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PHARMACOKINETICS

Pharmacokinetics of obinutuzumab in Chinese patients with B-cell lymphomas

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AIM

The Phase Ib GERSHWIN study (NCT01680991) assessed the pharmacokinetic (PK) profile of obinutuzumab following multiple intravenous (i.v.) doses to Chinese patients with B-cell lymphomas, and compared findings with previous obinutuzumab PK studies in mainly Caucasian (non-Chinese) patients.

METHODS

GERSHWIN was an open-label, single-arm intervention study. Patients aged >18 years with CD20+ relapsed/refractory chronic lymphocytic leukaemia (CLL), diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma (FL) were enrolled from four centres in China. The treatment period was 24 weeks; patients received obinutuzumab 1000 mg i.v. on Days (D)1, 8 and 15 of Cycle (C)1 (CLL patients: first infusion split over 2 days) and on D1 of C2–8 (all cycles: 21 days). PK parameters were estimated using non-compartmental analysis (NCA), and a population PK analysis was used to determine whether observed GERSHWIN PK data were in accordance with previous obinutuzumab PK studies in non-Chinese patients.

RESULTS

The PK analysis population included 48 patients: 28 patients completed all treatment cycles. NCA showed a similar PK profile in Chinese patients with FL, DLBCL and CLL. Steady-state concentrations of obinutuzumab appeared to be reached at the start of C2 irrespective of histology. There was no apparent relationship between body weight and systemic exposure. Most PK profiles observed in GERSHWIN lay within the 90% prediction interval of simulated profiles.

CONCLUSIONS

Obinutuzumab exposure was comparable in CLL, DLBCL and FL patients. NCA and population PK analysis indicate that PK characteristics of Chinese patients with B-cell lymphomas are similar to those in non-Chinese patients.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The PK profile of obinutuzumab is well described by a two-compartment PK model comprising both a linear and nonlinear time-varying clearance pathway.
- This is based on PK data from mainly Caucasian patients in previous studies such as GAUGUIN, GAUDI, GAUSS, GATHER and GADOLIN.

WHAT THIS STUDY ADDS

- NCA showed a similar PK profile in Chinese patients with FL, DLBCL and CLL.
- The current study confirms that obinutuzumab exposure is similar in Chinese and non-Chinese patients with CD20+ malignant B-cell lymphomas.

Tables of Links

TARGETS
Other protein targets [2]
CD20

LIGANDS
Obinutuzumab
Rituximab

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2].

Introduction

B-cell lymphoproliferative diseases are a heterogeneous group of malignancies that range from slow-growing indolent and incurable diseases, such as follicular lymphoma (FL) or chronic lymphocytic leukaemia (CLL), to more aggressive diffuse large B-cell lymphomas (DLBCL). In China, there are few epidemiological data for lymphoma. According to a nationwide collaborative study of 10 002 lymphoma cases diagnosed in 2010, DLBCL is the most common B-cell lymphoma subtype in China, accounting for 50.2% of all cases, compared with 8.3% for FL and 6.4% for CLL/small lymphocytic lymphoma [3]. The relatively low incidence of CLL among the Chinese population was also highlighted in a North American survey, which reported a world age-standardized rate (per 100 000) for CLL of 0.40 among the Chinese population in British Columbia compared with 1.71 among the non-Chinese population [4]. Despite the availability of various agents for the treatment of non-Hodgkin lymphoma (NHL) and CLL, there is an ongoing need for the development of safe and effective therapies to prolong remission in patients and to improve cure rates.

Obinutuzumab (GAZYVA/GAZYVARO) is a novel glycoengineered type II monoclonal antibody (mAb). The main characteristics of obinutuzumab are high-affinity binding to the CD20 antigen, and high antibody-dependent cellular toxicity, antibody-dependent cellular phagocytosis and cell death induction, combined with low complement-dependent cytotoxic activity [5, 6]. Regulatory approval has recently been granted in Europe, the United States and other countries worldwide for use of obinutuzumab in combination with chlorambucil to treat previously untreated patients with CLL [7, 8]. The basis for this approval was data from the Phase III CLL11 study showing a statistically significant improvement in progression-free survival (PFS) with obinutuzumab plus chlorambucil compared with rituximab plus chlorambucil in treatment-naïve CLL patients (n = 781) with comorbidities (median PFS 29.2 *vs*. 15.4 months; hazard ratio [HR] 0.40, 95% confidence interval [CI] 0.33, 0.50; $P < 0.001$) [9, 10]. Obinutuzumab also demonstrated promising activity in patients with rituximab-refractory CLL and NHL in the single-arm Phase II GAUGUIN study [11, 12] and a higher overall response rate compared with rituximab in patients with relapsed indolent lymphoma in the Phase II GAUSS study [13]. Subsequently, the Phase III GADOLIN study in patients with rituximab-refractory indolent NHL showed that independently-assessed PFS was longer after treatment with obinutuzumab plus bendamustine than after bendamustine alone (HR 0.55, 95% CI 0.4, 0.74; P = 0.00011) [14].

The pharmacokinetics (PK) of obinutuzumab are well described by a two-compartment PK model comprising linear and nonlinear time-varying clearance pathways [15]. To date, several studies have examined the PK of obinutuzumab in patients with NHL and CLL, for example the Phase II GAUGUIN study (NCT00517530 [11, 12]) in Caucasian patients [11, 12, 16–18], and a Phase I Japanese study [19]. Other studies assessing obinutuzumab PK include CLL11 (NCT01010061 [9]), GAUDI (NCT00825149 [20, 21], GAUSS (NCT00576758 [13]), GATHER (NCT01414855) and GADOLIN (NCT01059630 [22]). However, PK bridging studies are a frequent requirement of Asian drug regulatory authorities when considering a new therapeutic entity [23]. The primary purpose of the current study (GERSHWIN; NCT01680991) was to assess the PK profile of obinutuzumab following administration of multiple intravenous (i.v.) doses to Chinese patients with CD20+ malignant B-cell lymphomas and to compare the findings with those from other obinutuzumab PK studies in mainly Caucasian (non-Chinese) patients using a population PK approach. Safety, tolerability and efficacy of obinutuzumab were secondary objectives of the current study and will be published separately.

Methods

Study design and treatment

This was a Phase Ib, open-label, single-arm interventional study (GERSHWIN) enrolling patients from four centres in China from 6 September 2012 to 15 August 2013. GERSHWIN was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. This study was approved by the Ethics Committee of the Cancer Institute and Hospital, Chinese Academy of Medical Sciences, in May 2012 (12–047/581). All patients provided written informed consent to participate in the study.

The treatment period was 24 weeks; patients received obinutuzumab 1000 mg i.v. on Days 1, 8 and 15 of Cycle 1 and on Day 1 of Cycles 2 to 8 (each cycle lasted 21 days). The first infusion of obinutuzumab on Cycle 1, Day 1 was given as a split dose over 2 days in CLL patients. For the first infusion, obinutuzumab was administered at an initial rate of 50 mg h^{-1} in patients with NHL. In the absence of infusion-related reactions, the infusion rate was increased by 50 mg h^{-1} every 30 min to a maximum of 400 mg h^{-1}. In CLL patients, the first two infusions were given at a dose of 100 mg at a rate of 25 mg h^{-1} over 4 h on Day 1 and at a dose of 900 mg starting at 50 mg h^{-1} on Day 2, increasing by 50 mg h^{-1} every 30 min to a maximum of 400 mg h^{-1}. If the first obinutuzumab infusion was well tolerated by the patient (CLL or NHL), subsequent infusions were given at an initial rate of 100 mg h^{-1} and increased by 100 mg h^{-1} increments at 30-min intervals (as tolerated) to a maximum rate of 400 mg h^{-1}.

Obinutuzumab aqueous solution was supplied in a 50 ml glass vial containing 1000 mg of drug in 40 ml of solution (25 mg ml^{-1}), together with the excipients histidine, trehalose and poloxamer 188. Before infusion, obinutuzumab was diluted by adding 40 ml of solution to 210 ml of 0.9% sodium chloride solution in an infusion bag, to produce a final concentration for infusion of 4 mg ml^{-1}.

Study population

Patients were aged >18 years with histologically documented CD20+ relapsed/refractory CLL, DLBCL or FL, an Eastern Co-operative Oncology Group (ECOG) performance status of 0 or 1 and a life expectancy of >6 months. Patients with FL or DLBCL could be included if they had failed (relapsing after, or refractory to) at least one chemotherapy regimen with or without rituximab at any point in their treatment history. CLL patients could be included if they had relapsed after, or were refractory to at least one chemotherapy regimen at any point in their treatment history. Relapse was defined as disease recurrence after any documented history of response (complete response [CR], CR with incomplete bone marrow recovery [CRi; patients with CLL only] or partial response [PR]) that lasted at least 6 months. Refractory was defined as progression on treatment or stable disease (SD), or any response that was followed by progression less than 6 months after treatment.

With the exception of CLL patients, all patients must have had at least one bi-dimensionally measurable lesion (>1.5 cm in its largest dimension by computed tomography). For CLL patients, circulating lymphocyte count assessments were an acceptable method of measurement. All measurable and evaluable disease was required to be assessed and documented before study treatment initiation. Tumour response was assessed according to the International Workshop to Standardize Response criteria for NHL [24], and the 2008 guidelines of the International Workshop on CLL [25].

Full inclusion criteria and details of patient exclusion criteria can be found in Appendix I.

Study endpoints and procedures

Blood samples for the measurement of obinutuzumab serum concentrations (5 ml pre-dose on Cycle 1, Day 1; 2 ml for all other samples) were collected as follows. For NHL patients, Day 1 samples were collected pre-dose, at the end of infusion, and at 4, 24, 72 and 120 h post-infusion. For CLL patients, Day 1 and Day 2 samples were collected pre-dose and at the end of infusion, and also at 4, 24, 72 and 120 h post-infusion on Day 2. The additional sampling for CLL patients reflected the split dosing of obinutuzumab over Days 1 and 2 in this group. Additional blood samples (all patients) were collected pre-dose and at the end of infusion for all subsequent doses, and at 4, 24, 72, 120, 168, 336, 504 and 672 h and 3 and 6 months after the final infusion (Cycle 8, Day 1).

Obinutuzumab serum concentrations were measured using a specific and validated enzyme-linked immunosorbent assay (ELISA) method. Samples were pre-incubated with a cocktail containing biotinylated and digoxigenin-labelled anti-idiotype antibodies directed to the antigen binding site of obinutuzumab. Using a streptavidin-coated microplate, immune complexes bound to the microplate were detected by addition of horseradish peroxidase-conjugated Fab fragments directed to digoxigenin. Bound peroxidase was detected through a chromogenic reaction. The absorbance (405 nm for detection absorbance and 490 nm for reference absorbance) was proportional to the amount of obinutuzumab present in the sample. PK parameters were either read directly from plasma concentration–time profiles or calculated using standard non-compartmental methods. The lower limit of quantification in undiluted serum was 0.00405 μg ml^{-1}. The calibration range concentrations were 0.00405–0.400 μg ml^{-1} in 100% human serum. The accuracy of the ELISA method (using quality control samples) for determination of obinutuzumab serum sample concentrations was consistent throughout the study: precision ranged from 4.43% to 25.2% and accuracy ranged from 95.1% to 100.0%.

Pharmacokinetic analyses

The PK analysis population included all patients randomized and adherent to the study protocol.

Pharmacokinetic analyses using non-compartmental analysis (NCA). PK parameters of obinutuzumab for each patient were estimated using NCA (Phoenix WinNonlin® version 6.2; Certara® USA, Inc.). Time to maximum observed serum concentration (t_{max}), maximum observed serum concentration (C_{max}), and trough concentration before the next dose (C_{trough}) were obtained directly from plasma *vs.* time profiles. The following PK parameters were calculated: apparent terminal half-life ($t_{1/2}$), area under the serum concentration–time curve from 0 to Day 7 (AUC_{7d}), area

under the serum concentration–time curve from 0 to Day 21 (AUC_{21d}) at Cycle 8, systemic clearance (CL_{ss}), and volume of distribution at steady state (V_{ss}).

All computed PK parameters were presented as summary statistics, including arithmetic means, geometric means (e.g. *AUC* and C_{max}), medians, ranges, standard deviations and coefficients of variation (CV%). Individual and mean serum concentrations of obinutuzumab *vs*. time were graphically displayed.

Population pharmacokinetic analysis. To determine whether observed obinutuzumab PK data from GERSHWIN (available for 48 Chinese patients) were in accordance with obinutuzumab PK data from previous clinical studies, a robust population PK model previously developed in a large database of 961 lymphoma patients (mainly Caucasian [95%]: 342 CLL; 469 indolent NHL [406 FL]; 130 DLBCL; 20 mantle cell lymphoma]) was used to simulate PK profiles in the GERSHWIN study (unpublished data on file, F. Hoffmann-La Roche Ltd, Clinical Pharmacology, Basel, Switzerland). Simulations were conducted by taking into account patients' baseline characteristics (e.g. tumour size, body weight, gender) in the current study, and were run 100 times to determine the median, 5th and 95th predicted PK profile. The adequacy of matching between observed obinutuzumab concentrations in GERSHWIN and predicted PK profiles was assessed graphically by overlaying the observed PK data with the predicted mean profile and its associated 90% prediction interval. Full details of the population PK model have been published previously by Gibiansky *et al.* [15].

Results

Patients

Of 56 Chinese patients screened, 48 patients (FL, n = 13; DLBCL, n = 23; CLL, n = 12) were enrolled and 28 patients (58.3%) completed treatment. Seventeen patients discontinued obinutuzumab during Cycles 1–4 and three patients discontinued obinutuzumab during Cycles 5–8. Reasons for discontinuation of obinutuzumab included progressive disease (n = 9), physician decision (n = 6), withdrawal by patient (n = 3), adverse event (pneumonia) and protocol violation (n = 1 each). A total of 141 adverse events were reported by 35 patients, most of which were of mild or moderate severity (116; 82.3%). The most commonly reported adverse events were infusion-related reactions (15 patients; 31.2%), all of which occurred after the first obinutuzumab infusion. A full report of safety results from the study will be published separately.

The PK analysis population included 48 patients: 28 patients (FL, n = 11; DLBCL, n = 8; CLL, n = 9) completed the eight-cycle PK sample collection. Three patients (DLBCL, n = 2; CLL, n = 1) were excluded from the Cycle 1 PK analysis due to limited PK sampling and an additional two patients (DLBCL, n = 2) were excluded from the analysis of $t_{1/2}$ and V_{ss} at Cycle 8 only, because their values could not be reliably estimated.

Most patients had advanced-stage disease (Binet B or C for CLL, Ann Arbor 3–4 for FL or DLBCL) and the median number of prior treatment lines was similar across lymphoma types (CLL, 2.0; DLBCL, 2.0; FL, 3.0) (Table 1).

Pharmacokinetic analyses using NCA

The mean serum concentration–time profiles of obinutuzumab for patients with FL, DLBCL and CLL on Cycle 1, Day 1 (and Day 2 for CLL) and for Cycle 8 are shown in Figure 1. The mean serum concentration–time profiles for obinutuzumab for patients from Cycle 1 to Cycle 8 are shown in Figure 2. Derived PK parameters for all patient populations for Cycle 1 and Cycle 8 are summarized in Table 2.

Overall, comparison of C_{max} and AUC_{21d} as well as other derived PK parameters showed the PK profile of obinutuzumab to be very similar for the three lymphoma types (Table 2). Mean serum concentrations of obinutuzumab over Cycles 1–8 showed that C_{max} and C_{trough} steady-state levels appeared to be achieved at the start of Cycle 2, irrespective of histology. Concentration–time profiles were similar for the three lymphoma types (Figure 2), with a slight increase in serum levels of obinutuzumab from Cycles 5/6–8 in patients with DLBCL or CLL. Systemic exposure to obinutuzumab after the Cycle 8 dose (AUC_{21d} value) was not dependent on body weight for any of the three lymphoma types (Figure 3), although a slight trend for decreased *AUC* with increased body weight was seen for FL patients (P = 0.286; P = 0.876 for DLBCL; P = 0.897 for CLL). Inter-subject variability of obinutuzumab exposure appeared to be slightly higher for patients with CLL (CV% estimated to be <43% for *AUC* and <33% for C_{max} for both cycles) than for patients with DLBCL or FL (CV% estimated to be <38% for *AUC* and <29% for C_{max} for both cycles).

Population pharmacokinetic analysis

Population PK analysis showed that most PK profiles from Chinese patients observed in GERSHWIN lay within the 90% prediction interval of the simulated profiles, indicating that PK data in Chinese patients were in agreement with the PK characteristics in non-Chinese lymphoma patients (which were established previously using population PK methods) (Figure 4).

Discussion

Non-compartmental analysis of Chinese patients in the Phase Ib GERSHWIN study showed that the PK profile of obinutuzumab is similar in patients with FL, DLBCL and CLL. Steady-state concentrations of obinutuzumab appeared to be reached at the start of Cycle 2 dosing irrespective of histology, and there was no apparent relationship between body weight and *AUC*. In addition, estimated exposure at steady state (e.g. Cycle 8 AUC_{21d} and C_{max}) for Chinese patients with DLBCL and FL was generally similar to that for Chinese patients with CLL.

A two-compartment PK model comprising linear and nonlinear time-varying clearance pathways has been shown to adequately describe serum obinutuzumab concentration data. The initial clearance of obinutuzumab is more than

Table 1

Patient demographic and baseline characteristics

	FL (*n* = 13)	DLBCL (*n* = 23)	CLL (*n* = 12)	Safety population[a] (*n* = 48)
Median age (range), years	56 (34–67)	58 (18–75)	63 (34–76)	59 (18–76)
Female, *n* (%)	5 (38.5)	12 (52.2)	5 (41.7)	22 (45.8)
Median weight (range), kg	61 (47–88)	61 (45–83)	60 (43–84)	61 (43–88)
Median height (range), cm	167 (151–183)	164 (152–181)	161 (154–170)	163 (151–183)
ECOG, n/N[b] (%)				
0	8/13 (61.5)	8/23 (34.8)	2/12 (16.7)	18/48 (37.5)
1	5/13 (38.5)	15/23 (65.2)	10/12 (83.3)	30/48 (62.5)
Ann Arbor stage, n/N[b] (%)				
I	2/13 (15.4)	0	–	2/36 (5.6)
II	0	4/23 (17.4)	–	4/36 (11.1)
III	5/13 (38.5)	8/23 (34.8)	–	13/36 (36.1)
IV	3/13 (23.1)	7/23 (30.4)	–	10/36 (27.8)
Missing	3/13 (23.1)	4/23 (17.4)	–	7/36 (19.4)
Binet stage, n/N[b] (%)				
A	–	–	1/12 (8.3)	1/12 (8.3)
B	–	–	6/12 (50.0)	6/12 (50.0)
C	–	–	2/12 (16.7)	2/12 (16.7)
Unknown	–	–	3/12 (25.0)	3/12 (25.0)
Median no. of previous treatment lines (range)	3.0 (1–6)	2.0 (1–11)	2.0 (1–7)	2.0 (1–11)

CLL, chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Co-operative Oncology Group; FL, follicular lymphoma. SD, standard deviation.

[a]All patients who received at least one dose of obinutuzumab.

[b]Evaluable patients.

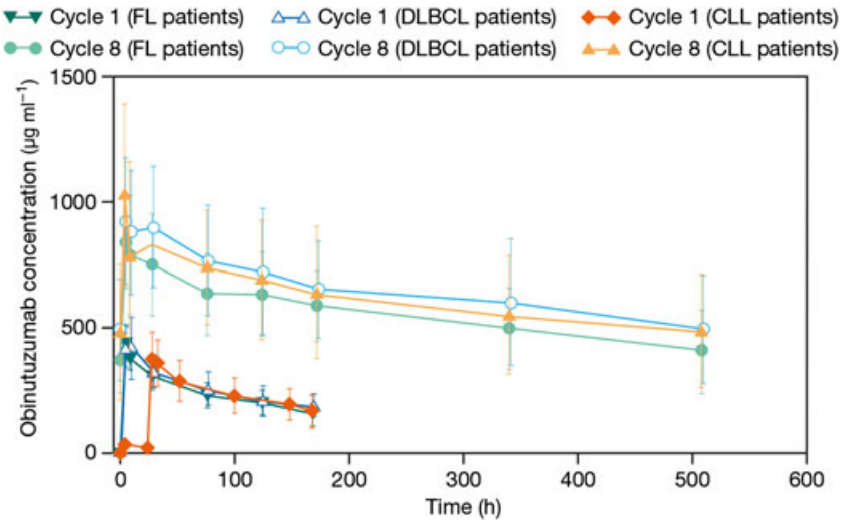

Figure 1

Mean (standard deviation) obinutuzumab serum concentration–time profiles post-obinutuzumab administration (1000 mg i.v.) during Cycle 1, Day 1 (and Day 2 for chronic lymphocytic leukaemia [CLL]) and Cycle 8 for follicular lymphoma (FL), diffuse large B cell lymphoma (DLBCL) and CLL patients

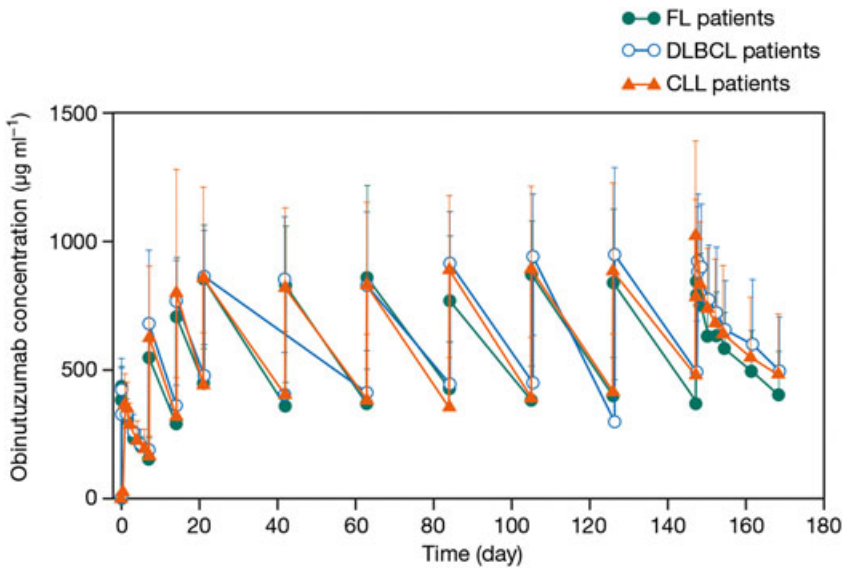

Figure 2

Mean (standard deviation) obinutuzumab serum concentration–time profiles post-obinutuzumab administration (1000 mg i.v.) during the eight treatment cycles for follicular lymphoma (FL), diffuse large B cell lymphoma (DLBCL) and chronic lymphocytic leukaemia (CLL) patients

Table 2

Summary of serum PK parameters in patients with FL, DLBCL or CLL post-obinutuzumab administration (1000 mg i.v.) at Cycle 1, Day 1 and Cycle 8

Time point	Parameter, geometric mean (CV%)	FL (n = 13)	DLBCL[a] (n = 21)	CLL[a,b] (n = 11)
Cycle 1, Day 1[b]	C_{max}, μg ml^{-1}	437 (16.7)	442 (21.1)	369 (31.8)
	AUC_{7d}, day·μg ml^{-1}	1750 (20.5)	1647 (20.7)	1458 (34.8)
Time point	**Parameter, geometric mean (unit)[c]**	**FL (n = 11)**	**DLBCL (n = 8)**	**CLL (n = 9)**
Cycle 8	Median t_{max}, h (range)	4.0 (3.2–7.8)	7.25 (3.3–27.5)	3.5 (3.3–25.5)
	$t_{1/2}$, day	26.7 (49.6)	33.3[d] (68.6)	21.5 (71.8)
	C_{max}, μg ml^{-1}	867 (19.6)	966 (28.3)	1050 (32.6)
	AUC_{7d}, day·μg ml^{-1}	4546 (24.1)	5211 (31.1)	5017 (30.2)
	AUC_{21d}, day·μg ml^{-1}	11 285 (26.7)	13 000 (37.3)	12 289 (42.7)
	V_{ss}, l	4.03 (21.5)	4.49[d] (38.2)	3.32 (27.9)
	CL_{ss}, ml day^{-1}	88.6 (26.7)	76.9 (37.3)	81.4 (42.7)

AUC_{7d}, area under the serum concentration *vs.* time curve (Day 0 to Day 7); AUC_{21d}, area under the serum concentration *vs.* time curve (Day 0 to Day 21); C_{max}, maximum observed serum concentration; CLL, chronic lymphocytic leukaemia; CL_{ss}, clearance at steady state; CV, coefficient of variation; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; PK, pharmacokinetic; $t_{1/2}$, terminal half-life; V_{ss}, volume of distribution at steady state.
[a]One patient was excluded from the CLL group, and two from the DLBCL group due to limited pharmacokinetic sampling.
[b]For CLL, parameters were from Cycle 1 Day 1 and Day 2 due to split dosing.
[c]Except t_{max} which is shown as median (range).
[d]n = 6, since two patients were excluded from the analysis because parameters could not be reliably estimated.

two times higher than the steady-state clearance; this is consistent with a decrease in the time-varying clearance component, which is high at the start of treatment and then declines with administration of repeated cycles of obinutuzumab. The time-varying clearance pathway is consistent with target-mediated drug disposition, such that at the start of treatment, obinutuzumab is bound to a large quantity of CD20+ cells. With repeated dosing of obinutuzumab, the pool of CD20+ cells becomes saturated, hence reducing the contribution of this component to overall clearance. The linear clearance pathway is consistent with catabolism of immunoglobulin G antibodies, and is therefore independent of CD20+ cells. These observations support the need to minimize the time-varying clearance component quickly, and led to the proposed obinutuzumab dose regimen of 1000 mg for both induction and extended treatment [15].

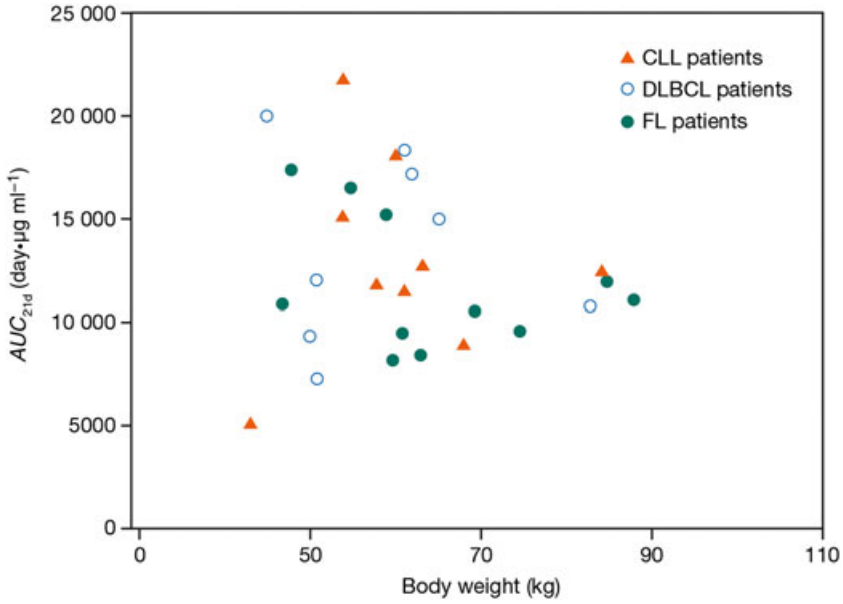

Figure 3

Relationship between body weight and obinutuzumab area under the serum concentration–time curve (Day 0 to Day 21) (AUC_{21d}) in patients with follicular lymphoma (FL), diffuse large B cell lymphoma (DLBCL) or chronic lymphocytic leukaemia (CLL) post-obinutuzumab administration (1000 mg i.v.) at Cycle 8

In addition to the non-compartmental PK analysis, a population PK assessment was performed to determine whether data from GERSHWIN were in accordance with previously collected PK data in mainly Caucasian patients for obinutuzumab. A population PK model comprising 961 patients was used to simulate PK profiles in the current study. The results from this population PK analysis support our main finding that observed obinutuzumab PK parameters are similar across Chinese and non-Chinese patients with CLL, DLBCL and FL.

The PK profile of obinutuzumab reported in the current study was similar to that reported in two previous studies evaluating obinutuzumab PK in relapsed or refractory CLL and NHL patients from Europe (GAUGUIN, Phase II) [11, 12, 16] and Japan (Phase I) [19] (Table 3). In a Phase II update of the GAUGUIN study, 12 CLL and 47 NHL (relapsed/refractory) patients had PK data available at Cycle 8. The NHL patients comprised 30 cases of indolent NHL (including FL) and 17 cases of aggressive NHL (including DLBCL), and all patients were Caucasian except for one Asian patient with CLL. The doses of obinutuzumab were 1000 mg for CLL and 400/800 mg for NHL. Notably, the primary PK parameters for obinutuzumab at Cycle 8, i.e. geometric mean dose-adjusted C_{max}, C_{trough} and AUC_{21d}, were similar between GAUGUIN and the current study for both NHL and CLL (C_{max}/dose 0.75–0.94 *vs.* 0.87–1.05 μg ml^{-1} mg^{-1}; C_{trough}/dose 0.40–0.52 *vs.* 0.35–0.46 μg ml^{-1} mg^{-1}; AUC_{21d}/dose 11.0–14.7 *vs.* 11.3–13.0 day·μg ml^{-1} mg^{-1}) (Table 3). In the Phase I Japanese study, PK data were available for 10 patients with NHL across four dose cohorts at Cycle 8. Each cohort received a lower initial obinutuzumab dose, which was then increased for the second and subsequent doses (i.e. 200/400 mg, 400/800 mg, 800/1200 mg, and 1200/2000 mg). All patients were Japanese and the majority had FL. Despite the small sample size, the dose-adjusted PK data for obinutuzumab (C_{max}/dose 0.87–1.50 μg ml^{-1} mg^{-1}; C_{trough}/dose 0.36–1.05 μg ml^{-1} mg^{-1}; AUC_{21d}/dose 9.0–14.9 day·μg ml^{-1} mg^{-1}) were comparable with the data reported in the current study, which also had a relatively small sample size (n = 48).

Notably, our finding that the PK profile of obinutuzumab is similar in Chinese *vs.* non-Chinese patients is consistent with the similar PK profiles observed for other mAbs across ethnic populations. Both intrinsic (e.g. genetic and physiological differences) and extrinsic ethnic factors (e.g. cultural and environmental differences) can impact on drug disposition, safety and efficacy; however, there is an increasing body of evidence to suggest that ethnicity, after accounting for body weight differences, may not influence the PK profile of biologics to the same degree that it does for small molecules [26]. Reasons for this include a lack of involvement of hepatic metabolism in the clearance and elimination of mAbs and the fact that mAbs are administered parenterally, thereby avoiding any impact of dietary factors on systemic exposure. This is also borne out by a recent review by Zhou *et al.* showing that the dosing regimens of 12 mAbs approved in the USA and Japan are identical or very similar in both countries [23].

In conclusion, we provide evidence that obinutuzumab exposure is comparable in Chinese patients with CLL, DLBCL and FL. Results indicate that PK characteristics in Chinese patients are similar to those reported in non-Chinese patients with CD20+ malignant B-cell lymphomas. Furthermore, our population PK analysis confirms that the PK data observed are in agreement with the previously established PK characteristics of obinutuzumab in non-Chinese patients with CLL, DLBCL and FL.

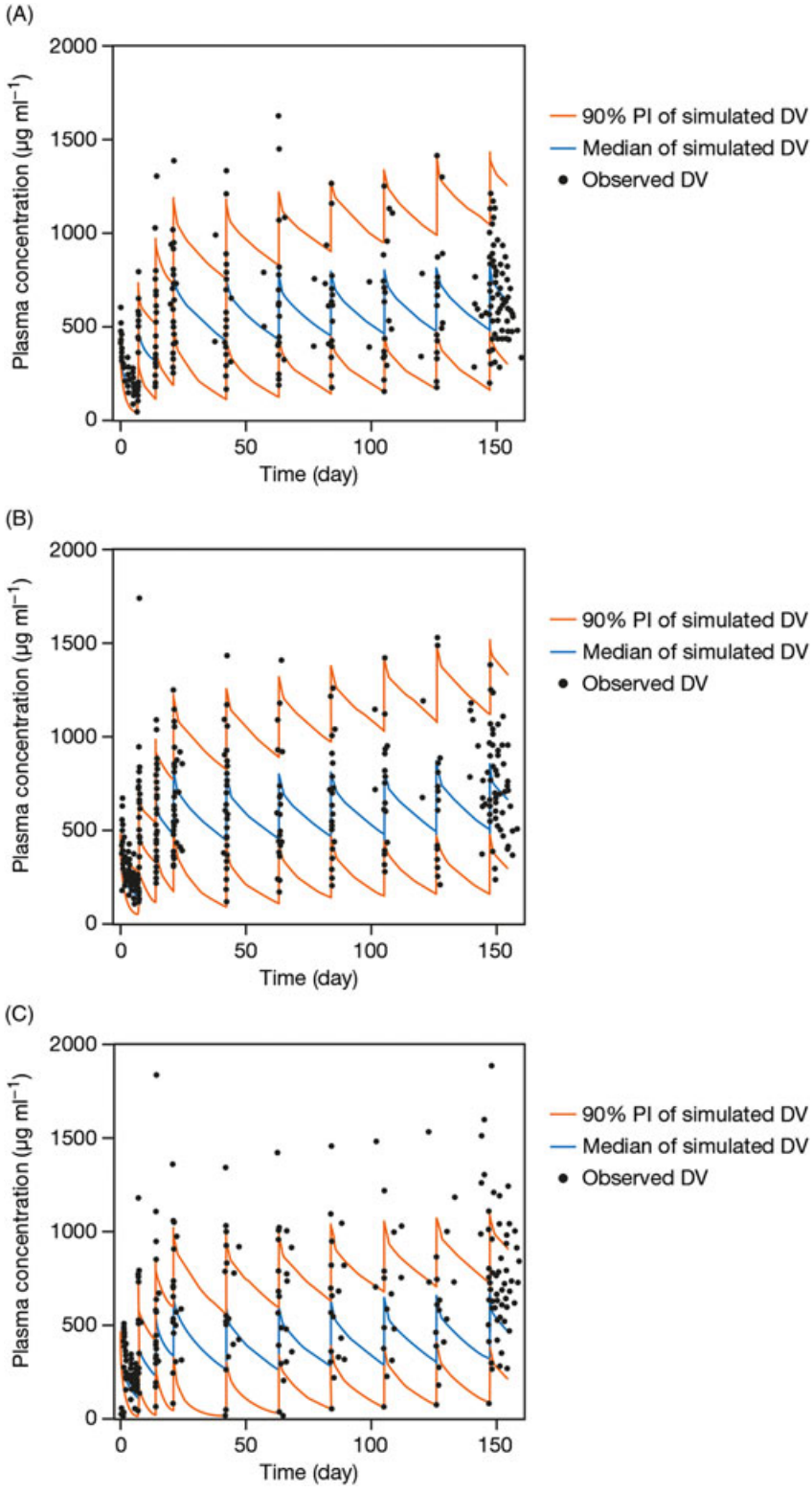

Figure 4

Comparison of simulated pharmacokinetic (PK) profiles and observed PK data in GERSHWIN for (A) follicular lymphoma (FL), (B) diffuse large B cell lymphoma (DLBCL) and (C) chronic lymphocytic leukaemia (CLL) patients from Cycle 1 to Cycle 8. DV, dependent variable; PI, prediction interval

Table 3

Comparison of obinutuzumab PK at Cycle 8 in FL, DLBCL and CLL patients in the GERSHWIN, GAUGUIN and the Japanese Phase I clinical studies

Study	Disease	No. of patients	Obinutuzumab dose (mg)	C_{max} (μg ml^{-1})	C_{max}/dose (μg ml^{-1} mg^{-1})	C_{trough} (μg ml^{-1})	C_{trough}/dose (μg ml^{-1} mg^{-1})	AUC_{21d} (day·μg ml^{-1})	AUC_{21d}/dose (day·μg ml^{-1} mg^{-1})
GAUGUIN[a] Phase II	CLL	12	1000	799	**0.799**	437	**0.437**	11 001	11.0
	αNHL	9	400	374	**0.935**	195	**0.488**	5870	14.7
		8	800	601	**0.751**	416	**0.520**	9159	11.4
	iNHL	11	400	335	**0.838**	160	**0.400**	4905	12.3
		19	800	654	**0.818**	350	**0.438**	10 223	12.8
JO21900[b] Phase I	NHL	3	400	359	**0.898**	218	**0.545**	3740	9.35
		2	800	1200	**1.500**	836	**1.045**	11 900	14.9
		3	1200	1040	**0.867**	432	**0.360**	10 800	9.00
		2	2000	1910	**0.955**	1250	**0.625**	25 100	12.6
GERSHWIN Phase Ib	CLL	9	1000	1050	**1.050**	403	**0.403**	12 289	12.3
	DLBCL	8	1000	966	**0.966**	455	**0.455**	13 000	13.00
	FL	11	1000	867	**0.866**	352	**0.352**	11 285	11.3

αNHL, aggressive NHL; AUC_{21d}, area under the serum concentration *vs.* time curve (Day 0 to Day 21); CLL, chronic lymphocytic leukaemia; C_{max}, maximum observed serum concentration; C_{trough} trough observed serum concentration; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; iNHL, indolent lymphoma; /dose, dose-adjusted (i.e. pharmacokinetic value divided by the dose administered); PK, pharmacokinetics.
[a]Data are geometric mean values, median body weight 72 (52–100) kg for CLL, 73.2 (49.5–122) kg for αNHL,73.8 (49.8–104) kg for iNHL.
[b]Data are arithmetic mean values, median body weight 55.4 (41.2–94.5).

Competing Interests

J. Zhai, C. Jamois and J. Shi are employed by F. Hoffmann-La Roche Ltd. M. Brewster is employed by and holds stock options in F. Hoffmann-La Roche Ltd. Y. Qin, J. Zhu, Y. Song, X. Du, Y. Shi and Z. Shen report no conflicts of interest.

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Contributors

J. Zhai, Y. Shi and J. Shi were responsible for the conception and design. J. Zhai, Y. Qin, Y. Shi and X. Du were responsible for the collection and assembly of data. J. Zhai, Y. Qin, J. Zhu, Y. Song, C. Jamois, M. Brewster, J. Shi and Z. Shen were responsible for data analysis and interpretation. J. Zhai, Y. Qin, J. Zhu, Y. Song, Z. Shen, X. Du, C. Jamois, M. Brewster, Y. Shi and J. Shi wrote the manuscript. J. Zhai, Y. Qin, J. Zhu, Y. Song, Z. Shen, X. Du, C. Jamois, M. Brewster, Y. Shi and J. Shi approved the final version of the manuscript.

Appendix I

Inclusion criteria

A patient could be included if they met all of the following criteria:

1. Histologically documented CD20+ malignant disease (B-cell lymphoma or B-CLL [B-CLL confirmed by International Workshop on CLL [25]).
2. Relapsed or refractory FL, DLBCL or CLL:

   a) Patients with FL or DLBCL could be included if they had failed (relapsing after or refractory to) at least one standard chemotherapy (recommended by the Chinese guideline or judged to be appropriate by the investigator) with or without rituximab at any point in their treatment history.
   b) Patients with CLL could be included if they had relapsed or were refractory to at least one chemotherapy regimen at any point in their treatment history.

   Relapse and refractoriness were defined as follows:

   - *Relapse was defined as disease recurrence after any documented history of response (complete response [CR], complete response with incomplete bone marrow recovery [CRi (CLL only)] or partial response [PR]) of ≥6 months.*
   - *Refractoriness was defined as progression on treatment or stable disease (SD), or any response that was followed by progression <6 months after treatment.*

3. Patients with FL and DLBCL had to have at least one bi-dimensionally measurable lesion (>1.5 cm in its largest dimension by computerized tomography scan). For CLL patients, circulating lymphocyte cell assessments were an acceptable method of measurement. Note that all measurable and evaluable disease must have been assessed and documented prior to initiation of obinutuzumab

treatment. Tumour response was assessed according to the International Workshop to Standardize Response criteria for NHL [24], and the 2008 guidelines of the International Workshop on CLL [25].
4. Able and willing to provide written informed consent and to comply with the study protocol.
5. Age > 18 years.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
7. Life expectancy >6 months.

Exclusion criteria

A patient was excluded if they met any of the following criteria:

1. Prior use of any investigational monoclonal antibody therapy within 6 months of study start.
2. Prior use of any anti-cancer vaccine.
3. Prior administration of rituximab within 3 months of study entry.
4. Prior administration of radioimmunotherapy within 3 months of study entry.
5. History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies. Known sensitivity or allergy to murine products.
6. Central nervous system lymphoma.
7. History of other malignancy that could affect compliance with the protocol or interpretation of results. Patients with a history of curatively treated basal or squamous cell carcinoma of the skin or *in situ* carcinoma of the cervix were generally eligible, provided the tumour was treated with curative intent at least 2 years prior to study entry.
8. Evidence of significant, uncontrolled concomitant diseases which could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or pulmonary disease (including obstructive pulmonary disease and history of symptomatic bronchospasm).
9. Known active bacterial, viral (including human immunodeficiency virus [HIV]), fungal, mycobacterial, or other infection (excluding fungal infections of nail beds) or any major episode of infection requiring hospitalization or treatment with intravenous antibiotics (for intravenous antibiotics this pertains to completion of last course of antibiotic treatment) within 4 weeks of receiving the first dose of obinutuzumab.
10. Recent major surgery (within 4 weeks prior to receiving first dose of obinutuzumab), other than for diagnosis.
11. Any of the following abnormal laboratory values:
    - Creatinine clearance of ≤40 ml min^{-1}, calculated according to the Cockcroft-Gault formula
    - Aspartate aminotransferase or alanine aminotransferase >2.5 × upper limit of normal (ULN) for >2 weeks; bilirubin >3 × ULN unless due to underlying disease
    - Platelet count $<75 \times 10^9$/l
    - Neutrophils $<1.5 \times 10^9$/l
    - Haemoglobin <8 g dl^{-1}
    - Prothrombin time (PT)/international normalized ratio (INR) >2 × ULN if not on therapeutic/prophylactic anticoagulation.

NOTE: Patients with cell counts below the thresholds listed above could be considered eligible if, in the investigator's opinion, this was due to bone marrow infiltration.

12. Positive test result for HIV.
13. History of confirmed progressive multifocal leukoencephalopathy.
14. Positive hepatitis serology:

Hepatitis B (HBV): Patients with positive serology for hepatitis B, defined as positive for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (anti-HBc). Patients with CLL who were positive for anti-HBc and negative for HbsAg could be included if HBV DNA is undetectable as confirmed by a central lab. These patients had to be willing to undergo monthly DNA testing.

Hepatitis C (HCV): Patients with positive hepatitis C serology unless HCV (RNA) was confirmed negative.

15. Women who were pregnant or lactating.
16. Fertile men or women of childbearing potential unless: (1) surgically sterile or ≥2 years after the onset of menopause, (2) willing to use a highly effective contraceptive method such as oral contraceptives, intrauterine device, sexual abstinence or barrier method of contraception in conjunction with spermicidal jelly during study treatment and in female patients for 12 months (male patients for 3 months) after end of obinutuzumab treatment.
17. Treatment within a clinical study within 30 days prior to study entry.
18. Vaccination with a live vaccine within 28 days prior to the first dose.

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