7	8
Primary cause of death, no. (%)			
Recurrence of B-cell ALL	0	3 (43)	3 (38)
GVHD	0	2 (29)	2 (25)
Infection	0	1 (14)	1 (13)
Septic shock	0	1 (14)	1 (13)
Thrombotic microangiopathy (TMA)	1	0	1 (13)
Time from first dose of inotuzumab ozogamicin to death, no. (%), months			
< 3	0	0	0
3-5	0	3 (43)	3 (38)
6-11	1	4 (57)	5 (63)
Median (95% CI)	10.91	6.77 (4.01 - 11.33)	7.47 (5.55-11.33)
Range	NE	(4.01-11.33)	(4.01-11.33)
Mean	10.91	7.52	7.94
Standard deviation	NE	2.79	2.84

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who have not yet completed a follow-up form are not included in the data and estimates shown in this table. Patients with a reported outcome event beyond 12 months post-transplant (or post-inotuzumab ozogamicin) are not shown in this table, as follow-up among survivors in the population is approximately 12 months post-transplant.
Outcomes are not evaluable (NE) if sample size is < 20.
Post-inotuzumab ozogamicin survival is time from first dose of inotuzumab ozogamicin to death from any cause. Patients are censored at the last date that the patient was known to be alive. There are no competing risks.

Figure 13 Post-inotuzumab ozogamicin overall survival in adult patients in first complete remission prior to HSCT



16.4 Transplant-related mortality subgroups

Table 39 Transplant-related mortality within 12 months in patients who had relapsed or refractory B-Cell ALL prior to HSCT

	Pediatric patients (< 18 y)	Adults (≥ 18 y)	All patients
No. patients with relapsed or refractory B-Cell ALL prior to HSCT and with post-transplant follow-up	**21**	**91**	**112**
Transplant-related mortality (95% CI)	NE	18 (11-27)%	17 (11-25)%
6 months	NE	23 (14-33)%	21 (14-30)%
12 months			
No. patients with TRM within 12 months	3	19	22
No. patients with competing risk (post-transplant relapse)	7	29	36
Primary cause of death, among patients with TRM, no. (%)			
GVHD	0	4 (21)	4 (18)
VOD/SOS	2 (67)	6 (32)	8 (36)
Interstitial pneumonitis	1 (33)	1 (5)	2 (9)
Infection	0	1 (5)	1 (5)
Septic shock	0	1 (5)	1 (5)
Hemorrhage	0	3 (16)	3 (14)
Organ failure	0	3 (16)	3 (14)
Time from transplant to TRM, no. (%), months			
< 3	3	13 (68)	16 (73)
3-5	0	3 (16)	3 (14)
6-11	0	3 (16)	3 (14)
Median (95% CI)	1.81 (0.92 - 2.92)	1.97 (1.58 - 3.84)	1.91 (1.58-3.35)
Range	(0.92-2.92)	(0.62-11.27)	(0.62-11.27)
Mean	1.88	3.18	3
Standard deviation	1	2.86	2.7

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who have not yet completed a follow-up form are not included in the data and estimates shown in this table. Patients with a reported outcome event beyond 12 months post-transplant (or post-inotuzumab ozogamicin) are not shown in this table, as follow-up among survivors in the population is approximately 12 months post-transplant.
Outcomes are not evaluable (NE) if sample size is < 20.
Transplant-related mortality (post-transplant non-relapse mortality) is time from HSCT to death within the first 28 days post-HSCT, or death from any cause without prior relapse/progression post-HSCT.

Figure 14 Transplant-related mortality within 12 months in patients who had relapsed or refractory B-Cell ALL prior to HSCT

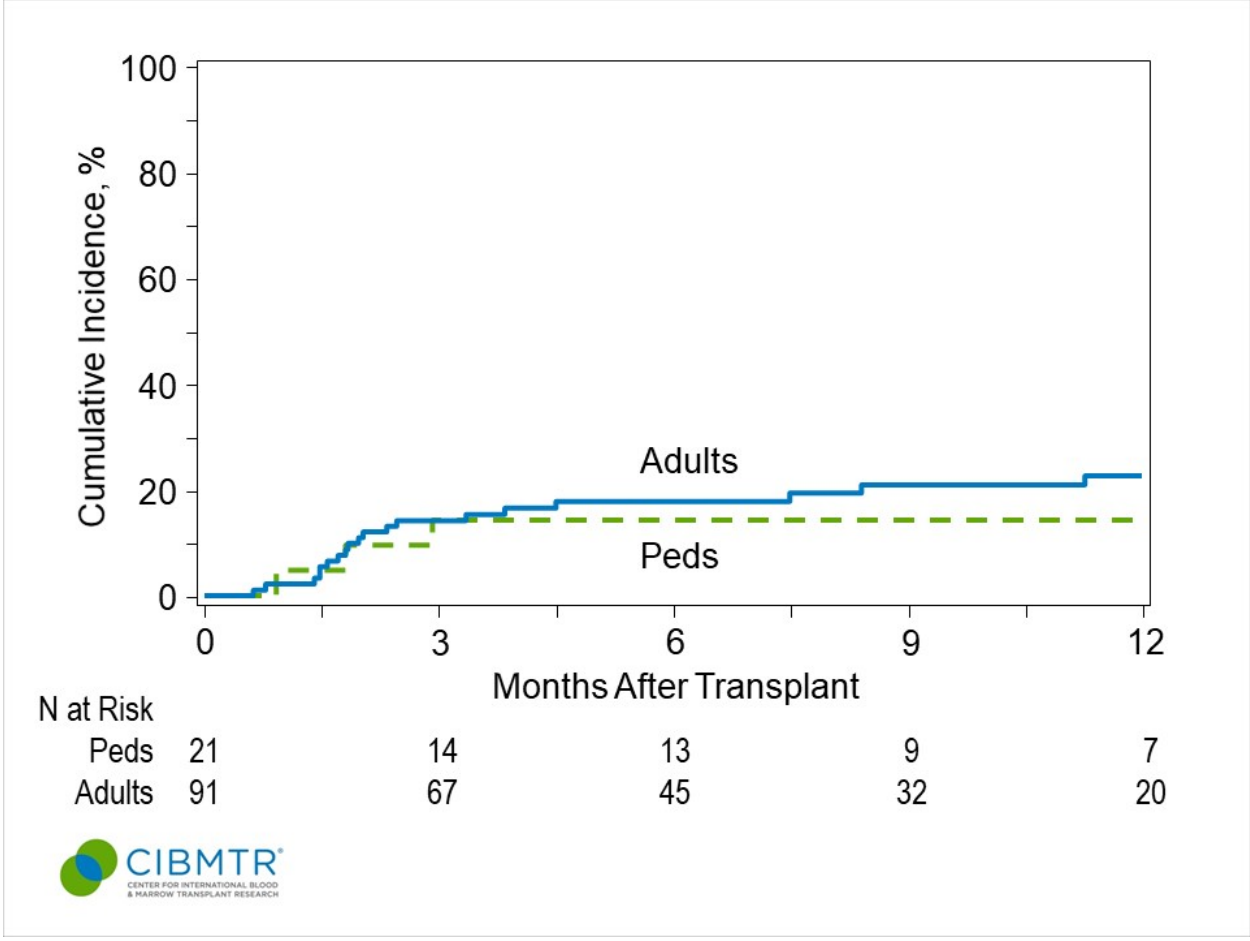
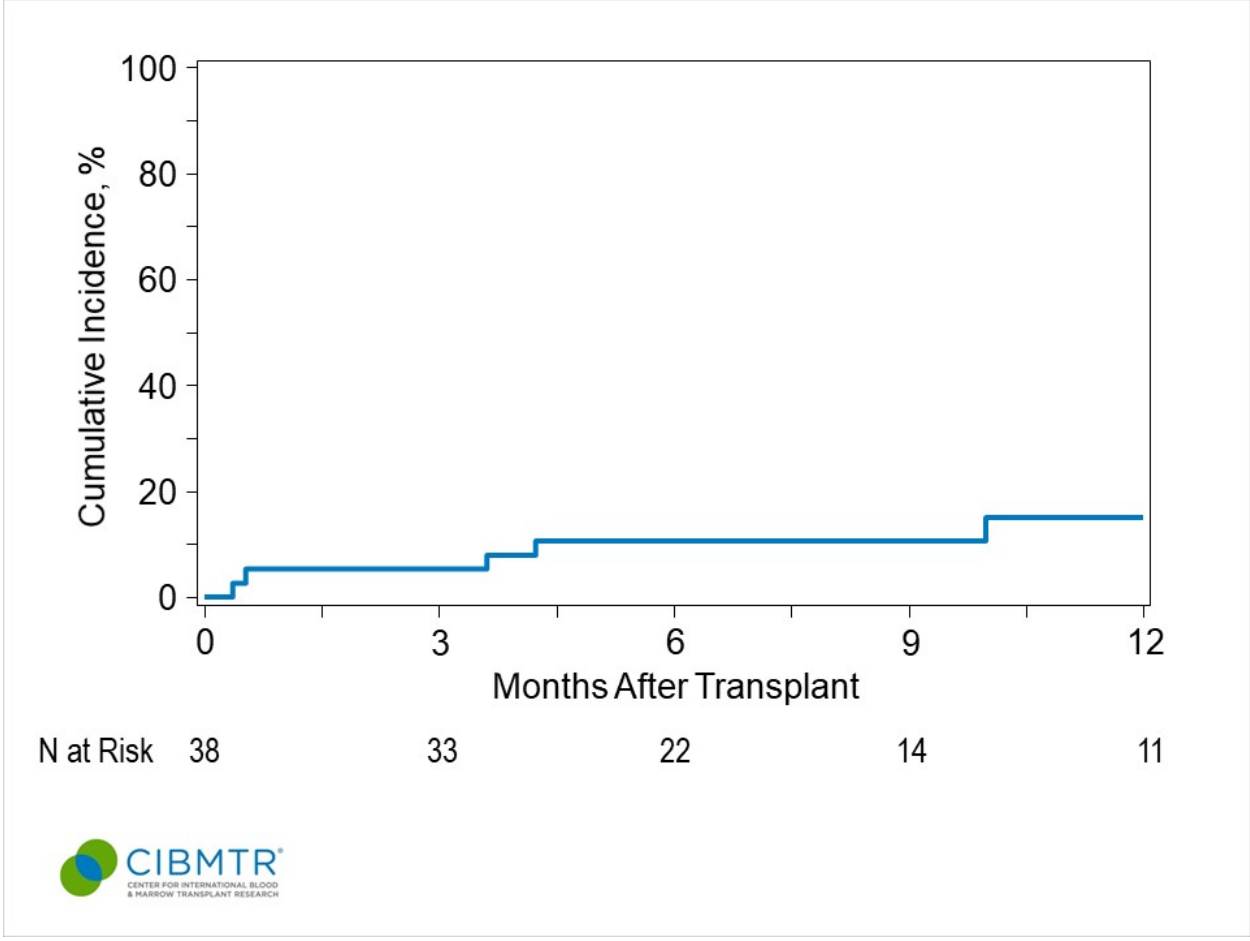


Table 40 Transplant-related mortality within 12 months in patients in first complete remission prior to HSCT

	Pediatric patients (< 18 y)	Adults (≥ 18 y)	All patients
No. patients with first complete remission prior to HSCT and with post-transplant follow-up	**6**	**40**	**46**
Transplant-related mortality (95% CI)			
6 months	NE	11 (3-22)%	9 (2-20)%
12 months	NE	NE	NE
No. patients with TRM within 12 months	1	5	6
No. patients with competing risk (post-transplant relapse)	2	11	13
Primary cause of death, among patients with TRM, no. (%)			
GVHD	0	3 (60)	3 (50)
Infection	0	1 (20)	1 (17)
Septic shock	0	1 (20)	1 (17)
Thrombotic microangiopathy (TMA)	1	0	1 (17)
Time from transplant to TRM, no. (%), months			
< 3	0	2 (40)	2 (33)
3-5	0	2 (40)	2 (33)
6-11	1	1 (20)	2 (33)
Median (95% CI)	8.05	3.61 (0.36 - 9.99)	3.93 (0.36-9.99)
Range	NE	(0.36-9.99)	(0.36-9.99)
Mean	8.05	3.75	4.46
Standard deviation	NE	3.91	3.91

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who have not yet completed a follow-up form are not included in the data and estimates shown in this table. Patients with a reported outcome event beyond 12 months post-transplant (or post-inotuzumab ozogamicin) are not shown in this table, as follow-up among survivors in the population is approximately 12 months post-transplant.
Outcomes are not evaluable (NE) if sample size is < 20.
Transplant-related mortality (post-transplant non-relapse mortality) is time from HSCT to death within the first 28 days post-HSCT, or death from any cause without prior relapse/progression post-HSCT.

Figure 15 Transplant-related mortality within 12 months in adult patients in first complete remission prior to HSCT



16.5 Non-transplant-related mortality subgroups

Table 41 Non-transplant-related mortality within 12 months in patients who had relapsed or refractory B-Cell ALL prior to HSCT

	Pediatric patients (< 18 y)	Adults (≥ 18 y)	All patients
No. patients with relapsed or refractory B-Cell ALL prior to HSCT and with post-transplant follow-up	**21**	**91**	**112**
Non-transplant-related mortality (95% CI)			
6 months	NE	11 (5-18)%	11 (6-18)%
12 months	NE	27 (18-37)%	27 (19-36)%
No. patients with NTRM within 12 months	5	20	25
No. patients with competing risk (transplant-related mortality)	3	19	22
Time from transplant to NTRM, no. (%), months			
< 3	2 (40)	1 (5)	3 (12)
3-5	1 (20)	8 (40)	9 (36)
6-11	2 (40)	11 (55)	13 (52)
Median (95% CI)	3.88 (1.12 - 9.82)	6.13 (4.7 - 7.13)	6.05 (4.21-7.13)
Range	(1.12-9.82)	(2.69-11.07)	(1.12-11.07)
Mean	5.32	6.28	6.09
Standard deviation	4	2.42	2.73

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who have not yet completed a follow-up form are not included in the data and estimates shown in this table. Patients with a reported outcome event beyond 12 months post-transplant (or post-inotuzumab ozogamicin) are not shown in this table, as follow-up among survivors in the population is approximately 12 months post-transplant.
Outcomes are not evaluable (NE) if sample size is < 20.
Non-transplant-related mortality is time from HSCT to death after the first 28 days post-HSCT from any cause after prior relapse/progression post-HSCT.

Figure 16 Non-transplant-related mortality within 12 months in patients who had relapsed or refractory B-Cell ALL prior to HSCT

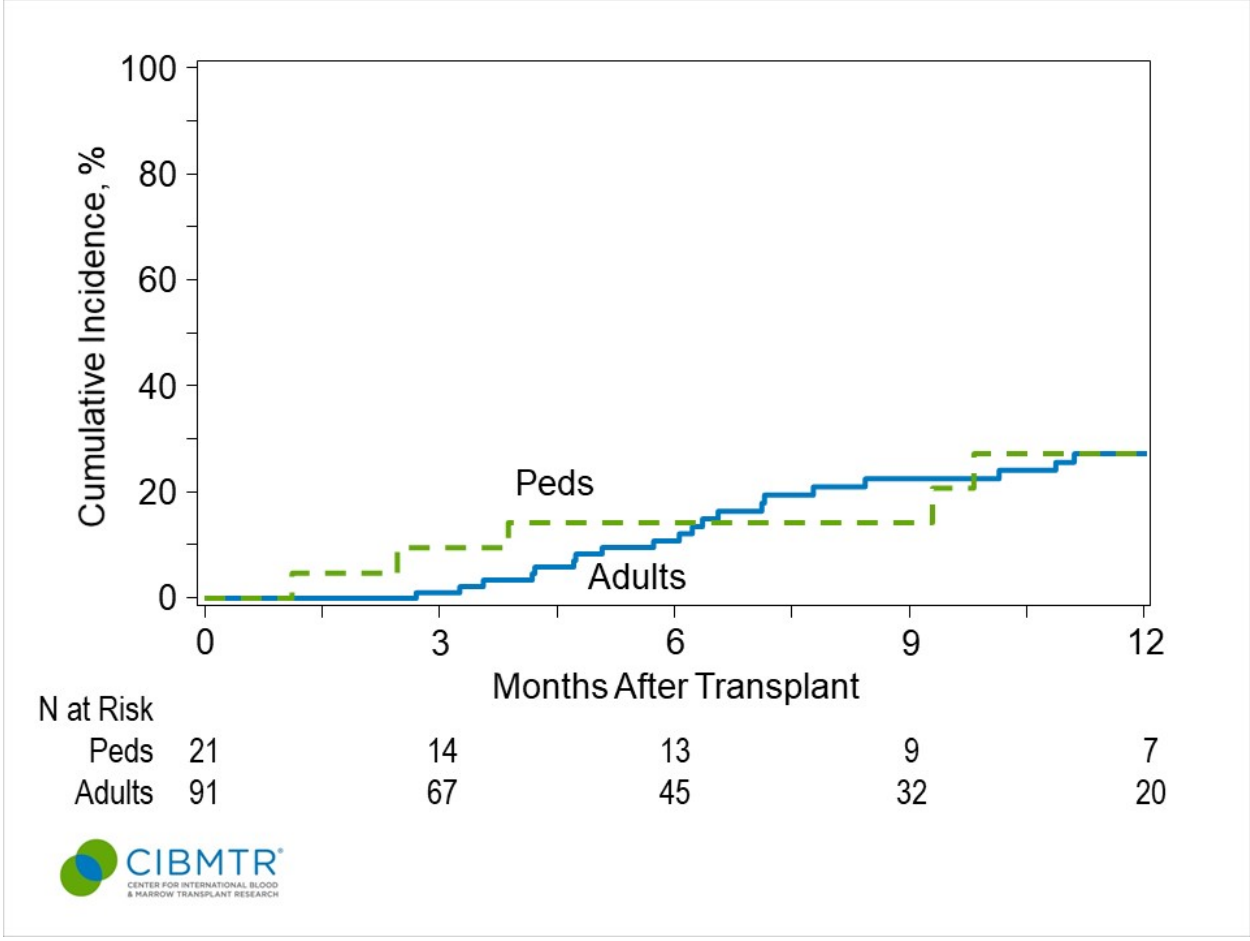
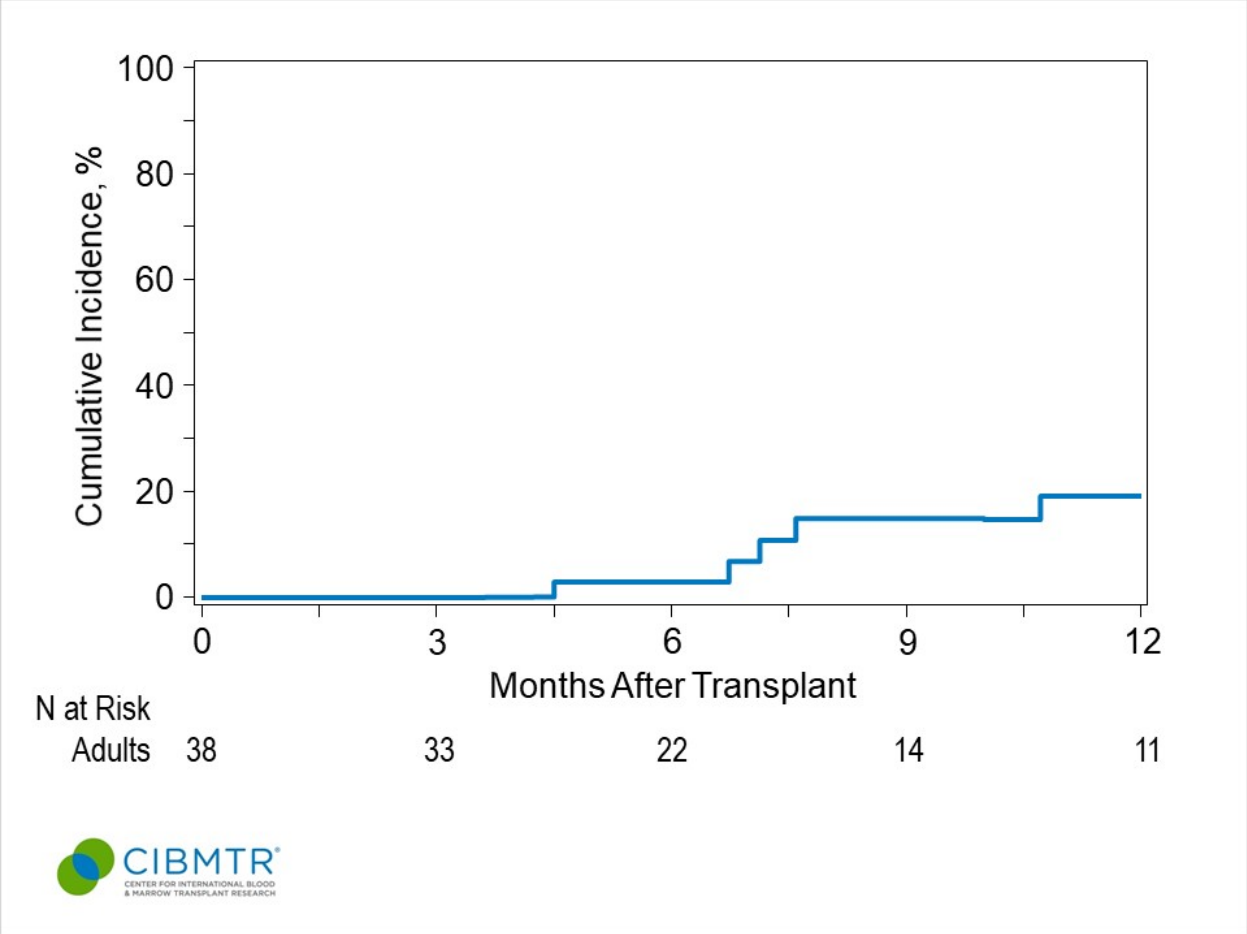


Table 42 Non-transplant-related mortality within 12 months in patients in first complete remission prior to HSCT

	Pediatric patients (< 18 y)	Adults (≥ 18 y)	All patients
No. patients in first complete remission prior to HSCT and with post-transplant follow-up	**6**	**40**	**46**
Non-transplant-related mortality (95% CI)			
6 months	NE	3 (0-12)%	2 (0-10)%
12 months	NE	NE	NE
No. patients with NTRM within 12 months	0	5	5
No. patients with competing risk (transplant-related mortality)	1	5	6
Time from transplant to NTRM, no. (%), months			
< 3	0	0	0
3-5	0	1 (20)	1 (20)
6-11	0	4 (80)	4 (80)
Median (95% CI)	NE	7.13 (4.5 - 10.71)	7.13 (4.5-10.71)
Range	NE	(4.5-10.71)	(4.5-10.71)
Mean	NE	7.33	7.33
Standard deviation	NE	2.23	2.23

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who have not yet completed a follow-up form are not included in the data and estimates shown in this table. Patients with a reported outcome event beyond 12 months post-transplant (or post-inotuzumab ozogamicin) are not shown in this table, as follow-up among survivors in the population is approximately 12 months post-transplant.
Outcomes are not evaluable (NE) if sample size is < 20.
Non-transplant-related mortality is time from HSCT to death after the first 28 days post-HSCT from any cause after prior relapse/progression post-HSCT.

Figure 17 Non-transplant-related mortality within 12 months in adults in first complete remission prior to HSCT



16.6 Post-transplant relapse subgroups

Table 43 Post-transplant relapse within 12 months in patients who had relapsed or refractory B-cell ALL prior to HSCT

	Pediatric patients (< 18 y)	Adults (≥ 18 y)	All patients
No. patients with relapsed or refractory B-Cell ALL prior to HSCT and with post-transplant follow-up	**21**	**91**	**112**
Post-transplant relapse (95% CI)			
6 months	NE	25 (17-35)%	25 (17-34)%
12 months	NE	37 (26-48)%	36 (27-47)%
No. patients with post-transplant relapse within 12 months	7	29	36
No. patients with competing risk (transplant-related mortality)	3	19	22
Time from transplant to post-transplant relapse, no. (%), months			
< 3	4 (57)	10 (34)	14 (39)
3-5	1 (14)	12 (41)	13 (36)
6-11	2 (29)	7 (24)	9 (25)
Median (95% CI)	2.2 (1.12 - 9.66)	3.45 (2.99 - 5.22)	5.88 (4.7-7.1)
Range	(1.12-9.66)	(1.61-11.89)	(1.12-11.89)
Mean	3.8	4.72	4.54
Standard deviation	3.14	3.16	3.13

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who have not yet completed a follow-up form are not included in the data and estimates shown in this table. Patients with a reported outcome event beyond 12 months post-transplant (or post-inotuzumab ozogamicin) are not shown in this table, as follow-up among survivors in the population is approximately 12 months post-transplant.
Outcomes are not evaluable (NE) if sample size is < 20.
Post-transplant relapse is time from HSCT to first relapse post-HSCT without death post-relapse, or with death after the first 28 days post-HSCT.

Figure 18 Post-transplant relapse within 12 months in patients who had relapsed or refractory B-cell ALL prior to HSCT

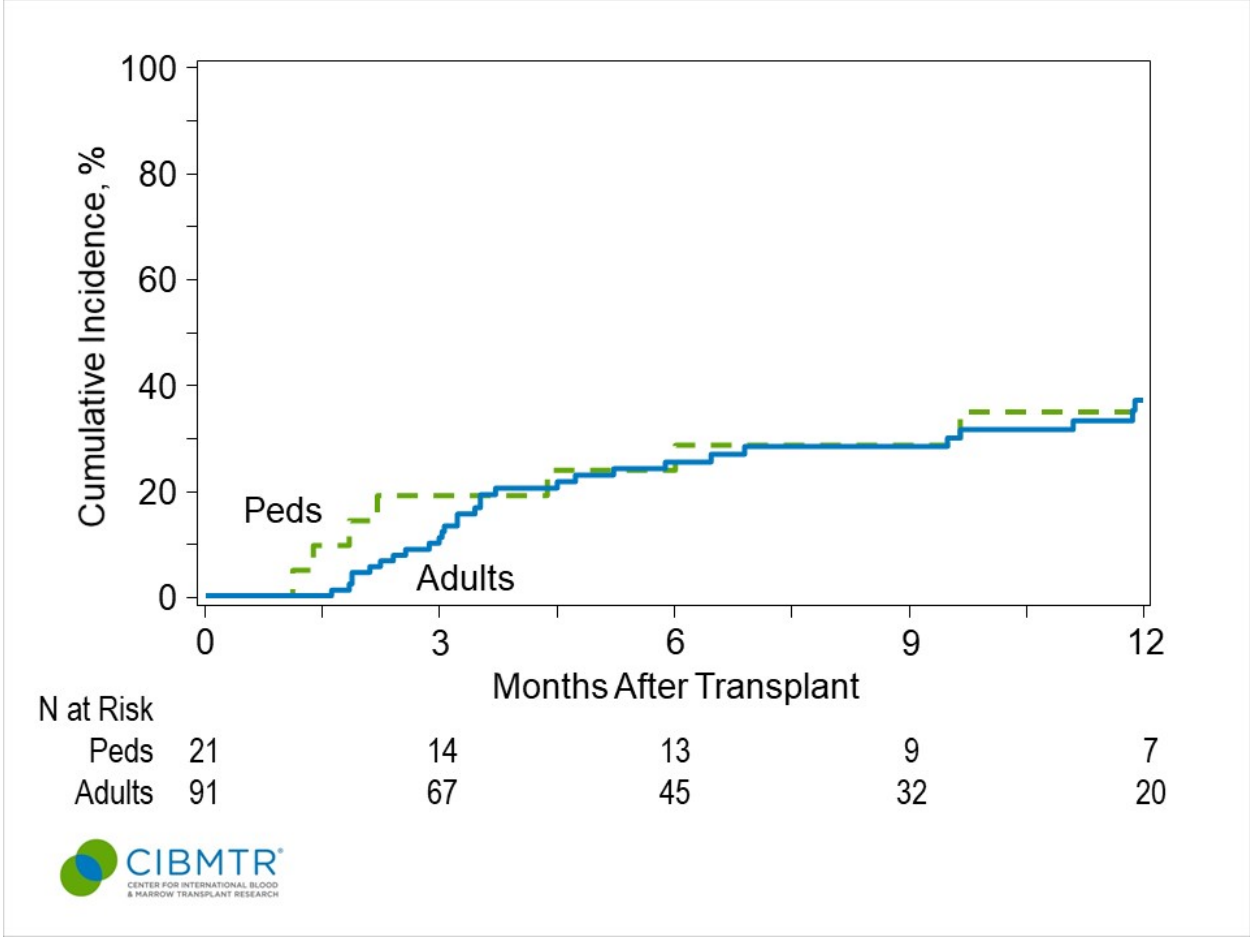
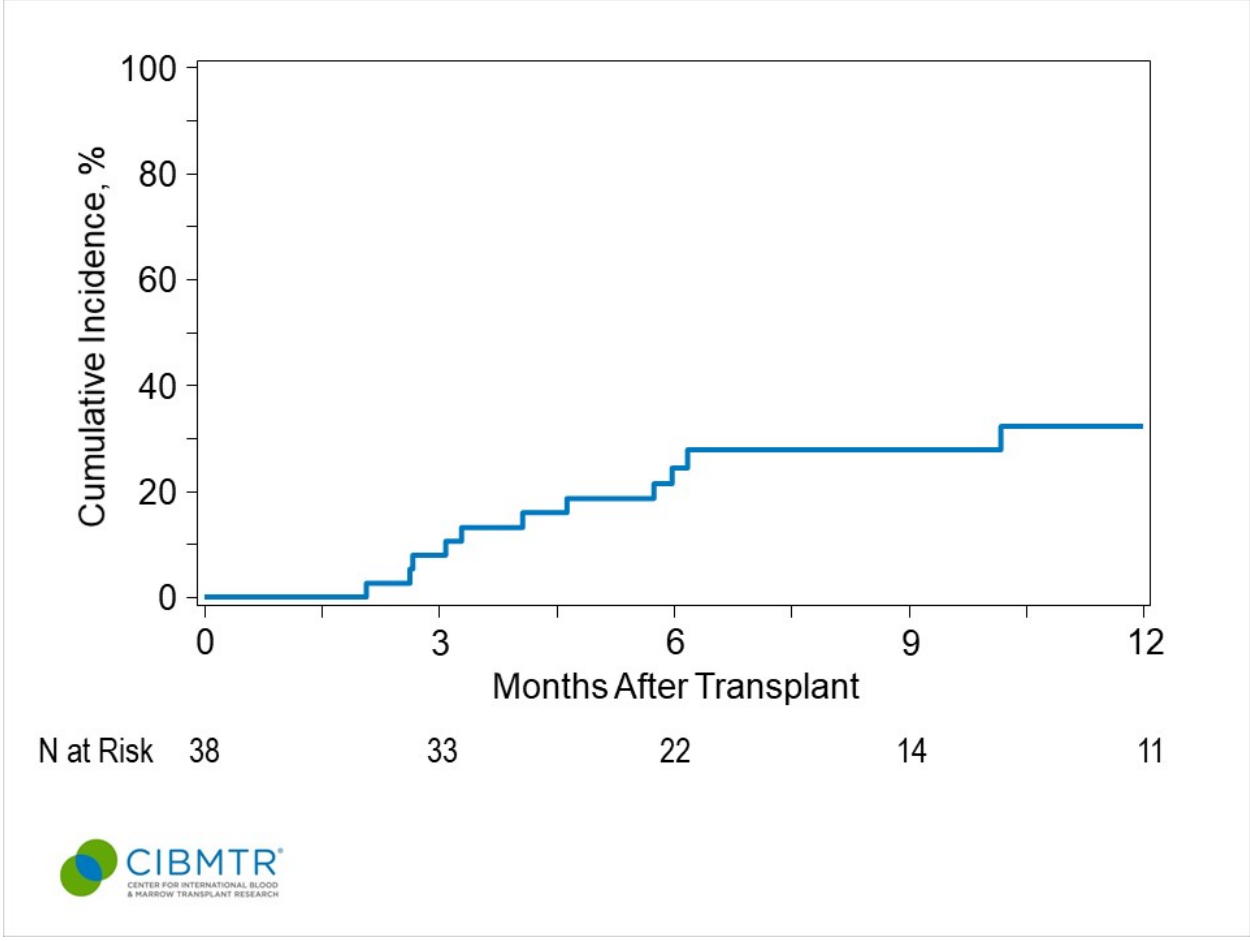


Table 44 Post-transplant relapse within 12 months in patients in first complete remission prior to HSCT

	Pediatric patients (< 18 y)	Adults (≥ 18 y)	All patients
No. patients in first complete remission prior to HSCT and with post-transplant follow-up	**6**	**40**	**46**
Post-transplant relapse (95% CI)			
6 months	NE	24 (12-40)%	26 (14-40)%
12 months	NE	NE	NE
No. patients with post-transplant relapse within 12 months	2	11	13
No. patients with competing risk (transplant-related mortality)	1	5	6
Time from transplant to post-transplant relapse, no. (%), months			
< 3	1 (50)	3 (27)	4 (31)
3-5	1 (50)	6 (55)	7 (54)
6-11	0	2 (18)	2 (15)
Median (95% CI)	NE	4.07 (2.66 - 6.18)	6.74 (3.48-10.71)
Range	(1.97-5.26)	(2.07-10.18)	(1.97-10.18)
Mean	3.61	4.59	4.44
Standard deviation	2.32	2.35	2.28

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who have not yet completed a follow-up form are not included in the data and estimates shown in this table. Patients with a reported outcome event beyond 12 months post-transplant (or post-inotuzumab ozogamicin) are not shown in this table, as follow-up among survivors in the population is approximately 12 months post-transplant.
Outcomes are not evaluable (NE) if sample size is < 20.
Post-transplant relapse is time from HSCT to first relapse post-HSCT without death post-relapse, or with death after the first 28 days post-HSCT.

Figure 19 Post-transplant relapse within 12 months in adults in first complete remission prior to HSCT



16.7 100-Day post-HSCT adverse events subgroups

Table 45 100-Day post-HSCT adverse events of interest in patients with B-Cell ALL who received inotuzumab ozogamicin and had relapsed or refractory B-Cell ALL prior to HSCT

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
Number of patients with relapsed or refractory B-Cell ALL prior to HSCT and with post-transplant follow-up	**21**	**91**	**112**
Viral infection, up to day 100			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Yes	8 (38)	42 (46)	50 (45)
No	12 (57)	45 (49)	57 (51)
Not reported	1 (5)	2 (2)	3 (3)
Bacterial infection, up to day 100			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Yes	9 (43)	45 (49)	54 (48)
No	11 (52)	40 (44)	51 (46)
Not reported	1 (4)	4 (4)	5 (5)
Fungal infection, up to day 100			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Yes	2 (10)	10 (11)	12 (11)
No	18 (86)	78 (86)	96 (86)
Not reported	1 (5)	1 (1)	2 (2)
SIRS development, up to day 100			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Yes	2 (10)	5 (6)	7 (6)
No	19 (90)	84 (92)	103 (92)
Septic shock, up to day 100			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Yes	1 (5)	10 (11)	11 (10)
No	20 (95)	79 (87)	99 (88)
Maximum grade of acute GVHD, up to day 100[a]			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
None	12 (57)	42 (46)	54 (48)
I	2 (10)	9 (10)	11 (10)
II	3 (14)	22 (24)	25 (22)
III	2 (10)	8 (9)	10 (9)
IV	2 (10)	7 (8)	9 (8)
Not reported	0	1 (1)	1 (1)
Time from HSCT to date of maximum acute GVHD, months			
Number evaluable	9	46	55
Median	0.9	1.3	1.2
Range	(0.6-1.4)	(0.6-3.2)	(0.6-3.2)
Mean	0.9	1.5	1.4
Standard deviation	0.3	0.6	0.6

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
Number of patients with relapsed or refractory B-Cell ALL prior to HSCT and with post-transplant follow-up	**21**	**91**	**112**
Chronic GVHD, up to 1 year post-transplant			
Yes	0	18 (20)	18 (16)
No	21	70 (77)	91 (81)
Not reported	0	3 (3)	3 (3)
Time from HSCT to chronic GVHD, months			
Number evaluable	0	18	18
Median	0	6.1	6.1
Range	0	(2-13.9)	(2-13.9)
Mean	0	6.5	6.5
Standard deviation	0	3.4	3.4
VOD/SOS within 100 days post-transplant			
Yes	6 (29)	16 (18)	22 (20)
No	15 (71)	75 (82)	90 (80)
Time from HSCT to VOD/SOS, months			
Number evaluable	6	16	22
Median	0.4	0.4	0.4
Range	(0.2-0.8)	(0.2-2.6)	(0.2-2.6)
Mean	0.5	0.7	0.6
Standard deviation	0.3	0.7	0.6
Secondary malignancy			
Yes [b]	0	1 (1)	1 (1)
No	20 (95)	89 (98)	109 (97)
Not reported	1 (5)	1 (1)	2 (2)
Time from HSCT to secondary malignancy, months			
Number evaluable	0	1	1
Median	NE	4	4
Range	NE	NE	NE
Mean	NE	4	4
Standard deviation	NE	NE	NE
Pulmonary AEs within 100 days post-transplant			
IPN / Idiopathic pneumonia syndrome			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Yes	3 (14)	4 (4)	7 (6)
No	18 (86)	83 (91)	101 (90)
Not reported	0	2 (2)	2 (2)
Bronchiolitis obliterans			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Yes	0	1 (1)	1 (1)
No	21	88 (97)	109 (97)
COP/BOOP			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Yes	0	0	0
No	21	89 (98)	110 (98)

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
Number of patients with relapsed or refractory B-Cell ALL prior to HSCT and with post-transplant follow-up	**21**	**91**	**112**
Diffuse alveolar hemorrhage			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Yes	0	2 (2)	2 (2)
No	21	87 (96)	108 (96)
Cardiovascular AEs within 100 days post-transplant			
Arrhythmia			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Yes	0	0	0
No	21	82 (90)	103 (92)
Not reported	0	7 (8)	7 (6)
Congestive heart failure			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Yes	0	1 (1)	1 (1)
No	21	88 (97)	109 (97)
Coronary artery disease			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Yes	0	0	0
No	21	89 (98)	110 (98)
Myocardial infarction or unstable angina			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Yes	0	1 (1)	1 (1)
No	21	88 (97)	109 (97)
Hypertension (HTN) requiring therapy			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Yes	1 (5)	6 (7)	7 (6)
No	20 (95)	82 (90)	102 (91)
Not reported	0	1 (1)	1 (1)
Thrombotic microangiopathy (TMA)			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Yes	0	2 (2)	2 (2)
No	21	87 (96)	108 (96)
Renal AEs within 100 days post-transplant			
Acute renal failure requiring dialysis			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Yes	2 (10)	11 (12)	13 (12)
No	19 (90)	78 (86)	97 (87)
Musculoskeletal AEs within 100 days post-transplant			
Avascular necrosis			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Yes	0	1 (1)	1 (1)
No	21	88 (97)	109 (97)

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
Number of patients with relapsed or refractory B-Cell ALL prior to HSCT and with post-transplant follow-up	**21**	**91**	**112**
Endocrine dysfunction within 100 days post-transplant			
Diabetes or hyperglycemia requiring chronic treatment			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Yes	0	4 (4)	4 (4)
No	21	85 (93)	106 (95)
Growth hormone deficiency or short stature			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Yes	0	0	0
No	21	89 (98)	110 (98)
Hypothyroidism requiring replacement therapy			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Yes	0	0	0
No	21	89 (98)	110 (98)
Pancreatitis			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Yes	0	0	0
No	21	89 (98)	110 (98)
Depression requiring therapy			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Yes	0	1 (1)	1 (1)
No	21	87 (96)	108 (96)
Not reported	0	1 (1)	1 (1)
Anxiety requiring therapy			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Yes	1 (5)	1 (1)	2 (2)
No	20 (95)	86 (95)	106 (95)
Not reported	0	2 (2)	2 (2)
CNS hemorrhage and stroke			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Yes	1 (5)	2 (2)	3 (3)
No	20 (95)	87 (96)	107 (96)
PTSD requiring therapy			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Yes	0	0	0
No	21	89 (98)	110 (98)

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who have not yet completed a follow-up form are not included in the data and estimates shown in this table.
Outcomes are not evaluable (NE) if sample size is < 20.
All events were evaluated up to 100 days post-transplant unless noted otherwise.
[a] Acute GVHD grading follows the Consensus criteria (Przepiorka D, Weisdorf D, Martin P, et al. [1995] 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant 15:825–828.) Acute GVHD was evaluated up to 100 days post-transplant.
[b] Secondary malignancy reported was squamous cell cancer of the skin.

Table 46 100-Day post-HSCT adverse events of interest in patients with B-Cell ALL who received inotuzumab ozogamicin and were in first complete remission prior to HSCT

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
Number of patients in first complete remission prior to HSCT and with post-transplant follow-up	**6**	**40**	**46**
Viral infection, up to day 100			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Yes	1 (17)	13 (33)	14 (30)
No	4 (67)	27 (68)	31 (67)
Bacterial infection, up to day 100			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Yes	1 (17)	18 (45)	19 (41)
No	4 (67)	22 (55)	26 (57)
Fungal infection, up to day 100			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Yes	0	4 (10)	4 (9)
No	5 (83)	36 (90)	41 (89)
SIRS development, up to day 100			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Yes	1 (17)	0	1 (2)
No	4 (67)	40	44 (96)
Septic shock, up to day 100			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Yes	2 (33)	5 (13)	7 (15)
No	3 (50)	35 (88)	38 (83)
Maximum grade of acute GVHD, up to day 100[a]			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
None	2 (33)	21 (53)	23 (50)
I	1 (17)	3 (8)	4 (9)
II	1 (17)	11 (28)	12 (26)
III	0	2 (5)	2 (4)
IV	1 (17)	3 (8)	4 (9)
Time from HSCT to date of maximum acute GVHD, months			
Number evaluable	3	19	22
Median	1.4	1.1	1.2
Range	(0.4-2.9)	(0.5-3)	(0.4-3)
Mean	1.5	1.3	1.3
Standard deviation	1.3	0.6	0.7

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
Number of patients in first complete remission prior to HSCT and with post-transplant follow-up	**6**	**40**	**46**
Chronic GVHD, up to 1 year post-transplant			
Yes	2 (33)	10 (25)	12 (26)
No	4 (67)	30 (75)	34 (74)
Time from HSCT to chronic GVHD, months			
Number evaluable	2	10	12
Median	NE	8.2	8.2
Range	(3.3-12.4)	(2.2-12.9)	(2.2-12.9)
Mean	7.9	8.3	8.2
Standard deviation	6.5	3.6	3.8
VOD/SOS within 100 days post-transplant			
Yes	1 (17)	1 (3)	2 (4)
No	5 (83)	39 (98)	44 (96)
Time from HSCT to VOD/SOS, months			
Number evaluable	1	1	2
Median	0.3	0.6	NE
Range	NE	NE	(0.3-0.6)
Mean	0.3	0.6	0.5
Standard deviation	NE	NE	0.2
Secondary malignancy			
Yes [b]	0	1 (3)	1 (2)
No	6	38 (95)	44 (96)
Not reported	0	1 (3)	1 (2)
Time from HSCT to secondary malignancy, months			
Number evaluable	0	1	1
Median	NE	2	2
Range	NE	NE	NE
Mean	NE	2	2
Standard deviation	NE	NE	NE
Pulmonary AEs within 100 days post-transplant			
IPN / Idiopathic pneumonia syndrome			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Yes	0	4 (10)	4 (9)
No	5 (83)	36 (90)	41 (89)
Bronchiolitis obliterans			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Yes	0	0	0
No	5 (83)	40	45 (98)
COP/BOOP			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Yes	0	0	0
No	5 (83)	40	45 (98)

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
Number of patients in first complete remission prior to HSCT and with post-transplant follow-up	**6**	**40**	**46**
Diffuse alveolar hemorrhage			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Yes	0	0	0
No	5 (83)	40	45 (98)
Cardiovascular AEs within 100 days post-transplant			
Arrhythmia			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Yes	0	0	0
No	4 (67)	40	44 (96)
Not reported	1 (17)	0	1 (2)
Congestive heart failure			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Yes	0	0	0
No	5 (83)	40	45 (98)
Coronary artery disease			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Yes	0	0	0
No	5 (83)	40	45 (98)
Myocardial infarction or unstable angina			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Yes	0	0	0
No	5 (83)	40	45 (98)
Hypertension (HTN) requiring therapy			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Yes	4 (67)	3 (8)	7 (15)
No	1 (17)	37 (93)	38 (83)
Thrombotic microangiopathy (TMA)			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Yes	1 (17)	1 (3)	2 (4)
No	4 (67)	39 (98)	43 (93)
Renal AEs within 100 days post-transplant			
Acute renal failure requiring dialysis			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Yes	1 (17)	1 (3)	2 (4)
No	4 (67)	39 (98)	43 (93)
Musculoskeletal AEs within 100 days post-transplant			
Avascular necrosis			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Yes	0	0	0
No	5 (83)	40	45 (98)

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
Number of patients in first complete remission prior to HSCT and with post-transplant follow-up	**6**	**40**	**46**
Endocrine dysfunction within 100 days post-transplant			
Diabetes or hyperglycemia requiring chronic treatment			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Yes	1 (17)	1 (3)	2 (4)
No	4 (67)	39 (98)	43 (93)
Growth hormone deficiency or short stature			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Yes	0	0	0
No	5 (83)	40	45 (98)
Hypothyroidism requiring replacement therapy			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Yes	0	0	0
No	5 (83)	40	45 (98)
Pancreatitis			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Yes	0	0	0
No	5 (83)	40	45 (98)
Depression requiring therapy			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Yes	1 (17)	0	1 (2)
No	4 (67)	40	44 (96)
Anxiety requiring therapy			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Yes	1 (17)	0	1 (2)
No	4 (67)	40	44 (96)
CNS hemorrhage and stroke			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Yes	0	0	0
No	5 (83)	40	45 (98)
PTSD requiring therapy			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Yes	0	0	0
No	5 (83)	40	45 (98)

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who have not yet completed a follow-up form are not included in the data and estimates shown in this table.
Outcomes are not evaluable (NE) if sample size is < 20.
All events were evaluated up to 100 days post-transplant unless noted otherwise.
[a] Acute GVHD grading follows the Consensus criteria (Przepiorka D, Weisdorf D, Martin P, et al. [1995] 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant 15:825–828.) Acute GVHD was evaluated up to 100 days post-transplant.
[b] Secondary malignancies reported were acute myeloid leukemia and other acute leukemia.

16.8 Veno-occlusive disease subgroups

Table 47 Post-transplant VOD/SOS within 100 days in patients who had relapsed or refractory B-cell ALL prior to HSCT

	Pediatric patients (< 18 y)	Adults (≥ 18 y)	All patients
No. patients with relapsed or refractory B-Cell ALL and with post-transplant follow-up	**21**	**91**	**112**
Veno-occlusive disease, (95% CI)			
100 days	NE	18 (10-26)%	20 (13-28)%
Number of patients with veno-occlusive disease	6	16	22
Number of patients with competing risk (death without VOD)	4	29	33
Time from transplant to veno-occlusive disease, no. (%), months			
< 3	6	16	22
Median (95% CI)	0.44 (0.23 - 0.82)	0.38 (0.3 - 0.95)	0.38 (0.30-0.82)
Range	(0.23-0.82)	(0.16-2.6)	(0.16-2.6)
Mean	0.5	0.66	0.62
Standard deviation	0.28	0.66	0.58

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who have not yet completed a follow-up form are not included in the data and estimates shown in this table.
Outcomes are not evaluable (NE) if sample size is < 20.
VOD is the occurrence of veno-occlusive disease/sinusoidal obstruction syndrome reported on the CIBMTR Form 2100. VOD is only considered within the first 100 days post-HSCT. Death without VOD is the competing risk.

Figure 20 Post-transplant VOD/SOS within 100 days in patients who had relapsed or refractory B-Cell ALL prior to HSCT

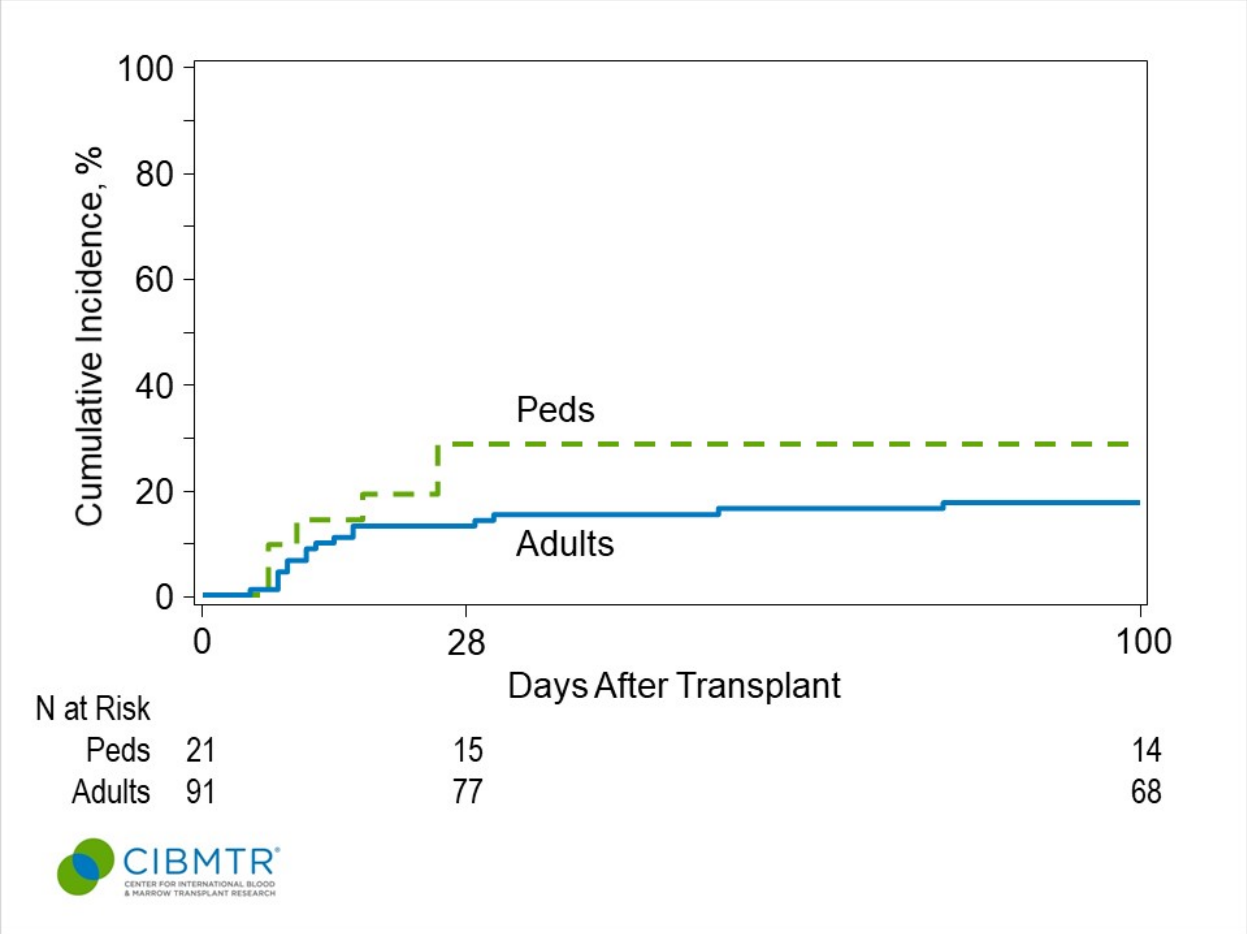


Table 48 Post-transplant VOD/SOS within 100 days, in patients who were in first complete remission prior to HSCT

	Pediatric patients (< 18 y)	Adults (≥ 18 y)	All patients
No. patients in first complete remission prior to HSCT and with post-transplant follow-up	**6**	**40**	**46**
Veno-occlusive disease, (95% CI)			
100 days	NE	3 (0-10)%	4 (0-12)%
Number of patients with veno-occlusive disease	1	1	2
Number of patients with competing risk (death without VOD)	1	8	9
Time from transplant to veno-occlusive disease, no. (%), months			
< 3	1	1	2
Median	0.33	0.59	NE
Range	NE	NE	(0.33-0.59)
Mean	0.33	0.59	0.46
Standard deviation	NE	NE	0.19

Notes: The CIBMTR collects follow-up data at specific time points post-HSCT, specifically at 100 days, 6 months and annually until year 6 post-HSCT and biennially thereafter until death. Patients who have not yet completed a follow-up form are not included in the data and estimates shown in this table.
Outcomes are not evaluable (NE) if sample size is < 20.
VOD is the occurrence of veno-occlusive disease/sinusoidal obstruction syndrome reported on the CIBMTR Form 2100. VOD is only considered within the first 100 days post-HSCT. Death without VOD is the competing risk.

Figure 21 Post-transplant VOD/SOS within 100 days in adults in first complete remission prior to HSCT

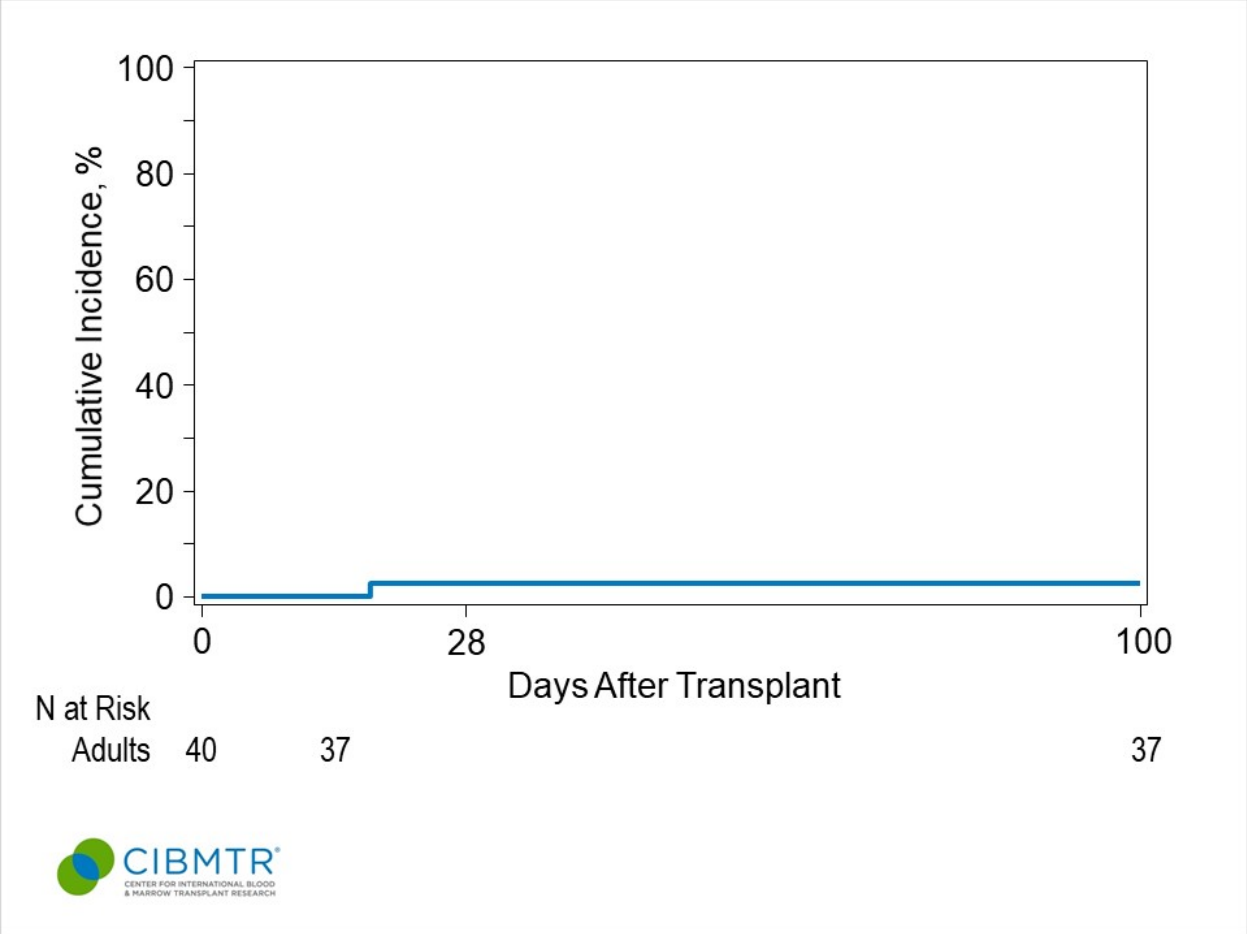


Table 49 VOD characteristics within 100 days post-transplant, with and without and defibrotide as liver toxicity prophylaxis, in patients who had relapsed or refractory B-cell ALL prior to HSCT

	Pediatric patients (< 18 years) No. (%)		Adult patients (≥ 18 years) No. (%)		All patients No. (%)	
	Defibrotide	No defibrotide	Defibrotide	No defibrotide	Defibrotide	No defibrotide
Number of patients with relapsed or refractory B-Cell ALL prior to HSCT and post-transplant follow-up	**10**	**11**	**9**	**82**	**19**	**93**
Number of patients with post-transplant VOD/SOS	2	4	5	11	7	15
Time to post-transplant VOD/SOS, days						
Median	NE	16	16	11	16	11
Range	(10-17)	(7-25)	(8-31)	(5-79)	(8-31)	(5-79)
Mean	14	16	19	21	17	19
Standard deviation	5	10	10	24	9	21
Grade of VOD/SOS						
N/A; no VOD/SOS	8 (80)	7 (64)	4 (44)	71 (87)	12 (63)	78 (84)
Mild VOD/SOS (no other organs involved within 60 days of VOD/SOS diagnosis)	2 (20)	1 (9)	3 (33)	3 (4)	5 (26)	4 (4)
Severe VOD/SOS (multiple organ dysfunction within 60 days of VOD/SOS diagnosis)	0	3 (27)	2 (22)	8 (10)	2 (11)	11 (12)
Liver toxicity prophylaxis						
None (or no additional)	0	5 (45)	1 (11)	6 (7)	1 (5)	11 (12)
Ursodiol	0	3 (27)	0	72 (88)	0	75 (81)
Ursodiol + defibrotide	5 (50)	0	7 (78)	0	12 (63)	0
Ursodiol + defibrotide + others	5 (50)	0	1 (11)	0	6 (32)	0
Ursodiol + others	0	3 (27)	0	3 (4)	0	6 (6)
Not reported	0	0	0	1 (1)	0	1 (1)

	Pediatric patients (< 18 years) No. (%)		Adult patients (≥ 18 years) No. (%)		All patients No. (%)	
	Defibrotide	**No defibrotide**	**Defibrotide**	**No defibrotide**	**Defibrotide**	**No defibrotide**
Number of patients with relapsed or refractory B-Cell ALL prior to HSCT and post-transplant follow-up	**10**	**11**	**9**	**82**	**19**	**93**
Treatment for VOD/SOS						
N/A; no VOD/SOS	8 (80)	7 (64)	4 (44)	71 (87)	12 (63)	78 (84)
None	0	0	1 (11)	2 (2)	1 (5)	2 (2)
Defibrotide	0	1 (9)	1 (11)	1 (1)	1 (5)	2 (2)
Defibrotide + ursodiol	1 (10)	0	0	0	1 (5)	0
Defibrotide + ursodiol + diuretics	0	1 (9)	0	3 (4)	0	4 (4)
Diuretics	0	0	0	1 (1)	0	1 (1)
Defibrotide + ursodiol + methylprednisolone + diuretics + heparin	0	1 (9)	0	1 (1)	0	2 (2)
Defibrotide + ursodiol + methylprednisolone + N-acetylcysteine + rifaximin/lactulose	0	0	0	1 (1)	0	1 (1)
Defibrotide + ursodiol + methylprednisolone + diuretics	0	0	0	1 (1)	0	1 (1)
Defibrotide + diuretics	0	0	0	1 (1)	0	1 (1)
Defibrotide + ursodiol + methylprednisolone + diuretics + N-acetylcysteine + tissue plasminogen activator	0	0	1 (11)	0	1 (5)	0
Not reported	1 (10)	1 (9)	2 (22)	0	3 (16)	1 (1)
Post-VOD/SOS survival						
N/A; no VOD/SOS	8 (80)	7 (64)	4 (44)	71 (87)	12 (63)	78 (84)
Alive	1 (10)	1 (9)	3 (33)	3 (4)	4 (21)	4 (4)
Dead	1 (10)	3 (27)	2 (22)	8 (10)	3 (16)	11 (12)

Note: Outcomes are not evaluable (NE) if sample size is < 20.

Table 50 VOD characteristics within 100 days post-transplant, with and without and defibrotide as liver toxicity prophylaxis, in patients who were in first complete remission prior to HSCT

	Pediatric patients (< 18 years) No. (%)		Adult patients (≥ 18 years) No. (%)		All patients No. (%)	
	Defibrotide	No defibrotide	Defibrotide	No defibrotide	Defibrotide	No defibrotide
Number of patients in first complete remission prior to HSCT and post-transplant follow-up	**3**	**3**	**2**	**38**	**5**	**41**
Number of patients with post-transplant VOD/SOS	1	0	0	1	1	1
Time to post-transplant VOD/SOS, days						
Median	10	NE	NE	18	10	18
Range	NE	NE	NE	NE	NE	NE
Mean	10	NE	NE	18	10	18
Standard deviation	NE	NE	NE	NE	NE	NE
Grade of VOD/SOS						
N/A; no VOD/SOS	2 (67)	3	2	37 (97)	4 (80)	40 (98)
Mild VOD/SOS (no other organs involved within 60 days of VOD/SOS diagnosis)	0	0	0	1 (3)	0	1 (2)
Severe VOD/SOS (multiple organ dysfunction within 60 days of VOD/SOS diagnosis)	1 (33)	0	0	0	1 (20)	0
Liver toxicity prophylaxis						
None (or no additional)	1 (33)	1 (33)	0	5 (13)	1 (20)	6 (15)
Ursodiol	0	1 (33)	0	32 (84)	0	33 (80)
Ursodiol + defibrotide	2 (67)	0	1 (50)	0	3 (60)	0
Ursodiol + defibrotide + others	0	0	1 (50)	0	1 (20)	0
Ursodiol + others	0	1 (33)	0	1 (3)	0	2 (5)
Treatment for VOD/SOS						
N/A; no VOD/SOS	2 (67)	3	2	37 (97)	4 (80)	40 (98)
Defibrotide + ursodiol + diuretics	0	0	0	1 (3)	0	1 (2)
Not reported	1 (33)	0	0	0	1 (20)	0

	Pediatric patients (< 18 years) No. (%)		Adult patients (≥ 18 years) No. (%)		All patients No. (%)	
	Defibrotide	**No defibrotide**	**Defibrotide**	**No defibrotide**	**Defibrotide**	**No defibrotide**
Number of patients in first complete remission prior to HSCT and post-transplant follow-up	**3**	**3**	**2**	**38**	**5**	**41**
Post-VOD/SOS survival						
N/A; no VOD/SOS	2 (67)	3	2	37 (97)	4 (80)	40 (98)
Alive	1 (33)	0	0	1 (3)	1 (20)	1 (2)
Dead	0	0	0	0	0	0

Note: Outcomes are not evaluable (NE) if sample size is < 20.

16.9 Post-HSCT clinical status subgroups

Table 51 Post-HSCT clinical status, in patients who had relapsed or refractory B-Cell ALL prior to HSCT

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
Number of patients with relapsed or refractory B-Cell ALL prior to HSCT and with follow-up	**21**	**91**	**112**
Best response to HSCT			
Continued complete remission (CR)[a]	20 (95)	78 (86)	98 (88)
CR	0	8 (9)	8 (7)
Not in CR	1 (5)	4 (4)	5 (4)
Not reported	0	1 (1)	1 (1)
Granulopoiesis / neutrophil recovery[b]			
Yes	21	88 (97)	109 (97)
No	0	2 (2)	2 (2)
Not reported	0	1 (1)	1 (1)
Time from HSCT to granulopoiesis/neutrophil recovery, days			
Number evaluable	21	88	109
Median	17	17	17
Range	(10-30)	(9-52)	(9-52)
Mean	18	18	18
Standard deviation	6	7	7
Megakaryopoiesis / platelet recovery[c]			
Yes	17 (81)	73 (80)	90 (80)
No	4 (19)	17 (19)	21 (19)
Not reported	0	1 (1)	1 (1)
Time from HSCT to megakaryopoiesis/platelet recovery, days			
Number evaluable	17	73	90
Median	25	27	27
Range	(13-43)	(13-97)	(13-97)
Mean	27	32	31
Standard deviation	10	16	15
Engraftment syndrome within 100 days post-transplant			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Yes	5 (24)	10 (11)	15 (13)
No	16 (76)	79 (87)	95 (85)
Time from HSCT to engraftment syndrome, days			
Number evaluable	5	10	15
Median	12	15	13
Range	(11-13)	(2-42)	(2-42)
Mean	12	16	15
Standard deviation	1	10	8

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
Number of patients with relapsed or refractory B-Cell ALL prior to HSCT and with follow-up	**21**	**91**	**112**
Weight, most recent post-HSCT, kg			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Not reported	0	3 (3)	3 (3)
Number evaluable	21	86	107
Median	32	74	66
Range	(8-85)	(33-210)	(8-210)
Mean	36	78	70
Standard deviation	20	27	30
Height, most recent post-HSCT, cm			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Not reported	7 (33)	89 (98)	96 (86)
Number evaluable	14	0	14
Median	122	NE	122
Range	(81-158)	NE	(81-158)
Mean	123	NE	123
Standard deviation	23	NE	23
Performance scale and status, post-HSCT			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
Karnofsky			
90-100	3 (14)	35 (38)	38 (34)
10-80	12 (57)	28 (31)	40 (36)
Not reported	6 (29)	26 (29)	32 (29)
Total inpatient days in first 100 days post-HSCT [d]			
N/A; CIBMTR Form 2100 not yet received	0	2 (2)	2 (2)
< 30	4 (19)	40 (44)	44 (39)
30-59	10 (48)	26 (29)	36 (32)
60-100	2 (10)	12 (13)	14 (13)
Not reported	5 (24)	11 (12)	16 (14)
Number evaluable	16	78	94
Median	39	29	31
Range	(21-60)	(6-94)	(6-94)
Mean	40	36	37
Standard deviation	13	22	20
Time from HSCT to date of last contact, months			
< 3	5 (24)	15 (16)	20 (18)
3-5	2 (10)	20 (22)	22 (20)
6-11	6 (29)	31 (34)	37 (33)
≥ 12	8 (38)	25 (27)	33 (29)
Number evaluable	21	91	112
Median	9.3	6.54	6.95
Range	(0.92-28.39)	(0.62-26.18)	(0.62-28.39)
Mean	10.73	8.46	8.89
Standard deviation	8.7	6.04	6.64

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
Number of patients with relapsed or refractory B-Cell ALL prior to HSCT and with follow-up	**21**	**91**	**112**

Note: Outcomes are not evaluable (NE) if sample size is < 20.

[a] Continued complete remission is defined as a patient who underwent transplant during complete remission, and the complete remission is sustained post-transplant. Complete remission is defined as all the following: < 5% blasts in bone marrow, no blasts with Auer rods, no extramedullary disease and no disease progression for at least 4 weeks.

[b] Absolute neutrophil count (ANC) > 500/mm^3 sustained for 3 lab values; evaluated ≤ 100 days post-transplant.

[c] Initial platelet count > 20 × 10^9/L achieved; evaluated ≤ 100 days post-transplant.

[d] The form asks for the number of inpatient days in the first 100 days (day 0 to day 100) post-HSCT.

Table 52 Post-HSCT clinical status, in patients who were in first complete remission prior to HSCT

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
Number of patients in first complete remission prior to HSCT and with follow-up	**6**	**40**	**46**
Best response to HSCT			
Continued complete remission (CR)[a]	6	39 (98)	45 (98)
CR	0	1 (3)	1 (2)
Granulopoiesis / neutrophil recovery [b]			
Yes	5 (83)	39 (98)	44 (96)
No	0	0	0
Not reported	1 (17)	1 (3)	2 (4)
Time from HSCT to granulopoiesis/neutrophil recovery, days			
Number evaluable	5	39	44
Median	21	17	17
Range	(12-29)	(10-29)	(10-29)
Mean	20	17	17
Standard deviation	7	4	5
Megakaryopoiesis / platelet recovery [c]			
Yes	4 (67)	35 (88)	39 (85)
No	1 (17)	3 (8)	4 (9)
Not reported	1 (17)	2 (5)	3 (7)
Time from HSCT to megakaryopoiesis/platelet recovery, days			
Number evaluable	4	35	39
Median	40	29	29
Range	(32-49)	(15-96)	(15-96)
Mean	40	30	31
Standard deviation	7	14	14
Engraftment syndrome within 100 days post-transplant			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Yes	1 (17)	1 (3)	2 (4)
No	4 (67)	39 (98)	43 (93)
Time from HSCT to engraftment syndrome, days			
Number evaluable	1	1	2
Median	12	19	NE
Range	NE	NE	(12-19)
Mean	12	19	16
Standard deviation	NE	NE	5
Weight, most recent post-HSCT, kg			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Not reported	0	1 (3)	1 (2)
Number evaluable	5	39	44
Median	33	83	81
Range	(14-64)	(43-130)	(14-130)
Mean	39	84	79

	Pediatric patients (< 18 y) No. (%)	Adults (≥ 18 y) No. (%)	All patients No. (%)
Number of patients in first complete remission prior to HSCT and with follow-up	**6**	**40**	**46**
Standard deviation	23	21	26
Height, most recent post-HSCT, cm			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Not reported	1 (17)	40	41 (89)
Number evaluable	4	0	4
Median	128	NE	128
Range	(88-156)	NE	(88-156)
Mean	125	NE	125
Standard deviation	31	NE	31
Performance scale and status, post-HSCT			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
Karnofsky			
90-100	0	22 (55)	22 (48)
10-80	5 (83)	9 (23)	14 (30)
Not reported	0	9 (23)	9 (20)
Total inpatient days in first 100 days post-HSCT [d]			
N/A; CIBMTR Form 2100 not yet received	1 (17)	0	1 (2)
< 30	1 (17)	24 (60)	25 (54)
30-59	3 (50)	8 (20)	11 (24)
60-100	1 (17)	5 (13)	6 (13)
Not reported	0	3 (8)	3 (7)
Number evaluable	5	37	42
Median	39	23	25
Range	(27-70)	(7-92)	(7-92)
Mean	44	31	32
Standard deviation	16	20	19
Time from HSCT to date of last contact, months			
< 3	0	2 (5)	2 (4)
3-5	0	8 (20)	8 (17)
6-11	2 (33)	15 (38)	17 (37)
≥ 12	4 (67)	15 (38)	19 (41)
Number evaluable	6	40	46
Median	12.19	7.26	7.82
Range	(6.34-24.05)	(0.36-24.64)	(0.36-24.64)
Mean	12.54	9.66	10.04
Standard deviation	6.19	6.07	6.1

Note: Outcomes are not evaluable (NE) if sample size is < 20.

[a] Continued complete remission is defined as a patient who underwent transplant during complete remission, and the complete remission is sustained post-transplant. Complete remission is defined as all the following: < 5% blasts in bone marrow, no blasts with Auer rods, no extramedullary disease and no disease progression for at least 4 weeks.

[b] Absolute neutrophil count (ANC) > 500/mm^3 sustained for 3 lab values; evaluated ≤ 100 days post-transplant.

[c] Initial platelet count > 20 × 10^9/L achieved; evaluated ≤ 100 days post-transplant.

[d] The form asks for the number of inpatient days in the first 100 days (day 0 to day 100) post-HSCT.

17 Appendices

Appendices are separate documents.

17.1 Appendix 1: Protocol

Study B1931028 protocol

17.2 Appendix 2: Statistical Analysis Plan

Study B1931028 SAP version 4.0 dated 21 July 2020

17.3 Appendix 3: CIBMTR Data Collection Forms

CIBMTR data collection forms:

- 2400: Pre-Transplant Essential Data
- 2402: Pre-Transplant Essential Data: Disease Classification
- 2000: Recipient Baseline Data
- 2011: ALL Pre-HSCT Data
- 2111: ALL Post-HSCT Data
- 2541: Inotuzumab Ozogamicin Supplemental Data Collection
- 2100: Post-HSCT Data
- 2450: Post-Transplant Essential Data
- 2553: VOD/SOS Supplemental Data Collection Form
- 2900: Recipient Death Data

17.4 Appendix 4: Statistical programming plan for additional analyses

Study B1931028 Version 1.1 dated 14 Sept. 2020

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