

ARTICLE

Characterization of the Relationship of Inotuzumab Ozogamicin Exposure With Efficacy and Safety End Points in Adults With Relapsed or Refractory Acute Lymphoblastic Leukemia

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Inotuzumab ozogamicin (InO), an anti-CD22 monoclonal antibody conjugated to calicheamicin, is approved in Europe and the United States for treatment of adults with relapsed or refractory acute lymphoblastic leukemia (ALL). Population analyses were performed to evaluate the relationship between InO exposure and efficacy and safety end points in patients with ALL. The probability of achieving complete remission/complete remission with incomplete hematologic recovery (CR/CRi) and minimal residual disease (MRD)-negativity for InO relative to chemotherapy was also investigated. Data from study 1010 (NCT01363297) and INO-VATE (NCT01564784) were pooled for exposure–response (InO, $n = 234$) and treatment–response (InO, $n = 234$; chemotherapy, $n = 143$) analyses. The analyses demonstrated that InO exposure was significantly correlated with achieving CR/CRi and MRD-negativity, as well as with hepatic event adjudication board-reported veno-occlusive disease/sinusoidal obstruction. Patients with ALL treated with InO had significantly greater odds of achieving CR/CRi (7-times higher) and MRD-negativity (13-times higher) than those receiving chemotherapy.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Prior to this analysis, there was no knowledge of the relationship between inotuzumab ozogamicin (InO) exposure and InO efficacy and safety end points.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ By evaluating safety and efficacy end points via generalized binomial logistic regression, this analysis characterized the relationship between the observed response with InO exposure.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ This analysis demonstrated a significant relationship between InO exposure and achieving complete remission/complete remission with incomplete hematologic recovery (CR/CRi) and minimal residual disease (MRD)-negativity, and that the percentage of CD22-positive leukemic blasts at baseline was a predictive covariate.

Additionally, baseline cytogenetic characteristics were a significant predictor of achieving MRD-negativity. Patients receiving InO had significantly greater odds of achieving CR/CRi and MRD-negativity than those receiving chemotherapy. Veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) was the only safety end point that showed a statistically significant positive relationship with InO exposure; post-therapy hematopoietic stem cell transplant was also a significant predictor of VOD/SOS.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

☑ This study will aid medical professionals to make informed decisions regarding dose modifications and the impact it will have on safety and efficacy for their patients with acute lymphoblastic leukemia.

Inotuzumab ozogamicin (InO), an anti-CD22 monoclonal antibody conjugated to calicheamicin, is approved in Europe and the United States for treatment of adults with relapsed or refractory (R/R) acute lymphoblastic leukemia (ALL).^{1,2} Efficacy and safety of InO in patients with R/R ALL was demonstrated in the phase I/II study 1010 (ClinicalTrials.gov, NCT01363297) and the phase III

INO-VATE trial (ClinicalTrials.gov, NCT01564784).^{3,4} In the INO-VATE primary intent-to-treat analysis ($n = 218$), patients randomized to InO had a significantly higher ($P < 0.001$) rate of complete remission/complete remission with incomplete hematologic recovery (CR/CRi; 80.7% vs. 29.4%), with a higher rate of minimal residual disease (MRD)-negativity among those achieving CR/CRi (78.4% vs. 28.1%) vs.

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control arm (investigator's choice of chemotherapy).³ With long-term follow-up (≥ 24 months; intent-to-treat, $n = 326$), rates of remission and MRD-negativity remained higher and overall survival (OS) was longer (hazard ratio 0.751; 97.5% confidence interval (CI) 0.568–0.993; $P = 0.01$) with InO.⁴ In clinical studies, InO was generally well-tolerated, with frequently reported adverse events (AEs) being hematologic cytopenias, elevated liver function tests, and veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS).^{3–5}

The objective of this analysis was to determine the relationship between InO exposure and efficacy and safety end points. The analyses explored baseline demographic variables and disease status factors as potential explanatory variables (covariates) of the selected end points. Further, it was of high clinical interest to perform a treatment–response analysis for selected efficacy end points to quantify the superiority of InO treatment in this patient population relative to investigator's choice of chemotherapy.

METHODS

Study design

Data were pooled from two studies in patients with R/R CD22-positive B-cell ALL treated with InO (study 1010 and long-term INO-VATE data) vs. control (INO-VATE only). Control comprised investigator's choice of chemotherapy (fludarabine/cytarabine/granulocyte colony-stimulating factor, mitoxantrone/cytarabine, or high-dose cytarabine). Full methodology for these trials has been previously published^{3,4} and is described in brief in the **Supplementary Material S1**.

Efficacy (CR/CRi and MRD-negativity) and safety (see **Supplementary Material S1**) end points were monitored. Individual pharmacokinetic (PK) parameters were estimated using a previously reported InO population PK model.⁶ InO exposure parameters were calculated for the time of event, or for the duration of treatment if no response was achieved, and included: maximum observed concentration prior to response ($C_{\max\text{event}}$), maximum observed concentration for the duration of treatment ($C_{\max\text{overall}}$), cumulative area under the concentration-time curve (cAUC), average plasma concentration (C_{avg}), and cumulative area under the concentration-time curve in the first cycle of treatment (cAUCP1).

Modeling software and strategy

All models utilized events as dependent variable or response, which was defined as yes/no for CR/CRi, MRD-negativity, any hepatic event (defined by a prespecified cluster term), VOD/SOS, and grade ≥ 3 AEs based on laboratory abnormality data for neutropenia, thrombocytopenia, elevated alanine aminotransferase (ALT), elevated aspartate aminotransferase (AST), and elevated total bilirubin. The standard Medical Dictionary for Regulatory Activities queries were based on version 18.1. The preferred terms included in the “any hepatic event” cluster were VOD in the liver, hepatic vein occlusion, hepatic vein thrombosis, portal vein thrombosis, Budd-Chiari syndrome, chronic graft vs. host disease in the liver, or acute graft vs. host disease in the liver.

Analyses were performed using generalized binomial logistic regression as implemented with the glm

(family = “binomial”) function in the R programming language, version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria). The models developed for this analysis consisted of three components: (i) base model, which included either treatment arm (treatment–response) or InO exposure (exposure–response); (ii) full covariate model, which included all potential explanatory variables as fixed effects that may influence response; and (iii) final model, which included all statistically significant fixed effects that influenced response.

Base model development. Base models were developed for each safety and efficacy end point. Any parameter included in the base model was not subject to removal during the development of the final model. During model development, the major aspects captured by the base model were treatment arm in the treatment–response analysis, exposure to InO (exposure–response for efficacy and safety end points), and associated baseline laboratory parameters (exposure–response for safety end points).

To assess the exposure–response or treatment–response relationship for each of the efficacy and safety end points, a logistic regression of the following form was used:

$$\text{logit}(p(Y)) = \theta_1 + \theta_2 \cdot \text{InO exposure/ARM} + \theta_3 \cdot \text{covariates}$$

where θ_1 represents the cutoff or intercept, θ_2 represents a linear effect of the exposure to InO (exposure–response) or the effect of treatment arm (treatment–response) on the probability of the event occurring, θ_3 represents the estimate of the effect of an additional covariate, and ARM represents the treatment arm.

Covariate selection and full model development.

Covariates initially deemed clinically relevant were considered for model inclusion for each efficacy and safety end point. Potential predictors of response for the end points included ARM (treatment–response analysis only), race, sex, age, body surface area, baseline Eastern Cooperative Oncology Group Performance Status (ECOG PS), salvage status, hematopoietic stem cell transplant (HSCT) post-therapy (VOD/SOS only), prior study HSCT (PSCT), baseline laboratory measurements (albumin, alkaline phosphatase, baseline bilirubin (BBIL), baseline ALT (BALT), baseline AST (BAST), creatinine clearance, B-lymphocytes, platelets, and neutrophils), baseline cytogenetics, baseline total blast counts in peripheral blood, percentage of bone marrow blasts, percentage of CD22-positive blasts (assessed by bone marrow and/or peripheral blood), *Ph/bcr-abl* status, and prior liver disease (hepatic-related end points only). Concomitant treatment with P-glycoprotein inhibitors and growth factor stimulatory treatments were also explored for potential association to the endpoint of interest. Both categorical and continuous covariates were included as a linear function.

Final model development. Final model development began with the full model and was subjected to a backward elimination algorithm. In this algorithm, significance was

determined using deviance (D), which can be shown to be approximately χ^2 distributed with degrees of freedom equal to the difference in the number of parameters estimated. Smaller values of D indicate a better fit. To compare two nested models, the difference in the D of each of the models also follows approximately χ^2 distribution with degrees of freedom equal to the difference in the number of parameters estimated.

This difference was used to judge whether a covariate should remain in the model during the backward elimination by using a removal threshold of a change in D greater than $\chi^2_{0.99} = 6.63$ for safety and $\chi^2_{0.95} = 3.84$ for efficacy. This corresponds to a $P \leq 0.01$ and $P \leq 0.05$ for the safety and efficacy analyses, respectively. When the removal of any of the remaining covariates resulted in a significant increase in ΔD , the elimination process stopped and the model was considered final. Variables specified in the base model were not subject to removal from the model regardless of statistical significance. Hosmer-Lemeshow test and area under the receiver-operating characteristic curve were utilized to evaluate the final model for model adequacy and predictive performance.

RESULTS

Study population

The pooled study population for the exposure-response analysis included patients who had PK information available and received at least one dose of InO (study 1010, $n = 72$; INO-VATE, $n = 162$). For the treatment-response analysis, the exposure-response study population and the control arm from INO-VATE ($N = 143$) were included. Baseline categorical and continuous covariates are shown in **Table 1**. Overall, 62% of patients were men, 72% were white, and median age was 46 years (range 18–79 years). The majority of patients were receiving salvage 1 or 2 therapy (59% and 33%, respectively), and 20% of patients had HSCT prior to the study. **Table 2** details the number of patients and the efficacy outcomes for the 377 patients included in the study population. In INO-VATE, the rate of CR/CRi was approximately twofold higher in the InO arm (74%) vs. the control arm (35%); MRD-negativity was achieved by 62% ($n = 97/156$) and 17% ($n = 23/138$) of patients, respectively. In study 1010, 68% of patients achieved CR/CRi and 57% achieved MRD-negativity.

Exposure-response analysis for efficacy end points

CR/CRi and MRD-negativity are binomially distributed variables (yes/no). Logistic regression analysis allowed construction of a linear predictor for probabilities of response ranging from 0 to 100%. Moreover, the odds ratio (OR) is considered better than probability to represent the chance of an event occurring relative to a reference situation (i.e., InO vs. control). This exposure-response analysis explored intrinsic and extrinsic factors as potential predictors of response and intended to characterize, if any, relationships between InO exposure and response.

Statistically significant predictors ($\alpha = 0.05$) of the efficacy end point (CR/CRi) were: (i) the C_{avg} , which was calculated as the ratio of cAUC over the timeframe for the cumulative exposure, and (ii) the percentage of leukemic blasts that were CD22-positive at baseline. The percentage of leukemic blasts that

were CD22-positive at baseline used in this model (BMCD22h) was a hybrid variable created using values from the percentage of leukemic blasts that were CD22-positive in bone marrow at baseline; when this value was missing, it was imputed by using the percentage of leukemic blasts that were CD22-positive from peripheral blood at baseline, in place of the missing value. The final model parameters are presented in **Table 3**. The logistic regression equation for the final model was:

$$\text{Logit}(P) = \log\left(\frac{P}{1-P}\right) = -11.202 + 0.051 \cdot \text{BMCD22h} + 2.108 \cdot \log(C_{avg}).$$

The coefficients represent the effect on the probability of achieving CR/CRi that one unit change in value of a variable has (BMCD22h and C_{avg}).

To better understand the obtained logistic regression parameters, the predicted probabilities were calculated categorizing the continuous variable BMCD22h in two groups: $< 90\%$ and $\geq 90\%$ leukemic blasts CD22-positive at baseline. **Figure 1** illustrates the differences in predicted probabilities by percent CD22-positive leukemic blasts at baseline and InO exposure represented by C_{avg} .

For the MRD-negativity end point, C_{avg} , the percentage of leukemic blasts that are CD22-positive at baseline and baseline cytogenetic characteristics were found to be statistically significant predictors ($\alpha = 0.05$). The variable baseline cytogenetic characteristics (normal, Philadelphia chromosome-positive (Ph+), complex, t(4;11), other, and missing) were regrouped after testing the overall effect of the six categories on MRD-negativity into three new groups:

- Reference group: normal baseline cytogenetics (20 or more metaphases) with Ph(+) and other.
- BCYTOC2: missing information and normal baseline cytogenetics with fewer than 20 metaphases or with an unknown number of metaphases.
- BCYTOC1: abnormalities designated as t(4;11) and complex cytogenetics.

The coefficients in the two baseline cytogenetic characteristic terms indicate an increase (> 0) or decrease (< 0) in the probability of achieving MRD-negativity relative to the baseline cytogenetic characteristics in the reference group. The final model parameters are presented in **Table 3**. The logistic regression equation for the final model was:

$$\begin{aligned} \text{Logit}(P) &= \log\left(\frac{P}{1-P}\right) \\ &= -14.104 - 1.184 \cdot \text{BCYTO1} - 0.6 \cdot \text{BCYTO2} \\ &\quad + 2.325 \cdot \log(C_{avg}) + 0.066 \cdot \text{BMCD22h} \\ &\quad + 2.325 \cdot \log(C_{avg}) + 0.066 \cdot \text{BMCD22h} \end{aligned}$$

The coefficients represent the effect on the probability of achieving MRD-negativity when a factor is present vs. absent (categorical variables, such as BCYTOC) or the effect that one unit change in value of a variable has on the probability of achieving MRD-negativity.

Table 1 Summary of patient characteristics by study and treatment

Characteristic	Study 1010 InO n = 72 ^a	INO-VATE InO n = 162 ^b	INO-VATE Control n = 143 ^c	Total N = 377
Male, n (%)	51 (71)	90 (56)	92 (64)	233 (62)
Age, median (range), years	45.0 (20–79)	46.5 (20–78)	47.0 (18–79)	46.0 (18–79)
Race, n (%)				
White	55 (76)	110 (68)	105 (73)	270 (72)
Black	2 (3)	4 (2)	3 (2)	9 (2)
Asian	6 (8)	31 (19)	20 (14)	57 (15)
Other	9 (12)	17 (10)	15 (10)	41 (11)
BL ECOG PS, n (%)				
0	12 (17)	62 (38)	55 (38)	129 (34)
1	41 (57)	79 (49)	70 (49)	190 (50)
2	16 (22)	21 (13)	17 (12)	54 (14)
3	3 (4)	0 (0)	0 (0)	3 (1)
Missing	0 (0)	0 (0)	1 (1)	1 (0)
BL CD22-positivity, n (%) ^d				
< 70%	5 (7)	5 (3)	17 (12)	27 (7)
70–90%	8 (11)	30 (19)	15 (10)	53 (14)
≥ 90%	58 (81)	107 (66)	85 (59)	250 (66)
Missing	1 (1)	20 (12)	26 (18)	47 (12)
Salvage therapy, n (%)				
1	17 (24)	111 (69)	95 (66)	223 (59)
2	28 (39)	49 (30)	47 (33)	124 (33)
3	27 (38)	0 (0)	0 (0)	27 (7)
Missing	0 (0)	2 (1)	1 (1)	3 (1)
BL cytogenetics, n (%)				
Normal	11 (15)	35 (22)	29 (20)	75 (20)
Ph+	16 (22)	21 (13)	23 (16)	60 (16)
Complex	15 (21)	27 (17)	21 (15)	63 (17)
t(4;11)	2 (3)	6 (4)	6 (4)	14 (4)
Other	18 (25)	42 (26)	37 (26)	97 (26)
Missing/unknown	10 (14)	31 (19)	27 (19)	68 (18)
Dual alkylator treatment, n (%)	2 (3)	11 (7)	7 (5)	20 (5)
PSCT, n (%)	23 (32)	28 (17)	26 (18)	77 (20)
Post-study therapy HSCT, n (%)	24 (33)	77 (48)	32 (22)	133 (35)
BL WT, median (range), kg	77.7 (30.9–153.5)	72.0 (45.0–133.9)	76.6 (39.0–192.0)	76.0 (30.9–192.0)
BL BSA, median (range), m ²	1.9 (1.3–2.8)	1.9 (1.3–2.5)	1.9 (1.4–3.1)	1.9 (1.3–3.1)
BL CCL, median (range), mL/min	128.8 (29.4–367.7)	118.6 (36.3–350.5)	122.3 (57.5–501.6)	122.1 (29.4–501.6)
BL albumin, median (range), g/dL	3.7 (1.8–4.6)	3.8 (2.0–4.9)	3.7 (2.1–5.0)	3.7 (1.8–5.0)
BL ALT, median (range), U/L	36.0 (5.0–161.0)	31.0 (5.0–138.0)	31.9 (7.0–180.0)	32.2 (5.0–180.0)
BL ALK median (range), U/L	94.5 (44.0–283.0)	76.0 (36.0–1209.0)	84.0 (26.0–432.0)	83.0 (26.0–1209.0)
BL AST, median (range), U/L	33.0 (11.0–131.0)	24.00 (5.0–187.0)	27.0 (5.0–153.0)	27.0 (5.0–187.0)
BL bilirubin, median (range), mg/dL	0.5 (0.1–1.2)	0.5 (0.1–2.2)	0.5 (0.1–1.4)	0.5 (0.1–2.2)
BL BM blasts, median (range), %	82.8 (10.0–100.0)	71.0 (5.0–100.0)	74.8 (5.0–100.0)	76.0 (5.0–100.0)
BL PB blasts, median (range), %	11.5 (0.0–95.0)	4.0 (0.0–100.0)	2.0 (0.0–92.0)	4.0 (0.0–100.0)
BL neutrophils, median (range), 10 ⁹ cells/L	1.7 (0.0–20.0)	1.5 (0.0–17.9)	1.8 (0.0–17.5)	1.6 (0.0–20.0)
BL platelets, median (range), 10 ⁹ cells/L	38.0 (7.0–302.0)	54.5 (2.0–319.0)	54.0 (4.0–285.0)	53.1 (2.0–319.0)

ALK, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, baseline; BM, bone marrow; BSA, body surface area; CCL, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group Performance Status; InO, inotuzumab ozogamicin; HSCT, hematopoietic stem cell transplantation; PB, peripheral blood; Ph+, Philadelphia chromosome-positive; PSCT, prior study HSCT; U/L, upper/lower; WT, body weight.

^aFor study 1010, the number of patients corresponds to all patients who were randomized and treated by the cutoff date, January 30, 2016.

^bINO-VATE randomized and treated 164 patients in the InO arm. Pharmacokinetic information was not available for two patients, and therefore they were excluded from the current study. Data cutoff date, March 8, 2016.

^cINO-VATE randomized 162 patients into the SC arm, with 143 patients receiving treatment. Data cutoff date, March 8, 2016.

^dThe percentage of leukemic blasts that were CD22-positive was assessed using BM samples; when BM samples were missing, the percentage of leukemic blasts that were CD22-positive was assessed using PB samples.

Table 2 Eligible patients by study and treatment

Variable	Category	Study 1010 InO	INO-VATE InO	INO-VATE Control	Total
<i>n</i> ^a		72	162	143	377
CR/CRi	CR/CRi (-)	23 (32%)	42 (26%)	93 (65%)	158 (42%)
	CR/CRi (+)	49 (68%)	120 (74%)	50 (35%)	219 (58%)
HSCT:CR/CRi	CR/CRi (+):No HSCT	27 (38%)	51 (31%)	29 (20%)	107 (28%)
	CR/CRi (+):HSCT	22 (31%)	69 (43%)	21 (15%)	112 (30%)
	CR/CRi (-)	23 (32%)	42 (26%)	93 (65%)	158 (42%)
<i>n</i> ^a		72	156	138	366
MRD	MRD-negativity not achieved	31 (43%)	59 (38%)	115 (83%)	205 (56%)
	MRD-negativity achieved	41 (57%)	97 (62%)	23 (17%)	161 (44%)
HSCT:MRD	MRD-negativity achieved: No HSCT	21 (29%)	42 (27%)	14 (10%)	77 (21%)
	MRD-negativity achieved: HSCT	20 (28%)	55 (35%)	9 (7%)	84 (23%)
	MRD-negativity not achieved	31 (43%)	59 (38%)	115 (83%)	205 (56%)

CR, complete remission; CRi, complete remission with incomplete hematological recovery; HSCT, hematopoietic stem cell transplant; InO, inotuzumab ozogamicin; MRD, minimal residual disease; PK, pharmacokinetics.

^aNumber corresponds to all patients receiving treatment with available PK information for each efficacy end point.

Figure 1a,b illustrates differences in predicted probabilities for both efficacy end points by the identified statistically significant variables.

Exposure-response analysis for safety end points

During final model development, the best exposure predictor based on the lowest change in deviance (*D*) value (ΔD) was selected for each of the different safety end points. For the AE end points of hepatic events, investigator-reported VOD/SOS, and grade ≥ 3 AEs (neutropenia, thrombocytopenia, elevated bilirubin, AST, and ALT), InO exposure did not have a statistically significant positive relationship ($\alpha = 0.05$). Hepatic Event Adjudication Board (HEAB)-assessed VOD/SOS was the only analyzed end point that showed a statistically significant positive relationship with InO exposure ($\log(\text{cAUCP1})$) in the final model ($\alpha = 0.05$ (**Table 3**)). In addition, post-therapy HSCT was found to be a statistically significant predictor of HEAB-assessed VOD/SOS ($\alpha = 0.01$). The final model parameters for HEAB-assessed VOD/SOS are presented in **Table 3**, with the logistic regression equation presented as:

$$\begin{aligned} \text{Logit}(P) = \log\left(\frac{P}{1-P}\right) = & -6.31 + 0.02 \cdot \text{BALT} + 0.086 \cdot \text{BBIL} \\ & + 1.974 \cdot \text{Post Therapy HSCT} \\ & + 1.008 \cdot \log(\text{cAUCP1}) \end{aligned}$$

Figure 1c shows the predicted probabilities of patients experiencing HEAB-assessed VOD/SOS following InO treatment. Patients who received post-therapy HSCT had an increased probability of experiencing HEAB-assessed VOD/SOS with increasing $\log(\text{cAUCP1})$.

Treatment-response analysis

For the efficacy end point CR/CRi, three variables in the final model were significant predictors: ARM, BECOG PS,

and baseline absolute blasts in peripheral blood (BLSTABL). Because BECOG PS included only three patients with a PS 3, these patients were grouped with BECOG PS 2. The final model was further reduced after testing the overall effect of BECOG PS as ordered variable taking the values 0 to 2 vs. BECOG PS as dichotomous variable (BECOGC) taking the values 0 (for baseline ECOG = 0) and 1 (for baseline ECOG ≥ 1). The final model parameters are shown in **Table 4**.

The logistic regression equation for the final model was:

$$\begin{aligned} \text{Logit}(P) = \log\left(\frac{P}{1-P}\right) = & 0.573 + 1.964 \cdot \text{ARM} - 0.873 \cdot \text{BECOGC} \\ & - 0.063 \cdot \log(\text{BLSTABL}). \end{aligned}$$

Based on the OR estimated in the final model, the odds of achieving CR or CRi for InO treatment were 7.1-times higher (OR 7.1; 95% CI 4.3–12.3) than in the control arm for a given BECOG PS and for a given amount of total blasts in peripheral blood (Table 4). The predicted probabilities were calculated for both treatment arms and stratified by BECOG PS over the range of BLSTABL values. **Figure 2** illustrates the differences in predicted probabilities by ARM, BECOG PS, and BLSTABL.

For the efficacy end point MRD-negativity, five variables were found to be statistically significant predictors of achieving MRD-negativity. These included ARM, BECOG PS, baseline cytogenetic characteristics, whether or not patients underwent PSCT, and BLSTABL. The final model parameters are shown in **Table 4**. The logistic regression equation for the final model was:

$$\begin{aligned} \text{logit}(P) = \log\left(\frac{P}{1-P}\right) = & -0.63 + 2.544 \cdot \text{ARM} - 0.73 \cdot \text{BECOGC} - 0.958 \cdot \text{BCYTOC1} \\ & - 0.738 \cdot \text{BCYTOC2} - 0.059 \cdot \log(\text{BLSTABL}) + 0.939 \cdot \text{PSCT} \end{aligned}$$

Table 3 Parameter estimates of final exposure–response logistic regression models

Variables	Estimate	95% CI	P-value
Exposure-response analysis with CR/CRi as efficacy endpoint and C_{avg} as exposure metric			
Intercept	-11.202	-15.7610, 7.2808	<0.0001
Baseline CD22+, % ^a	0.051	0.0233, 0.0829	0.0007
Log (C_{avg}), ng/mL	2.108	1.4830, 2.8237	<0.0001
OR, baseline CD22+, % ^a	1.052	1.0236, 1.0864	NA
OR, log (C_{avg}), ng/mL	8.229	4.4060, 16.8385	NA
ΔD	66.75759	NA	NA
P-value (HL test) ^b	0.1261	NA	NA
Exposure-response analysis with MRD-negativity as efficacy endpoint and C_{avg} as exposure metric			
Intercept	-14.104	-19.4441, 9.5273	<0.0001
Baseline cytogenetics ^c	-1.184	-2.0554, 0.3366	0.0067
Baseline cytogenetics (missing/unknown) ^d	-0.600	-1.5550, 0.3729	0.2191
Log (C_{avg}), ng/mL	2.325	1.6490, 3.1069	<0.0001
Baseline CD22+, %	0.066	0.0348, 0.1028	0.0001
OR, baseline cytogenetics ^c	0.306	0.1280, 0.7142	NA
OR, baseline cytogenetics ^d (missing/unknown)	0.549	0.2112, 1.4519	NA
OR, log (C_{avg})	10.222	5.2020, 22.3523	NA
OR, baseline CD22+, %	1.069	1.0354, 1.1083	NA
ΔD	86.54063	NA	NA
P-value (HL test) ^b	0.21	NA	NA
Exposure-response analysis with HEAB-assessed VOD/SOS as safety endpoint and cAUCP1 as exposure metric			
Intercept	-6.310	-9.9488, -3.3227	0.0002
Baseline ALT	0.002	-0.0171, 0.0190	0.8132
Baseline bilirubin	0.086	-1.4983, 1.5530	0.9099
Post-therapy HSCT	1.974	0.8154, 3.4690	0.0026
Log(cAUCP1)	1.008	0.0910, 2.0473	0.0424
OR, baseline ALT	1.002	0.9831, 1.0192	NA
OR, baseline bilirubin	1.090	0.2235, 4.7256	NA
OR, post-therapy HSCT	7.197	2.2600, 32.1036	NA
OR, log(cAUCP1)	2.741	1.0953, 7.7469	NA
ΔD	21.706	NA	NA
P-value (HL test) ^b	0.469	NA	NA

ALT, alanine aminotransferase; ^aD, deviance difference between null and final model; cAUCP1, cumulative area under the inotuzumab ozogamicin concentration–time on cycle 1; C_{avg} , average concentration calculated as the ratio of cAUC over its respective timeframe; CI, confidence interval; CR/CRi, complete response/complete response with incomplete hematological recovery; HEAB, hepatic event adjudication board; HL, Hosmer-Lemeshow; HSCT, hematopoietic stem cell transplant; MRD, minimal residual disease; NA, not applicable; OR, odds ratio; P-value, level of marginal significance within a statistical hypothesis test; |z|, represents the tail area in a two-tail test, VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome.

^aThe percentage of leukemic blasts that were CD22-positive was assessed using bone marrow samples; when bone marrow samples were missing, the percentage of leukemic blasts that were CD22-positive was assessed using peripheral blood samples.

^bP-value for Hosmer-Lemeshow goodness of fit test; when there is good agreement between the observed and predicted values, the P-value does not indicate any statistically significant differences between observed and predicted.

^cThis term represents grouped baseline cytogenetic abnormalities for complex and t(4;11).

^dThis term represents grouped baseline cytogenetic abnormalities for missing information and normal baseline cytogenetics with fewer than 20 metaphases or with an unknown number of metaphases.

The odds of achieving MRD-negativity for InO treatment were 12.7-times higher (OR 12.7; 95% CI 7.0–24.3) relative to the control arm for a given BECOG PS and baseline cytogenetic characteristics, with or without PSCT, and for a given amount of BLSTABL (Table 4). The predicted probabilities were calculated for both treatment arms and stratified by the significant predictors.

Figure 2 illustrates the predicted probabilities by ARM, BECOG PS, presence vs. absence of PSCT, and baseline cytogenetic characteristics over the range of BLSTABL. Further, no chemotherapy regimen was found to perform better ($\alpha = 0.01$) than another in achieving CR/CRi or MRD-negativity.

DISCUSSION

This study investigated InO exposure–response for efficacy and safety end points based on pooled data from phase III INO-VATE and phase I/II study 1010 in adult patients with R/R CD22-positive B-cell ALL. Two different logistic regression analyses were performed for the efficacy end points CR/CRi and MRD. The first analysis included only the InO-treated population defined in the efficacy analysis set. This exposure–response analysis intended to characterize, if any, the potential relationships between InO exposure and response. The second analysis included the exposure–response study population along with the control arm from

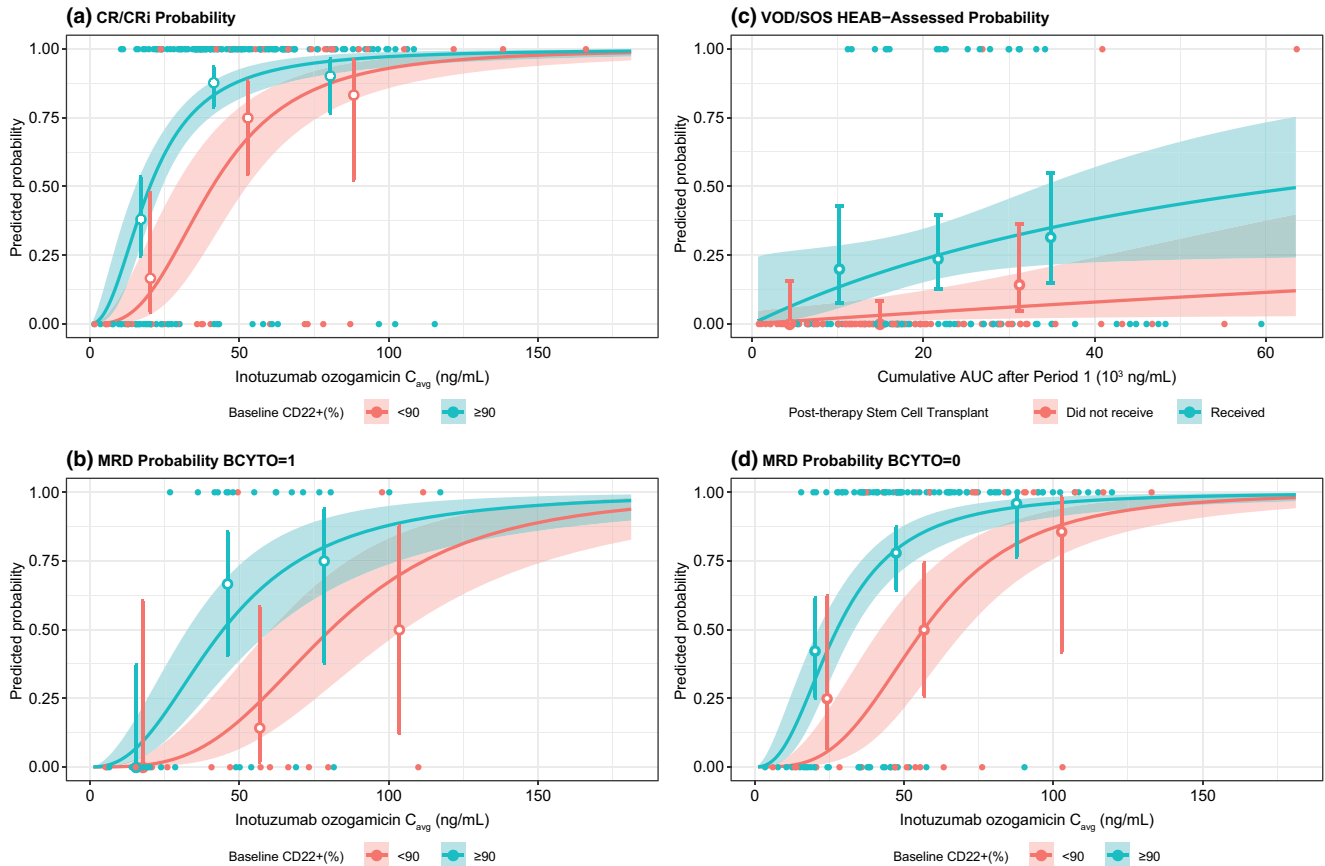


Figure 1 Predicted probabilities for exposure–response logistic regression models. The percentage of leukemic blasts that were CD22-positive was assessed using bone marrow samples; when bone marrow samples were missing, the percentage of leukemic blasts that were CD22-positive was assessed using peripheral blood samples. The observed values (0 = no event, 1 = event) are represented as points on the plot. The observed probabilities and associated 90% CIs are represented on the plot as empty circles and error bars, binned according to the following exposure quantiles: 0–< 25% (low exposure), 25–< 75% (medium exposure), and 75–100% (high exposure). BCYTO = 0 refers to grouped baseline cytogenetic characteristics normal, Philadelphia chromosome (+), and other. BCYTO = 1 refers to grouped baseline cytogenetic characteristic complex and t(4;11). AUC, area under the inotuzumab ozogamicin concentration–time curve; CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematological recovery; HEAB, Hepatic Event Adjudication Board; HSCT, hematopoietic stem cell transplant; MRD, minimal residual disease; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome.

INO-VATE and did not include any InO parameter of exposure, and was intended to quantify the odds of a positive outcome for InO relative to control. Given that this treatment–response analysis compared two treatments with different mechanisms of action (targeted vs. nonspecific), none of the covariates identified were specific for targeted therapy; this is in contrast to the exposure–response analysis, which was focused only on a CD22-positive targeted therapy (InO). Additionally, both analyses explored intrinsic and extrinsic factors as predictors of response.

The exposure–response analysis performed for CR/CRi per investigator’s assessment demonstrated that InO C_{avg} to the time to event, or for the duration of treatment if no response was achieved, was a statistically significant predictor of achieving CR/CRi. The percentage of leukemic blasts that were CD22-positive was also retained as a significant predictor, independent of InO exposure. The exposure–response analysis performed with MRD as an

efficacy end point demonstrated that InO C_{avg} to the time to event, or for the duration of treatment if no response was achieved, was a statistically significant predictor of achieving MRD-negativity. The percentage of leukemic blasts that were CD22-positive at baseline and baseline cytogenetic characteristics were also retained as significant predictors, independent of InO exposure. A previous analysis of INO-VATE identified the rate of achieving CR/CRi, and MRD-negativity was significantly higher with InO-treated vs. chemotherapy-treated patients with both high ($\geq 90\%$) and low ($< 90\%$) leukemic blast CD22-positivity, with the greatest benefit from InO treatment observed in patients with high CD22-positivity leukemic blast.⁷

The treatment–response analysis using CR/CRi as an efficacy end point indicated total blast cells in peripheral blood and BECOG PS were significant predictors of achieving CR/CRi. This analysis also indicated the choice of treatment (InO vs. control) had a significant impact on achieving CR/

Table 4 Parameter estimates of final treatment–response logistic regression models

Variables	Estimate	95% CI	P-value
Treatment-response analysis with CR/CRi as efficacy endpoint			
Intercept	0.573	0.0559, 1.1042	0.0317
ARM	1.964	1.4524, 2.5065	<0.0001
BECOG> 0	-0.873	-1.4084, 0.3583	0.0011
Log(BLSTABL)	-0.063	-0.0865, 0.0410	<0.0001
OR, ARM	7.128	4.2733, 12.2623	NA
OR, BECOG> 0	0.418	0.2445, 0.6989	NA
OR, Log(BLSTABL)	0.939	0.9171, 0.9598	NA
ΔD	94.1272	NA	NA
P-value (HL test) ^a	0.6076	NA	NA
Treatment-response analysis with MRD-negativity as efficacy endpoint			
Intercept	-0.630	-1.2502, 0.0350	0.0412
ARM	2.544	1.9502, 3.1911	<0.0001
BECOG> 0	-0.730	-1.2833, 0.1916	0.0086
Baseline cytogenetics ^b	-0.958	-1.6251, 0.3152	0.0040
Baseline cytogenetics (missing/unknown) ^c	-0.738	-1.4315, 0.0651	0.0335
Log(BLSTABL)	-0.059	-0.0836, 0.0362	<0.0001
PSCT	0.939	0.3291, 1.5671	0.0029
OR, ARM	12.735	7.0300, 24.3163	NA
OR, BECOG> 0	0.482	0.2771, 0.8256	NA
OR, baseline cytogenetics ^b	0.383	0.1969, 0.7296	NA
OR, baseline cytogenetics (missing/unknown) ^c	0.478	0.2389, 0.9370	NA
OR, Log(BLSTABL)	0.942	0.9198, 0.9644	NA
OR, PSCT	2.557	1.3897, 4.7929	NA
ΔD	121.5361	NA	NA
P-value (HL test) ^a	0.351	NA	NA

ARM, inotuzumab ozogamicin arm of the study; BECOG, baseline Eastern Cooperative Oncology Group; BLSTABL, baseline absolute blasts in peripheral blood; CI, confidence interval; CR/CRi, complete response/complete response with incomplete hematological recovery; ΔD , deviance difference between null and final model; HL, Hosmer-Lemeshow; MRD, minimal residual disease; NA, not applicable; OR, odds ratio; PSCT, prior study hematopoietic stem cell transplant; P-value, level of marginal significance within a statistical hypothesis test; |z|, it represents the tail area in a two-tail test.

^aP-value for Hosmer-Lemeshow goodness of fit test; when there is good agreement between the observed and predicted values, the P-value does not indicate any statistically significant differences between observed and predicted.

^bThis term represents grouped baseline cytogenetic abnormalities for complex and t(4;11).

^cThis term represents grouped baseline cytogenetic abnormalities for missing information and normal baseline cytogenetics with fewer than 20 metaphases or with an unknown number of metaphases.

CRi. Based on the final model, the odds of achieving CR/CRi for InO treatment were predicted to be approximately 7-times higher than for control for a given BECOG PS and for a given total blast count in peripheral blood. Treatment–response analysis using MRD-negativity as an efficacy end point indicated that BECOG PS, baseline cytogenetic characteristics, whether or not patients underwent prior study therapy HSCT, and total blast cells in peripheral blood were significant predictors of MRD outcome. This analysis also

indicated the choice of treatment (InO vs. control) had a significant impact on achieving MRD-negativity. Based on the final model, the odds of achieving MRD-negativity were predicted to be ~ 13-times higher in InO-treated patients than those in the control arm for a given ECOG PS, presence or absence of prior study therapy HSCT, and for a given total blast count in peripheral blood.

One limitation of this study is the fact that MRD-negativity and CR/CRi did not directly translate to OS. Unlike CR/CRi and MRD-negativity, OS is confounded by subsequent therapy, including HSCT. Although InO therapy greatly improves a patient’s chance of proceeding to HSCT, HSCT itself has its own inherent risks, which can confound the evaluation of OS for InO. Furthermore, the OS data appeared to deviate from the proportional-hazards assumption, so an exploratory *post hoc* analysis based on restricted mean survival time was conducted. The results from this analysis demonstrated a significantly longer mean OS with InO than with standard therapy (13.9 vs. 9.9 months; $P = 0.005$).³ The 2-year survival probability in the InO and standard therapy groups was 23% and 10%, respectively.³ Due to the heterogeneity of the data, subgroup analyses were also performed.^{8–10} For instance, *post hoc* subgroup analyses found that the OS with InO was significantly longer in patients aged < 55 vs. ≥ 55 years (8.6 vs. 5.6 months; hazard ratio 0.61; 95% CI 0.43–0.87; one-sided $P = 0.0032$).

Based on the incidence and severity of treatment-related AEs following treatment with InO, eight prespecified safety outcomes were included in the exposure–response safety analysis. No exposure–response relationship was found with hepatic events (defined by a prespecified cluster); investigator-assessed VOD/SOS; grade ≥ 3 myelosuppression; or elevated ALT, AST, or bilirubin. HEAB-assessed VOD/SOS was the only end point that showed a statistically significant positive relationship with InO exposure. Post-therapy HSCT was also shown to be a significant predictor of HEAB-assessed VOD/SOS. A similar exposure–response relationship was found for another antibody drug conjugate with calicheamicin as a payload, gemtuzumab ozogamicin (Mylotarg).¹¹ The incidence of VOD related to gemtuzumab ozogamicin post-therapy HSCT was not assessed, as the majority of patients that underwent post-therapy HSCT developed VOD from the earlier studies. The most recent gemtuzumab ozogamicin studies had 0% incidence of VOD, likely due to the reduction in gemtuzumab ozogamicin exposure (fractionated dose of 3 mg/m² on days 1, 4, and 7 vs. 9 mg/m² on days 1 and 15).¹¹

HSCT is the ultimate goal of post-relapse ALL treatment, with HSCT a prognostic indicator of survival and a potentially curative treatment option.¹² Long-term follow-up of InO-VATE demonstrated that patients receiving InO are more likely to proceed directly to HSCT vs. those receiving chemotherapy (48.2% vs. 24.5%), which reinforces the role of InO as an effective bridge to HSCT in patients with R/R ALL.⁴ Among patients who proceeded to HSCT, 23% treated with InO developed VOD/SOS vs. 9% in the control arm.⁴ Due to the increased risk of VOD/SOS in InO patients proceeding to HSCT, the current prescribing recommendations are to limit InO treatment to two cycles; a third cycle may be considered for patients who have not achieved CR/CRi and MRD-negativity after two cycles.¹

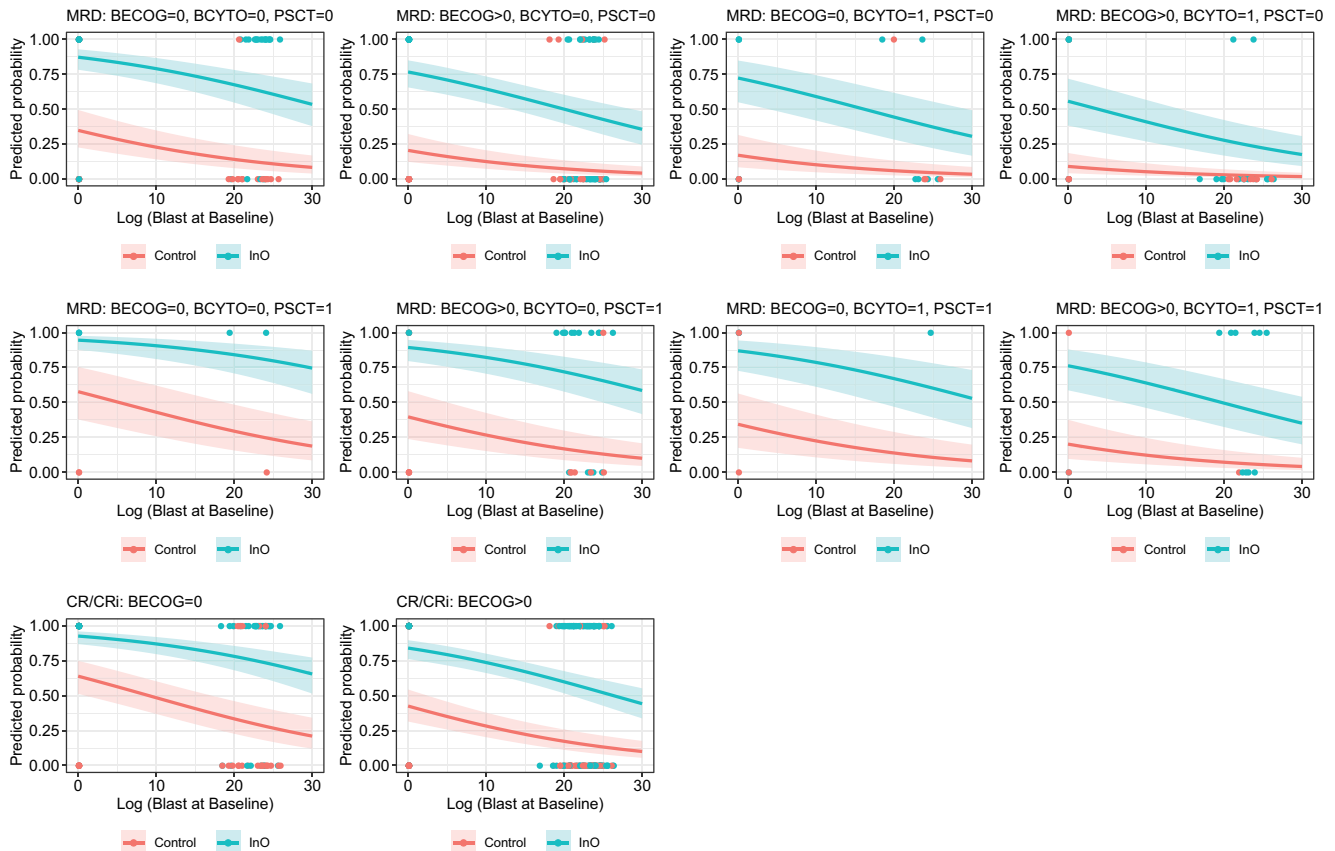


Figure 2 Predicted probabilities for treatment–response logistic regression models. The observed values (0 = no event, 1 = event) are represented as points on the plot. BECOG = 0 corresponds to a BECOG value of 0, BECOG > 0 corresponds to a BECOG value > 0 (from 1 to 3). BCYTO = 0 refers to grouped baseline cytogenetic characteristics normal, Philadelphia chromosome (+), and other. BCYTO = 1 refers to grouped baseline cytogenetic characteristic complex and t(4;11). PSCT = 0 refers to absence of HSCT prior to InO therapy, PSCT = 1 refers to HSCT prior to InO therapy. BCYTO, baseline cytogenetic characteristics; BECOG, Baseline Eastern Cooperative Oncology Group; Control, choice of fludarabine/cytarabine/granulocyte colony-stimulating factor, mitoxantrone/cytarabine, or high-dose cytarabine; CR, complete remission; CRI, complete remission with incomplete hematological recovery; HSCT, hematopoietic stem cell transplant; InO, inotuzumab ozogamicin; MRD, minimal residual disease; PSCT, prior study hematopoietic stem cell transplant.

Further, the results from this study support the current recommended dose of 1.8 mg/m² for InO as well as the dose recommendations provided on the current product label. There is also an ongoing postmarketing requirement study (NCT03677596) comparing two dose levels of InO (starting dose of 1.2 mg/m²/cycle vs the labeled dose of 1.8 mg/m²/cycle) in patients at higher risk for VOD to further investigate the potential impact of dose on response (CR/CRI) and safety (VOD).

In conclusion, the exposure–response analysis indicated that InO exposure was significantly correlated with achieving CR/CRI and MRD-negativity, as well as with HEAB-reported VOD/SOS. Further, the treatment–response analysis indicated that patients receiving InO had significantly greater odds of achieving CR/CRI and MRD-negativity than those receiving chemotherapy.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

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