

## ORIGINAL ARTICLE

# Pharmacokinetics, exposure, efficacy and safety of obinutuzumab in rituximab-refractory follicular lymphoma patients in the GADOLIN phase III study

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**Aims:** Rituximab is standard care in a number of lymphoma subtypes, including follicular lymphoma (FL), although many patients are resistant to rituximab, or develop resistance with repeated treatment, and a high proportion relapse. Obinutuzumab is a novel anti-CD20 monoclonal antibody with improved efficacy over rituximab. It is approved for previously untreated chronic lymphocytic leukaemia (CLL), and for use with bendamustine in patients with rituximab-relapsed/refractory FL.

**Methods:** Using a previously described population pharmacokinetic (PK) model of obinutuzumab in patients with non-Hodgkin lymphoma and CLL, we conducted an exposure-response analysis using data from 6 clinical trials in patients with CD20+ B-cell malignancies (CLL11, GADOLIN, GATHER, GAUDI, GAUGUIN and GAUSS) to describe the PK properties of obinutuzumab, identify covariates influencing exposure, and explore how exposure affects safety, efficacy and pharmacodynamics.

**Results:** A 2-compartment model with linear and time-dependent clearance described obinutuzumab PK. Disease type and subtype, body weight, baseline tumour size, and sex had the largest effects on PK. Obinutuzumab exposure was not associated with occurrence or severity of adverse events, but higher exposure appeared to be associated with greater efficacy, particularly longer progression-free survival. However, in multivariate Cox regression analysis, progression-free survival benefit in the obinutuzumab plus bendamustine arm was independent of exposure.

**Conclusion:** The updated population PK model reported here accurately describes the PK of obinutuzumab patients with non-Hodgkin lymphoma and CLL. The selected obinutuzumab dosing regimen offers clinical benefit in a majority of rituximab-refractory FL patients treated with bendamustine, irrespective of variability in exposure, whilst minimising adverse events.

## KEYWORDS

drug exposure, follicular lymphoma, obinutuzumab, pharmacokinetics

Clinicaltrials.gov identifiers: NCT01010061, NCT01059630, NCT01414855, NCT000825149, NCT00517530, NCT00576758.

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## 1 | INTRODUCTION

Follicular lymphoma (FL) is the most common type of indolent non-Hodgkin lymphoma (iNHL).<sup>1</sup> Lymphomas of this subtype are characterised by an ongoing pattern of relapse and are usually incurable in their advanced stages.<sup>1-3</sup> **Rituximab** was the first monoclonal antibody (mAb) to target the **CD20** B-cell surface antigen,<sup>4</sup> and its use in conjunction with chemotherapy significantly improved outcomes in patients with advanced (stage 3-4) FL in first-line and salvage settings.<sup>5-10</sup> Although rituximab is standard care in FL and a number of other lymphoma subtypes,<sup>11</sup> management of rituximab relapse and resistance presents a significant challenge.<sup>12</sup>

**Obinutuzumab** (GA101) is a novel, humanised anti-CD20 mAb. In contrast to rituximab, which works primarily via complement-dependent cytotoxicity and localises CD20 in lipid rafts by binding it as a tetramer,<sup>4</sup> obinutuzumab is a type II mAb<sup>13-15</sup> that binds to CD20 without forming cross-links to CD20 tetramers, and so remains dispersed throughout the entire surface of the B cell. Obinutuzumab is glycoengineered to enhance binding affinity to FcγRIIIA/B expressed on effector cells such as natural killer cells, macrophages/dendritic cells and neutrophils, and works mainly by promoting direct cell death and antibody-dependent cellular cytotoxicity.<sup>4</sup> In clinical trials, obinutuzumab showed improved efficacy compared with rituximab<sup>16-19</sup>; in particular, a retrospective pharmacokinetic (PK)/pharmacodynamic (PD) analysis of the CLL11 trial demonstrated that obinutuzumab exhibited superior efficacy over rituximab, regardless of alternative dosing schedules; even when the dose of rituximab was tripled, it could not match the levels of B-cell depletion achieved by obinutuzumab.<sup>20</sup> Obinutuzumab is approved for previously untreated chronic lymphocytic leukaemia (CLL), and for use with bendamustine in patients with rituximab-relapsed/refractory FL.<sup>4</sup>

A predictive model describing the population PK of obinutuzumab, based on data from 678 patients with CLL or iNHL, has been described previously.<sup>21</sup> This model used data from 4 clinical studies: CLL11 (NCT01010061; patients with CLL)<sup>22</sup>; GAUDI (NCT00825149; patients with iNHL)<sup>23</sup>; GAUGUIN (NCT00517530; patients with CLL, iNHL, diffuse large B-cell lymphoma [DLBCL] or mantle cell lymphoma [MCL])<sup>18,24</sup>; and GAUSS (NCT00576758; patients with CLL, iNHL, DLBCL or MCL).<sup>25</sup> We report the development of an updated model based on a larger database including patients from 2 additional studies: GADOLIN (NCT01059630; patients with rituximab relapsed/refractory iNHL)<sup>26</sup>; and GATHER (NCT01414855; patients with DLBCL).<sup>27</sup> Our objectives were to further characterise the PK of obinutuzumab in different CD20 B-cell malignancies and to explore whether differences in drug exposure in patients from the GADOLIN study affected PD, safety or efficacy.

## 2 | METHODS

### 2.1 | Patients and study designs

Serum obinutuzumab concentrations from 961 patients with CD20+ B-cell malignancies from 6 clinical studies (GAUSS [*n* = 105: 4 CLL,

#### What is already known about this subject

- Rituximab, a type I anti-CD20 monoclonal antibody, is the current standard of care in follicular lymphoma and a number of other lymphoma subtypes, although management of rituximab relapse and resistance presents a significant challenge.
- Obinutuzumab is a novel, humanised, type II anti-CD20 monoclonal antibody that has exhibited superior efficacy over rituximab, regardless of alternative dosing schedules.

#### What this study adds

- The study provides a population pharmacokinetic model that accurately describes the pharmacokinetics of obinutuzumab in patients with non-Hodgkin lymphoma and chronic lymphocytic leukaemia.
- No association was found between obinutuzumab exposure and adverse events in rituximab-relapsed/refractory follicular lymphoma patients, confirming the favourable safety profile of the fixed-dose obinutuzumab regimen that is now approved for use with bendamustine in these patients.

96 iNHL, 4 DLBCL, 1 MCL]; GAUGUIN [*n* = 131: 30 CLL, 56 iNHL, 26 DLBCL, 19 MCL]; GAUDI [*n* = 134 iNHL]; CLL11 [*n* = 308 CLL]; GADOLIN [*n* = 183 iNHL]; and GATHER [*n* = 100 DLBCL]) were analysed using a validated sandwich enzyme-linked immunosorbent assay with a lower limit of quantitation of 4.05 ng/mL,<sup>21</sup> and were included in a population PK analysis using nonlinear mixed effect modelling techniques with NONMEM software (Version 7.3.0, ICON Development Solutions<sup>28</sup>; Table S1). Across the studies, obinutuzumab was given intravenously at doses of 50–2000 mg. All studies were carried out in accordance with the Declaration of Helsinki and the International Guidelines for Good Clinical Practice. Protocols were approved by the ethics committees at participating centres.

### 2.2 | Population PK analysis

The population PK analysis was performed as described previously.<sup>21</sup> The base model, a 2-compartment model in which clearance was a sum of time-dependent clearance ( $CL_T$ ) and time-independent clearance ( $CL_{inf}$ ), was updated with clinical data from the GATHER and GADOLIN studies. GATHER is an open-label phase II trial to evaluate the safety and efficacy of obinutuzumab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy in patients with advanced DLBCL. In GATHER, patients received eight 21-day cycles of obinutuzumab (1000 mg given intravenously on Day 1 of each cycle) alongside standard CHOP therapy for 6 cycles. GADOLIN, a phase III trial to assess the efficacy, safety and PK of obinutuzumab plus bendamustine (G-Benda) vs bendamustine

monotherapy in rituximab-refractory iNHL, is described in detail elsewhere.<sup>29,30</sup> In GADOLIN, a fixed dose of 1000 mg obinutuzumab was given on days 1, 8 and 15 of cycle 1, and on day 1 of cycles 2–6 (28-day cycles). Obinutuzumab maintenance therapy was subsequently given as 1000 mg every 2 months for 2 years, or until disease progression.

$CL_T$  decreased with time with a decay coefficient ( $K_{des}$ ). The Monte Carlo importance sampling expectation-maximisation assisted by mode *a posteriori* (IMPMP) estimation method was used (Supplementary Methods).<sup>31</sup>

Covariates investigated in the model are listed in Table S2. Graphical evaluation of the models and visual predictive check<sup>32</sup> simulations were performed as described previously.<sup>21</sup> Normalised prediction-distribution-error procedures<sup>33,34</sup> and stratification of model evaluation diagnostics were also undertaken (Supplementary Methods and Table S3). Individual predicted PK parameters were computed and summarised based on the standard iNHL dosing regimen, and individual concentration–time courses simulated (Supplementary Methods).

### 2.3 | Exposure–safety and exposure–efficacy relationships for FL patients (GADOLIN study)

Exposure–safety and exposure–efficacy relationships in rituximab-relapsed/refractory FL patients from the GADOLIN trial were explored using graphical analyses. Among patients with available PK assessments ( $n = 183$ ), only patients who received at least 5 doses of obinutuzumab (i.e.  $\geq 3$  dosing cycles) were included in the analyses. Baseline patient/disease characteristics of the subpopulation treated with G-Benda who contributed to the PK analysis were consistent with those of the intention-to-treat population.<sup>29,30</sup>

Safety outcomes explored were occurrence of serious adverse events (SAEs), severity of infusion-related reactions (IRRs), occurrence and severity of neutropenia and thrombocytopenia adverse events (AEs) and change in neutrophil/platelet counts. Relationships between exposure and PD outcomes were also explored (Supplementary Methods). Analyses included patients who received  $\geq 1$  dose of obinutuzumab.

For the exposure–efficacy analysis, mean obinutuzumab concentration over the induction period ( $C_{mean}$ ) was used to represent obinutuzumab exposure as it accounted for the actual dosing history (including dosing delays and modifications) over the entire induction period. This is similar to using cumulative area under the curve (AUC) over induction period, but it better accounts for differences in the duration of induction between patients. This exposure measure has been used previously for obinutuzumab.<sup>35</sup> Minimum serum concentration at a specific timepoint ( $C_{trough}$ ) would have been a better predictor of target saturation; however, it mainly accounts for the latest dose before  $C_{trough}$ . Distributions of  $C_{mean}$  were compared for different best overall response (BOR) categories. Relationships of progression-free survival (PFS) and overall survival (OS) with exposure were assessed by comparing  $C_{mean}$  in patients with or without events (progression, relapse, or death for PFS; death for OS). The risk of PFS

and OS events associated with 3 categories of exposure (low, medium and high, defined using tertiles of exposure) was compared graphically using Kaplan–Meier plots for all patients (analysis cut-off: 1 September 2014) and for patients with low and high baseline tumour size (defined based on the median value calculated from the sum of the products of diameters of the target lesion; Figure S1).

### 2.4 | Cox proportional hazards analysis of PFS and OS

In a *post-hoc* exploratory analysis, relationships between PK exposure, PFS and OS were characterised by semi-parametric Cox proportional hazards (CPH) models to investigate the effect of potential confounding factors on exposure (Supplementary Methods). Models where exposure was treated as a continuous or categorical covariate were evaluated during model development. CPH models were based on a 120-day safety update analysis of the GADOLIN trial (cut-off: 1 May 2015).

### 2.5 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY,<sup>36</sup> and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18.<sup>37</sup>

## 3 | RESULTS

### 3.1 | Population PK analysis in CLL, DLBCL and NHL

A total of 16 301 serum obinutuzumab concentrations from 961 patients were captured for the population PK analysis; 469 of these patients had iNHL, of whom 406 had FL (8545 serum samples) and 183 were from the GADOLIN trial (2178 serum samples). Other disease types were CLL ( $n = 342$ ), DLBCL ( $n = 130$ ) and MCL ( $n = 20$ ).

Summary statistics for the continuous covariates are presented in Table S4. The 2-compartment linear model with both linear ( $CL_{inf}$ ) and time-dependent clearances ( $CL_T$ ) described previously<sup>21</sup> accurately described obinutuzumab PK in patients from the 6 clinical studies.

Parameter estimates for the final covariate model are summarised in Table S5. Values for  $CL_{inf}$ , central volume of distribution ( $V_1$ ) and intercompartmental clearance ( $Q$ ) were similar to previous estimates based on 678 patients,<sup>21</sup> but estimates for the decay coefficient of time dependent clearance ( $k_{des}$ ) and peripheral volume of distribution ( $V_2$ ) were higher (0.11 vs 0.036  $day^{-1}$  and 1.23 vs 1.01 L, respectively) and  $CL_T$  was lower (0.154 vs 0.231 L  $day^{-1}$ ). Unexplained interindividual variability was moderate (44.6%) for  $CL_{inf}$  and was high for  $CL_T$  (110%) and  $k_{des}$  (90.6%). These values are consistent with the previously reported values for obinutuzumab,<sup>21</sup> except for  $k_{des}$ , where

incorporation of additional covariates in the current analysis allowed lower unexplained interindividual variability from 201% ( $\ln^{21}$ ) to 90.6%. The interindividual variability values were also consistent with those reported for rituximab in CLL patients.<sup>38</sup>

As baseline B-cell counts and disease type were confounded (e.g. by high B-cell counts in CLL patients); of these 2 variables, disease type was tested as a covariate in the model.

According to the model, a patient with FL or DLBCL would have a  $CL_{inf}$  of 74 mL day<sup>-1</sup>,  $V_1$  of 2.72 L,  $Q$  of 1.32 L day<sup>-1</sup> and  $V_2$  of 1.23 L (analysed covariates set to reference values). The initial value of  $CL_T$  was 154 mL day<sup>-1</sup>, with an estimated half-life of 6.3 days.  $CL_T$  half-life varied according to disease type and treatment (marginal zone lymphoma, 21.1 days; CLL treated with chlorambucil, 20.4 days; iNHL treated with bendamustine, 10.7 days; FL treated with fludarabine and cyclophosphamide, 2.4 days). Initial  $CL_T$  was higher in CLL or MCL than the reference subtype (FL or DLBCL), higher in men than women, and increased with increasing baseline tumour size (Table 1). Relative to a reference patient (65-year-old female with FL or DLBCL, baseline tumour size 3000 mm<sup>2</sup>), initial  $CL_T$  was ~100% greater in a patient with high baseline tumour size (22 400 mm<sup>2</sup>) and 55% lower

in a patient with low baseline tumour size (304 mm<sup>2</sup>). For  $CL_{inf}$ , the variance from the reference value was ~20% for the same 2 baseline tumour size values (Table 1).

Several other covariates had an effect on  $CL_{inf}$ ; the most marked differences relative to reference values were in patients with MCL, CLL and small lymphocytic lymphoma (Table 1).

Covariate model evaluation showed no model deficiencies (diagnostic plots) or unaccounted trends (dependencies of random effects). Visual predictive checks showed good agreement between simulated and observed data for all studies.

Sensitivity analyses were performed by refitting the final model developed on data from the 6 clinical studies from only those patients with iNHL and FL. Population predictions and goodness-of-fit for these 2 models were very similar to those for the final model, and individual predictions were nearly identical.

Summaries of mean PK parameters are shown in Table S6 and results of model-based simulations with the iNHL dosing regimen are reported in Supplementary Results and Figures S2 and S3. Simulations showed that the loading doses enable concentrations to reach steady-state values at the end of cycle 1, and that concentrations

**TABLE 1** Effects of covariates on key pharmacokinetic parameters in the final covariate model

Parameter	Covariate	Reference value for covariate*	Illustrative value for covariate*	Effect on parameter, % (mean, 95% CIs)
$CL_{inf}$	Body weight	75 kg	52 kg	-20.9 (-26, -15.4)
			115 kg	31.4 (21.6, 42)
	Serum albumin	40 g/L	28.7 g/L	25.4 (35.1, 16.4)
			48.7 g/L	-12.6 (-16.3, -8.6)
	Sex	Female	Male	17.6 (9.8, 26)
			Disease type	FL or DLBCL
	CLL	38 (10.2, 72.9)		
MCL	106.9 (44.6, 195.9)			
Age	65 years	38 years	13.8 (5.7, 22.6)	
		83 years	-5.7 (-8.9, -2.5)	
Baseline tumour size	3000 mm <sup>2</sup>	304 mm <sup>2</sup>	-18.6 (-24.4, -12.4)	
		22 400 mm <sup>2</sup>	19.8 (12.3, 27.8)	
$CL_T$	Sex	Female	Male	45.1 (19.3, 76.6)
			Disease type	FL or DLBCL
	CLL	180.3 (28, 513.7)		
	MCL	102.3 (63.6, 150.1)		
Baseline tumour size	3000 mm <sup>2</sup>	304 mm <sup>2</sup>	-55.2 (-64.8, -42.9)	
		22 400 mm <sup>2</sup>	102.3 (63.6, 150.1)	
$V_1$	Body weight	75 kg	52 kg	-12.9 (-15.3, -10.5)
			115 kg	17.5 (13.9, 21.4)
Sex	Female	Female	Male	19.4 (15.8, 23)
			$V_2$	Body weight
115 kg	58.4 (39, 80.5)			
$K_{des}$	Received CHOP	No	Yes	-69.1 (-75.1, -61.6)
	Received fludarabine + cyclophosphamide	No	Yes	164.4 (38.5, 404.8)
	Received bendamustine	No	Yes	-40.9 (-55.5, -21.6)
	Disease type	FL or DLBCL	MZL	-70.1 (-81.9, -50.7)

CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone; CL: confidence limit;  $CL_{inf}$ : nonspecific time-independent clearance;  $CL_T$ : initial value of time-dependent clearance; CLL: chronic lymphocytic leukaemia; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma;  $k_{des}$ : decay coefficient of time-dependent clearance; MCL: mantle cell lymphoma; MZL: marginal zone lymphoma; PK: pharmacokinetic; SLL: small lymphocytic lymphoma;  $V_1$ : central volume of distribution;  $V_2$ : peripheral volume of distribution.

\*For continuous covariates, reference values are medians and illustrative values are the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles of the values in the analysis data set.

differ slightly according to lymphoma type, iNHL subtype, weight, sex and baseline tumour size, as well as the accompanying chemotherapy.

### 3.2 | Relationships between exposure and study outcomes in GADOLIN relapsed/refractory FL patients

These analyses used efficacy and safety data from the 145 FL patients from GADOLIN.

### 3.3 | Exposure–safety analysis

Analysis of the relationships between exposure and SAE occurrence were done for all reported SAEs and for seven System Organ Classes in which 4 or more SAEs (occurring at any time) were reported (Table S7). Graphical analysis showed no relationship between the severity of IRRs and the predicted obinutuzumab  $C_{max}$  after the dose that preceded the IRR (Figure S4). The time course of reductions in neutrophil counts and platelet counts was similar for low ( $C_{mean} < 293 \mu\text{g mL}^{-1}$ ), middle ( $C_{mean} 293\text{--}388 \mu\text{g mL}^{-1}$ ) and high ( $C_{mean} > 388 \mu\text{g mL}^{-1}$ ) tertiles of obinutuzumab exposure. Distribution of  $C_{mean}$  values showed no relationship with the occurrence or severity of neutropenia or thrombocytopenia, although the numbers of patients with thrombocytopenia AEs of Common Terminology Criteria for Adverse Event grades 1–4 was small (data not shown).

Anti-drug antibodies were detected in 1 patient from GADOLIN treated with G-Benda; no influence on obinutuzumab PK was seen.

### 3.4 | Exposure–pharmacodynamic relationships

In all obinutuzumab exposure tertiles, B-cell counts decreased rapidly from baseline after the start of obinutuzumab treatment and remained depressed for the whole observation period ( $n = 143$ ; data not shown).

The reduction in tumour size between baseline and end of induction was similar across exposure groups with a slightly higher reduction in the middle and high tertiles (median 80%, 86% and 84% in the low, middle and high tertiles, respectively; data not shown) suggestive of a possible relationship between exposure and tumour burden reduction. However, this might be subject to confounding by higher baseline tumour size in patients with low PK exposure (Figure S5), and is a visual comparison only that was not subject to formal statistical analysis.

### 3.5 | Exploratory exposure–efficacy relationships

Graphical analyses of exposure–efficacy relationships in FL patients who received obinutuzumab in GADOLIN were performed on 128 patients for BOR and PFS. Patients with complete response had apparently higher obinutuzumab  $C_{mean}$  than patients in other response categories (partial response, stable disease or progressive disease; Figure S6), especially in the subset of patients with low baseline tumour size (below median value).

Patients with PFS events appeared to have a lower median obinutuzumab  $C_{mean}$  than patients without events, both for all patients and those with high baseline tumour size; in patients with low baseline tumour size,  $C_{mean}$  distributions were similar for patients with and without PFS events (Figure 1).

### 3.6 | CPH analysis of exposure–efficacy relationships

The CPH models included 294 patients for PFS (obinutuzumab [G-Benda],  $n = 128$ ; control [bendamustine-only],  $n = 166$ ) and 295 for OS (129 and 166, respectively). Parameters of the final models are presented in Table 2. OS data were not analysed by exposure tertiles because of immaturity of the data. Model predictions were in good agreement with observed data for both PFS and OS.

The PFS analysis with continuous exposure confirmed that the risk of a PFS event was lower in the G-Benda arm than the bendamustine-only arm, as previously reported.<sup>18</sup>

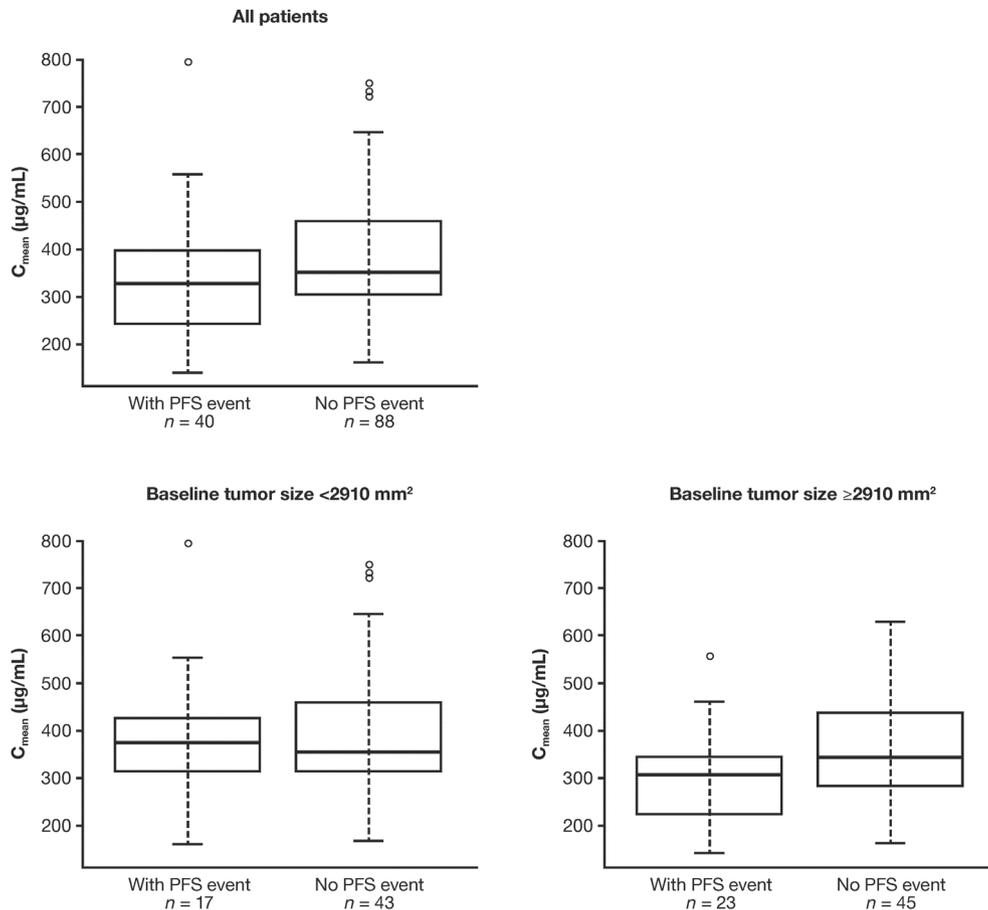
CPH models indicated that the risk of progression or death decreased with increasing obinutuzumab PK exposure; by approximately 40% and 80% at the 5<sup>th</sup> ( $C_{mean} 195 \mu\text{g/mL}$ ) and 95<sup>th</sup> ( $C_{mean} 604 \mu\text{g/mL}$ ) percentiles of exposure, respectively (hazard ratio [HR] [95% confidence interval (CI)] 0.60 [0.50–0.71] and 0.20 [0.12–0.35], respectively). In patients with bone marrow involvement at baseline, the risk of progression or death increased by 69% (HR [95% CI] 1.69 [1.22–2.35]).

For OS, patient age was a significant predictor of shorter survival, although the effect was small. No effect of baseline tumour size on PFS or OS was seen. Figure 2 illustrates the effects of exposure and prognostic factors on the PFS hazard. Longer PFS was observed in all obinutuzumab groups compared to the bendamustine-only group, with longer PFS for patients in the higher tertile of exposure vs those in the lower and middle tertiles (Figure 3), particularly in patients with high baseline tumour size (data not shown).

A CPH model with a categorical exposure (defined by tertiles of  $C_{mean}$ ) was also implemented for PFS (Table 2). For all 3 exposure groups, risk of progression was significantly lower than for the bendamustine-only arm. However, HRs were not ordered between exposure categories (0.37, 0.45, and 0.30 for low, middle and high exposure categories relative to the bendamustine-only arm) and 95% CIs overlapped for all 3 categories.

## 4 | DISCUSSION

The obinutuzumab population PK model described here is consistent with an earlier model based on a smaller number of CLL and NHL patients,<sup>21</sup> and with previous experience with rituximab that showed time-dependent PK in the targeting of CD20 on B-cells by antibody.<sup>38–40</sup> The expanded model, based on data from 6 rather than 4 clinical studies (283 additional patients) and examining a greater number of covariates, describes a 2-compartment linear PK model with both time-independent and time-dependent clearance components.



**FIGURE 1** Relationships between PFS and obinutuzumab exposure ( $C_{\text{mean}}$ ) in patients with FL participating in GADOLIN who received at least 3 dosing cycles of obinutuzumab ( $n = 128$ ). Lines inside boxes denote medians. Boxes denote IQR. Error bars: limits of  $1.5 \times$  IQR. Circles show outliers.  $C_{\text{mean}}$ : mean obinutuzumab exposure over induction period; FL: follicular lymphoma, IQR: interquartile range; PFS: progression-free survival

The time-dependent pathway is thought to be due to target-mediated drug disposition. CD20+ B-cells, the therapeutic target of obinutuzumab, also mediate its clearance; as treatment continues, fewer target cells are able to bind to and clear obinutuzumab. Once the majority of target cells are destroyed after being bound by obinutuzumab, target-mediated drug disposition contributes much less to drug clearance. The model showed that clearance increased with increases in baseline tumour size, with a much more profound effect on  $CL_T$  than  $CL_{\text{inf}}$ , which is consistent with target-mediated elimination. The model also showed substantial differences in clearance between types of lymphoma. This was most evident for MCL patients, in whom both  $CL_T$  and  $CL_{\text{inf}}$  were higher when compared with a typical FL or DLBCL patient. Rate of clearance decline was also affected by lymphoma type; this may reflect differences between disease types in how CD20 is expressed or distributed<sup>41</sup> and/or the number of circulating lymphocytes in blood.

The clearance parameters estimated by our model for a reference patient are typical for mAbs.<sup>42,43</sup> Based on our model estimate for  $CL_T$ , it would take approximately 1 month (5 half-lives) for  $CL_T$  to reach a near-zero value, suggesting that most CD20 target cells are saturated within the first month of dosing. Conditional simulations confirmed that steady state exposure to obinutuzumab is reached by

the end of the first dosing cycle. By administering 2 extra 1000-mg doses during cycle 1, the saturation of CD20+ cells is reached rapidly in a majority of patients and maintained throughout the treatment period.<sup>44</sup>

The increase in obinutuzumab  $CL_{\text{inf}}$ ,  $V_1$  and  $V_2$  with body weight is typical for mAbs, but model-based conditional simulations of concentration-time profiles following the iNHL dosing regimen and the absence of a clear relationship between exposure and efficacy suggest that this association is probably not clinically relevant for dosing in patients with iNHL. Higher  $CL_{\text{inf}}$  in patients with low albumin levels may be linked to the correlation of albumin levels with efficiency of the neonatal Fc receptor.<sup>45</sup> There were also associations of  $CL_{\text{inf}}$  and  $V_1$  with sex and of  $CL_{\text{inf}}$  with age, but the dependencies were mild and are not considered clinically relevant. The association between  $CL_T$  and baseline tumour size was deemed to be not clinically relevant, because 2 loading doses were able to provide sufficient exposure during cycle 1 even in subjects with high baseline tumour size. The large interindividual variability in the parameters characterising the time dependency, even if unexplained, was expected as it reflects the large heterogeneity in the individual target expression at baseline, and in the reduction of target over time following treatment initiation.

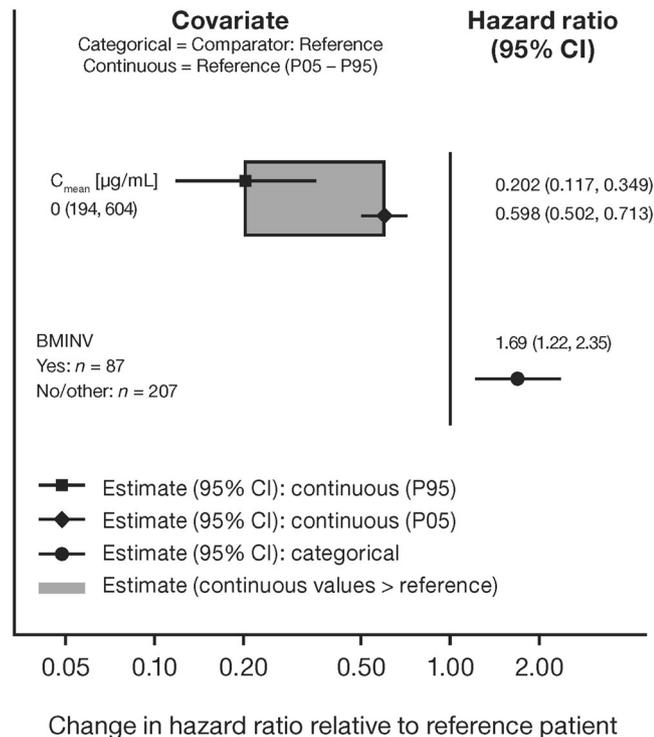
**TABLE 2** Parameters of the final cox proportional hazards models for PFS and OS based on data in patients with follicular lymphoma in GADOLIN

Covariate/tertile	HR (95% CI)*	$\beta$	SE	RSE
<b>PFS, model with exposure as continuous covariate (<math>C_{\text{mean}}</math>)</b>				
$C_{\text{mean}}$ (as a continuous covariate)	0.9974 (0.9965 to 0.9983)	-0.0027	0.0005	17.42
Bone marrow involvement at baseline, yes vs no	1.689 (1.217 to 2.346)	0.5244	0.1675	31.95
<b>PFS, with exposure as categorical covariate (<math>C_{\text{mean}}</math> tertiles)</b>				
Low tertile of $C_{\text{mean}}$	0.3695 (0.2219 to 0.6154)	-0.9956	.2603	26.14
Middle tertile of $C_{\text{mean}}$	0.4466 (0.2701 to 0.7383)	-0.8062	0.2565	31.82
High tertile of $C_{\text{mean}}$	0.3031 (0.1782 to 0.5156)	-1.194	0.2711	22.71
Bone marrow involvement at baseline, yes vs no	1.758 (1.259 to 2.454)	0.564	0.1703	30.19
<b>OS</b>				
Log $C_{\text{mean}}$ (as a continuous covariate)	0.8484 (0.7731 to 0.9309)	-0.1645	0.04736	28.8
Age (as a continuous covariate), increase of 1 y	1.06 (1.034 to 1.086)	0.05785	0.01257	21.73
Bone marrow involvement at baseline, yes vs no	2.401 (1.473 to 3.914)	0.8759	0.2494	28.47

CI: confidence interval;  $C_{\text{mean}}$ : mean obinutuzumab exposure over induction period; FL: follicular lymphoma; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; SE: standard error; RSE: relative standard error.

Patients in obinutuzumab + bendamustine arm who received <5 obinutuzumab doses (3 cycles) were excluded from this analysis.  $C_{\text{mean}}$  tertiles: low = 141–313  $\mu\text{g/mL}$ ; middle = 313–400  $\mu\text{g/mL}$ ; high = 400–794  $\mu\text{g/mL}$ .

\*Computed as  $\exp(\beta)$ .

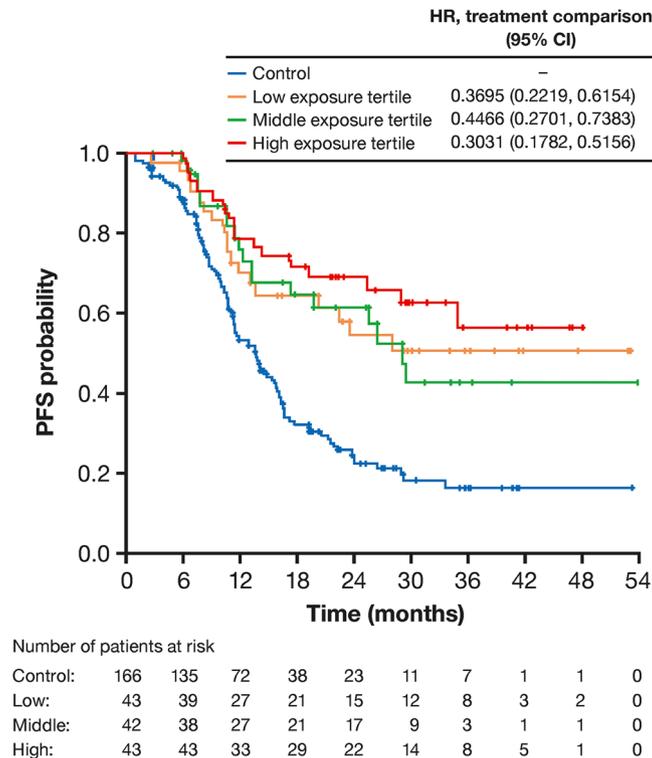


**FIGURE 2** Covariate effects on HR in the final cox proportional hazards model for PFS ( $n = 128$ ) in patients with FL participating in GADOLIN who received at least 3 dosing cycles of obinutuzumab (combined with bendamustine). BMINV: bone marrow involvement at baseline; CI: confidence interval;  $C_{\text{mean}}$ : mean obinutuzumab exposure over induction period; FL: follicular lymphoma; HR: hazard ratio; PFS: progression-free survival

Simulations of the iNHL dosing regimen in FL patients, i.e. 28-day dosing cycles, showed that obinutuzumab concentrations were lower during cycles 2–5 of induction therapy for CHOP than for other partner chemotherapy. The recommended higher dosing frequency of obinutuzumab when given with CHOP (eight 21-day cycles) compared to bendamustine (6 28-day cycles) accounts for this difference.

In patients with FL participating in GADOLIN, graphical analysis revealed no relationships between exposure and safety parameters, and changes in neutrophil and platelet counts during study treatment were unaffected by the level of obinutuzumab exposure. This is not entirely surprising, as cytopenia during treatment with anti-CD20 mAbs appears to have several possible causes.<sup>46</sup> In early treatment cycles, tumour destruction by the immune system leads to release of cytokines such as interleukins, which have the potential to induce cytopenia. In later cycles, other causes of cytopenia, such as reduction in bone marrow reserve, are more likely.

As stated previously, B-cell counts decrease rapidly after initiation of obinutuzumab treatment, and remain low during the entire dosing period in all exposure groups. This finding is consistent with our hypothesis that with the optimised dosing regimen of obinutuzumab (i.e. 1000-mg fixed dose on days 1, 8 and 15 of cycle 1 and then on day 1 of subsequent cycles), the CD20 pool in the body is saturated quickly, with saturation maintained throughout the entire dosing period in all patients despite the between-patient variability in PK exposure. Although there was a tendency for a greater reduction in tumour size during induction in patients with higher exposure, a confounding effect of tumour burden on exposure cannot be excluded. Recently, Tout *et al.*<sup>47</sup> reported that lower rituximab exposure in



**FIGURE 3** Kaplan–Meier plot, showing relationship between PFS ( $n = 128$ ) and obinutuzumab exposure (by tertiles of  $C_{\text{mean}}$ ) in patients with FL participating in GADOLIN who received at least 3 dosing cycles of obinutuzumab (combined with bendamustine). The upper table shows HR for PFS in obinutuzumab plus bendamustine arm relative to control arm ( $n = 166$ ; bendamustine monotherapy) from the final CPH model.  $C_{\text{mean}}$  tertile ranges: lower, 141–313  $\mu\text{g}/\text{mL}$ ; middle, 313–400  $\mu\text{g}/\text{mL}$ ; higher, 400–794  $\mu\text{g}/\text{mL}$ . CI: confidence interval;  $C_{\text{mean}}$ : mean obinutuzumab exposure over induction period; FL: follicular lymphoma; HR: hazard ratio; PFS: progression-free survival

DLBCL patients was a consequence of high tumour burden leading to poorer prognosis rather than a cause of inferior response. Similarly, exposure–response analyses of trastuzumab in patients with HER2+ cancers suggested that patients with low exposure had shorter overall survival times; however, they also had poor clinical factors at baseline and increasing the dose in this type of patient did not improve efficacy.<sup>48</sup>

Exploratory analysis of exposure–efficacy relationships suggested that patients with higher exposure to obinutuzumab could have better efficacy results (BOR, PFS), especially in patients with high tumour burden at baseline; however, this analysis was limited as it did not account for other prognostic factors. These results are consistent with graphical analyses for patients with CLL who received obinutuzumab that similarly were not adjusted for prognostic factors.<sup>21</sup> In cancer patients, exposure–response analyses often indicate poorer response in the low exposure group; however, it is often not a causal relationship as poor prognostic factors lead to low exposure.<sup>48</sup>

CPH modelling confirmed that G-Benda treatment significantly increased PFS compared with bendamustine alone in patients with FL, while differences in PFS between obinutuzumab exposure groups (tertiles of  $C_{\text{mean}}$ ) were small, with overlapping CIs. In addition, bone marrow involvement at baseline significantly shortened both PFS and OS, consistent with the published literature.<sup>49–51</sup> Increasing age

also had a statistically relevant effect on survival (for OS only), in agreement with existing data.<sup>21</sup> Differences in OS between patients with low and high exposure were not meaningful; however, at the time of the analysis cut off (1 May 2015), OS data were too immature to allow any definite conclusions. These results suggest that the current dosing regimen of obinutuzumab is offering clinical benefit to a majority of FL patients in GADOLIN, irrespective of the variability in drug exposure.

## 5 | CONCLUSION

In conclusion, the updated population PK model reported here accurately describes the concentration–time course of obinutuzumab in patients with NHL and CLL, in accordance with earlier findings in this patient population.<sup>21</sup> In rituximab-relapsed/refractory FL patients in the GADOLIN study, no association was found between obinutuzumab exposure and AEs, confirming the favourable safety profile of the fixed-dose regimen that is now approved for use with bendamustine in these patients. Graphical analysis suggested that an increase in obinutuzumab exposure was associated with better response rate and PFS in FL patients, but a multivariate Cox analysis of PFS that accounted for prognostic factors produced less conclusive

results. These findings confirm the suitability of the recommended fixed dose regimen of 1000 mg of obinutuzumab for rituximab-relapsed/refractory FL that provides clinical benefit in a majority of patients whilst minimising AEs.

## ACKNOWLEDGEMENTS

Support for third-party writing assistance under the directions of the lead authors was provided by Helen Cathro at Gardiner-Caldwell Communications and was funded by F. Hoffmann-La Roche Ltd.

This work was supported by F. Hoffmann-La Roche Ltd.

## COMPETING INTERESTS

The authors declare the following conflicts of interest: E.G. and L.G. were consultants for F. Hoffmann-La Roche Ltd, and V.B., N.F., M.B. and C.J. are employees of F. Hoffmann-La Roche Ltd. G.F.-R. is a former employee of F. Hoffmann-La Roche. G.F.-R. owns stock in F. Hoffmann-La Roche Ltd.

## CONTRIBUTORS

E.G. and L.G.: data analysis and data interpretation. V.B.: data analysis. N.F.: study, analyses and interpretation of the results. M.B.: study conduct and data collection, analysis and interpretation. G.F.-R.: study conduct, data analysis and data interpretation. C.J.: study, analyses, interpretation of the results and co-wrote the paper. All authors reviewed and contributed to the manuscript and approved the final version.

## DATA AVAILABILITY STATEMENT

Qualified researchers may request access to individual patient level data through the clinical study data request platform.<sup>52</sup> Further details on Roche's criteria for eligible studies are available from this site.<sup>53</sup> Further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents are available from the Roche website.<sup>54</sup>

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**How to cite this article:** Gibiansky E, Gibiansky L, Buchheit V, et al. Pharmacokinetics, exposure, efficacy and safety of obinutuzumab in rituximab-refractory follicular lymphoma patients in the GADOLIN phase III study. *Br J Clin Pharmacol.* 2019;85:1935–1945. <https://doi.org/10.1111/bcp.13974>

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