Pharmacokinetic/Pharmacodynamic Modeling to Support the Re-approval of Gemtuzumab Ozogamicin

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Gemtuzumab ozogamicin (Mylotarg; Pfizer, New York, NY) was the first antibody–drug conjugate to be approved for CD33-positive acute myeloid leukemia (AML). However, it was voluntarily withdrawn from the US market due to lack of clinical benefit in the confirmatory phase III trial. In 2012, several investigator cooperative studies using a different dosing regimen showed efficacy, but pharmacokinetic (PK) data were not collected in these trials. Through simulation of expected concentrations for new dosing regimens, PK/pharmacodynamic modeling was able to support the safety and efficacy of these regimens. Significant exposure–response relationships were found for the attainment of complete remission with and without platelet recovery, attainment of blast-free status, the time course of myelosuppression, several grade ≥ 3 hepatic adverse events, and veno-occlusive disease. Gemtuzumab ozogamicin received full approval by the US Food and Drug Administration (FDA) in September 2017 for newly diagnosed and relapsed AML in adult patients and relapsed AML in pediatric patients aged 2–17 years.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Acute myeloid leukemia (AML) is a major area of unmet medical need in the United States. Selecting a safe and effective dosing regimen is essential to developing life-saving treatments. Because oncology programs rarely study more than one dose after phase I, modeling and simulation (M&S) is an essential tool for evaluating the safety and efficacy of a dosing regimen.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ How does M&S provide a rationale for a new dosing regimen for gemtuzumab ozogamicin in adult and pediatric patients with AML?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ M&S provides a rationale for new, fractionated dosing regimens of gemtuzumab ozogamicin in combination with and without cytotoxic chemotherapy.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ M&S was able to assess the probability of achieving a given end point based on prior data and new observed information. Despite the limited data in the pediatric population, M&S was able to sufficiently characterize the risk vs. benefit supporting the pediatric indication.

Gemtuzumab ozogamicin was the first antibody–drug conjugate approved by the US Food and Drug Administration (FDA). It is composed of a CD33-directed monoclonal antibody hP67.6 (recombinant humanized immunoglobulin G4) covalently linked to the cytotoxic agent *N*-acetyl gamma calicheamicin. The antibody portion binds specifically to the CD33 antigen, which is expressed on leukemic blasts in > 90% of patients with acute myeloid leukemia (AML) but not on normal hematopoietic stem cells.[1,2] Gemtuzumab ozogamicin was approved by the FDA in May 2000 as a single agent (9 mg/m^2 on days 1 and 15) for the treatment of patients who are 60 years of age or older with CD33-positive AML in first relapse and who are not considered candidates for other cytotoxic chemotherapy.[3,4] In 2005, gemtuzumab ozogamicin was also approved in Japan. However, in 2010, gemtuzumab ozogamicin was voluntarily withdrawn from the US market when the postapproval confirmatory trial using a single gemtuzumab ozogamicin dose of 6 mg/m^2 on day 4 in combination with daunorubicin and cytarabine failed to verify clinical benefit vs. conventional chemotherapy in patients with previously untreated *de novo* AML.[5] Despite the withdrawal from US markets, there remained interest in gemtuzumab ozogamicin because of the continued poor outcome of patients with AML.

The recommended dose in the initial approval along with the dose selected for the confirmatory phase III trial were based on target site saturation after a single dose.[6] It was later determined that rapid and continuous re-expression of the CD33 antigen on the

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cell surface occurs after a single dose of gemtuzumab ozogamicin. It was, therefore, hypothesized that more frequent dosing of gemtuzumab ozogamicin (i.e., additional doses administered sooner after the first administration) would saturate the newly expressed CD33 antigens and increase internalization of gemtuzumab ozogamicin into leukemic blasts.[7–9] Additionally, given that efficacy was observed at lower doses in the phase I trials (1–4 mg/m^2), and that >90% saturation was observed at 3 mg/m^2, it was proposed that fractionating the 9 mg/m^2 dose would be safer and at least as efficacious.[10] Hence, a lower but more frequent dose schedule (fractionated regimen) was evaluated in several investigator cooperative studies, including MyloFrance-1, Acute Leukemia French Association (ALFA)-0701, and EORTC/GIMEMA AML-19[11–14] (see **Table 1**).

MyloFrance-1 was a phase II, single-arm, open-label study in adults with CD33-positive AML in first relapse, which included a single course of gemtuzumab ozogamicin 3 mg/m^2 on days 1, 4, and 7. The median duration of first remission was 10 months. Of the 57 patients who received treatment, 15 patients (26%) achieved complete remission (CR), and 4 patients (7%) achieved CR without platelet recovery (CRp). These rates were similar to the 13% CR and 13% CRp observed in the registrational phase II studies, which used a 9 mg/m^2 on days 1 and 15 monotherapy regimen.[14] The duration of myelosuppression was also shorter using the fractionated monotherapy regimen, and there were no cases of veno-occlusive disease (VOD).[11]

The ALFA-0701 study was a randomized phase III study evaluating standard chemotherapy (control arm) vs. standard chemotherapy in combination with gemtuzumab ozogamicin (3 mg/m^2 on days 1, 4, and 7) followed by two additional doses of gemtuzumab ozogamicin (3 mg/m^2) on the first day of each of two consolidation cycles (treatment arm).[12,13] Results of the ALFA-0701 study showed a statistically significant and clinically meaningful improvement in the primary end point of event-free survival (hazard ratio = 0.56; 95% confidence interval (CI): 0.42–0.76; median: 9.5 for the control arm vs. 17.3 months for the treatment arm; P = 0.0002) when gemtuzumab ozogamicin was added to standard intensive first-line induction chemotherapy in patients with untreated AML.

The AML-19 study was a randomized, open-label phase III study comparing gemtuzumab ozogamicin to best supportive care in patients with previously untreated AML who were considered ineligible for intensive chemotherapy, where gemtuzumab ozogamicin was given as monotherapy on day 1 (6 mg/m^2) and on day 8 (3 mg/m^2) during induction.[14] Efficacy was established on the basis of improvement in overall survival (OS). The hazard ratio for OS was 0.69 (95% CI: 0.53–0.90; two-sided P = 0.005 by log-rank test) with a median OS of 4.9 months in the gemtuzumab ozogamicin arm vs. 3.6 months in the control arm.

Based on the results observed in these three studies, and the increasing use of gemtuzumab ozogamicin under Pfizer's compassionate care program, a biologic license application (BLA) for gemtuzumab ozogamicin was submitted to the FDA. To support the BLA, population pharmacokinetic (PK) modeling of total hP67.6 antibody serum concentration was conducted for both adult and pediatric patients.[15,16] For both populations, the final model was a two-compartment model with time-dependent clearance. These models were used to predict gemtuzumab ozogamicin exposure for patients in the phase III pivotal study (ALFA-0701), in which no PK was collected.

The current report describes the pharmacodynamic (PD) modeling performed to support the efficacy and safety of the fractionated dosing regimens. Models were developed that adequately represent the exposure–response (ER) relationships between total hP67.6 antibody exposure (maximum serum concentration (C_{max})) with safety and efficacy end points. The attainment of CR/CRp and blast-free status were the efficacy end points used for the ER models. CR/CRp was derived using the revised International Working Group criteria (see **Table S1**).[17] Blast-free status was defined as the absence of blasts in the peripheral blood and <5% blasts in the bone marrow. Using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03,[18] the clinically relevant safety end points were the occurrence of VOD, neutropenia, low platelet counts, and the occurrence of grade ≥ 3 adverse events (AEs) for elevated aspartate transaminase (AST), elevated alkaline phosphatase (ALP), hypoalbuminemia, and elevated bilirubin. For the observed myelosuppression (low neutrophil and platelet counts), the relationship between total hP67.6 antibody exposure and the time course of the depletion and regeneration of neutrophils and platelets was assessed using a semimechanistic model.[19,20]

The PK/PD modeling was an integral component of the BLA, which resulted in the approval of gemtuzumab ozogamicin by the FDA in 2017. Patients with newly diagnosed *de novo* AML are approved to receive 3 mg/m^2 (up to one 4.5 mg vial) on days 1, 4, and 7 in combination with daunorubicin and cytarabine. Patients with newly diagnosed AML and considered ineligible for intensive chemotherapy are approved to receive a single-agent regimen of 6 mg/m^2 on day 1 and 3 mg/m^2 on day 8 during induction. Single-agent gemtuzumab ozogamicin 3 mg/m^2 on days 1, 4, and 7 is also approved for relapsed or refractory AML in adult and pediatric (aged 2–17 years) patients.[21] Full approval was received by the European Medicines Agency in 2018 for patients aged 15 years and older with previously untreated *de novo* CD33-positive AML administered as 3 mg/m^2 (up to one vial) on days 1, 4, and 7 in combination with daunorubicin and cytarabine.[22]

RESULTS

The ER analyses included pooled data from eight phase I–III clinical trials comprised of 597 patients with AML. Responses in pediatric patients were predicted based on the estimated parameters from the eight trials in adults and compared with the observed responses. A description of each trial is provided in **Table 1**. All of the PK samples collected were from Pfizer-sponsored trials conducted between 1995 and 2001. Total hP67.6 antibody exposure was predicted for patients in ALFA-0701 using the adult population PK model. Available data included baseline Eastern Cooperative Oncology Group-Performance Status score, occurrence of a prior stem cell transplant, *de novo* status, baseline bone marrow blast percentage, race, and sex. Longitudinal data on dosing, standard hematology laboratory measurements, total hP67.6

Table 1 Summary of the studies considered for the PK/PD modeling

Study number	*N* (with PK)	Population	Study design	Induction dosing schedule
Study 101	40 (40)	Patients aged ≥ 16 years to ≤ 70 years with relapsed or refractory CD33-positive AML	Phase I, single-arm, dose-escalation study to examine the safety and PK of GO	GO: 0.25, 0.5, 1, 2, 4, 5, 6, and 9 mg/m^2 as a single 2-hour i.v. infusion/dose (≥ 14 days apart); maximum of 3 doses
Study 102	29 (29)	Children (≤ 17 yo) with refractory or relapsed AML	Phase I, pediatric, single-arm, dose-escalation study to assess safety of GO	GO: 6, 7.5, and 9 mg/m^2 as a single 2-hour i.v. infusion/dose (≥ 14 days apart) for up to 2 doses. For patients < 3 yo, per kg dosing was used
Study 103	Phase I: 20 (20) Phase II: 20 (20)	Japanese adults 18–70 years with relapsed or refractory CD33-positive AML	Phase I/II, single-arm, dose-escalation, study to assess safety and efficacy of GO	Phase I: GO: 6, 7.5, and 9 mg/m^2 as a single 2-hour i.v. infusion/dose (≥ 14 days apart) for up to 2 doses. Phase II: GO; 9 mg/m^2 as a single 2-hour i.v. infusion/dose (≥ 14 days apart) for up to 2 doses
Study 201	84 (84)	Adults with CD33-positive AML in first relapse	Phase II, single arm, multidose study to assess safety and efficacy of GO	GO: 9 mg/m^2 as a single 2-hour i.v. infusion/dose for 2 or 3 doses
Study 202	95 (95)	Adults with CD33-positive AML in first relapse	Phase II, single arm, multidose study to assess safety and efficacy of GO	GO: 9 mg/m^2 as a single 2-hour i.v. infusion/dose for 2 or 3 doses
Study 203	98 (98)	Adults ≥ 60 years with CD33-positive AML in first relapse	Phase II, single arm, multidose study to assess safety and efficacy of GO	GO: 9 mg/m^2 as a single 2-hour i.v. infusion/dose for 2 or 3 doses
Study 205	Phase I: 21 (21) Phase II: 17 (17)	Phase I: Adults ≥ 18 years with relapsed or refractory CD33-positive AML or patients ≥ 60 years with *de novo* untreated CD33-positive AML. Phase 2: Untreated adults ≥ 60 years with *de novo* CD33-positive AML	Phase I/II, open-label, single-arm, multicenter study to assess the safety and efficacy of GO given in combination with AraC	Phase I: 4 dose schedules: (1) GO 6 mg/m^2, D1 and D15; (1a) GO 6 mg/m^2 D1 and 4 mg/m^2 D8; (2a) GO 6 mg/m^2 D1 and 4 mg/m^2 D8; (3a) GO 9 mg/m^2 D1 and 6 mg/m^2 D8. All GO doses except step 1a were combined with AraC 100 mg/m^2/d D1–7. Phase II: Dose schedule "2a" from phase I
Study 206	Phase I: 22 (22) Phase II: 49 (49)	Part 1: Adults ≥ 18 and < 60 years with *de novo* AML or adults ≥ 60 years with relapsed or refractory AML. Part 2: Adults ≥ 18 and < 60 years with *de novo* CD33-positive AML	Phase I/II, open-label, single-arm, multicenter study to assess safety and efficacy of GO given in combination with AraC and DNR in patients with CD33-positive AML between 18 and 60 years with untreated *de novo* AML	Part 1: Three dose schedules: (1) AraC 100 mg/m^2/d D1–7; DNR 45 mg/m^2 D1–3; GO 6 mg/m^2 D4. (2) AraC 100 mg/m^2/d D1–7; DNR 45 mg/m^2 D1–3; GO 9 mg/m^2 GO D4. (3) AraC 200 mg/m^2/d D1–7; DNR 45 mg/m^2 D1–3; GO 9 mg/m^2 D4. Part 2: Dose schedule "1" from Part 1
Study ALFA-0701[a]	GO: 131 (0) Control: 137 (0) (PK simulated)	Adults 50–70 years with untreated *de novo* AML	Phase III, open-label, randomized 1:1 study to assess benefit and toxicity of adding fractionated GO to standard induction therapy	DNR 60 mg/m²/d D1–3; AraC 200 mg/m²/d D1–7; GO 3 mg/m² (maximum dose 5 mg) D1, 4, and 7
MyloFrance 1[b]	57 (0)	Adults 50–70 years with AML in first relapse	Phase II, single-arm, multicenter study to assess the safety and efficacy of fractionated doses of GO	GO: 3 mg/m^2 on D1, 4, and 7
Study AML-19[b]	237 (0)		Phase III, open-label, randomized 1:1 study to assess overall survival of GO compared with best supportive care	GO monotherapy including 2 i.v. infusions administered at 6 mg/m^2 on D1 and 3 mg/m^2 on D8

ALFA, Acute Leukemia French Association; AML, acute myeloid leukemia; AraC, cytarabine; d, day; D, nominal day; DNR, daunorubicin; GO, gemtuzumab ozogamicin; PD, pharmacodynamic; PK, pharmacokinetic; yo, years old.
[a]PK concentrations were simulated for patients in ALFA-0701. [b]Data from the Mylofrance-1 and AML-19 studies were not included in the PK/PD modeling.

antibody area under the time-concentration curve (AUC) and C_{max} for each dose, dose regimen, number of doses, and treatment (monotherapy or combination) were available and evaluated as predictors for the models. Summary statistics and frequencies of the efficacy and safety end points used in these analyses, calculated for each study, are provided in **Table 2**.

Logistic regression

Logistic regression models (with a logit link function) were developed for the attainment of CR/CRp and the attainment of blast-free status. A model was developed using the first-dose C_{max}, overall C_{max}, and overall AUC. Only the first-dose C_{max} models are presented herein (see **Table 3**). To control for

Table 2 Summary information about the frequency and severity of the adverse events

		Study number								
		101	102	103	201	202	203	205	206	701
CR/CRp, *n*	Yes	4	7	5	32	33	32	10	43	99
	No	36	22	15	49	61	62	11	10	31
BF, *n*	Yes	8	11	8	53	52	49	11	43	116
	No	32	18	12	28	42	45	10	10	14
VOD, *n*	Yes	1	3	0	3	4	1	1	1	5
	No	39	26	20	78	90	93	37	70	125
AST, *n*	Grade 0	5	3	2	17	4	19	6	14	21
	Grade 1	18	13	10	46	48	54	15	38	73
	Grade 2	7	9	7	7	23	7	4	5	20
	Grade 3	8	3	1	9	16	12	8	13	10
	Grade 4	2	1	0	2	3	2	5	0	5
	Missing	0	0	0	0	0	0	0	1	1
ALP, *n*	Grade 0	11	21	9	37	35	29	6	25	39
	Grade 1	21	7	11	32	37	51	28	37	54
	Grade 2	7	1	0	9	17	10	3	6	21
	Grade 3	1	0	0	3	5	4	1	3	14
	Grade 4	0	0	0	0	0	0	0	0	1
	Missing	0	0	0	0	0	0	0	0	1
Albumin, *n*	Grade 0	5	5	4	11	19	4	2	7	4
	Grade 1	6	11	13	30	33	24	7	22	16
	Grade 2	26	11	3	37	34	60	26	37	64
	Grade 3	3	1	0	2	5	3	3	5	6
	Grade 4	0	0	0	0	0	0	0	0	0
	Missing	0	1	0	1	3	3	0	0	40
Bilirubin, *n*	Grade 0	19	21	14	34	29	45	17	44	69
	Grade 1	8	4	5	28	25	21	5	14	24
	Grade 2	9	1	1	11	28	21	10	6	23
	Grade 3	4	2	0	7	9	5	5	6	8
	Grade 4	0	1	0	1	3	2	1	1	1
	Missing	0	0	0	0	0	0	0	0	5
Absolute neutrophil count, 10^9/L	Median (range)	0.8 (0.0–9.2)	1.1 (0.0–5.8)	0.5 (0.1–3.2)	0.5 (0.0–4.8)	0.4 (0.0–45.0)	0.5 (0.0–10.0)	0.5 (0.0–5.7)	0.7 (0.0–20.0)	0.6 (0.01–67.9)
Absolute platelet count, 10^9/L	Median (range)	27 (5–193)	37 (10–102)	58.5 (29–184)	44 (5–192)	44 (3–192)	41 (1–283)	43.5 (3–183)	51.7 (6–279)	67 (9–393)
Bone marrow blast, %	Median (range)	23 (0–91)	60 (5–100)	70 (25–90)	84 (0–100)	90.5 (0–100)	80 (0–100)	60 (9.5–100)	66.5 (5–100)	55 (7–97)

ALP, alkaline phosphatase; AST, aspartate transaminase; BF, blast-free; CR, complete remission; CRp, complete remission without platelet recovery; VOD, veno-occlusive disease.

Table 3 Parameter estimates for the logistic regression models

	Models						
Parameters	**ALP**	**ALB**	**Bilirubin**	**VOD**	**AST**	**CR/CRp**	**Blast free**
Intercept	−4.989 (*P* < 0.001)	2.023 (*P* = 0.009)	−3.706 (*P* < 0.001)	−4.24 (*P* < 0.001)	−2.009 (*P* < 0.001)	−3.856 (*P* < 0.001)	−2.225 (*P* < 0.001)
AraC + GO	−4.102 (*P* = 0.500)	.981 (*P* = 0.206)	.967 (*P* = 0.08)	1.487 (*P* = 0.228)	1.417 (*P* < 0.001)	3.504 (P0 < .001)	1.962 (*P* < 0.001)
AraC + DNR + GO	1.506 (*P* = 0.003)	1.304 (*P* = 0.028)	0.755 (*P* = 0.086)	1.683 (*P* = 0.043)	0.382 (*P* = 0.256)	4.917 (*P* < 0.001)	3.873 (*P* < 0.001)
GO single agent: multiple doses	NA	NA	NA	NA	NA	2.916 (*P* < 0.001)	1.918 (*P* < 0.001)
Log-cumulative AUC	0.189 (*P* = 0.378)	NA	NA	NA	NA	NA	NA
First dose total hP67.6 antibody C_{max}	NA	0.517 (*P* = 0.023)	NA	0.543 (*P* = 0.008)	NA	0.262 (*P* = 0.014)	0.366 (*P* < 0.001)
Log-first dose total hP67.6 antibody C_{max}	NA	NA	0.625 (*P* = 0.010)	NA	0.458 (*P* = 0.007)	NA	NA
Baseline ALP	0.005 (*P* < 0.001)	NA	NA	NA	−0.005 (*P* = 0.008)	NA	NA
Baseline ALB	NA	−1.934 (*P* < 0.001)	NA	NA	NA	NA	NA
Baseline bilirubin	NA	NA	1.161 (*P* < 0.001)	NA	NA	NA	NA
Baseline AST	NA	NA	NA	NA	0.021 (*P* = 0.001)	NA	NA
Prior stem cell transplant	NA	NA	1.216 (*P* = 0.009)	2.166 (*P* = 0.004)	1.045 (*P* = 0.010)	NA	NA
Bone marrow blast percentage	NA	NA	NA	−0.027 (*P* = 0.005)	NA	NA	NA

The parameters estimates in the models for each end point are presented vertically. The model estimates are provided for each of the models with the *P* value in parentheses. First dose total hP67.6 antibody C_{max}, numerical value or its logarithm, represents the C_{max} value of total hP67.6 after the first given dose of gemtuzumab ozogamicin.

ALB, albumin; ALP, alkaline phosphatase; AraC, cytarabine; AST, aspartate transaminase; AUC, area under the time-concentration curve; C_{max}, maximum serum concentration; CR, complete remission; CRp, complete remission without platelet recovery; DNR, daunorubicin; GO, gemtuzumab ozogamicin; NA, not applicable, the variable was not included in the final model; VOD, veno-occlusive disease.

the different dosing regimens and the number of doses, indicator variables were added to the model to identify monotherapy (single vs. multiple doses) as well as the combination treatments (gemtuzumab ozogamicin + cytarabine and gemtuzumab ozogamicin + cytarabine + daunorubicin).

Total hP67.6 antibody exposure and dosing regimen were significant predictors for each of the efficacy models such that higher exposure, after accounting for the dosing regimen and treatment, was related to higher probability of response (CR/CRp and blast-free status). No additional variables were statistically significant at the 0.01 level and consequently were not included in the final models.

Logistic regression models were also developed for the occurrence of grade ≥ 3 AEs and VOD using the same stepwise covariate modeling approach used for the efficacy models. For each end point, the baseline value was included in the model. For grade ≥ 3 ALP, there was no evidence of an ER relationship. For the other safety end points, there was a statistically significant ER relationship with the C_{max} after the first dose. Prior stem cell transplantation was associated with a statistically significant increase in the risk of experiencing grade ≥ 3 bilirubinemia, and grade ≥ 3 elevated AST. For elevated ALP, elevated AST, bilirubinemia, and hypoalbuminemia, the baseline value of each measurement, respectively, was the strongest predictor of the risk of experiencing a grade ≥ 3 AE. For elevated AST, the baseline value of ALP was a significant predictor for a grade ≥ 3 AE. A higher percentage of leukemic blasts at baseline were associated with a lower probability of VOD, whereas a prior stem cell transplant was associated with a higher probability of VOD. The parameter estimates for all of the logistic regression models are provided in **Table 3** and the receiver operating characteristic curves assessing model adequacy are presented in **Figure S1**.

Because gemtuzumab ozogamicin is a CD33-targeted compound, an assessment of the effect, if any, of CD33 expression on CR/CRp and blast-free status was performed. Unfortunately, the percentage of patients with missing CD33 expression information was very high (around 50% missing) and, therefore, this assessment was considered exploratory. Additionally, the majority of patients had CD33 expression (mean fluorescence intensity) > 80%. The

exploratory analysis did not find any statistically significant relationships between efficacy and either of the two baseline CD33 metrics: percentage of leukemic blasts that were CD33-positive and mean fluorescence intensity (data not shown).

The logistic regression models developed with data from the adult patients were tested on pediatric patient data using the Hosmer–Lemeshow test[23] (**Table S2**). For all efficacy end points, there was no evidence of lack of fit between the observed pediatric data and predicted rate using the adult model ($P > 0.05$). For safety end points, only VOD and elevated albumin showed evidence of a lack of fit with the adult models. In the pediatric population, three patients experienced VOD within 28 days of any gemtuzumab ozogamicin dose and one patient experienced grade ≥ 3 elevated albumin. Comparatively, incidence of VOD was substantially lower (n = 16/552) and elevated albumin was higher (n = 28/550) in the adult population. In the three cases of VOD, it is possible that another factor, not considered in the adult model, is driving the occurrence of VOD in pediatric patients. However, the number of events is very small for both end points and more data would be required for a proper assessment.

Myelosuppression

The semimechanistic myelosuppression model (**Figure S2**) was able to successfully describe the platelet and neutrophil counts over time following gemtuzumab ozogamicin monotherapy and in combination with chemotherapy (cytarabine or cytarabine + daunorubicin). Platelet and neutrophil profiles were also well characterized when several treatment cycles were modeled continuously in time, and this characterization could be applied to different schedules of administration. The model assumption that gemtuzumab ozogamicin suppressed the proliferation rate of stem cells was considered mechanistically reasonable given the known cytotoxic mechanism of action of gemtuzumab ozogamicin. Visual predictive checks (VPCs) for adults and pediatric patients for both neutrophil and platelet counts are presented in **Figure S3**. Final parameter estimates are shown in **Tables 4 and 5**. The pediatric VPCs were based on the model developed for the adult population. The VPCs show that the model fits the data well for both the adult and pediatric patients. Simulations were performed using the model to assess the differences in myelosuppression for the different approved regimens. The predicted time courses for both neutrophils and platelets are illustrated in **Figure 1**.

Clinical utility index

To quantitatively determine optimal tradeoffs among key drug attributes (CR/CRp and VOD), a clinical utility index for the different approved dosing regimens was calculated using a 1:1 weighting scheme with the probability of CR/CRp and the probability of VOD (the AE of greatest clinical concern during the FDA oncology drug advisory committee meeting). The curves were calculated for the different dosing regimens of gemtuzumab ozogamicin monotherapy (9 mg/m^2 on day 1 and day 15, 6 mg/m^2 on day 1 and 3 mg/m^2 on day 8, and 3 mg/m^2 on days 1, 4, and 7) as well as in combination with chemotherapy (gemtuzumab ozogamicin 3 mg/m^2 on days 1, 4, and 7 in combination with cytarabine and daunorubicin in newly diagnosed patients). In addition, the impact of having a prior stem cell transplant is shown, as it is a strong predictor of VOD. The estimated clinical utility indices are presented in **Figure 2**.

DISCUSSION

In the BLA for gemtuzumab ozogamicin, it was necessary to characterize potential ER relationships between gemtuzumab ozogamicin exposure with efficacy and safety during the induction phase of treatment. Despite the fact that all the PK samples available were from the original submission using a different regimen, statistically significant ER relationships were found for CR/CRp and blast-free status with predicted total hP67.6 antibody exposure (first dose C_{max}). The three-drug combination therapies (gemtuzumab ozogamicin + daunorubicin + cytarabine) in studies 206 and ALFA-0701 showed significant increases in the probability of achieving CR/CRp and achieving blast-free status over all gemtuzumab ozogamicin monotherapy regimens as well as single-dose gemtuzumab ozogamicin in combination with cytarabine. Based on the available data, gemtuzumab ozogamicin + cytarabine + daunorubicin seems to be superior to gemtuzumab ozogamicin monotherapy; however, patient population (refractory and *de novo*) and combination therapy were confounded variables that may have an important role in the efficacy outcomes, as all *de novo* patients received combination therapy, whereas gemtuzumab ozogamicin monotherapy was given to relapsed/refractory patients. Although other research has subsequently found a CD33 expression relationship with both efficacy and safety,[24–27] no significant ER relationships were found between CD33 expression and any of the end points in the exploratory analyses.

Based on the incidence and severity of treatment-related AEs following treatment with gemtuzumab ozogamicin, seven safety terms were selected as the safety end points of interest for ER analyses. A higher C_{max} after the first dose was found to be associated with a higher probability of experiencing VOD and a grade ≥ 3 AE for elevated AST, bilirubinemia, and hypoalbuminemia. Additionally, the corresponding baseline laboratory value was statistically significant for each of the respective models. The percent of leukemic blasts in the bone marrow was found to be inversely related to the probability of experiencing VOD. It is possible that a higher disease burden results in more leukemic cells to which the antibody may bind, thus reducing the exposure elsewhere. Caution is warranted for patients who have had a stem cell transplant prior to receiving gemtuzumab ozogamicin, as this was associated with a higher risk of VOD, bilirubinemia, and elevated AST. VOD can be fatal and is a known serious risk to patients receiving a stem cell transplant.

The majority of patients experienced grade ≥ 3 myelosuppression. The data show that nearly all patients who achieved remission or blast-free status experienced grade 4 depletion of leukocytes, neutrophils, and platelets. The time course of the myelosuppression model was originally developed to describe the chemotherapy-induced antiproliferative effect through drug-specific parameters (slope or maximum effect (E_{max}) and half-maximal effective concentration (EC_{50})) and also system-related parameters that should be common to all drugs. The EC_{50} estimated parameter was significantly below the achieved

Table 4 Parameter estimates for the neutropenia model

Parameter	Estimate	Shrinkage (%)	Bootstrap Mean	Bootstrap 95% CI lower	Bootstrap 95% CI upper
Structural model					
MMT (hours)	64.99	54.0	60.55	23.706	72.65
E_{max}, maximum effect of GO concentration on the overall drug effect	0.818	63.9	0.91	0.728	1.176
EC_{50}, total hP67.6 antibody concentration that led to half of the maximum antiproliferative effect (ng/mL)	113.30	58.4	166.71	62.35	425.65
CIR_0, Baseline level of circulating cells (10^9 cells/L)	0.814	18.2	0.812	0.689	0.940
γ, feedback parameter on cell proliferation	0.286	60.4	0.268	0.180	0.353
SLO_a, linear effect of AraC on overall drug effect	0.539	93.5	0.597	0.524	0.670
SLO_d, linear effect of DNR on overall drug effect	0.184	95.8	0.213	0.188	0.253
Proportional residual error	1.06	31.28	1.045	0.960	1.135
Covariates					
GO + AraC on CIR_0	−0.173	—	−0.151	−0.443	0.211
GO monotherapy on CIR_0	−0.138	—	−0.121	−0.294	0.097
GO + AraC on E_{max}	0.273	—	0.281	−0.109	0.773
GO monotherapy on E_{max}	−0.136	—	−0.191	−0.310	−0.033
Multidrug resistance efflux on E_{max}	0.0004	—	0.001	−0.001	0.003
Prior stem cell transplant on MMT	0.411	—	0.418	−0.779	1.734
Baseline bone marrow blast percentage on CIR_0	−0.005	—	−0.005	−0.009	−0.002
	Estimate	**CV (%)**	**Mean**	**95% CI lower**	**95% CI upper**
Interindividual variability parameters					
MMT	0.173	41.63	0.211	0.045	1.112
E_{max}	0.111	33.38	0.123	0.055	0.231
EC_{50}	3.9	197.48	4.560	2.317	7.904
CIR_0	1.229	110.88	1.281	1.055	1.527
γ	0.248	49.76	0.209	0.009	0.316
SLO_a	0.025	FIXED	—	—	—
SLO_d	0.025	FIXED	—	—	—
Variance–covariance parameters					
MMT and E_{max} interaction	0.113	33.64	0.095	0.016	0.214
MMT and EC_{50} interaction	0.701	83.75	0.557	0.096	1.205
E_{max} and EC_{50} interaction	0.619	78.67	0.669	0.302	1.205
MMT and CIR_0 interaction	−0.218	46.71	−0.149	−0.432	0.134
E_{max} and CIR_0 interaction	−0.018	13.44	0.032	−0.122	0.196
EC_{50} and CIR_0 interaction	−0.795	89.14	−0.716	−1.518	0.161
Objective function value	4,917.409	—	4,925.27	4,596.44	5,253.43

Interindividual variability of parameter estimates has been reported as the CV(%) scale (i.e., $\sqrt{(\omega^2)\cdot 100}$) as the parameters follow a log-normal distribution. The bootstrap CIs were calculated using the percentiles from the 1,000 bootstrap samples with stratification by study. The reference patient is male, *de novo* patient receiving GO + DNR + AraC with a multidrug resistance efflux value of 47.50, a baseline leukemic bone marrow blast of 60%, and did not receive a prior stem cell transplant. The covariates were parameterized as follows:

$MMT = 64.99\cdot(1+0.411\cdot PSCT)$, where PSCT = 1 if the patient received a prior stem cell transplant and 0 otherwise;

$E_{max} = 0.818\cdot(1+0.273\cdot THER1)\cdot(1-0.136\cdot THER2)\cdot(1+0.0004\cdot(MDREFX-47.50))$, where THER1 = 1 for AraC+GO and THER2 = 1 for GO monotherapy and 0 otherwise;

$CIR0 = 0.814\cdot(1-0.173\cdot THER1)\cdot(1-0.138\cdot THER2)\cdot(1-0.005\cdot(BMAR-60))$, where THER1 = 1 for AraC+GO and THER2 = 1 for GO monotherapy and 0 otherwise.

AraC, cytarabine; CI, confidence interval; CV (%), percentage of coefficient of variation; DNR, daunorubicin; EC_{50}, half-maximal effective concentration; E_{max}, maximum effect; GO, gemtuzumab ozogamicin; MMT, mean maturation time.

concentrations under the gemtuzumab ozogamicin dosing regimen of 9 mg/m^2 at least 14 days apart and the fractionated dosing schedule of 3 mg/m^2 on days 1, 4, and 7. The estimated EC_{50} values for myelosuppression of platelets and neutrophils were 21 and 113 ng/mL, respectively. The low EC_{50} values estimated by the model relative to the plasma concentration achieved under the recommended dosing schedules (predicted geometric C_{max} over the treatment course for 9 mg/m^2 on days 1 and 15 and

for 3 mg/m^2 on days 1, 4, and 7 were 2,620 ng/mL and 632 ng/mL, respectively) confirms the almost complete depletion of neutrophils and platelets observed in the trials presented in this report. In the current study population, the mean maturation time (MMT) is lower than what was previously reported and is expected for neutrophils (120 hours vs. 65 hours) and platelets (240 hours vs. 125 hours). This discrepancy in MMT could be due to the nature of the disease and/or previous antiproliferative treatments not accounted for in the model. Combination therapy and *de novo* AML were found to be statistically significant covariates affecting MMT and E_{max} for both platelet counts and neutropenia. However, the majority of patients receiving combination therapy with cytarabine + daunorubicin had *de novo* AML and, therefore, based on the available data, it does not seem possible to distinguish between those two effects, as they are confounded variables.

The observed data in pediatric patients from Study 102 were used to evaluate the adequacy of the models developed with the adult populations for making inferences regarding the pediatric population. For CR/CRp and blast-free status, there was no evidence of lack of fit ($P > 0.05$) between the observed pediatric data and the adult models. This suggests that inferences regarding the ER relationships with CR/CRp and blast-free status for the adult population can be extended to the pediatric population. For the safety end points, only the models for VOD and hypoalbuminemia showed a lack of fit between the pediatric patient data and the model predictions. The prevalence of VOD was higher than predicted ($P < 0.0001$) in the pediatric patient population consistent with other research suggesting an increased risk for pediatric patients, particularly patients under 10 years old.[28] The prevalence of grade ≥ 3 hypoalbuminemia was lower than predicted ($P = 0.0015$) for the adult population. Hypoalbuminemia can also occur in patients due to comorbid conditions, which may be more frequent in adults. The differences in the prevalence of VOD and hypoalbuminemia (along with the small number of events) suggest that inferences regarding the pediatric population for these two safety end points should be made with caution. Myelosuppression in the pediatric population was determined to be adequately characterized with the adult models, because the VPCs (simulated using the adult models) did not show any evidence of lack of fit. This bridging of the ER relationship characterized in the adult models to the pediatric population supports a favorable risk/benefit profile for treatment with gemtuzumab ozogamicin in the relapsed/refractory pediatric population. The optimal dose for pediatric patients is currently being evaluated in the MyeChild study.[29]

When gemtuzumab ozogamicin was administered in a first-line *de novo* AML setting in combination with daunorubicin and cytarabine, the fractionated dose regimen (3 mg/m^2 on days 1, 4, and 7) resulted in the highest clinical utility index at the expected total hP67.6 antibody C_{max} values after the first given dose of gemtuzumab ozogamicin. Comparable clinical utility index values were calculated for each of the approved regimens for refractory AML (3 mg/m^2 on days 1, 4, and 7 as monotherapy) or in newly diagnosed patients with AML who are considered ineligible for intensive chemotherapy (6 mg/m^2 on day 1 and 3 mg/m^2 on day 8) relative to the initially approved two 9 mg/m^2 doses at least 14 days apart. More than one dose of gemtuzumab ozogamicin was associated with improved efficacy of gemtuzumab ozogamicin relative to a single dose, consistent with literature suggesting that gemtuzumab ozogamicin activity is increased by more frequent dosing because CD33 is rapidly re-expressed on leukemic cells following the first dose, thereby increasing drug uptake into leukemic blasts with subsequent doses. Furthermore, it is important to note that the clinical utility index presented in **Figure 2** only accounts for CR/CRp and occurrence of VOD; however, other factors were also considered when the different dosing regimens were evaluated. The time course of myelosuppression indicated that when dosing 9 mg/m^2 every 14 days, it takes a longer time for blood cell counts to recover relative to lower doses given closer in time (**Figure 1**; i.e., 3 mg/m^2 on days 1, 4, and 7 and 6 mg/m^2 on day 1 and 3 mg/m^2 on day 8).

The results of these analyses support the important role of modeling and simulation in drug development. Earlier correlations with gemtuzumab ozogamicin exposure could have informed the risk of some of the presented AEs for the first approved dose (9 mg/m^2 14 days apart). However, the role of a more frequent schedule of administration, which was likely key to the efficacy improvement of the new regimens, could not have been estimated without data from the cooperative studies supported by the quick re-expression of the CD33 antigen after exposure to a single dose of gemtuzumab ozogamicin. By combining the observed PD end points with both observed and predicted exposures, the safety and efficacy of new dosing regimens for new patient populations were supported using PK/PD modeling and simulation. Given the previous withdrawal of gemtuzumab ozogamicin from the US market, the reapproval with new dosing regimens underscores the importance of selecting the best dose regimen. Together with the study outcomes, the PK/PD modeling supports the three approved gemtuzumab ozogamicin regimens in patients with newly diagnosed or relapse/refractory AML.

METHODS

Analyses were performed using R software version 3.2.2 or later,[30] NONMEM version 7.3,[31] and Perl-speaks-NONMEM (PsN) version 4.2.0.[32]

Logistic regression

Base models were developed for each of the efficacy end points and hepatic-related safety end points. The major aspects of the treatment with gemtuzumab ozogamicin that needed to be captured by the model were:

- Total hP67.6 antibody exposure (i.e., cumulative AUC, overall C_{max}, or C_{max} for the first dose)
- The number of doses of gemtuzumab ozogamicin as a monotherapy during the induction phase
- The combination with chemotherapy (gemtuzumab ozogamicin + cytarabine or gemtuzumab ozogamicin + daunorubicin + cytarabine)

For the safety end points, the baseline laboratory value of each event was included in the base model. A backward stepwise elimination approach was used to assess potential covariates with an inclusion criteria

Table 5 Parameter estimates for the time course of platelets model

Parameter	Estimate	Shrinkage (%)	Bootstrap Mean	Bootstrap 95% CI lower	Bootstrap 95% CI upper
Structural model					
MMT (hours)	125.216	67.7	157.752	111.286	233.69
E_{max}, maximum effect of GO concentration on the overall drug effect	0.667	64	0.8	0.536	1.151
EC_{50}, total hP67.6 antibody concentration that led to half of the maximum antiproliferative effect (ng/mL)	21.45	79.1	17.987	8.696	30.584
CIR_0, baseline level of circulating cells (10^9 cells/L)	53.90	20.1	52.844	47.876	58.523
γ, feedback parameter on cell proliferation	0.550	74.1	0.518	0.458	0.561
SLO_a, linear effect of AraC on overall drug effect	0.220	96.5	0.234	0.2	0.264
SLO_d, linear effect of DNR on overall drug effect	0.085	97.2	0.092	0.08	0.117
Proportional residual error	0.713	29.3	0.699	0.653	0.745
Covariates					
Relapsed/refractory on CIR_0	−0.278	—	−0.246	−0.348	−0.137
Relapsed/refractory on E_{max}	−0.520	—	−0.571	−0.724	−0.406
GO + AraC on MMT	−0.158	—	0.167	−0.588	4.96
GO monotherapy on MMT	−0.514	—	−0.571	−0.736	−0.427
Female on MMT	−0.068	—	−0.09	−0.235	0.04
	Estimate	**CV (%)**	**Mean**	**95% CI lower**	**95% CI upper**
Interindividual variability parameters					
MMT	0.017	13.033	0.04	0.005	0.116
E_{max}	0.07	26.533	0.083	0.021	0.161
EC_{50}	0.236	48.624	0.969	0.257	2.329
CIR_0	0.356	59.668	0.381	0.303	0.46
γ	0.009	9.735	0.019	0.004	0.046
SLO_a	0.025	FIXED	—	—	—
SLO_d	0.025	FIXED	—	—	—
Variance–covariance parameters					
MMT and E_{max} interaction	0.009	9.673	0.005	−0.032	0.071
MMT and EC_{50} interaction	−0.025	15.77	−0.064	−0.249	0.113
E_{max} and EC_{50} interaction	0.082	28.65	0.141	−0.092	0.394
MMT and CIR_0 interaction	−0.012	10.974	−0.033	−0.126	0.039
E_{max} and CIR_0 interaction	0.05	22.316	0.046	−0.035	0.126
EC_{50} and CIR_0 interaction	0.025	15.729	0.019	-0.604	0.601
Objective function value	2,562.60	—	2,574.84	2,267.02	2,921.10

Interindividual variability of parameter estimates has been reported as the CV (%) scale (i.e., $\sqrt{(\omega^2)} \cdot 100$) as the parameters follow a log-normal distribution. The bootstrap CIs were calculated using the percentiles from the 1,000 bootstrap samples with stratification by study. The reference patient is a male, *de novo* patient receiving GO + DNR + AraC. The covariates were parameterized as follows:

$MMT = 125.216 \cdot (1 - 0.068 \cdot SEX) \cdot (1 - 0.158 \cdot THER1) \cdot (1 - 0.514 \cdot THER2)$, where SEX=1 for female and 0 for male, THER1 = 1 for AraC+GO,THER2 = 1 for GO monotherapy and 0 otherwise;

$CIR0 = 53.90 \cdot (1 - 0.278 \cdot RR)$, where RR =1 if the patient is Relapse/Refractory and 0 otherwise; $E_{max} = 0.667 \cdot (1 - 0.520 \cdot RR)$, where RR =1 if the patient is Relapse/Refractory and 0 otherwise.

AraC, cytarabine; CI, confidence interval; CV (%), percentage of coefficient of variation; DNR, daunorubicin; EC_{50}, half-maximal effective concentration; E_{max}, maximum effect; GO, gemtuzumab ozogamicin; MMT, mean maturation time.

of $\alpha = 0.01$. The following covariates were tested for potential inclusion in the final model: sex; age; baseline bone marrow blasts (%); baseline values of ALP, bilirubin, albumin, neutrophils, leukocytes, and platelets; concomitant hydroxyurea treatment; prior stem cell transplant; two or more doses of gemtuzumab ozogamicin monotherapy; and baseline Eastern Cooperative Oncology Group-Performance Status (≤1 vs. ≥2).

Myelosuppression time course

The time courses of platelet and neutrophil counts were modeled using a semimechanistic PK/PD model described elsewhere[19,20] and shown in **Figure S2**. The semimechanistic myelosuppression model consisted of 12 compartments, with 7 PK compartments (3 for gemtuzumab ozogamicin,[16] 2 for cytarabine, and 2 for daunorubicin[33]) and 5 PD compartments, to characterize the longitudinal change of

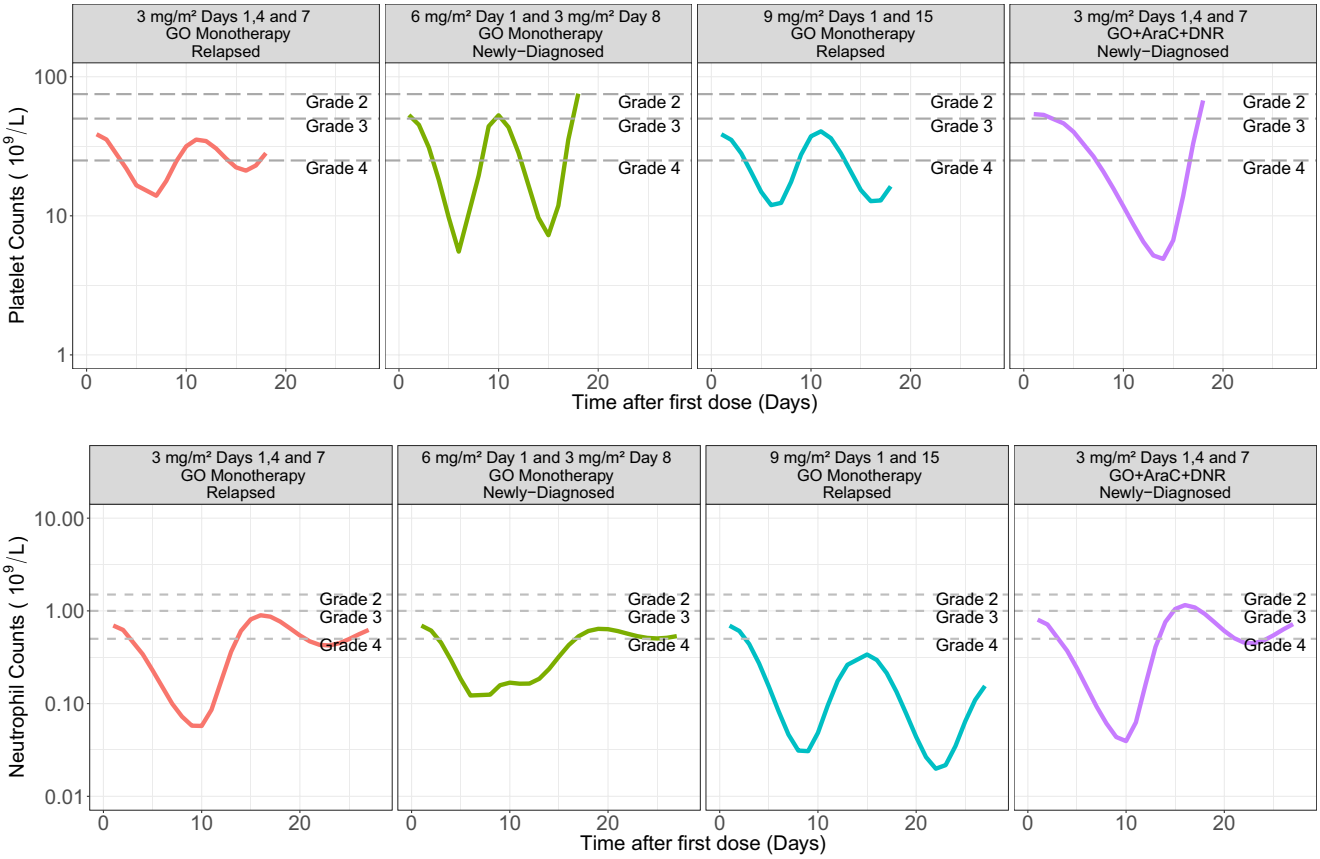

Figure 1 Predicted time course of myelosuppression for the initial and recently approved regimens. The predicted time course of neutrophils and platelets for the different approved dosing regimens are shown. The dashed lines show the grade severity using the National Cancer Institute Common Terminology Criteria for Adverse Events, v4.03 definitions. AraC, cytarabine; DNR, daunorubicin; GO, gemtuzumab ozogamicin.

cell count following administration of gemtuzumab ozogamicin as a single agent, in combination with cytarabine or in combination with daunorubicin + cytarabine. The drug effect for the different agents was considered additive with a linear (daunorubicin and cytarabine) and an E_{max} function (gemtuzumab ozogamicin). The form of the five PD compartments is as follows:

$$\mathrm{dProl}/\mathrm{d}t = k_{\mathrm{prol}} \cdot \mathrm{Prol} \cdot (1 - \mathrm{ED}) \cdot (\mathrm{Circ}_0/\mathrm{Circ})^{\gamma} - k_{tr} \cdot \mathrm{Prol}$$

$$\mathrm{d}T_1/\mathrm{d}t = k_{tr} \cdot \mathrm{Prol} - k_{tr} \cdot T_1$$

$$\mathrm{d}T_2/\mathrm{d}t = k_{tr} \cdot T_1 - k_{tr} \cdot T_2$$

$$\mathrm{d}T_3/\mathrm{d}t = k_{tr} \cdot T_2 - k_{tr} \cdot T_3$$

$$\mathrm{dCirc}/\mathrm{d}t = k_{tr} \cdot T_3 - k_{\mathrm{circ}} \cdot \mathrm{Circ}$$

with

$$\mathrm{ED} = \mathrm{E}_{\max} \cdot \left(\frac{C_1}{C_1 + \mathrm{EC}_{50}} \right) + \mathrm{SLO}_a \cdot C_9 + \mathrm{SLO}_d \cdot C_{11}$$

where ED is the overall drug effect with C_1 is the total hP67.6 antibody serum concentration, C_9 is the cytarabine concentration, and C_{11} is the daunorubicin concentration, each at time t. Circ represents platelets and neutrophils in their respective models. Following the approach of Friberg, the models were parameterized such that k_{prol} and k_{circ} were equal to $k_{tr} = 4/\mathrm{MMT}$ where 4 is the number of transit compartments (T_1, T_2, and T_3) plus one. Prol represents stem cells and progenitor cells (i.e., proliferative cells). SLO_a and SLO_d represent the linear effect of cytarabine and daunorubicin on the total drug effect.

For both neutrophils and platelets, interindividual variability was assumed to be lognormally distributed with a mean of 0 and covariance matrix of $\boldsymbol{\Omega}$. Interindividual variability was evaluated for MMT, E_{max}, EC_{50}, CIR_0, and γ, variability was fixed to 15% for $\theta_{\mathrm{slope,AraC}}$, and $\theta_{\mathrm{slope,DNR}}$. Off-diagonal elements of the $\boldsymbol{\Omega}$ matrix were estimated for MMT, E_{max}, EC_{50}, CIR_0, and γ.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

Figure S1. Receiver operating characteristic curves for logistic regression models.
Figure S2. Semimechanistic myelosuppression model.
Figure S3. Visual predictive check of the myelosuppression time course models.
Table S1. Definitions of treatment outcome based on the 2003 IWG criteria.
Table S2. Goodness of fit of logistic regression models to the pediatric data.

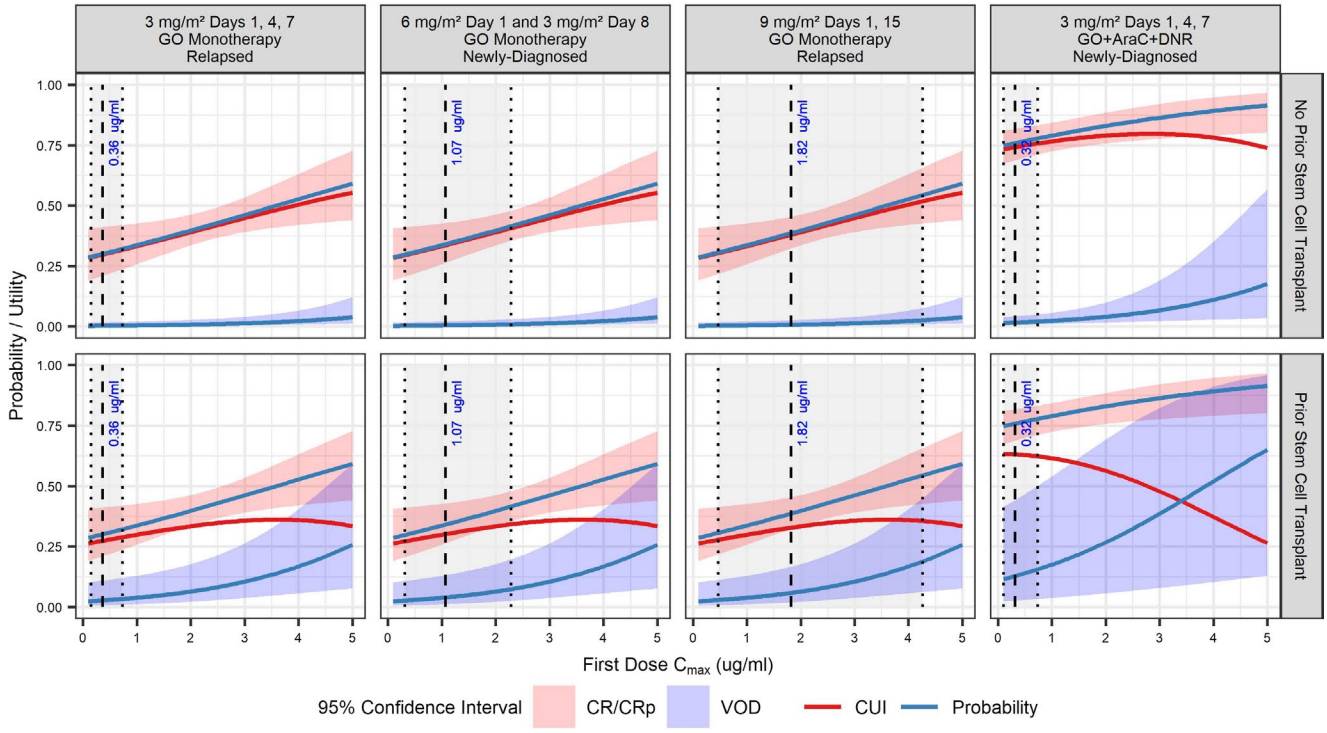

Figure 2 Clinical utility index for the initial and the recently approved regimens. The red line is the clinical utility index calculated using the probability of achieving CR/CRp and the probability of experiencing VOD (blue lines). The shaded blue and pink areas are the 95% confidence intervals around the predicted probabilities of VOD and CR/CRp, respectively. The fine dotted lines represent the 10th and 90th percentiles of the total hP67.6 antibody maximum serum concentration (C_{max}) after the first given dose of gemtuzumab ozogamicin. The dashed line is the total hP67.6 antibody geometric mean C_{max} after the first given dose of gemtuzumab ozogamicin from patients in the analysis dataset. AraC, cytarabine; CUI, clinical utility index; CR, complete response with platelet recovery; CRp, complete response without platelet recovery; DNR, daunorubicin; GO, gemtuzumab ozogamicin; VOD, veno-occlusive disease.

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CONFLICT OF INTEREST

The authors are all directly employed by Pfizer Inc.

AUTHOR CONTRIBUTIONS

L.K.F., A.R.G., J.C.M., J.E.H., and E.V. wrote the manuscript. L.K.F., A.R.G., J.C.M., J.E.H., and E.V. designed the research. L.K.F., A.R.G., J.C.M., and J.E.H. performed the research. L.K.F., A.R.G., J.C.M., and J.E.H. analyzed the data.

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