1. NAME OF THE MEDICINAL PRODUCT

BESPONSA

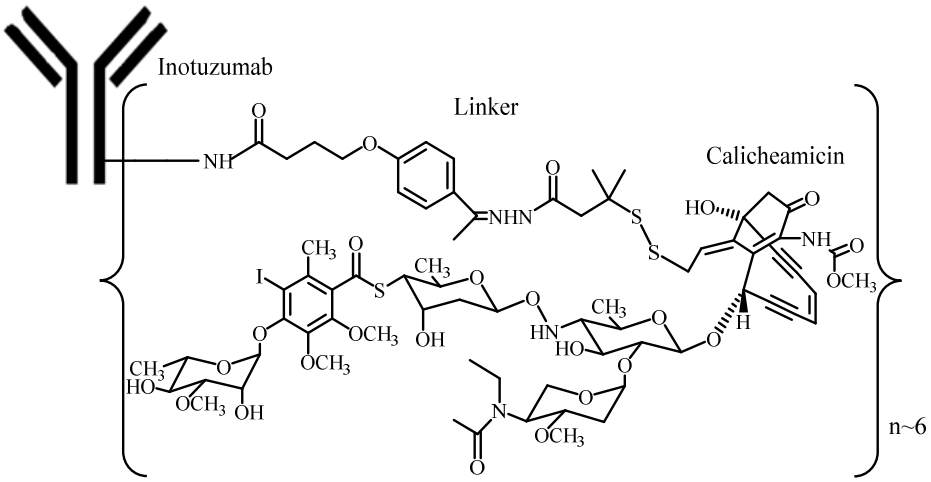
2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1 mg inotuzumab ozogamicin.

After reconstitution (see Section 6.6), 1 mL of solution contains 0.25 mg inotuzumab ozogamicin.

For the full list of excipients, see Section 6.1.

Chemical structure:



Inotuzumab ozogamicin is a CD22-directed antibody-drug conjugate (ADC) consisting of 3 components: 1) the recombinant humanized immunoglobulin class G subtype 4 (IgG4) kappa antibody inotuzumab, specific for human CD22, 2) N-acetyl-gamma-calicheamicin that causes double-stranded DNA breaks, and 3) an acid-cleavable linker composed of the condensation product of 4-(4'-acetylphenoxy)-butanoic acid (AcBut) and 3-methyl-3-mercaptobutane hydrazide (known as dimethylhydrazide) that covalently attaches N-acetyl-gamma-calicheamicin to inotuzumab.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to off-white, lyophilized cake or powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Inotuzumab ozogamicin is indicated for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

4.2. Posology and method of administration

For patients with circulating lymphoblasts, cytoreduction with a combination of hydroxyurea, steroids, and/or vincristine to a peripheral blast count ≤10,000/mm^3 is recommended prior to the first dose.

Premedication with a corticosteroid, antipyretic, and antihistamine is recommended prior to dosing (see Section 4.4).

Patients should be observed during and for at least 1 hour after the end of the infusion for symptoms of infusion related reactions (see Section 4.4).

Posology

Administer inotuzumab ozogamicin in 3- to 4-week cycles.

For patients proceeding to a hematopoietic stem cell transplant (HSCT), the recommended duration of treatment with inotuzumab ozogamicin is 2 cycles. A third cycle should be considered for those patients who do not achieve a complete remission (CR) or a complete remission with incomplete hematologic recovery (CRi) and minimal residual disease (MRD) negativity after 2 cycles (see Section 4.4).

For patients not proceeding to HSCT, a maximum of 6 cycles may be administered.

Any patients who do not achieve a CR or CRi within 3 cycles should discontinue treatment.

Table 1 shows the recommended dosing regimens.

For the first cycle, the recommended total dose of inotuzumab ozogamicin for all patients is 1.8 mg/m^2 per cycle, administered as 3 divided doses on Days 1 (0.8 mg/m^2), 8 (0.5 mg/m^2), and 15 (0.5 mg/m^2). Cycle 1 is 3 weeks in duration, but may be extended to 4 weeks if the patient achieves a CR or CRi, and/or to allow recovery from toxicity.

For subsequent cycles, the recommended total dose of inotuzumab ozogamicin is 1.5 mg/m^2 per cycle, administered as 3 divided doses on Days 1 (0.5 mg/m^2), 8 (0.5 mg/m^2), and 15 (0.5 mg/m^2) for patients who achieve a CR or CRi or 1.8 mg/m^2 per cycle given as 3 divided doses on Days 1 (0.8 mg/m^2), 8 (0.5 mg/m^2), and 15 (0.5 mg/m^2) for patients who do not achieve a CR or CRi. Subsequent cycles are 4 weeks in duration.

Table 1. Dosing Regimen for Cycle 1 and Subsequent Cycles Depending on Response to Treatment

	Day 1	**Day 8[a]**	**Day 15[a]**
Dosing regimen for Cycle 1			
All patients:			
Dose (mg/m^2)[b]	0.8	0.5	0.5
Cycle length	21 days[c]		
Dosing regimen for subsequent cycles depending on response to treatment			
Patients who have achieved a CR[d] or CRi[e]:			
Dose (mg/m^2)[b]	0.5	0.5	0.5
Cycle length	28 days[f]		
Patients who have not achieved a CR[c] or CRi[d]:			

Table 1. Dosing Regimen for Cycle 1 and Subsequent Cycles Depending on Response to Treatment

	Day 1	Day 8[a]	Day 15[a]
Dose (mg/m^2)[b]	0.8	0.5	0.5
Cycle length	28 days[f]		

Abbreviations: CR=complete remission; CRi=complete remission with incomplete hematologic recovery.

[a] +/- 2 days (maintain a minimum of 6 days between doses).

[b] Dose is based on the patient's body surface area (m^2).

[c] For patients who achieve a CR or a CRi, and/or to allow for recovery from toxicity, the cycle length may be extended up to 28 days (i.e., 7-day treatment-free interval starting on Day 21).

[d] CR is defined as <5% blasts in the bone marrow and the absence of peripheral blood leukemic blasts, full recovery of peripheral blood counts (platelets $\geq 100 \times 10^9$/L and absolute neutrophil counts [ANC] $\geq 1 \times 10^9$/L) and resolution of any extramedullary disease.

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

[f] 7-day treatment-free interval starting on Day 21.

Dose modifications

Dose modification of inotuzumab ozogamicin may be required based on individual safety and tolerability (see Section 4.4). Management of some adverse drug reactions may require dosing interruptions and/or dose reductions, or permanent discontinuation of inotuzumab ozogamicin (see Sections 4.4 and 4.8). If the dose is reduced due to inotuzumab ozogamicin-related toxicity, the dose must not be re-escalated.

Table 2 and Table 3 show the dose modification guidelines for hematologic and nonhematologic toxicities, respectively. Inotuzumab ozogamicin doses within a treatment cycle (i.e., Days 8 and/or 15) do not need to be interrupted due to neutropenia or thrombocytopenia, but dosing interruptions within a cycle are recommended for nonhematologic toxicities.

Table 2. Dose Modifications for Hematologic Toxicities

Hematologic Toxicity	Dose Modification(s)
If prior to inotuzumab ozogamicin treatment:	
ANC was $\geq 1 \times 10^9$/L	If ANC decreases, then interrupt the next cycle of treatment until recovery of ANC to $\geq 1 \times 10^9$/L.
Platelet count was $\geq 50 \times 10^9$/L[a]	If platelet count decreases, then interrupt the next cycle of treatment until platelet count recovers to $\geq 50 \times 10^9$/L.[a]
ANC was $<1 \times 10^9$/L and/or platelet count was $<50 \times 10^9$/L[a]	If ANC and/or platelet count decreases, then interrupt the next cycle of treatment until at least one of the following occurs: - ANC and platelet count recover to at least baseline levels for the prior cycle, or - ANC recovers to $\geq 1 \times 10^9$/L and platelet count recovers to $\geq 50 \times 10^9$/L,[a] or - Stable or improved disease (based on most recent bone marrow assessment) and the ANC and platelet count decrease is considered to be due to the underlying disease (not considered to be inotuzumab ozogamicin-related toxicity).

Abbreviation: ANC=absolute neutrophil count.

[a] Platelet count used for dosing should be independent of blood transfusion.

Table 3. Dose Modifications for Nonhematologic Toxicities

Nonhematologic Toxicity	Dose Modification(s)
VOD/SOS or other severe liver toxicity	Permanently discontinue treatment (see Section 4.4).
Total bilirubin >1.5 × ULN and AST/ALT >2.5 × ULN	Interrupt the dosing until recovery of total bilirubin to ≤1.5 × ULN and AST/ALT to ≤2.5 × ULN prior to each dose unless due to Gilbert's syndrome or hemolysis. Permanently discontinue treatment if total bilirubin does not recover to ≤1.5 × ULN or AST/ALT does not recover to ≤2.5 × ULN (see Section 4.4).
Infusion related reaction	Interrupt the infusion and institute appropriate medical management. Depending on the severity of the infusion related reaction, consider discontinuation of the infusion or administration of steroids and antihistamines. For severe or life-threatening infusion reactions, permanently discontinue treatment (see Section 4.4).
Grade ≥2[a] nonhematologic toxicity (inotuzumab ozogamicin-related)	Interrupt treatment until recovery to Grade 1 or pretreatment grade levels prior to each dose.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal; VOD/SOS=venoocclusive liver disease/sinusoidal obstruction syndrome.

[a] Severity grade according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0.

Table 4 shows the dose modification guidelines depending on the duration of dosing interruptions due to toxicity.

Table 4. Dose Modifications Depending on Duration of Dosing Interruption Due to Toxicity

Duration of Dosing Interruption Due to Toxicity	Dose Modification(s)
<7 days (within a cycle)	Interrupt next dose (maintain a minimum of 6 days between doses).
≥7 days	Omit next dose within the cycle.
≥14 days	Once adequate recovery is achieved, decrease the total dose by 25% for the subsequent cycle. If further dose modification is required, then reduce the number of doses to 2 per cycle for subsequent cycles. If a 25% decrease in the total dose followed by a decrease to 2 doses per cycle is not tolerated, then permanently discontinue treatment.
>28 days	Consider permanent discontinuation of treatment.

Special populations

Elderly patients

No adjustment to the starting dose is required based on age (see Section 5.2). Increased age may be associated with an increased risk of venoocclusive liver disease/sinusoidal obstruction syndrome (VOD/SOS) after HSCT (see Section 4.4).

Hepatic impairment

No adjustment to the starting dose is required in patients with hepatic impairment defined by total bilirubin ≤1.5 × upper limit of normal (ULN) and aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤2.5 × ULN (see Section 5.2). There is limited safety information available in patients with total bilirubin >1.5 × ULN and AST/ALT >2.5 × ULN prior to dosing. Interrupt dosing until recovery of total bilirubin to ≤1.5 × ULN and AST/ALT to ≤2.5 × ULN prior to each dose unless due to Gilbert's syndrome or hemolysis.

Permanently discontinue treatment if total bilirubin does not recover to ≤1.5 × ULN or AST/ALT does not recover to ≤2.5 × ULN (see Table 3 and Section 4.4).

Renal impairment

No adjustment to the starting dose is required in patients with mild, moderate, or severe renal impairment (creatinine clearance [CL_{cr}] 60-89 mL/min, 30-59 mL/min, or 15-29 mL/min, respectively) (see Section 5.2). The safety and efficacy of inotuzumab ozogamicin have not been studied in patients with end-stage renal disease.

Pediatric population

The safety and efficacy of inotuzumab ozogamicin in the pediatric population (<18 years) have not been established. Currently available data are described in Sections 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration

Inotuzumab ozogamicin is for intravenous use. The infusion must be administered over 1 hour.

Do not administer inotuzumab ozogamicin as an intravenous push or bolus.

Inotuzumab ozogamicin must be reconstituted and diluted before administration. For instructions on reconstitution and dilution of inotuzumab ozogamicin before administration, see Section 6.6.

4.3. Contraindications

- Hypersensitivity to inotuzumab ozogamicin or to any of the excipients.
- Patients who have ongoing VOD/SOS.
- Patients with serious ongoing hepatic disease (e.g., cirrhosis, nodular regenerative hyperplasia, active hepatitis).

4.4. Special warnings and precautions for use

Hepatotoxicity, including venoocclusive liver disease/sinusoidal obstruction syndrome (VOD/SOS)

In a randomized clinical study of inotuzumab ozogamicin in patients with relapsed or refractory ALL (Study 1), hepatotoxicity, including severe, life-threatening, and sometimes fatal hepatic VOD/SOS and increases in liver tests, was reported (see Section 4.8).

VOD/SOS was reported in 23/164 (14%) patients during or following treatment or following a HSCT after completion of treatment. Grade 3/4 AST, ALT, and total bilirubin abnormal liver tests occurred in 7/160 (4%), 7/161 (4%), and 8/161 (5%) patients, respectively.

Among all 164 patients treated, VOD/SOS was reported in 5/164 (3%) patients during study therapy or in follow-up without an intervening HSCT. Among the 79 patients who proceeded to a subsequent HSCT (8 of whom received additional salvage therapy after treatment with

inotuzumab ozogamicin before proceeding to HSCT), VOD/SOS was reported in 18/79 (23%) patients. Five of the 18 VOD/SOS events that occurred post-HSCT were fatal (see Section 5.1).

VOD/SOS was reported up to 56 days after the final dose during treatment or during follow-up without an intervening HSCT. The median time from HSCT to onset of VOD/SOS was 15 days (range: 3-57 days).

Some patients may be at increased risk for developing VOD/SOS.

Patients who have experienced prior VOD/SOS or have serious ongoing hepatic liver disease (e.g., cirrhosis, nodular regenerative hyperplasia, active hepatitis) may be at increased risk for worsening of liver disease, including developing VOD/SOS, following treatment with inotuzumab ozogamicin.

Prior HSCT may be associated with an increased risk of VOD/SOS. Of the 5 patients who experienced VOD/SOS during treatment with inotuzumab ozogamicin but without an intervening HSCT, 2 patients had also received a HSCT before inotuzumab ozogamicin treatment. Among patients who proceeded to HSCT, VOD/SOS was reported after the HSCT that followed treatment with inotuzumab ozogamicin in 5/11 (46%) patients who received a HSCT both prior to and after inotuzumab ozogamicin treatment and 13/68 (19%) patients who only received a HSCT after inotuzumab ozogamicin treatment.

Among patients who proceed to HSCT, use of HSCT conditioning regimens containing 2 alkylating agents and last total bilirubin level ≥ULN before follow-up HSCT are significantly associated with an increased risk of VOD/SOS after HSCT. Other factors that may also be associated with an increased risk of VOD/SOS after HSCT include increased age, a history of liver disease and/or hepatitis before treatment, later salvage lines, and a greater number of treatment cycles.

Due to the risk of VOD/SOS, especially after HSCT, monitor closely for signs and symptoms of VOD/SOS; these may include elevations in total bilirubin, hepatomegaly (which may be painful), rapid weight gain, and ascites. Monitoring only total bilirubin may not identify all patients at risk of VOD/SOS. In all patients, monitor liver tests, including ALT, AST, total bilirubin, and alkaline phosphatase, prior to and following each dose of inotuzumab ozogamicin. For patients who develop abnormal liver tests, more frequent monitoring of liver tests and clinical signs and symptoms of hepatotoxicity is recommended. For patients who proceed to HSCT, monitor liver tests closely during the first month post-HSCT, then less frequently thereafter, according to standard medical practice.

Elevation of liver tests may require dosing interruption, dose reduction, or permanent discontinuation of inotuzumab ozogamicin (see Section 4.2).

Carefully consider the benefit/risk before administering inotuzumab ozogamicin to patients who have experienced prior VOD/SOS. If these patients are treated with inotuzumab ozogamicin, monitor closely for signs and symptoms of VOD/SOS and permanently discontinue treatment if VOD/SOS occurs (see Section 4.2). If severe VOD/SOS occurs, the patient should be treated according to standard medical practice.

Particular attention should be paid when administering inotuzumab ozogamicin to patients who are older, have had a prior HSCT, are in later lines of salvage, or have a prior history of liver disease and/or hepatitis. Due to the risk of VOD, for patients proceeding to HSCT, the recommended duration of treatment with inotuzumab ozogamicin is 2 cycles; a third cycle should be considered for those patients who do not achieve a CR or CRi and MRD negativity after 2 cycles (see Section 4.2). Avoid the use of HSCT conditioning regimens containing 2 alkylating agents.

Increased Risk of Post-Transplant Non-Relapse Mortality

In a randomized clinical study of inotuzumab ozogamicin in patients with relapsed or refractory ALL (Study 1), a higher post-HSCT non-relapse mortality rate was observed in patients receiving inotuzumab ozogamicin compared to the Investigator's choice of chemotherapy arm, resulting in a higher Day 100 post-HSCT mortality rate.

Overall, 79/164 patients (48%) in the inotuzumab ozogamicin arm and 35/162 patients (22%) in the Investigator's choice of chemotherapy arm had a follow-up HSCT. The post-HSCT non-relapse mortality rate was 31/79 (39%) and 8/35 (23%) in the inotuzumab ozogamicin arm compared to the Investigator's choice of chemotherapy arm, respectively.

In the inotuzumab ozogamicin arm, the most common causes of post-HSCT non-relapse mortality included VOD and infections. Five of the 18 VOD events that occurred post-HSCT were fatal. In the inotuzumab ozogamicin arm, among patients with ongoing VOD at time of death, 6 patients died due to multiorgan failure (MOF) or infection (3 patients died due to MOF, 2 patients died due to infection, and 1 patient died due to MOF and infection).

Monitor closely for toxicities post-HSCT, including signs and symptoms of infection and VOD (see Section 4.4, Hepatotoxicity, including venoocclusive liver disease/sinusoidal obstruction syndrome (VOD/SOS) and Myelosuppression/cytopenias).

Myelosuppression/cytopenias

In a randomized clinical study of inotuzumab ozogamicin in patients with relapsed or refractory ALL (Study 1), neutropenia, thrombocytopenia, anemia, leukopenia, febrile neutropenia, lymphopenia, and pancytopenia, some of which were life-threatening, were reported (see Section 4.8).

Thrombocytopenia and neutropenia were reported in 83/164 (51%) and 81/164 (49%) patients, respectively. Grade 3 thrombocytopenia and neutropenia were reported in 23/164 (14%) patients and 33/164 (20%) patients, respectively. Grade 4 thrombocytopenia and neutropenia were reported in 46/164 (28%) patients and 45/164 (27%) patients, respectively. Febrile neutropenia, which may be life-threatening, was reported in 43/164 (26%) patients.

Complications associated with neutropenia and thrombocytopenia (including infections and bleeding/hemorrhagic events, respectively) were reported in some patients (see Section 4.8).

Infections, including serious infections, some of which were life-threatening or fatal, were reported in 79/164 (48%) patients. Fatal infections, including pneumonia, neutropenic sepsis,

sepsis, septic shock, and pseudomonal sepsis, were reported in 8/164 (5%) patients. Bacterial, viral, and fungal infections were reported.

Bleeding/hemorrhagic events, mostly mild in severity, were reported in 54/164 (33%) patients. Grade 3/4 bleeding/hemorrhagic events were reported in 8/164 (5%) patients. One Grade 5 bleeding/hemorrhagic event (intra-abdominal haemorrhage) was reported in 1/164 (1%) patients. The most common bleeding event was epistaxis which was reported in 24/164 (15%) patients.

Monitor complete blood counts prior to each dose of inotuzumab ozogamicin and monitor for signs and symptoms of infection during treatment and after HSCT (see Section 5.1), bleeding/hemorrhage, or other effects of myelosuppression during treatment with inotuzumab ozogamicin. As appropriate, administer prophylactic anti-infectives and employ surveillance testing during and after treatment with inotuzumab ozogamicin. Management of patients with severe infection, bleeding/hemorrhage, or other effects of myelosuppression, including severe neutropenia or thrombocytopenia, may require dosing interruption, dose reduction, or permanent discontinuation of inotuzumab ozogamicin (see Section 4.2).

Infusion related reactions

In a randomized clinical study of inotuzumab ozogamicin in patients with relapsed or refractory ALL (Study 1), infusion related reactions, all of which were Grade 2 in severity, were reported in 4/164 (2%) patients (see Section 4.8). Infusion related reactions generally occurred in Cycle 1 shortly after the end of the inotuzumab ozogamicin infusion and resolved spontaneously or with medical management.

Premedication with a corticosteroid, antipyretic, and antihistamine is recommended prior to dosing (see Section 4.2).

Monitor patients closely during and for at least 1 hour after the end of infusion for the potential onset of infusion related reactions, including symptoms such as hypotension, hot flush, rash, or breathing problems. If an infusion related reaction occurs, interrupt the infusion and institute appropriate medical management. Depending on the severity of the infusion related reaction, consider discontinuation of the infusion or administration of steroids and antihistamines. For severe or life-threatening infusion reactions, permanently discontinue inotuzumab ozogamicin (see Section 4.2).

Tumor lysis syndrome

In a randomized clinical study of inotuzumab ozogamicin in patients with relapsed or refractory ALL (Study 1), tumor lysis syndrome (TLS), which may be life-threatening or fatal, was reported in 4/164 (2%) patients (see Section 4.8). Grade 3/4 TLS was reported in 3/164 (2%) patients. TLS occurred shortly after the end of the inotuzumab ozogamicin infusion and resolved with medical management.

Monitor for signs and symptoms of TLS and treat according to standard medical practice.

QT interval prolongation

In a randomized clinical study of inotuzumab ozogamicin in patients with relapsed or refractory ALL (Study 1), increases in QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥60 msec from baseline were measured in 4/162 (3%) patients. No patients had QTcF values >500 msec. Grade 2 QT prolongation was reported in 2/164 (1%) patients. No Grade ≥3 QT prolongation or events of Torsade de Pointes were reported (see Sections 4.8 and 5.1).

Inotuzumab ozogamicin should be administered with caution in patients who have a history of, or predisposition for QT interval prolongation, who are taking medicinal products that are known to prolong QT interval, and in patients with electrolyte disturbances (see Section 4.5). Electrocardiograms (ECGs) and electrolytes should be obtained prior to the start of treatment and periodically monitored during treatment.

4.5. Interaction with other medicinal products and other forms of interaction

No clinical drug interaction studies have been performed with inotuzumab ozogamicin (see Section 5.2).

In a randomized clinical study of inotuzumab ozogamicin in patients with relapsed or refractory ALL (Study 1), prolonged QT interval was observed with inotuzumab ozogamicin (see Sections 4.4 and 5.1). Therefore, the concomitant use of inotuzumab ozogamicin with medicinal products known to prolong QT interval or able to induce Torsades de Pointes should be carefully considered. Monitor the QT interval in case of combinations of such medicinal products (see Section 4.4).

4.6. Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential should avoid becoming pregnant while receiving inotuzumab ozogamicin.

Women should be advised to use effective contraception during treatment with inotuzumab ozogamicin and for at least 8 months after the final dose. Men with female partners of childbearing potential should use effective contraception during treatment with inotuzumab ozogamicin and for at least 5 months after the final dose.

Pregnancy

There are no data in pregnant women using inotuzumab ozogamicin. Based on nonclinical safety findings, inotuzumab ozogamicin can cause embryo-fetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity (see Section 5.3).

Inotuzumab ozogamicin should not be used during pregnancy unless the potential benefit to the mother outweighs the potential risks to the fetus. Pregnant women, or patients becoming pregnant while receiving inotuzumab ozogamicin, or treated male patients as partners of pregnant women, should be apprised of the potential hazard to the fetus.

Breastfeeding

There are no data on the presence of inotuzumab ozogamicin or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. A risk to the newborn/infant cannot be excluded. Because of the potential for adverse reactions in breastfed infants, women should not breastfeed during treatment with inotuzumab ozogamicin and for at least 2 months after the final dose (see Section 5.3).

Fertility

Based on nonclinical findings, male and female fertility may be compromised by treatment with inotuzumab ozogamicin (see Section 5.3). Both men and women should seek advice for fertility preservation before treatment.

4.7. Effects on ability to drive and use machines

Inotuzumab ozogamicin can have an influence on the ability to drive and use machines. Patients may experience fatigue during treatment with inotuzumab ozogamicin (see Section 4.8). Therefore, caution should be recommended when driving or operating machines.

4.8. Undesirable effects

Summary of safety profile

The adverse reactions described in this section reflect exposure to inotuzumab ozogamicin in 164 patients with relapsed or refractory ALL who participated in a randomized clinical study of inotuzumab ozogamicin versus Investigator's choice of chemotherapy (fludarabine + cytarabine + granulocyte colony-stimulating factor [FLAG], mitoxantrone + cytarabine [MXN/Ara-C], or high dose cytarabine [HIDAC]) (Study 1) (see Section 5.1).

Of the 164 patients who received inotuzumab ozogamicin, the median age was 47 years (range: 18-78 years), 56% were male, 68% had received 1 prior treatment regimen for ALL, 31% had received 2 prior treatment regimens for ALL, 68% were White, 19% were Asian, and 2% were Black.

In patients who received inotuzumab ozogamicin, the median duration of treatment was 8.9 weeks (range: 0.1-26.4 weeks), with a median of 3 treatment cycles started in each patient. In patients who received Investigator's choice of chemotherapy, the median duration of treatment was 0.9 weeks (range: 0.1-15.6 weeks), with a median of 1 treatment cycle started in each patient.

The following adverse reactions, including appropriate management recommendations, are discussed in Section 4.4: hepatotoxicity (including VOD/SOS), myelosuppression/cytopenias (including complications of infections and bleeding/hemorrhagic events), infusion related reactions, TLS, and QT interval prolongation.

In patients who received inotuzumab ozogamicin, the most common (≥20%) adverse reactions were thrombocytopenia, neutropenia, infection, anaemia, leukopenia, fatigue, haemorrhage, pyrexia, nausea, headache, febrile neutropenia, transaminases increased, abdominal pain, gamma-glutamyltransferase increased, and hyperbilirubinaemia.

In patients who received inotuzumab ozogamicin, the most common (≥2%) serious adverse reactions were infection, febrile neutropenia, haemorrhage, abdominal pain, pyrexia, VOD/SOS, and fatigue.

In patients who received inotuzumab ozogamicin, the most common (≥2%) adverse reactions reported as the reason for permanent discontinuation of inotuzumab ozogamicin were infection (6%), thrombocytopenia (2%), hyperbilirubinaemia (2%), transaminases increased (2%), and haemorrhage (2%); the most common (≥5%) adverse reactions reported as the reason for dosing interruption were neutropenia (17%), infection (10%), thrombocytopenia (10%), transaminases increased (6%), and febrile neutropenia (5%); and the most common (≥1%) adverse reactions reported as the reason for dose reduction were neutropenia (1%), thrombocytopenia (1%), and transaminases increased (1%).

Tabulated list of adverse reactions

Table 5 shows the adverse reactions with ≥10% incidence reported in patients with relapsed or refractory ALL who received inotuzumab ozogamicin or Investigator's choice of chemotherapy.

Table 5. Adverse Reactions With ≥10% Incidence[a] in Patients With Relapsed or Refractory B-Cell Precursor ALL Who Received Inotuzumab Ozogamicin or Investigator's Choice of Chemotherapy (FLAG, MXN/Ara-C, or HIDAC)

	Inotuzumab Ozogamicin (N=164)		FLAG, MXN/Ara-C, or HIDAC (N=143[b])	
Body System	**All Grades**	**≥ Grade 3**	**All Grades**	**≥ Grade 3**
Adverse Reaction	**%**	**%**	**%**	**%**
Infections				
Infection[c]	48	28	76	54
Blood and lymphatic system disorders				
Thrombocytopenia[d]	51	42	61	59
Neutropenia[e]	49	48	45	43
Anemia[f]	36	24	59	47
Leukopenia[g]	35	33	43	42
Febrile neutropenia	26	26	53	53
Lymphopenia[h]	18	16	27	26
Metabolism and nutrition disorders				
Decreased appetite	12	1	13	2
Nervous system disorders				
Headache[i]	28	2	27	1
Vascular disorders				
Hemorrhage[j]	33	5	28	5
Gastrointestinal disorders				
Nausea	31	2	46	0
Abdominal pain[k]	23	3	23	1
Diarrhea	17	1	38	1
Constipation	16	0	24	0
Vomiting	15	1	24	0
Stomatitis[l]	13	2	26	3
Hepatobiliary disorders				
Hyperbilirubinemia	21	5	17	6

Table 5. Adverse Reactions With ≥10% Incidence[a] in Patients With Relapsed or Refractory B-Cell Precursor ALL Who Received Inotuzumab Ozogamicin or Investigator's Choice of Chemotherapy (FLAG, MXN/Ara-C, or HIDAC)

Body System Adverse Reaction	Inotuzumab Ozogamicin (N=164)		FLAG, MXN/Ara-C, or HIDAC (N=143[b])	
	All Grades %	≥ Grade 3 %	All Grades %	≥ Grade 3 %
General disorders and administration site conditions				
Fatigue[m]	35	5	25	3
Pyrexia	32	3	42	6
Chills	11	0	11	0
Investigations				
Transaminases increased[n]	26	7	13	5
Gamma-glutamyltransferase increased	21	10	8	4
Alkaline phosphatase increased	13	2	7	0

Adverse reactions included treatment-emergent all-causality events that commenced on or after Cycle 1 Day 1 within 42 days after the final dose of inotuzumab ozogamicin, but prior to the start of a new anticancer treatment (including HSCT).
Preferred terms were retrieved by applying the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1.
Severity grade of adverse reactions were according to NCI CTCAE version 3.0.
Abbreviations: ALL=acute lymphoblastic leukemia; FLAG=fludarabine + cytarabine + granulocyte colony-stimulating factor; HIDAC=high dose cytarabine; HSCT=hematopoietic stem cell transplant; MXN/Ara-C=mitoxantrone + cytarabine; N=number of patients; NCI CTCAE=National Cancer Institute Common Toxicity Criteria for Adverse Events.

[a] Only adverse reactions with ≥10% incidence in the inotuzumab ozogamicin arm are included.
[b] 19 patients randomized to FLAG, MXN/Ara-C, or HIDAC did not receive treatment.
[c] Infection includes any reported preferred terms for BESPONSA retrieved in the System Organ Class Infections and infestations.
[d] Thrombocytopenia includes the following reported preferred terms: Platelet count decreased and Thrombocytopenia.
[e] Neutropenia includes the following reported preferred terms: Neutropenia and Neutrophil count decreased.
[f] Anemia includes the following reported preferred terms: Anemia and Hemoglobin decreased.
[g] Leukopenia includes the following reported preferred terms: Leukopenia, Monocytopenia, and White blood cell count decreased.
[h] Lymphopenia includes the following reported preferred terms: B-lymphocyte count decreased, Lymphocyte count decreased, and Lymphopenia.
[i] Headache includes the following reported preferred terms: Headache, Migraine, and Sinus headache.
[j] Hemorrhage includes reported preferred terms for inotuzumab ozogamicin retrieved in the Standard MedDRA Query (narrow) for Hemorrhage terms (excluding laboratory terms), resulting in the following preferred terms: Conjunctival hemorrhage, Contusion, Ecchymosis, Epistaxis, Eyelid bleeding, Gastrointestinal hemorrhage, Gastritis hemorrhagic, Gingival bleeding, Hematemesis, Hematochezia, Hematotympanum, Hematuria, Hemorrhage intracranial, Hemorrhage subcutaneous, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Lip hemorrhage, Lower gastrointestinal hemorrhage, Mesenteric hemorrhage, Metrorrhagia, Mouth hemorrhage, Muscle hemorrhage, Oral mucosa hematoma, Petechiae, Post-procedural hematoma, Rectal hemorrhage, Shock hemorrhagic, Subcutaneous hematoma, Subdural hematoma, Upper gastrointestinal hemorrhage, and Vaginal hemorrhage.
[k] Abdominal pain includes the following reported preferred terms: Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Esophageal pain, and Hepatic pain.
[l] Stomatitis includes the following reported preferred terms: Aphthous ulcer, Mucosal inflammation, Mouth ulceration, Oral pain, Oropharyngeal pain, and Stomatitis.
[m] Fatigue includes the following reported preferred terms: Asthenia and Fatigue.
[n] Transaminases increased includes the following reported preferred terms: Aspartate aminotransferase increased, Alanine aminotransferase increased, Hepatocellular injury, and Hypertransaminasemia.

Additional adverse reactions (all grades) that were reported in less than 10% of patients treated with inotuzumab ozogamicin included: lipase increased (9%), abdominal distension (6%), amylase increased (5%), hyperuricemia (4%), ascites (4%), infusion related reaction (2%; includes the following: hypersensitivity and infusion related reaction), pancytopenia (2%; includes the following: bone marrow failure, febrile bone marrow aplasia, and pancytopenia), tumor lysis syndrome (2%), and electrocardiogram QT prolonged (1%).

Table 6 shows the clinically important laboratory abnormalities reported in patients with relapsed or refractory ALL who received inotuzumab ozogamicin or Investigator's choice of chemotherapy.

Table 6. Laboratory Abnormalities in Patients With Relapsed or Refractory B-Cell Precursor ALL Who Received Inotuzumab Ozogamicin or Investigator's Choice of Chemotherapy (FLAG, MXN/Ara-C, or HIDAC)

		Inotuzumab Ozogamicin		N	FLAG, MXN/Ara-C, or HIDAC	
		All Grades	Grade 3/4		All Grades	Grade 3/4
Laboratory Abnormality[a]	**N**	**%**	**%**		**%**	**%**
Hematology						
Platelet count decreased	161	98	76	142	100	99
Hemoglobin decreased	161	94	40	142	100	70
Leukocytes decreased	161	95	82	142	99	98
Neutrophil count decreased	160	94	86	130	93	88
Lymphocytes (absolute) decreased	160	93	71	127	97	91
Chemistry						
GGT increased	148	67	18	111	68	17
AST increased	160	71	4	134	38	4
ALP increased	158	57	1	133	52	3
ALT increased	161	49	4	137	46	4
Blood bilirubin increased	161	36	5	138	35	6
Lipase increased	139	32	13	90	20	2
Hyperuricemia	158	16	3	122	11	0
Amylase increased	143	15	2	102	9	1

Severity grade of laboratory abnormalities according to NCI CTCAE version 3.0.
Abbreviations: ALL=acute lymphoblastic leukemia; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; FLAG=fludarabine + cytarabine + granulocyte colony-stimulating factor; GGT=gamma-glutamyltransferase; HIDAC=high dose cytarabine; MXN/Ara-C=mitoxantrone + cytarabine; N=number of patients; NCI CTCAE=National Cancer Institute Common Toxicity Criteria for Adverse Events.

[a] Laboratory abnormalities were summarized up to the end of treatment + 42 days but prior to the start of a new anti-cancer therapy.

Immunogenicity

In clinical studies of inotuzumab ozogamicin in patients with relapsed or refractory ALL, the immunogenicity of inotuzumab ozogamicin was evaluated using an electrochemiluminescence (ECL)-based immunoassay to test for anti-inotuzumab ozogamicin antibodies (ADA). For patients whose sera tested positive for ADA, a cell-based assay was performed to detect neutralizing antibodies (NAb).

In clinical studies of inotuzumab ozogamicin in adult patients with relapsed or refractory ALL, 7/236 (3%) patients tested positive for ADA. No patients tested positive for NAb. In patients who tested positive for ADA, the presence of positive ADA did not affect clearance following inotuzumab ozogamicin treatment. The number of patients with positive ADA was too small to assess the impact of ADA on efficacy and safety.

In clinical study ITCC-059 of inotuzumab ozogamicin in pediatric patients with relapsed or refractory ALL (n=51), the incidence of ADA against inotuzumab ozogamcin was 0%.

4.9. Overdose

There is no specific treatment or antidote for inotuzumab ozogamicin overdose. Treatment of inotuzumab ozogamicin overdose should consist of general supportive measures.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Mechanism of action

Inotuzumab ozogamicin is a CD22-targeted ADC. Inotuzumab is a humanized IgG4 antibody which specifically recognizes human CD22. The small molecule, N-acetyl-gamma-calicheamicin, is a cytotoxic semisynthetic natural product. N-acetyl-gamma-calicheamicin is covalently attached to the antibody via a linker. Nonclinical data suggest that the anticancer activity of inotuzumab ozogamicin is due to the binding of the ADC to CD22-expressing tumor cells, followed by internalization of the ADC-CD22 complex, and the intracellular release of N-acetyl-gamma-calicheamicin dimethylhydrazide via hydrolytic cleavage of the linker. Activation of N-acetyl-gamma-calicheamicin dimethylhydrazide induces double-stranded DNA breaks, subsequently inducing cell cycle arrest and apoptotic cell death.

Pharmacodynamic effects

During the treatment period, the pharmacodynamic response to inotuzumab ozogamicin was characterized by the depletion of CD22-positive leukemic blasts.

Clinical efficacy and safety

Patients with relapsed or refractory ALL who have received 1 or 2 prior treatment regimens for ALL – Study 1

The safety and efficacy of inotuzumab ozogamicin in patients with relapsed or refractory ALL were evaluated in a randomized, open-label, international, multicenter Phase 3 study (Study 1). Eligible patients were ≥18 years of age with Philadelphia chromosome-negative or Philadelphia chromosome-positive relapsed or refractory B-cell precursor ALL. All patients were required to have ≥5% marrow blasts and to have received 1 or 2 previous induction chemotherapy regimens for ALL. Patients with Philadelphia chromosome-positive B-cell precursor ALL were required to have disease that failed treatment with at least 1 tyrosine kinase inhibitor and standard chemotherapy. Table 1 shows the dosing regimen used to treat patients.

In total, 326 patients were randomized to the study.

Among all 326 patients who were randomized to receive inotuzumab ozogamicin (N=164) or Investigator's choice of chemotherapy (N=162), 215 (66%) patients had received 1 prior treatment regimen for ALL and 108 (33%) patients had received 2 prior treatment regimens for ALL. The median age was 47 years (range: 18-79 years), 276 (85%) patients had Philadelphia chromosome-negative ALL, 206 (63%) patients had a duration of first remission <12 months, and 55 (18%) patients had undergone a HSCT prior to receiving inotuzumab ozogamicin or Investigator's choice of chemotherapy. The 2 treatment groups were generally balanced with respect to the baseline demographics and disease characteristics.

All evaluable patients had B-cell precursor ALL that expressed CD22, with >90% of evaluable patients exhibiting ≥70% leukemic blast CD22 positivity prior to treatment, as assessed by flow cytometry at a central laboratory.

The primary endpoints were CR/CRi, assessed by a blinded independent EAC, and overall survival (OS). The secondary endpoints included MRD negativity, duration of remission (DoR), HSCT rate, and progression-free survival (PFS). CR/CRi, MRD, and DoR were analyzed in the initial 218 randomized patients and OS, PFS, and HSCT rate were analyzed in all 326 randomized patients.

Table 7 shows the efficacy results from this study.

Table 7. Efficacy Results in Patients With Relapsed or Refractory B-Cell Precursor ALL Who Received Inotuzumab Ozogamicin or Investigator's Choice of Chemotherapy (FLAG, MXN/Ara-C, or HIDAC)

	CR[a]		**CRi[b]**		**CR/CRi[a,b]**	
	Inotuzumab Ozogamicin (N=109)	**HIDAC, FLAG, or MXN/Ara-C (N=109)**	**Inotuzumab Ozogamicin (N=109)**	**HIDAC, FLAG or MXN/Ara-C (N=109)**	**Inotuzumab Ozogamicin (N=109)**	**HIDAC, FLAG, or MXN/Ara-C (N=109)**
Responding (CR/CRi) patients						
n (%) [95% CI]	39 (35.8) [26.8-45.5]	19 (17.4) [10.8-25.9]	49 (45.0) [35.4-54.8]	13 (11.9) [6.5-19.5]	88 (80.7) [72.1-87.7]	32 (29.4) [21.0-38.8]
p-value[c]	0.0011		<0.0001		<0.0001	
MRD negativity[d]						
n	35	6	34	3	69	9
Rate[e] (%) [95% CI]	35/39 (89.7) [75.8-97.1]	6/19 (31.6) [12.6-56.6]	34/49 (69.4) [54.6-81.7]	3/13 (23.1) [5.0-53.8]	69/88 (78.4) [68.4-86.5]	9/32 (28.1) [13.7-46.7]
p-value[c]	<0.0001		0.0034		<0.0001	

Table 7. Efficacy Results in Patients With Relapsed or Refractory B-Cell Precursor ALL Who Received Inotuzumab Ozogamicin or Investigator's Choice of Chemotherapy (FLAG, MXN/Ara-C, or HIDAC)

DoR						
n	39	18	45	14	84	32
Median (mo) [95% CI]	8.0 [4.9-10.4]	4.9 [2.9-7.2]	4.6 [3.7-5.7]	2.9 [0.6-5.7]	5.4 [4.2-8.0]	3.5 [2.9-6.6]
HR[g] [95% CI]	0.352 [0.152-0.813]		0.401 [0.181-0.887]		0.502 [0.303-0.832]	
p-value[h]	0.0058		0.0104		0.0031	

	Inotuzumab ozogamicin (N=164)	**HIDAC, FLAG, or MXN/Ara-C (N=162)**
OS		
Median (mo) [95% CI]	7.7 [6.0-9.2]	6.2 [4.7-8.3]
HR[g] [97.5% CI]	0.751 [0.568-0.993]	
p-value[h]	0.0105	
PFS		
Median (mo) [95% CI]	5.0 [3.7-5.6]	1.8 [1.5-2.2]
HR[g] [97.5% CI]	0.452 [0.336-0.609]	
p-value[h]	<0.0001	
HSCT Rate		
n (%) [95% CI]	79 (48.2) [40.3-56.1]	35 (21.6) [15.5-28.7]
p-value[c]	<0.0001	

Abbreviations: ALL=acute lymphoblastic leukemia; CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete hematologic recovery; DoR=duration of remission; EAC=Endpoint Adjudication Committee; FLAG=fludarabine + cytarabine + granulocyte colony-stimulating factor; HIDAC=high dose cytarabine; HR=hazard ratio; HSCT=hematopoietic stem cell transplant; mo=months; MRD=minimal residual disease; MXN/Ara-C=mitoxantrone + cytarabine; N/n=number of patients; OS=overall survival; PFS=progression-free survival.

[a] CR, per EAC, was defined as <5% blasts in the bone marrow and the absence of peripheral blood leukemic blasts, full recovery of peripheral blood counts (platelets ≥100 x 10^9/L and absolute neutrophil counts [ANC] ≥1 x 10^9/L) and resolution of any extramedullary disease.

[b] CRi, per EAC, was defined as <5% blasts in the bone marrow and the absence of peripheral blood leukemic blasts, partial recovery of peripheral blood counts (platelets <100 x 10^9/L and/or ANC <1 x 10^9/L) and resolution of any extramedullary disease.

[c] 1-sided p-value using Chi-squared test.

[d] MRD negativity was defined by flow cytometry as leukemic cells comprising <1 x 10^{-4} (<0.01%) of bone marrow nucleated cells.

[e] Rate was defined as the number of patients who achieved MRD negativity divided by the total number of patients who achieved CR/CRi per EAC.

[f] DoR, based on a later cutoff date than the CR/CRi , was defined for patients who achieved CR/CRi per Investigator's assessment as time since first response of CR[a] or CRi[b] per Investigator's assessment to the date of a PFS event or censoring date if no PFS event was documented.

[g] Estimated using stratified Cox regression.

[h] 1-sided p-value using stratified log-rank test.

Among the initial 218 randomized patients, 64/88 (73%) and 21/88 (24%) of responding patients per Endpoint Adjudication Committee (EAC) achieved a CR/CRi in Cycles 1 and 2,

respectively, in the inotuzumab ozogamicin arm, and 29/32 (91%) and 1/32 (3%) of responding patients per EAC achieved a CR/CRi in Cycles 1 and 2, respectively, in the Investigator's choice of chemotherapy arm.

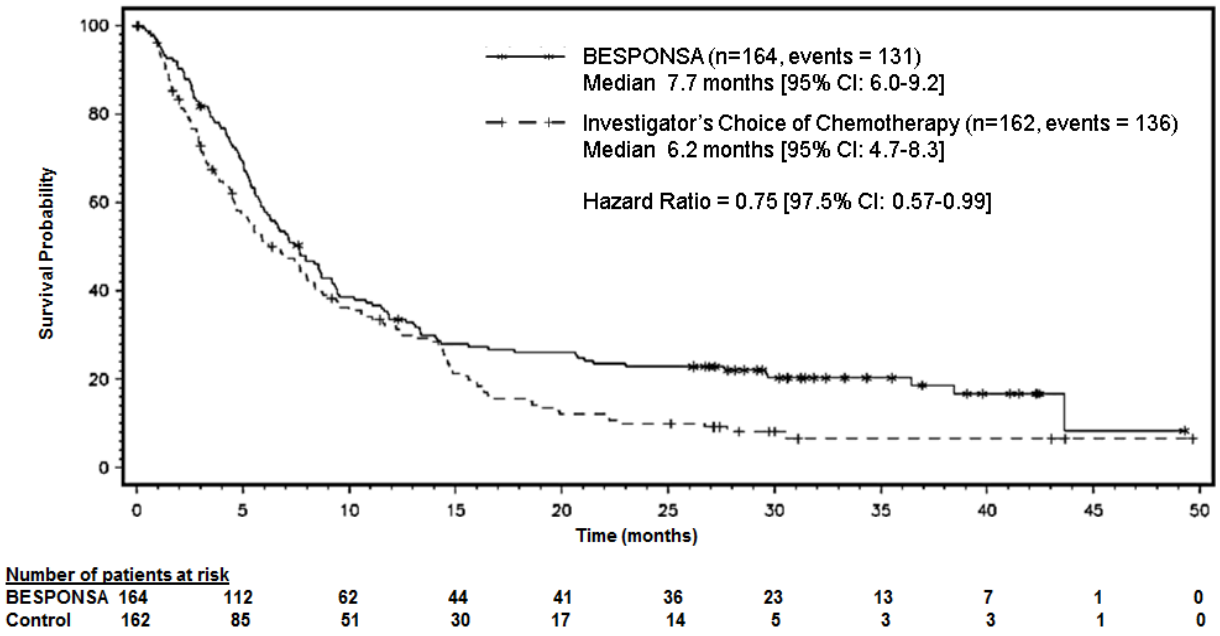
CR/CRi, MRD, and DoR results in the initial 218 randomized patients were consistent with those seen in all 326 randomized patients.

Among all 326 randomized patients, the survival probability at 24 months was 22.8% in the inotuzumab ozogamicin arm and 10.0% in the Investigator's choice of chemotherapy arm. Although there was a higher frequency of early deaths post-HSCT in the inotuzumab ozogamicin arm, an improvement in survival for inotuzumab ozogamicin versus Investigator's choice of chemotherapy was seen in patients who underwent HSCT.

Overall, 79/164 (48.2%) patients in the inotuzumab ozogamicin arm and 35/162 (21.6%) patients in the Investigator's choice of chemotherapy arm had a follow-up HSCT. This included 71 and 18 patients in the inotuzumab ozogamicin and Investigator's choice of chemotherapy arm, respectively, who proceeded directly to HSCT. In those patients who proceeded directly to HSCT, there was a median gap of 4.9 weeks (range: 1-19 weeks) between the final dose of inotuzumab ozogamicin and HSCT. In the inotuzumab ozogamicin arm, the most common causes of post-HSCT non-relapse mortality included VOD and infections (see Section 4.4). Five of the 18 VOD/SOS events that occurred post-HSCT were fatal (see Section 4.4). Six patients had ongoing VOD at time of death and died due to multiorgan failure (MOF) or infection (3 patients died due to MOF, 2 patients died due to infection, and 1 patient died due to MOF and infection). In patients who underwent a follow-up HSCT, the median OS was 11.9 months (95% CI: 9.2, 20.6) versus 18.6 months (95% CI: 14.6, 27.8) and the survival probability at Month 24 was 37.8% (95% CI: 27.2, 48.4) versus 36.2% (95% CI: 20.3, 52.3) for inotuzumab ozogamicin versus Investigator's choice of chemotherapy, respectively.

Figure 1 shows the analysis of OS. The analysis of OS did not meet the pre-specified boundary for statistical significance.

Figure 1. Kaplan-Meier Curve for Overall Survival (Intent-to-Treat Population)



Patient-reported outcomes were measured using the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30). Inotuzumab ozogamicin resulted in significantly better estimated mean postbaseline scores (inotuzumab ozogamicin and Investigator's choice of chemotherapy, respectively) in physical functioning (75.0 versus 68.1; p=0.0139), role functioning (64.7 versus 53.4; p=0.0065), social functioning (68.1 versus 59.8; p=0.0336), and appetite loss (17.6 versus 26.3; p=0.0193) compared to Investigator's choice of chemotherapy.

Patients with relapsed or refractory ALL who have received 2 or more prior treatment regimens for ALL - Study 2

The safety and efficacy of inotuzumab ozogamicin were evaluated in a single-arm, open-label, multicenter, Phase 1/2 study (Study 2). Eligible patients were ≥18 years of age with relapsed or refractory B-cell precursor ALL.

In the Phase 1 portion of the study, 37 patients received inotuzumab ozogamicin at a total dose of 1.2 mg/m^2 (n=3), 1.6 mg/m^2 (n=12), or 1.8 mg/m^2 (n=22). The recommended inotuzumab ozogamicin dose was determined to be 1.8 mg/m^2/cycle administered at a dose of 0.8 mg/m^2 on Day 1 and 0.5 mg/m^2 on Days 8 and 15 of a 28-day cycle with a dose reduction upon achieving CR/CRi.

Among the 35 patients in the Phase 2 portion who received inotuzumab ozogamicin at the recommended dose, 15 (43%) and 17 (49%) patients had received 2 or >2 prior treatment regimens for ALL, respectively. The median age was 34 years (range: 20-79 years), and 6 (17%) patients had a duration of first remission <12 months. Of these 35 patients, 24/35 (69% and 95% confidence interval [CI]: 50.7-83.2) patients achieved CR/CRi. Of the 24 patients who achieved CR/CRi, 18/24 (75%) patients also achieved MRD negativity. The median DoR was 3.8 months (95% CI: 2.2-5.8), the median PFS was 3.7 months (95% CI: 2.6-4.7), and the median OS was 6.4 months (95% CI: 4.5-7.9).

Pediatric patients

The safety and efficacy of inotuzumab ozogamicin in the pediatric population (<18 years) have not been established (see Section 4.2).

Study ITCC-059 was a Phase 1/2 multicenter, single-arm, open-label study conducted in 53 pediatric patients ≥1 and <18 years of age with relapsed or refractory CD22-positive B-cell precursor ALL to identify a recommended Phase 2 Dose (Phase 1) and to further evaluate the efficacy, safety, and tolerability of the selected inotuzumab ozogamicin dose as a monotherapy agent (Phase 2).The study also evaluated the pharmacokinetics and pharmacodynamics of inotuzumab ozogamicin as monotherapy (see Section 5.2).

In the Phase 1 Cohort (N=25), two dose levels were examined (initial dose of 1.4 mg/m^2 per cycle and an initial dose of 1.8 mg/m^2 per cycle). In the Phase 2 Cohort (N=28), patients were treated at the initial dose of 1.8 mg/m^2 per cycle (0.8 mg/m^2 on Day 1, 0.5 mg/m^2 on Days 8 and 15) followed by a dose reduction to 1.5 mg/m^2 per cycle for patients in remission. In both cohorts, patients received a median of 2 cycles of therapy (range: 1 to 4 cycles). In the Phase 1 Cohort, the median age was 11 years (range: 1-16 years), and 52% of patients had second or greater relapsed B-cell precursor ALL. In the Phase 2 Cohort, the median age was 7.5 years (range: 1-17 years), and 57% of patients had second or greater relapsed B-cell precursor ALL.

Efficacy was evaluated on the basis of Objective Response Rate (ORR), defined as the rate of patients with CR+CRp+CRi. In the Phase 1 Cohort, 20/25 (80%) patients had CR, the ORR was 80% (95% CI: 59.3-93.2), and the median Duration of Response (DoR) was 8.0 months (95% CI: 3.9-13.9). In the Phase 2 Cohort, 18/28 (64%) patients had CR, the ORR was 79% (95% CI: 59.0-91.7), and the DoR was 7.6 months (95% CI: 3.3-NE).

The most common adverse reactions (>30%) in the pediatric study ITCC-059 were thrombocytopenia (60%), pyrexia (52%), anaemia (48%), vomiting (48%), neutropenia (44%), infection (44%), haemorrhage (40%), febrile neutropenia (32%), nausea (32%), abdominal pain (32%) in the Phase 1 Cohort and pyrexia (46%), thrombocytopenia (43%), anemia (43%), vomiting (43%), neutropenia (36%), leukopenia (36%), nausea (32%), infection (32%), transaminase increased (32%), and hemorrhage (32%) in the Phase 2 Cohort.

In the Phase 1 Cohort, 2/25 (8.0%) patients had VOD (neither received transplant) and 6/28 (21.4%) patients in the Phase 2 Cohort had VOD, with a post-HSCT VOD rate of 5/18 (27.8% [95% CI: 9.69-53.48]). In the Phase 1 Cohort, 8/25 patients (32%) and 18/28 (64%) in the Phase 2 Cohort had a follow-up HSCT. The post-HSCT non-relapse mortality rate was 2/8 (25%) and 5/18 (28%) in the Phase 1 Cohort and the Phase 2 Cohort, respectively.

5.2. Pharmacokinetic properties

In patients with relapsed or refractory ALL, steady-state exposure was achieved by Cycle 4. The mean maximum observed concentration (C_{max}) of inotuzumab ozogamicin was 308 ng/mL. The mean simulated total area under the concentration-time curve (AUC) per cycle was 100,000 ng•h/mL.

Distribution

In vitro, the binding of N-acetyl-gamma-calicheamicin dimethylhydrazide to human plasma proteins is approximately 97%. *In vitro*, N-acetyl-gamma-calicheamicin dimethylhydrazide is a substrate of P-glycoprotein (P-gp). In humans, the total volume of distribution of inotuzumab ozogamicin was approximately 12 L.

Metabolism

In vitro, N-acetyl-gamma-calicheamicin dimethylhydrazide was primarily metabolized via nonenzymatic reduction. In humans, N-acetyl-gamma-calicheamicin dimethylhydrazide serum levels were typically below the limit of quantitation.

Elimination

Inotuzumab ozogamicin pharmacokinetics were well characterized by a 2-compartment model with linear and time-dependent clearance components. In 234 patients with relapsed or refractory ALL, the clearance of inotuzumab ozogamicin at steady state was 0.0333 L/h, and the terminal half-life ($t_{½}$) was 12.3 days. Following administration of multiple doses, a 5.3 times accumulation of inotuzumab ozogamicin was predicated by Cycle 4.

Based on a population pharmacokinetic analysis in 765 patients, body surface area was found to significantly affect inotuzumab ozogamicin disposition. The dose of inotuzumab ozogamicin is administered based on body surface area (see Section 4.2).

Drug interactions

Effect of other drugs on inotuzumab ozogamicin

In vitro, N-acetyl-gamma-calicheamicin dimethylhydrazide is primarily metabolized via nonenzymatic reduction. Therefore, coadministration of inotuzumab ozogamicin with inhibitors or inducers of cytochrome P450 (CYP) or uridine diphosphate glucuronosyltransferase (UGT) drug metabolizing enzymes are unlikely to alter exposure to N-acetyl-gamma-calicheamicin dimethylhydrazide.

Based on a population pharmacokinetic analysis in 736 patients, concomitant administration of cytoreductive drugs including hydroxyurea, granulocyte colony-stimulating factors including filgrastim or lenograstim, and P-gp inhibitors, had no apparent effect on inotuzumab ozogamicin clearance.

Effect of inotuzumab ozogamicin on other drugs

Effect on CYP substrates:

In vitro, N-acetyl-gamma-calicheamicin dimethylhydrazide and inotuzumab ozogamicin had a low potential to inhibit the activities of CYP1A2, CYP2A6 (tested only using inotuzumab ozogamicin), CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 or to

induce the activities of CYP1A2, CYP2B6, and CYP3A4 at clinically relevant concentrations.

Effect on UGT substrates:

In vitro, N-acetyl-gamma-calicheamicin dimethylhydrazide had a low potential to inhibit the activities of UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7 at clinically relevant concentrations.

Effect on drug transporter substrates:

In vitro, N-acetyl-gamma-calicheamicin dimethylhydrazide had a low potential to inhibit the activities of P-gp, breast cancer resistance protein (BCRP), organic anion transporter (OAT)1 and OAT3, organic cation transporter (OCT)2, and organic anion transporting polypeptide (OATP)1B1 and OATP1B3 at clinically relevant concentrations.

Pharmacokinetics in specific groups of subjects or patients

Age, race, and gender

Based on a population pharmacokinetic analysis, age, race, and gender did not significantly affect inotuzumab ozogamicin disposition.

Hepatic impairment

No formal pharmacokinetic studies of inotuzumab ozogamicin have been conducted in patients with hepatic impairment.

Based on a population pharmacokinetic analysis in 765 patients, the clearance of inotuzumab ozogamicin in patients with hepatic impairment defined by National Cancer Institute Organ Dysfunction Working Group (NCI ODWG) category B1 (total bilirubin ≤ULN and AST > ULN; n=133) or B2 (total bilirubin >1.0-1.5 × ULN and AST any level; n=17) was similar to patients with normal hepatic function (total bilirubin/AST ≤ULN; n=611) (see Section 4.2). In 3 patients with hepatic impairment defined by NCI ODWG category C (total bilirubin >1.5-3 × ULN and AST any level) and 1 patient with NCI ODWG category D (total bilirubin >3 × ULN and AST any level), inotuzumab ozogamicin clearance did not appear to be reduced.

Renal impairment

No formal pharmacokinetic studies of inotuzumab ozogamicin have been conducted in patients with renal impairment.

Based on population pharmacokinetic analysis in 765 patients, the clearance of inotuzumab ozogamicin in patients with mild renal impairment (CL_{cr} 60-89 mL/min; n=237), moderate renal impairment (CL_{cr} 30-59 mL/min; n=122), or severe renal impairment (CL_{cr} 15-29 mL/min; n=4) was similar to patients with normal renal function (CL_{cr} ≥90 mL/min; n=402) (see Section 4.2). The safety and efficacy of inotuzumab ozogamicin have not been studied in patients with end-stage renal disease (see Section 4.2).

Pediatric patients

Based on population pharmacokinetic analysis in 824 patients, patient age group (pediatric [≥1 and <18 years of age], n=59 vs adult, n=765) is not considered to have a significant effect on inotuzumab ozogamicin disposition over the treatment duration.

Cardiac electrophysiology

Based on a pharmacokinetic exposure-response analysis in 250 patients with relapsed or refractory ALL or other hematologic malignancies who received 1.8 mg/m^2/cycle inotuzumab ozogamicin administered as 3 divided doses on Days 1 (0.8 mg/m^2), 8 (0.5 mg/m^2), and 15 (0.5 mg/m^2) of a 21- to 28-day cycle or 1.8 mg/m^2/cycle administered once every 4 weeks, respectively, the median QTcF interval increased by 2.53 milliseconds (msec) from baseline (97.5th percentile: 4.92 msec) at the average C_{max} estimated for patients with relapsed or refractory ALL (371 ng/mL) and by 3.87 msec from baseline (97.5th percentile: 7.54 msec) at a 1.5 times higher average C_{max} (569 ng/mL).

In a randomized clinical study in patients with relapsed or refractory ALL (Study 1), increases in QTcF of ≥60 msec from baseline were measured in 4/162 (3%) patients in the inotuzumab ozogamicin arm and 3/124 (2%) patients in the Investigator's choice of chemotherapy arm. Increases in QTcF of >500 msec were observed in none of the patients in the inotuzumab ozogamicin arm and 1/124 (1%) patients in the Investigator's choice of chemotherapy arm. Mean (90% CI) maximum QTcF changes from baseline were 16.5 msec (14.3-18.7) in the inotuzumab ozogamicin arm and 10.8 msec (8.0-13.6) in the Investigator's choice of chemotherapy arm. Central tendency analysis of the QTcF interval changes from baseline showed that the highest upper bound of the 2-sided 90% CI for QTcF was 21.1 msec (observed at Cycle 4/Day 1/1 hour) in the inotuzumab ozogamicin arm and 21.2 msec (observed at Cycle 2/Day 1/1 hour) in the Investigator's choice of chemotherapy arm (see Section 4.4).

5.3. Preclinical safety data

Repeat-dose toxicity

In animals, the primary target organs included the liver, bone marrow and lymphoid organs with associated hematologic changes, and kidney and nervous system changes. Other observed changes included male and female reproductive organ effects and preneoplastic and neoplastic liver lesions (see below). Most effects were reversible to partially reversible except for effects in the liver and nervous system. The relevance of the irreversible animal findings to humans is uncertain.

Genotoxicity

Inotuzumab ozogamicin was clastogenic *in vivo* in the bone marrow of male mice. This is consistent with the known induction of DNA breaks by calicheamicin. N-acetyl-gamma-calicheamicin dimethylhydrazide (the cytotoxic agent released from inotuzumab ozogamicin) was mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay.

Carcinogenicity

Formal carcinogenicity studies have not been conducted with inotuzumab ozogamicin. In toxicity studies, rats developed oval cell hyperplasia, altered hepatocellular foci, and hepatocellular adenomas in the liver at approximately 0.3 times the human clinical exposure based on AUC. In 1 monkey, a focus of hepatocellular alteration was detected at approximately 3.1 times the human clinical exposure based on AUC at the end of the 26-week dosing period. The relevance of these animal findings to humans is uncertain.

Reproductive toxicity

Administration of inotuzumab ozogamicin to female rats at the maternally toxic dose (approximately 2.3 times the human clinical exposure based on AUC) prior to mating and during the first week of gestation resulted in embryo-foetal toxicity, including increased resorptions and decreased viable embryos. The maternally toxic dose (approximately 2.3 times the human clinical exposure based on AUC) also resulted in fetal growth retardation, including decreased fetal weights and delayed skeletal ossification. Slight fetal growth retardation in rats also occurred at approximately 0.4 times the human clinical exposure based on AUC (see Section 4.6).

Inotuzumab ozogamicin is considered to have the potential to impair reproductive function and fertility in men and women based on nonclinical findings. In repeat-dose toxicity studies in rats and monkeys, female reproductive findings included atrophy of ovaries, uterus, vagina, and mammary gland. The no observed adverse effect level (NOAEL) for the effects on female reproductive organs was approximately 2.2 and 3.1 times the human clinical exposure based on AUC, respectively. In repeat-dose toxicity studies in rats, male reproductive findings included testicular degeneration associated with hypospermia, and prostatic and seminal vesicle atrophy. The NOAEL was not identified for the effects on male reproductive organs, which were observed at approximately 0.3 times the human clinical exposure based on AUC (see Section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sucrose
Polysorbate 80
Sodium chloride
Tromethamine

6.2. Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in Section 6.6.

6.3. Shelf life

Unopened vials

Refer to outer carton for expiration date.

Reconstituted solution

Inotuzumab ozogamicin contains no bacteriostatic preservatives. The reconstituted solution must be used immediately. If the reconstituted solution cannot be used immediately, it may be stored for up to 4 hours in a refrigerator (2°-8°C; 36°-46°F). Protect from light and do not freeze.

Diluted solution

The diluted solution should be used immediately or stored at room temperature (20°-25°C; 68°-77°F) or in a refrigerator (2°-8°C; 36°-46°F). The maximum time from reconstitution through administration should be ≤8 hours, with ≤4 hours between reconstitution and dilution. Protect from light and do not freeze.

6.4. Special precautions for storage

Store in a refrigerator (2°-8°C; 36°-46°F).
Do not freeze.
Store in the original carton in order to protect from light.

For storage conditions after reconstitution and dilution, see Section 6.3.

6.5. Nature and contents of container

Type I amber glass vial with chlorobutyl rubber stoppers and crimp seal with flip-off cap containing 1 mg of powder.

Each carton contains 1 vial.

6.6. Special precautions for disposal and handling

Instructions for reconstitution, dilution, and administration

Use appropriate aseptic technique for the reconstitution and dilution procedures. Inotuzumab ozogamicin (which has a density of 1.02 g/mL at 20°C/68°F) is light sensitive and should be protected from ultraviolet light during reconstitution, dilution, and administration.

The maximum time from reconstitution through the end of administration should be ≤8 hours, with ≤4 hours between reconstitution and dilution.

Reconstitution

- Calculate the dose (mg) and number of vials of inotuzumab ozogamicin required.
- Reconstitute each 1 mg vial with 4 mL of sterile water for injection to obtain a single-use solution of 0.25 mg/mL of inotuzumab ozogamicin.
- Gently swirl the vial to aid dissolution. Do not shake.
- Inspect the reconstituted solution for particulates and discoloration. The reconstituted solution should be clear to slightly cloudy, colorless, and essentially free of visible foreign matter.

- Inotuzumab ozogamicin contains no bacteriostatic preservatives. The reconstituted solution should be used immediately. If the reconstituted solution cannot be used immediately, it may be stored in a refrigerator (2°-8°C; 36°-46°F) for up to 4 hours. Protect from light and do not freeze.

Dilution

- Calculate the required volume of the reconstituted solution needed to obtain the appropriate dose according to patient body surface area. Withdraw this amount from the vial(s) using a syringe. Protect from light. Discard any unused reconstituted solution left in the vial.
- Add the reconstituted solution to an infusion container with sodium chloride 9 mg/mL (0.9%) solution for injection to a total nominal volume of 50 mL. The final concentration should be between 0.01 and 0.1 mg/mL. Protect from light. An infusion container made of polyvinyl chloride (PVC) (di(2-ethylhexyl)phthalate [DEHP]- or non-DEHP-containing), polyolefin (polypropylene and/or polyethylene), or ethylene vinyl acetate (EVA) is recommended.
- Gently invert the infusion container to mix the diluted solution. Do not shake.
- The diluted solution must be used immediately, or after being stored at room temperature (20°-25°C; 68°-77°F) or in a refrigerator (2°-8°C; 36°-46°F). The maximum time from reconstitution through the end of administration should be ≤8 hours, with ≤4 hours between reconstitution and dilution. Protect from light and do not freeze.

Administration

- If the diluted solution is stored in a refrigerator (2°-8°C; 36°-46°F), it must be allowed to equilibrate at room temperature (20°-25°C; 68°-77°F) for approximately 1 hour prior to administration.
- Filtration of the diluted solution is not required. However, if the diluted solution is filtered, polyethersulfone (PES)-, polyvinylidene fluoride (PVDF)- or hydrophilic polysulfone (HPS)-based filters are recommended. Do not use filters made of nylon or mixed cellulose ester (MCE).
- Protect the intravenous bag from light using an ultraviolet light-blocking cover (i.e., amber, dark brown, or green bags or aluminum foil) during infusion. The infusion line does not need to be protected from light.
- Infuse the diluted solution for 1 hour at a rate of 50 mL/h at room temperature (20°-25°C; 68°-77°F). Protect from light. Infusion lines made of PVC (DEHP- or non-DEHP-containing), polyolefin (polypropylene and/or polyethylene), or polybutadiene are recommended.

Do not mix inotuzumab ozogamicin or administer as an infusion with other medicinal products.

Table 8 shows the storage times and conditions for reconstitution, dilution, and administration of inotuzumab ozogamicin.

Table 8. Storage Times and Conditions for Reconstituted and Diluted Inotuzumab Ozogamicin Solution

← Maximum time from reconstitution through administration ≤8 hours[a] →

Reconstituted Solution	Diluted Solution	
	After Start of Dilution	**Administration**
Use reconstituted solution immediately or after being stored in a refrigerator (2°-8°C; 36°-46°F) for up to 4 hours. Protect from light. Do not freeze.	Use diluted solution immediately or after being stored at room temperature (20°-25°C; 68°-77°F) or in a refrigerator (2°-8°C; 36°-46°F). The maximum time from reconstitution through the end of administration should be ≤8 hours, with ≤4 hours between reconstitution and dilution. Protect from light. Do not freeze.	If the diluted solution is stored in a refrigerator (2°-8°C; 36°-46°F), bring it to room temperature (20°-25°C; 68°-77°F) for approximately 1 hour prior to administration. Administer diluted solution as a 1 hour infusion at a rate of 50 mL/h at room temperature (20°-25°C; 68°-77°F). Protect from light.

[a] With ≤4 hours between reconstitution and dilution.

Disposal

Inotuzumab ozogamicin is for single use only.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT OWNER

Pfizer Inc
New York,
United States

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