Title

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Authors

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Fraser, Graeme AM
et al.

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Associations of ofatumumab exposure and treatment outcomes in patients with untreated CLL receiving chemoimmunotherapy

Roxanne C. Jewell[a,*], **Thomas J. Kipps**[b], **Jan Dürig**[c], **Laimonas Griskevicius**[d], **Stephan Stilgenbauer**[e], **Lukáš Smolej**[f], **Jiří Mayer**[g], **Georg Hess**[h], **Francisco J. Hernandez-Ilizaliturri**[i], **Swaminathan Padmanabhan-Iyer**[j], **Lei Fang**[k], **Nancy Goldstein**[a,*], **Michele Gorczyca**[l,*], **Ira Gupta**[m,*], **Steen Lisby**[n], **William G. Wierda**[o], **Hx-CD20-407 Study Investigators**

[a]Novartis Pharmaceuticals, Morrisville, NC, USA;

[b]UCSD Moores Cancer Center, La Jolla, CA, USA;

[c]Klinik für Hämatologie, Universitätsklinikum Essen, Essen, Germany;

[d]Vilnius University Hospital Santariskiu Klinikos, Vilnius University, Vilnius, Lithuania;

[e]Department of Internal Medicine III, Universitätsklinikum Ulm, Ulm, Germany;

[f]4th Department of Internal Medicine – Hematology, University Hospital and Faculty of Medicine, Hradec Králové, Czech Republic;

[g]Department of Internal Medicine/Hemato-Oncology, University Hospital Brno, Brno, Czech Republic;

[h]Johannes Gutenberg University, Mainz, Germany;

[i]Roswell Park Cancer Institute, Buffalo, NY, USA;

[j]Cancer Therapy and Research Center, San Antonio, TX, USA;

[k]Pharstat Inc., Raleigh, NC, USA;

[l]GlaxoSmithKline, Collegeville, PA, USA;

[m]Novartis Pharmaceuticals, King of Prussia, PA, USA;

[n]Genmab, Copenhagen, Denmark;

[o]MD Anderson Cancer Center, The University of Texas, Houston, TX, USA

Abstract

Relationships between patient characteristics, ofatumumab pharmacokinetics, and treatment outcomes were investigated in this phase 2 trial of ofatumumab plus fludarabine and cyclophosphamide (FC) in untreated chronic lymphocytic leukemia. Patients were randomized 1:1

CONTACT William G. Wierda, MD, PhD, wwierda@mdanderson.org, MD Anderson Cancer Center, The University of Texas, 1515 Holcombe Blvd., FC4.3020, Houston, TX 77030, USA.

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to receive 500 or 1000 mg ofatumumab (Cycle 1; 300 mg) plus FC every 4 weeks for six cycles. Median C_{max} and C_{trough} values were similar at Cycle 1 regardless of the ultimate clinical outcome. At later doses, these values were higher for patients with complete response (CR) than for other patients. Higher C_{max} and C_{trough} values at Cycles 3 and 6 were significantly associated with an increased likelihood of CR, whereas ofatumumab pharmacokinetics were not associated with an objective response (OR) on the basis of univariate analyses. Multivariate analyses indicated that baseline patient/disease factors were predominantly associated with CR (17p status) or OR (bulky lymphadenopathy, gender, and serum thymidine kinase), rather than ofatumumab pharmacokinetics. Trial registration: www.clinicaltrials.gov (NCT00410163).

Keywords

Chemoimmunotherapy; chronic lymphocytic leukemia; ofatumumab; pharmacokinetics

Introduction

Chronic lymphocytic leukemia (CLL) is characterized by progressive accumulation of mature B cells in the blood, lymph nodes, spleen, liver, and marrow, and largely remains incurable.[1] Chemoimmunotherapy represents an important clinical advance for patients with CLL,[2,3] yet little is known about the pharmacokinetics of monoclonal antibody (mAb) therapy when administered with chemotherapy in these patients.

Ofatumumab (Arzerra®; Novartis) is a human anti-CD20 mAb that binds to a unique, membrane-proximal epitope composed of both the large and small loops of the CD20 molecule expressed on B cells.[4] Ofatumumab elicits killing of primary tumor cells through complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis.[5–9] Ofatumumab demonstrates more potent complement-dependent cytotoxicity than rituximab, which may be a result of the close proximity of the small-loop binding site to the cell surface, potentially leading to more effective deposition of complement on the cell surface.[10]

Ofatumumab has demonstrated clinical activity as monotherapy for fludarabine-refractory CLL, including patients who were also refractory to alemtuzumab, an anti-CD52 mAb. [11,12] Ofatumumab in combination with chlorambucil (United States) [13] or with chlorambucil or bendamustine (European Union) [14] has also demonstrated clinical activity in patients with previously untreated CLL for whom fludarabine-based therapy was considered inappropriate.[15] Clinical activity was demonstrated in the current phase 2 trial of ofatumumab at two dose levels (500 mg and 1000 mg) in combination with fludarabine and cyclophosphamide (O-FC) in patients with previously untreated CLL.[16] Complete response (CR) rates in the previously untreated CLL population receiving O-FC were 32% and 50% in the 500 mg and 1000 mg dose groups, respectively, and the objective response (OR) rates were 77% and 73%.[16] At 22 months of follow-up, 88% of patients in the 500 mg group and 75% of patients in the 1000 mg group were progression-free.

The pharmacokinetic profile of ofatumumab and the relationships between ofatumumab pharmacokinetic parameters and clinical outcomes have been described in patients with

relapsed or refractory CLL.[12,17] In a phase 1–2 study in patients who received four weekly infusions of ofatumumab, higher ofatumumab area under the concentration–time curve (AUC) extrapolated to infinity (AUC(0–∞)), maximum observed concentration (C_{max}), minimum observed concentration prior to the next infusion (C_{trough}), and longer half-life ($t_{½}$) were associated with OR, and higher AUC(0–∞) and lower clearance (CL) were associated with longer progression-free survival (PFS), duration of response, and time to next CLL treatment.[17] In a study of patients with fludarabine-refractory CLL who received eight weekly intravenous infusions of ofatumumab, followed by four monthly infusions, ofatumumab pharmacokinetics (C_{max}, C_{trough}, and/or AUC values) at Dose 8 (eighth weekly dose) were significantly associated with OR, longer PFS, and longer overall survival in univariate analyses; however, in multivariate modeling, baseline disease factors and patient characteristics, rather than ofatumumab pharmacokinetics, were associated with clinical outcomes.[12]

The objective of this work was to evaluate relationships between pretreatment patient characteristics, ofatumumab pharmacokinetic parameter values, and treatment outcomes in a phase 2 trial of O-FC in patients with previously untreated CLL.[16]

Methods

Patients

The local Independent Ethics Committees or Institutional Review Boards of all participating institutions each approved the protocol, amendments, and consent forms. The study was initiated on 9 January 2007 and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Eligible adult patients (≥18 years of age) had active, treatment-naive CLL ($CD5^+/CD20^+/CD23^+$), circulating lymphocytes $>5 \times 10^9$/L, and an indication for treatment according to the 1996 National Cancer Institute-Working Group (NCI-WG) guidelines.[18] Exclusion criteria included known Richter transformation, central nervous system involvement, infection requiring systemic treatment, clinically significant cardiac disease, an uncontrolled medical condition, history of cerebrovascular disease, human immunodeficiency virus (HIV-1) infection, positive hepatitis B serology (unless consistent with vaccination), or Eastern Cooperative Oncology Group (ECOG) performance status >2.

Study design and treatment

This trial is registered at www.clinicaltrials.gov (NCT00410163). The study design was previously described.[16] This was a randomized, two-dose level, parallel cohort, open-label, phase 2 trial [Figure 1]. Patients were randomized 1:1 to receive 500 mg or 1000 mg ofatumumab (Day 1), combined with intravenous 25 mg/m^2 fludarabine and 250 mg/m^2 cyclophosphamide (Days 2–4 for Cycle 1, Days 1–3 for subsequent cycles) every 4 weeks for up to a total of six cycles [Figure 2]. The first dose of ofatumumab was 300 mg for both cohorts. Before all ofatumumab infusions, patients received 1000 mg acetaminophen and 10 mg cetirizine or equivalent. Glucocorticoid equivalent to 100 mg of prednisolone was also administered before the first and second infusions of ofatumumab; if no grade 3 or 4 adverse

events were observed with Infusion 2, the glucocorticoid dose could be reduced for subsequent infusions at the discretion of the investigator.

Baseline assessments included a physical examination, evaluation for constitutional symptoms, computed tomography (CT) scan, blood sampling for hematology and biochemistry, and marrow examination. Analyses of laboratory samples, including marrow biopsies and smears, were performed by a central laboratory (Bio-Analytical Research Corporation, Ghent, Belgium). Disease status was assessed by physical examination, presence of constitutional symptoms, and blood counts every 4 weeks until Week 24 and every 3 months after the last cycle until disease progression or Month 24. Bone marrow examination was performed after Cycle 3 and at 3 months after the end of treatment to confirm CR. After Month 24, patients were followed every 6 months to monitor B cells until the cell count recovered to the normal range or to at least to the baseline level, up to Month 60, or until the start of a new CLL treatment.

Response evaluations

Best overall response from the start of treatment until three months after the last infusion was determined for each patient by an Independent Review Committee based on the 1996 NCI-WG criteria.[18] Responders consisted of patients who met the 1996 NCI-WG criteria for CR, nodular partial response (nPR), or partial response (PR). Non-responders consisted of patients who met the criteria of stable disease (SD), progressive disease (PD), or were non-evaluable (NE).

Pharmacokinetics

Blood samples for quantification of serum ofatumumab concentration were collected prior to the start of the infusion, at the end of the infusion, and at 10 min, 1 h, and 2 h after the end of the infusion at the first (Cycle 1) and sixth (Cycle 6) doses, and at 1, 3, 6, and 9 months after the last infusion. Pre-infusion and post-infusion blood samples were collected at Cycles 2, 3, 4, and 5 [Figure 2]. Serum ofatumumab concentrations were determined using a validated ELISA with a lower limit of quantification of 0.1 μg/mL as previously described. [19]

Non-compartmental pharmacokinetic analyses of data at Cycles 1 and 6 were performed to determine C_{max}, C_{trough}, AUC, clearance (CL), volume of distribution at steady state (V_{ss}), and $t_{½}$ values. C_{max} and C_{trough} values were determined for the other cycles. Pharmacokinetic parameter values were summarized by cycle and by dose group.

Factors associated with ofatumumab pharmacokinetics and with clinical outcomes

Relationships between baseline patient characteristics, disease characteristics, and pharmacokinetic parameter values were evaluated by univariate and multivariate regression analyses. Associations between pharmacokinetic parameter values and baseline patient and disease characteristics and CR or OR were identified using univariate and multivariate logistic regression analyses. The factors identified as potentially significant ($p < 0.10$) in univariate analyses were combined in a multivariate analysis, and factors were removed by backward elimination with retention in the final model at $p < 0.05$.

Analyzed factors included gender; age at baseline; age group; height; weight; body mass index; β_2-microglobulin; thymidine kinase; *fluorescence in situ* hybridization (FISH) variables (del 17p, del 11q, trisomy 12q, del 13q alone, no abnormality, and del 6q); immunoglobulin heavy chain variable region (IgVH) mutational status; CD38 + cells among CD5 + CD19 + cells; absolute lymphocyte count (ALC) at baseline; hemoglobin at baseline; ECOG at screening; modified Rai stage at screening; modified Rai stage at diagnosis; Binet stage at screening; Binet stage at diagnosis; sum of the products of the greatest diameter (SPD) of lymph nodes as measured by CT scan at screening; percentage of marrow involvement by CLL (histology); number of lymph nodes at screening; largest lymph node at screening; bulky lymph nodes (>5 cm) at screening; completion of six cycles of ofatumumab; completion of six cycles of FC; C_{max} at Cycles 1, 3, and 6 (Visits 2, 15, and 29); C_{trough} at Cycles 2, 4, and 6 (Visits 9, 21, and 29); and AUC(0–∞) at Cycle 1 (Visit 2) and Cycle 6 (Visit 29).

Role of the funding source

This study was sponsored by GlaxoSmithKline and Genmab; ofatumumab is an asset of Novartis AG as of 2 March 2015. GlaxoSmithKline and Genmab provided the drug and worked closely together with the authors in development of study design and interpretation of the data. GlaxoSmithKline and Genmab funded the study and were also responsible for collection and analysis of the data.

Results

Patient characteristics

Sixty-one patients were enrolled from 17 centers in five countries and randomized to the ofatumumab 500 mg (n = 31) or 1000 mg (n = 30) dose groups. Pretreatment patient and disease characteristics were reported previously [16] [Table 1]. In the total population, the median (range) patient age was 56 years (38–73 years), and more male (70%) than female patients (30%) were enrolled. Thirty-eight patients (62%) completed all six cycles of O-FC.

Pharmacokinetics

Ofatumumab concentration–time data were available from 60 patients. Patients had measurable ofatumumab concentrations after the first infusion and an increase in serum concentrations was observed during subsequent cycles up to Cycle 4 [Figure 3].

Pharmacokinetic parameter values at Cycle 1 and Cycle 6 are summarized in Table 2. Ofatumumab pharmacokinetics at Cycle 6 appeared to be proportional to dose, with the possible exception of C_{trough}; however, there was large interpatient variability in C_{trough} values.

Mean serum ofatumumab CL values decreased substantially and mean terminal $t_{½}$ increased substantially after the first infusion. The average CL values were 139 mL/h and 6.7 mL/h following Cycle 1 and Cycle 6, respectively. The average terminal $t_{½}$ values were 19 h(0.79 days) following Cycle 1 and 551 h (23.0 days; 500 mg group) and 746 h (31.1 days; 1000

mg group) following Cycle 6. Mean V_{ss} values remained relatively consistent from Cycle 1 to Cycle 6 and ranged from 4.2 to 5.8 L.

Baseline factors associated with pharmacokinetic parameter values

Table 3 summarizes the pretreatment patient characteristics that were significantly associated with ofatumumab pharmacokinetic parameter values at Cycle 1 and Cycle 6 based on exploratory multivariate regression analysis. The factor most frequently associated with ofatumumab pharmacokinetics at Cycle 1 was gender, with higher C_{max} and AUC values in women than in men. Ofatumumab pharmacokinetics at Cycle 6 were not consistently associated with any factor analyzed, with different baseline disease and patient factors significant for the various pharmacokinetic parameters.

Ofatumumab pharmacokinetic parameters in responders versus non-responders

Median ofatumumab C_{max} and C_{trough} values at each cycle by best response are shown in Figure 4. Median C_{max} and C_{trough} values were similar at Cycle 1 between patients who ultimately had CR, PR/nPR, or SD/PD/NE. At later cycles, median C_{max} and C_{trough} values were higher for patients with CR than for patients with PR/nPR or SD/PD/NE. The number of patients decreased over time, particularly in the SD/PD/NE group.

Higher C_{max} and C_{trough} values at Cycle 3 and at Cycle 6 were significantly associated with an increased likelihood of CR based on univariate analyses [Table 4]. In a multivariate analysis, the significant factors associated with CR were FISH 17p (positive/negative) and C_{max} at Cycle 3 [Table 5].

No ofatumumab pharmacokinetic parameters were associated with an increased likelihood of OR based on univariate analyses [Table 6]. In a multivariate analysis, the significant factors associated with OR were bulky lymphadenopathy at screening, gender, and serum thymidine kinase [Table 7].

Discussion

Pharmacokinetic parameter values for ofatumumab after the first dose and after six doses at two dose levels in combination with fludarabine and cyclophosphamide chemotherapy in patients with previously untreated CLL are reported here. Ofatumumab CL values were much greater and half-life values were shorter at the first dose, consistent with previous studies of ofatumumab in patients with follicular lymphoma or CLL.[12,17,19] In addition to clearance via typical IgG clearance processes,[20–23] ofatumumab undergoes target-mediated clearance via binding to the CD20 epitope on B cells. Due to B-cell depletion, the total clearance of ofatumumab was lower after six infusions compared with the first infusion. V_{ss} values were consistent with distribution largely in the systemic circulation. After repeated administration, ofatumumab pharmacokinetic parameter values appeared to be proportional to dose.

In addition, this work evaluated relationships between pretreatment patient demographics, ofatumumab pharmacokinetic parameter values, and treatment outcomes. At Cycle 1, gender was the factor most frequently associated with ofatumumab pharmacokinetics, with higher

C_{max} and AUC values in women than in men. In contrast to Cycle 1, ofatumumab pharmacokinetics at Cycle 6 were not consistently associated with any factor analyzed, with factors such as β_2-micro- globulin, B-cell count at Dose 5, and lymph nodes (number or size category) as significant factors for the various pharmacokinetic parameters. The association of exposure with gender and/or body surface area (BSA) is consistent with distribution of mAbs largely in the systemic circulation and has been seen previously with both ofatumumab [24] and rituximab.[25] In the current study, the associations of ofatumumab exposure and clearance values with measures of disease burden at baseline are consistent with a large contribution of target-mediated clearance to ofatumumab total clearance in CLL.[24]

Higher ofatumumab C_{max} and C_{trough} values at Cycle 3 and at Cycle 6 were significantly associated with an increased likelihood of CR based on univariate analyses. However, in multivariate analyses, patient and disease factors, rather than measures of ofatumumab exposure, were predominantly associated with CR and OR, which was also seen with ofatumumab monotherapy in fludarabine-refractory CLL.[12] Thus, the observed correlations between ofatumumab exposure and clinical outcomes in CLL by univariate analyses should be interpreted with caution.

In this work, 17p deletion by FISH was associated with a lower probability of CR, consistent with its recognized role as an adverse prognostic factor.[26] Bulky lymphadenopathy at screening (≥5 cm) and higher thymidine kinase levels were associated with lower probabilities of OR. Thymidine kinase is correlated with proliferative activity and has been shown to be predictive of early progression in a subgroup of untreated patients with CLL.[27] With these findings in mind, the combination of ofatumumab with FC for treating previously untreated patients with CLL may be best targeted at patients without 17p deletion, bulky lymphadenopathy, or high levels of thymidine kinase.

In summary, an association between ofatumumab exposure and CR was found in patients with relapsed/refractory CLL based on univariate analyses. However, baseline patient and disease factors, rather than ofatumumab exposure, were associated with CR or OR based on multivariate analyses. Further investigation with ofatumumab will help elucidate the response kinetics of biologic therapy in combination with chemo-therapy, assessing factors such as ofatumumab dosing regimen, circulating ofatumumab concentrations, and disease burden on clinical outcomes in CLL.

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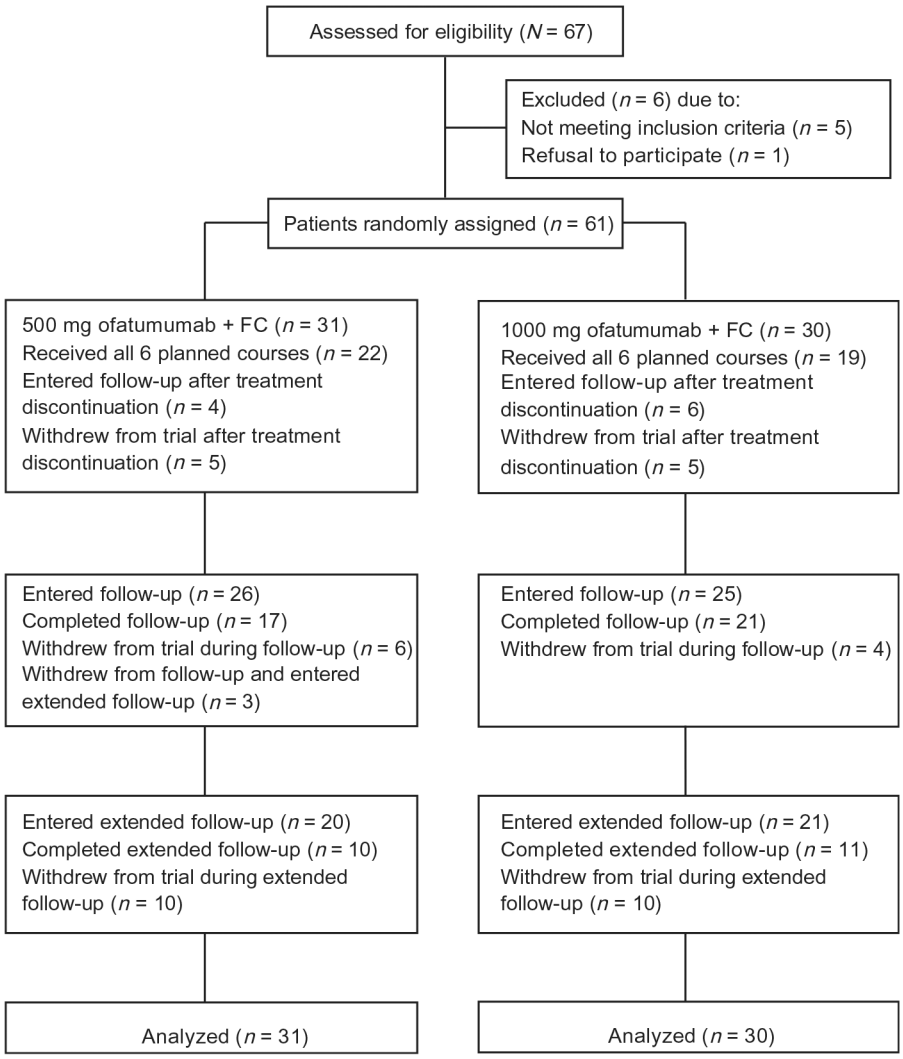

Figure 1.

CONSORT patient flow diagram. CONSORT: Consolidated Standards of Reporting Trials; FC: fludarabine and cyclophosphamide.

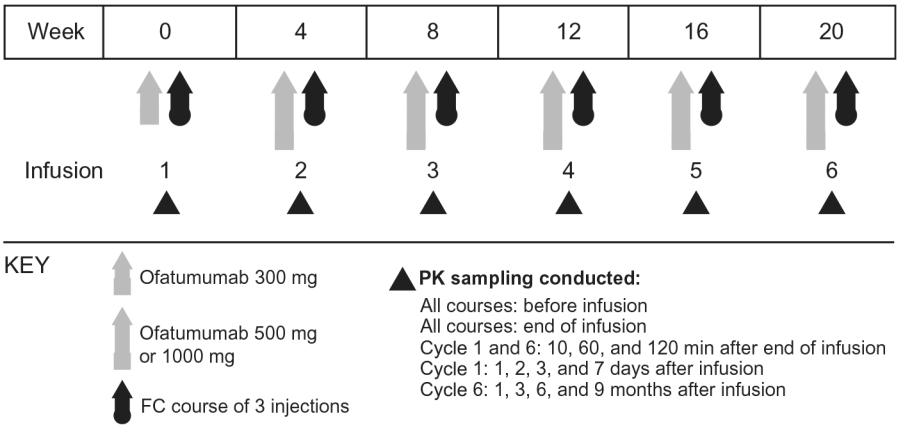

Figure 2.

Study treatment plan. Prednisolone 100 mg (or equivalent) was given prior to Infusions 1 and 2. If initial infusions were well tolerated, the glucocorticoid dose could be reduced to <100 mg for subsequent infusions. Pharmacokinetic sampling at 'end of infusion' was performed immediately after the infusion line was flushed with sterile, pyrogen-free 0.9% sodium chloride. FC: fludarabine and cyclophosphamide; PK: pharmacokinetic.

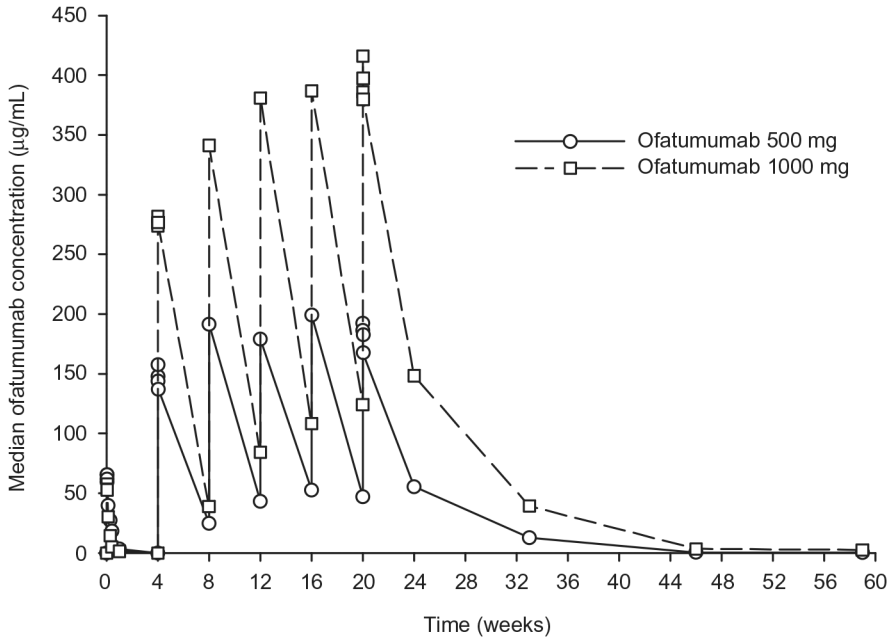

Figure 3.
Median ofatumumab concentration–time plots.

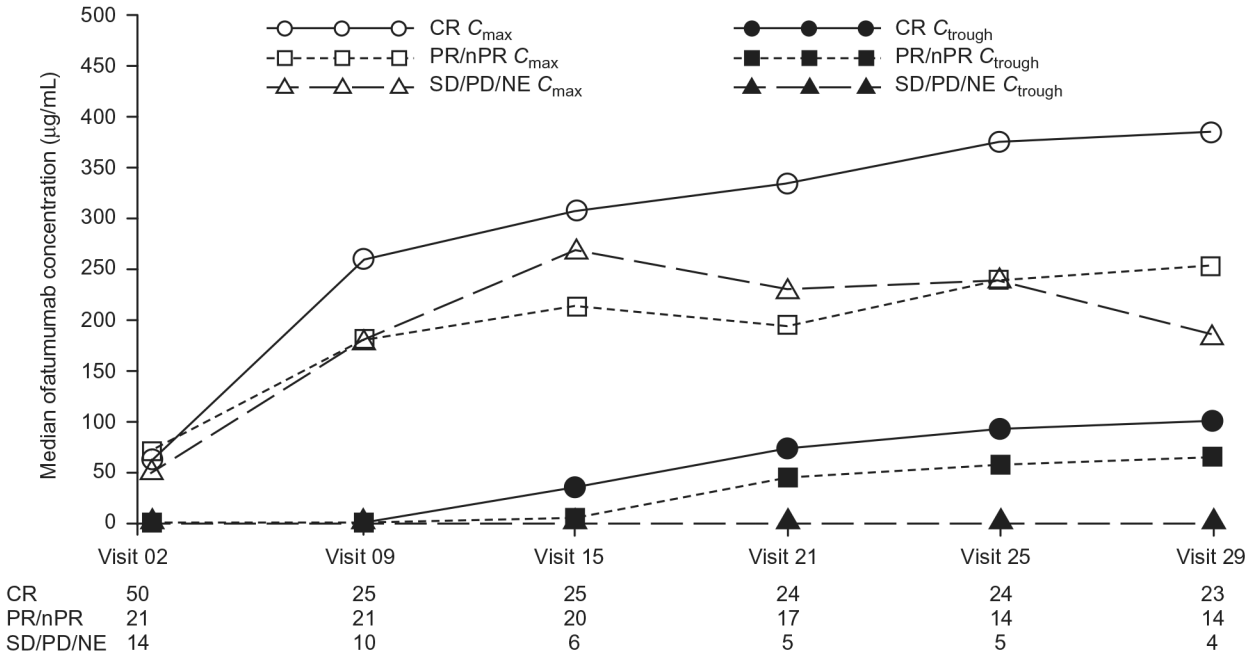

Figure 4.

Median ofatumumab C_{max} or C_{trough} values at each cycle by best response. C_{max}: maximum observed concentration; C_{trough}: minimum observed concentration prior to the next dose; CR: complete response; PR/nPR: partial response or nodal partial response; SD/PD/NE: stable disease, progressive disease, or not evaluable.

Table 1.

Pretreatment patient and disease characteristics.

Characteristic	Ofatumumab 500 mg (*n* = 31)	Ofatumumab 1000 mg (*n* = 30)
Age, years, median (range)	56 (38–73)	56 (38–72)
Gender, *n* (%)		
Male	20 (65)	23 (77)
Female	11 (35)	7 (23)
β_2-microglobulin (mg/L), median (range)	4.0 (1.8–11.5)	4.0 (2.1–10.7)
β_2-microglobulin (≥3.5 mg/L), *n* (%)	19 (61)	20 (69)
ALC ($\times 10^9$/L), median (range)	93 (4–302)	77 (8–307)
Rai stage III–IV at screening, *n* (%)	12 (39)	16 (53)
ECOG PS 1–2 at baseline, *n* (%)	16 (52)	12 (40)
Bulky lymph nodes (>5 cm), *n* (%)	5 (16)	5 (17)
Unmutated IGHV, *n* (%)	16 (52)	9 (30)
$CD38^+$ (≥20%), *n* (%)	9 (29)	7 (23)
FISH genomic abnormality[a], *n* (%)		
del 17p	2 (6)	6 (21)
del 11q	7 (23)	3 (10)
Trisomy 12	4 (13)	5 (17)
No abnormality	5 (16)	2 (7)
del 13q (sole)	12 (39)	13 (45)
del 6q	1 (3)	0

ALC: absolute lymphocyte count; ECOG PS: Eastern Cooperative Oncology Group performance status; FISH: fluorescence *in situ* hybridization; IGHV: immunoglobulin heavy chain variable region.

[a]FISH data were not available from one patient in the 1000 mg dose group.

Table 2.

Summary of ofatumumab pharmacokinetic parameter values.

Dose	*n*	C_{max} (mg/L)	AUC(0–∞) (mg.h/L)	AUC(0–τ) (mg.h/L)	$t_{½}$ (h)	CL (mL/h)	V_{ss} (L)	C_{trough} (mg/L)
Infusion 1 (Cycle 1, Visit 2)								
300 mg[a]	60	62.4	2156[b]	2156[b]	19.1[b]	139[a]	4.2[b]	NA
		(48)	(100)	(100)	(86)	(100)	(34)	
Infusion 6 (Cycle 6, Visit 29)								
500 mg	22	201	145,236[c]	74,728[d]	551[c]	6.7[d]	5.2[c]	19.9
		(30)	(54)	(39)	(31)	(39)	(27)	(1269)
1000 mg	19	427	397,577[c]	149,019	746[c]	6.7	5.8[c]	62.2
		(34)	(35)	(75)	(30)	(75)	(38)	(1036)

AUC(0–τ): area under the concentration–time curve over the dosing interval τ; AUC(0–∞): area under the concentration–time curve extrapolated to infinity; CL: clearance; C_{max}: maximum observed concentration; C_{trough}: minimum observed concentration prior to next dose; NA: not applicable; $t_{½}$: terminal phase half-life; Vss: volume of distribution at steady state.

Data are presented as geometric mean (% between-patient coefficient of variation).

[a] All patients received 300 mg ofatumumab at Cycle 1; ofatumumab concentration data were available from 60 patients.

[b] $n = 50$.

[c] $n = 16$.

[d] $n = 20$.

Table 3.

Baseline factors associated with pharmacokinetic parameter values at Cycle 1 and Cycle 6: multivariate analysis.

Pharmacokinetic parameter	Baseline factors[a]	Estimate[b]	*p*
Cycle 1			
C_{max}, mg/L	Gender (F/M)	0.766	<0.001
	Hemoglobin	0.103	<0.001
C_{trough}[c], mg/L	Gender (F/M)	0.524	0.006
	% bone marrow involvement	−0.040	<0.001
AUC, mg.h/L	Gender (F/M)	0.924	<0.001
CL, mL/h	Gender (F/M)	−0.924	<0.001
V_{ss}, L	Gender (F/M)	−0.555	<0.001
	Hemoglobin	−0.070	0.002
$t_{½}$, h	Gender (F/M)	0.739	0.001
	% Bone marrow involvement	−0.030	0.003
Cycle 6			
C_{max}, mg/L	β_2-microglobulin	−0.000	0.012
	BSA	−0.889	0.001
C_{trough}[c], mg/L	$CD5^+CD19^+$ at Dose 5	−0.003	0.001
	Bulky lymph nodes	−1.550	0.034
AUC, mg.h/L	del 17p	−;0.623	0.009
	Dose	0.001	<0.001
CL, mL/h	# of nodal sites	−0.041	0.027
	BSA	0.714	0.019
V_{ss}, L	del 17p	−0.749	0.004
$t_{½}$, h	$CD5^+CD19^+$ at Dose 5	−0.000	0.001
	Dose	0.001	0.017

AUC: area under the concentration–time curve; BSA: body surface area; CL: clearance; C_{max}: maximum observed concentration; C_{trough}: minimum observed concentration prior to next dose; F/M: female/male; $t_{½}$: terminal phase half-life; V_{SS}: volume of distribution at steady state.

[a] Results of backward elimination from full model.

[b] An estimate >0 is associated with a positive influence; an estimate <0 is associated with a negative influence.

[c] C_{trough} after the first infusion or before the sixth infusion.

Table 4.

Associations between pharmacokinetic parameter values and complete response: univariate analysis.

Parameter	*n*	Odds ratio	*p*
C_{max} (mg/L), Cycle 1	60	1.001	0.877
C_{trough} (mg/L), end of Cycle 1	56	8.834	0.184
AUC(0–∞) (mg.h/L), Cycle 1	50	1.000	0.414
C_{max} (mg/L), Cycle 3	51	1.008	0.013
C_{trough} (mg/L), end of Cycle 3	46	1.030	0.002
C_{max} (mg/L), Cycle 6	41	1.006	0.025
C_{trough} (mg/L), prior to Cycle 6	41	1.017	0.010
AUC(0–∞) (mg.h/L), Cycle 6	32	1.000	0.215

AUC(0–∞): area under the concentration–time curve extrapolated to infinity; C_{max}: maximum observed concentration; C_{trough}: minimum observed concentration prior to next dose.

Table 5.

Factors associated with complete response: multivariate analysis.

Prognostic factor	Odds ratio	p^a
FISH 17p (positive/negative) derived	52.078	0.020
C_{max} (mg/L) at Cycle 3	1.012	0.010

C_{max}: maximum observed concentration; FISH: fluorescence *in situ* hybridization.

[a]Based on Wald test in type 3 analysis of effects.

Table 6.

Associations between pharmacokinetic parameter values and objective response: univariate analysis.

Parameter	*n*	Odds ratio	*p*
C_{max} (mg/L), Cycle 1	60	1.017	0.167
C_{trough} (mg/L), end of Cycle 1	56	24.932	0.435
AUC(0–∞) (mg.h/L), Cycle 1	50	1.000	0.518
C_{max} (mg/L), Cycle 3	51	0.999	0.862
C_{trough} (mg/L), end of Cycle 3	46	1.035	0.070
C_{max} (mg/L), Cycle 6	41	1.003	0.510
C_{trough} (mg/L), prior to Cycle 6	41	1.025	0.100
AUC(0–∞) (mg.h/L), Cycle 6[a]	—	—	—

AUC(0–∞): area under the concentration–time curve extrapolated to infinity; C_{max}: maximum observed concentration; C_{trough}: minimum observed concentration prior to next dose.

[a]Not assessed; values missing for all non-responders.

Table 7.

Factors associated with objective response: multivariate analysis.

Prognostic factor	Odds ratio	p^a
Bulky lymphadenopathy at screening	35.410	0.011
Gender	0.155	0.089
Serum thymidine kinase	0.983	0.029

[a]Based on Wald test in type 3 analysis of effects.