Once-weekly ofatumumab in untreated or relapsed Waldenström's macroglobulinaemia: an open-label, single-arm, phase 2 study

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Summary

Background The development of more effective and safer treatments, especially non-chemotherapeutics, is needed for patients with Waldenström's macroglobulinaemia. The aim of the study was to assess the safety and clinical activity of intravenous ofatumumab monotherapy for untreated and relapsed Waldenström's macroglobulinaemia.

Methods We did a phase 2, open-label, single-arm study at six centres (hospitals and cancer clinics) in the USA. Patients aged at least 18 years who were diagnosed with untreated or relapsed Waldenström's macroglobulinaemia and required treatment, received up to three cycles of weekly ofatumumab for 5 weeks. For cycle 1, patients received one of two treatment regimens. Group A received ofatumumab 300 mg during week 1 followed by 1000 mg during weeks 2–4. Because of the acceptable safety of the 1000 mg dose in treatment group A and clinical activity of the 2000 mg dose established in chronic lymphocytic leukaemia, the study was amended on Dec 9, 2009, to change cycle 1 for group B who received ofatumumab 300 mg during week 1 and 2000 mg during weeks 2–5. We followed up patients during weeks 5–16 for treatment group A and during weeks 6–16 for treatment group B (no treatment was given during this follow-up). Patients in both groups with stable disease or a minor response after 16 weeks were eligible to then receive a redosing cycle of ofatumumab 300 mg during week 1 and 2000 mg during weeks 2–5. We followed up patients during weeks 6–16 after the redosing cycle (no treatment was given during this follow-up). Patients responding to cycle 1 or the redosing cycle who developed disease progression within 36 months could receive cycle 2 of ofatumumab 300 mg during week 1 and 2000 mg during weeks 2–5. The primary endpoint for this study was the proportion of patients who achieved an overall response (complete responses plus partial responses plus minor responses) after each treatment cycle in the intent-to-treat population every 4 weeks starting at week 8. This trial is registered at www.ClinicalTrials.gov, NCT00811733, and is now complete.

Findings Between March 17, 2009, and Feb 24, 2011, we enrolled and assigned 37 patients to treatment (15 in treatment group A and 22 in treatment group B). All 37 were included in the efficacy and safety analyses. 19 (51%, 95% CI 34·4–68·1) of 37 patients achieved an overall response after cycle 1 and 22 (59%, 42·1–75·2) of 37 achieved an overall response after the redosing cycle; 15 (41%) with partial responses, seven (19%) with minor responses. 13 patients received treatment cycle 2; ten (77%) of the 13 achieved a response. All 37 patients had at least one adverse event; 16 (43%) patients had events of grade 3 or more (30 grade 3, one grade 4). The most common grade 3 or 4 adverse events were infusion reactions (four [11%] of 37), chest pain (two [5%] of 37), haemolysis (two [5%] of 37), and neutropenia (two [5%] of 37). Two (9%) of 22 patients (both in treatment group B) had an IgM flare. 12 patients reported serious adverse events; haemolysis and pyrexia were the most common (each occurring in two [5%] of 37 patients).

Interpretation A high proportion of patients achieved an overall response with ofatumumab monotherapy and this treatment was well tolerated, with a low incidence of IgM flare. This therapy might be a non-chemotherapeutic treatment option for patients with Waldenström's macroglobulinaemia, especially those with high IgM concentrations.

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Introduction

Waldenström's macroglobulinaemia is a type of indolent B-cell non-Hodgkin lymphoma characterised by production of a monoclonal IgM paraprotein, bone marrow infiltration, and variable expression of CD20.[1–3] Patients have cytopenias resulting from bone marrow infiltration and complications arising from high serum concentrations of IgM such as hyperviscosity, haemolytic anaemia, and cryoglobulinemia.[4–8] Until recently, no treatments were specifically approved for Waldenström's macroglobulinaemia; in January, 2015, the US Food and Drug Administration approved ibrutinib for patients with this disease, however, some patients are unable to tolerate ibrutinib because of adverse events such as diarrhoea, bleeding risk, hypertension, arthralgias, and atrial fibrillation. Additionally, not all patients achieve adequate responses. Other drugs that are used, including alkylators and nucleoside analogues, cause myelosuppression and long-term marrow failure. 25% to 75% of patients with

Research in context

Evidence before this study

We searched PubMed for relevant English-language publications using the terms "Waldenström's treatment", "rituximab", "ofatumumab", "IgM flare", "rituximab mechanism of action", and "CD20 ligation", with no date restrictions. In January, 2015, the US Food and Drug Administration approved ibrutinib for patients with Waldenström's macroglobulinaemia; however, some patients are unable to tolerate ibrutinib because of adverse events such as diarrhoea, bleeding risk, hypertension, arthralgias, and atrial fibrillation. Additionally, not all patients achieve adequate responses. Alternative treatment options include alkylators and nucleoside analogues; however, these cause myelosuppression and long-term marrow failure. The chimeric anti-CD20 monoclonal antibody rituximab is clinically active in Waldenström's macroglobulinaemia (25% to 75% of patients treated with rituximab monotherapy had a response) but 40% to 50% of patients developed an IgM flare. Thus, development of new treatments, especially non-chemotherapeutics, is needed for patients with Waldenström's macroglobulinaemia.

Added value of this study

The results of our phase 2, open-label, single-arm study showed that ofatumumab monotherapy had clinical activity in Waldenström's macroglobulinaemia, including patients with a high tumour burden, and a manageable safety profile. The results compared favourably with those of rituximab and the incidence of IgM flare with ofatumumab (in two [9%] of 22 patients) was lower than previously reported for rituximab (40–50%). Re-treating patients who had initially responded to ofatumumab but later progressed, resulted in responses in most cases.

Implications of all the available evidence

Findings from this study might have major clinical significance for patients with Waldenström's macroglobulinaemia and warrant further assessment. Immunotherapy offers the potential of clinical efficacy without the marrow toxicity of cytotoxic chemotherapy. The large proportion of patients with a response and the low risk of IgM flare suggests that ofatumumab might be a non-chemotherapeutic treatment option for patients with Waldenström's macroglobulinaemia, particularly those with high IgM concentrations. Patients with Waldenström's macroglobulinaemia who respond to ofatumumab might also derive clinical benefit from retreatment at subsequent progression.

Waldenström's macroglobulinaemia achieve an overall response with the chimeric anti-CD20 monoclonal antibody rituximab,[9–14] with a median time to progression of 6–16 months;[9–11,14] however, 40–50% of patients treated with rituximab monotherapy have an IgM flare, defined as a transient increase in IgM that occurs with therapy and is followed by a sufficient decrease in IgM to qualify as a response. The acute rise in IgM is often sufficient to result in significant morbidity and mortality;[1,14,15] thus, development of new treatments that do not cause such flare, especially non-chemotherapeutics, is needed for patients with Waldenström's macroglobulinaemia.

See Online for appendix

Ofatumumab is a human anti-CD20 monoclonal antibody that binds to an epitope distinct from that which rituximab binds to.[16] Ofatumumab has more potent complement-dependent cytotoxicity than rituximab in vitro, especially in cells with low CD20 expression such as chronic lymphocytic leukaemia.[17,18] Ofatumumab is approved for the treatment of chronic lymphocytic leukaemia that is refractory to fludarabine and alemtuzumab[19,20] and for previously untreated chronic lymphocytic leukaemia in combination with chlorambucil,[21] and has shown clinical activity in patients with B-cell non-Hodgkin lymphoma.[22] Considering the established antitumour effects of rituximab, variable CD20 expression in Waldenström's macroglobulinaemia, and the enhanced complement-dependent cytotoxicity of ofatumumab, we did a phase 2 clinical trial to assess ofatumumab efficacy and tolerability in patients with Waldenström's macroglobulinaemia.

Methods

Study design and patients

We did a phase 2, open-label, single-arm study at six centres (hospitals and cancer clinics) in the USA (CA, NY, MN, and OH; appendix). Institutional review boards at participating centres approved the protocol; this study was done by the Waterfall Waldenström's Research Consortium and other centres.

Adult patients (≥18 years) with Waldenström's macroglobulinaemia, an Eastern Cooperative Oncology Group performance status of 2 or less, and life expectancy of more than 6 months were eligible. Patients had to have untreated or relapsed Waldenström's macroglobulinaemia, and require therapy according to criteria established by the Second International Workshop on Waldenström's macroglobulinaemia.[8,23,24] Other inclusion criteria were: detectable CD20-positive tumour by immunohisto-chemistry or flow cytometry; adequate organ function defined by an absolute neutrophil count of $1{\cdot}0\times10^9$ cells per L or more and a platelet count of more than 50×10^9 platelets per L unless due to marrow infiltration; transaminase concentrations of at least 2·5 times the upper level of normal (ULN); total bilirubin less than two times the ULN unless due to Gilbert's disease; and serum creatinine less than 265·2 µmol/L. Patients with monoclonal antibody therapy within 3 months before enrolment, other treatment for Waldenström's macroglobulinaemia within 28 days before enrolment, or uncontrolled chronic or active infections, HIV-positivity, or positive serology for

hepatitis B or C were excluded from the study. The 3-month exclusion for monoclonal antibody therapy is based upon the potential for responses to be noted in patients with Waldenström's macroglobulinaemia beyond the 3-month time point. Patients were recruited from physician practices at participating centres. Patients gave written informed consent.

Procedures

Patients received up to three cycles (cycle 1, redosing cycle, and cycle 2) of weekly ofatumumab (appendix). For cycle 1 we allocated patients into one of two treatment groups based on the timing of their enrolment and a protocol amendment made on Dec 9, 2009. Patients in treatment Group A received intravenous ofatumumab at 300 mg during week 1 and 1000 mg during weeks 2–4. Because of the acceptable safety of the 1000 mg dose in treatment group A and clinical activity of the 2000 mg dose established in chronic lymphocytic leukaemia, the study was amended to change cycle 1 for treatment group B who received ofatumumab 300 mg during week 1 and 2000 mg during weeks 2–5. We premedicated patients with paracetamol 1000 mg (or 975 mg) orally, diphenhydramine 50 mg orally or intravenously, and dexamethasone 8 mg orally or intravenously.

Responses were assessed centrally starting at week 8 of cycle 1, given the potential of IgM flare and the long time to response with rituximab. Patients with stable disease or a minor response at week 16 of cycle 1 were eligible to receive a redosing cycle of ofatumumab at 300 mg during week 1 and 2000 mg during weeks 2–5 of the cycle. Patients with progressive disease came off study and did not received further study drugs. We reassessed responses at week 16 of the redosing cycle. Patients who achieved a response after cycle 1 or the redosing cycle and subsequently developed progressive disease within 36 months were eligible to receive cycle 2 of ofatumumab at 300 mg during week 1 and 2000 mg during weeks 2–5.

No dose reductions were permitted during the study; if a patient experienced a treatment-related adverse event of grade 3 or 4 during treatment that did not resolve by the next scheduled dose, the next dose was held until the adverse event had resolved to grade 1 or better. If the adverse event did not sufficiently improve after 2 weeks, the patient was removed from treatment. Patients could be withdrawn from study participation for disease progression or initiation of alternative therapy, on the advice of the investigator, at the request of the patient, or if they were lost to follow-up or died.

The rationale for having a redosing cycle was to assess whether a second cycle of ofatumumab would be able to improve the response of a patient who was a poor responder or non-responder. Because the dosing of monoclonal antibodies is arbitrary, we felt it was important to include the responses at the different intervals to provide evidence of a dose effect. The rationale for having cycle 2 was to assess whether retreatment with ofatumumab would be able to generate responses in patients who previously showed a response and then progressed. Patients were required to wait until they at least showed progression as they would need to meet standard criteria for needing further treatment. Patients were required to meet at least one of the following criteria to be considered as requiring therapy in cycle 2: rising IgM, haemoglobin concentration of 100 g/L or less, platelet count of 100×10^9 platelets per L or less, symptomatic or bulky lymphadenopathy or organomegaly, or systemic manifestations of Waldenström's macroglobulinaemia, including hyperviscosity, neuropathy, amyloidosis, cryoglobulinaemia, and B symptoms.

We obtained blood samples during and after each treatment cycle. For each infusion, the maximum observed plasma ofatumumab concentration (C_{max}) and the plasma ofatumumab concentration before the start of the next infusion (C_{trough}) were determined directly from the raw concentration–time data.

Outcomes

We used National Cancer Institute Common Terminology Criteria for Adverse Events, v.3.0 to asssess toxicity from the first dose until 60 days after the last treatment dose. Patients were assessed for the primary endpoint of overall response (ie, best overall response irrespective of when it occurred) centrally using recommendations from the second and third international workshops on Waldenström's macroglobulinaemia.[25,26] Response criteria were: complete response (complete disappearance of monoclonal protein by immunofixation and lymphadenopathy or

	Treatment group A (1000 mg ofatumumab; n=15)	Treatment group B (2000 mg ofatumumab; n=22)	Total (n=37)
Age (years)	59 (43–85)	63·5 (45–79)	63 (43–85)
Aged ≥60 years	6 (40%)	17 (77%)	23 (62%)
Sex			
Male	9 (60%)	13 (59%)	22 (59%)
Female	6 (40%)	9 (41%)	15 (41%)
IgM at baseline (g/L)	34·9 (11·8–66·3)	30·0 (8·1–86·4)	31·1 (8·1–86·4)
Haemoglobin concentration at baseline (g/L)	98 (53–120)	96 (70–132)	9·8 (53–132)
No previous therapy	3 (20%)	6 (27%)	9 (24%)
Previous therapy	12 (80%)	16 (73%)	28 (76%)
Number of therapies*	3 (2–5)	2·5 (1–4)	3 (1–5)
Previous rituximab*	11/12 (92%)	14/16 (88%)	25/28 (89%)
Symptomatic or bulky lymphadenopathy or organomegaly at screening	6 (40%)	6 (27%)	12 (32%)

Data are median (range) or n (%) unless otherwise stated. Treatment group A=ofatumumab 300 mg during week 1 of the treatment cycle followed by 1000 mg during weeks 2–4. Treatment group B=ofatumumab 300 mg during week 1 of the treatment cycle followed by 2000 mg during weeks 2–5. *Includes only previously treated patients.

Table 1: **Baseline characteristics of the study population**

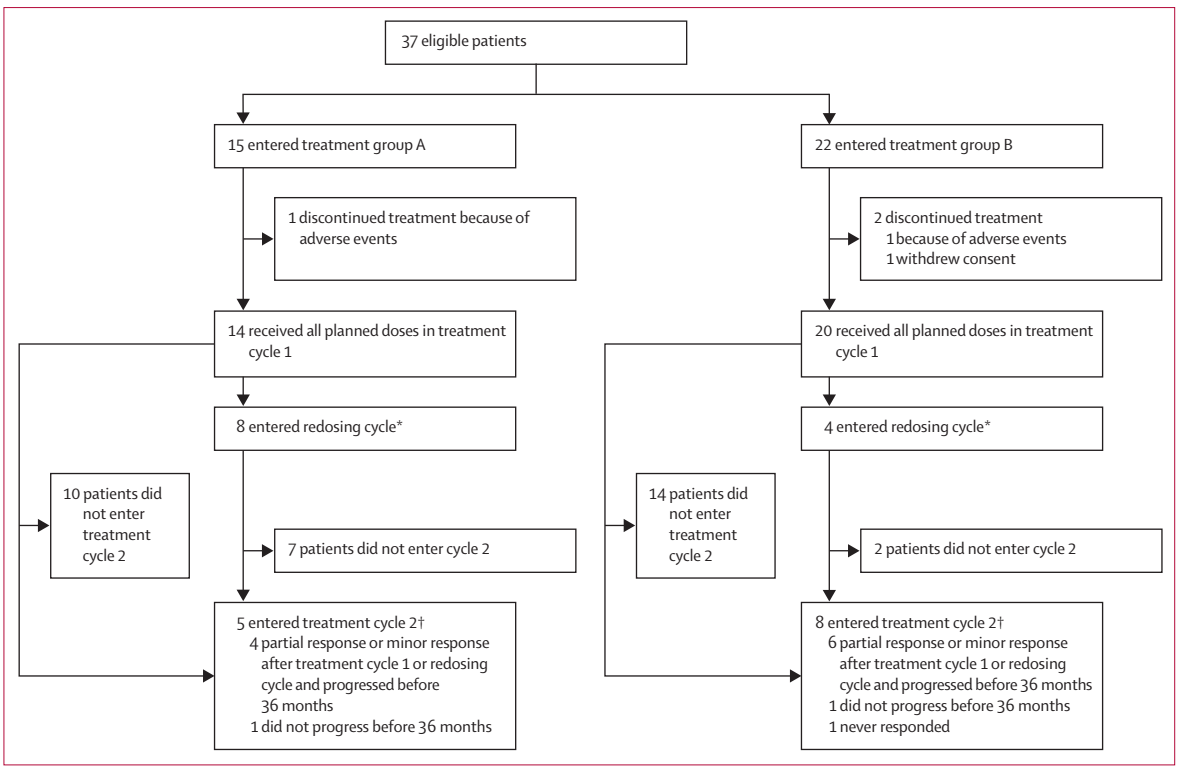

Figure 1: **Trial profile**
Treatment group A: in cycle 1, patients were administered ofatumumab 300 mg during week 1 followed by 1000 mg during weeks 2–4. Treatment group B: in cycle 1, patients were administered ofatumumab 300 mg during week 1 followed by 2000 mg during weeks 2–5. Patients received up to three cycles of treatment (cycle 1, redosing cycle, and cycle 2). Only patients who showed a response (complete, partial, or minor) during either cycle 1 or the redosing cycle and subsequently progressed within 36 months were eligible for cycle 2.

	Treatment group A (1000 mg ofatumumab; n=15)	Treatment group B (2000 mg ofatumumab; n=22)	Total (n=37)
All patients	47% (7/15)	68% (15/22)	59% (22/37)
Previous therapy			
Yes	42% (5/12)	69% (11/16)	57% (16/28)
No	67% (2/3)	67% (4/6)	67% (6/9)
Previous rituximab			
Yes	36% (4/11)	64% (9/14)	52% (13/25)
No	75% (3/4)	75% (6/8)	75% (9/12)
Baseline IgM concentration			
<40 g/L	67% (6/9)	63% (10/16)	64% (16/25)
≥40 g/dL	17% (1/6)	83% (5/6)	50% (6/12)

Data are % (n/N). Patients grouped by disease characteristics, responses assessed after treatment cycle 1 plus redosing cycle. Treatment group A=ofatumumab 300 mg during week 1 of the treatment cycle followed by 1000 mg during weeks 2–4. Treatment group B=ofatumumab 300 mg during week 1 of the treatment cycle followed by 2000 mg during weeks 2–5.

Table 2: **Patients with investigator-assessed responses**

organo-megaly confirmed at least 6 weeks later); partial response (>50% reduction in monoclonal protein and lympha-denopathy or organomegaly with no new signs or symptoms of disease); minor response (>25% but <50% reduction in serum monoclonal protein with no new signs or symptoms of disease); stable disease (<25% reduction and <25% increase in serum monoclonal protein without progression of lymphadenopathy or organomegaly or new signs or symptoms of disease); progressive disease (>25% increase in serum monoclonal protein confirmed by a second measurement or progression of clinically significant findings attributable to Waldenström's macroglobulinaemia). Overall response consisted of the number of patients who achieved a complete response, partial response, and minor response divided by the number of patients enrolled on to the study. We did baseline CT scans within 6 weeks of the first dose of cycle 1. CT scans were also required for patients whose initial response to ofatumumab treatment was progressive disease based on progressive lympha-denopathy (done at the time that the criteria for progressive disease were met) and for patients with measurable disease on their baseline CT scan whose IgM concentrations indicated complete response or partial response (at the time of response). The baseline IgM (average of screening and cycle 1, week 1 IgM concentrations) was used to assess response and results were reviewed centrally. IgM was measured weekly until week 8 of all cycles, then monthly for the first year.

	Treatment group A (1000 mg ofatumumab; n=15)	Treatment group B (2000 mg ofatumumab; n=22)	Total (n=37)
Responses to treatment cycle 1*			
Partial response	3 (20%)	9 (41%)	12 (32%)
Minor response	2 (13%)	5 (23%)	7 (19%)
Overall response (partial response plus minor response)	5 (33%; 95% CI 11·8–61·6)	14 (64%; 95% CI 40·7–82·8)	19 (51%; 95% CI 34·4–68·1)
Responses to treatment cycle 1 plus redosing cycle*			
Partial response	4 (27%)	11 (50%)	15 (41%)
Minor response	3 (20%)	4 (18%)	7 (19%)
Overall response (partial response plus minor response)	7 (47%; 95% CI 21·3–73·4)	15 (68%; 95% CI 45·1–86·1)	22 (59%; 95% CI 42·1–75·2)
Change in IgM concentrations			
IgM change from baseline to nadir (all patients, (n=37)	–43·6%	–39·1%	–39·8%
Median time to IgM nadir (all patients, n=37; days)	190	228	218
IgM change from baseline to nadir (responders, (n=22)	–61·0%	–72·2%	–64·0%
Median time to IgM nadir (responders, n=22; days)	351	289	298
Improvement in haemoglobin concentration			
Baseline haemoglobin <110 g/L (n)	12	14	26
≥30 g/L increase in haemoglobin	6 (50%)	9 (64%)	15 (58%)
†Normalisation of haemoglobin	6 (50%)	8 (57%)	14 (54%)
†Median time to reach normal haemoglobin (weeks)	25·0	20·9	20·9

Data are number (%) of patients achieving a response, or median, unless otherwise stated. Treatment group A=ofatumumab 300 mg during week 1 of the treatment cycle followed by 1000 mg during weeks 2–4. Treatment group B=ofatumumab 300 mg during week 1 of the treatment cycle followed by 2000 mg during weeks 2–5. *There were no complete responses in this study. †Normal haemoglobin concentration for men: 125 g/L; normal haemoglobin concentration for women: 115 g/L.

Table 3: **Clinical efficacy assessed by investigators**

IgM flare was defined as IgM concentrations increasing by more than 25% from baseline and associated with a response to treatment.

Secondary endpoints were time to response (defined as the time from baseline date to the first response date), duration of response (defined as the time from the initial response to relapse or progression, or death), time to relapse for complete responders (defined as the time from initial complete response to relapse or death), time to progression for partial or minor responders (defined as the time from the initial partial or minor response to progression or death), overall survival (defined as time from baseline date until death of any cause), and progression-free survival (defined as the time from baseline date to disease progression or death). Laboratory monitoring of haematology and chemistry were done weekly through week 8, then every 4 weeks through week 48, then every 12 weeks for the duration of the study.

Statistical analysis

This was an exploratory study with no formal hypothesis testing planned. For an expected 55% of patients (a similar proportion to those treated with rituximab) to achieve an overall response, the CI boundaries for the overall response were deemed to be 38%–72%. Responders included patients with complete response, partial response, or minor response. Patients with stable disease, progressive disease, or unknown or missing responses were considered non-responders.

The primary safety and efficacy population was the intention-to-treat (ITT) population which included all patients deemed eligible for treatment and who were exposed to ofatumumab irrespective of the planned course of treatment. Non-evaluable patients were those with insufficient data or insufficient time from treatment for a determination of response to be made at a given visit.

For the primary endpoint, we estimated and presented the proportion of patients with an overall response and corresponding exact 95% CI after cycle 1 and the redosing cycle in the ITT population. We generated summary statistics for the secondary endpoints. Progression-free survival, time to response, and duration of response were estimated using the Kaplan–Meier method with day 0 defined as the date of the first infusion. Progression-free survival estimates did not include the interval following disease progression for patients who received cycle 2.

For the pharmacokinetics analyses, we did non-linear mixed effects modelling of the concentration–time data using a two-compartment model with first-order elimination and combined additive and proportional error using the software NONMEM, v.7.2.0. The covariate model was adapted from the population pharmacokinetic model for ofatumumab monotherapy.[27] Individual post-hoc parameter estimates were generated for each patient, and pharmacokinetic parameter estimates were derived using standard equations. A data monitoring committee did not oversee the study. This study is registered at ClinicalTrials.gov (NCT00811733).

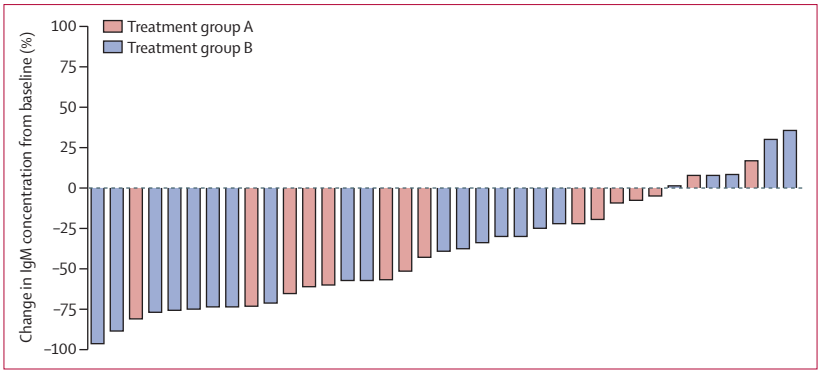

***Figure 2*: Changes in IgM concentration**
Data are changes from baseline to nadir for patients in cycle 1 plus redosing cycle for all patients (n=37). Treatment group A: in cycle 1, patients were administered ofatumumab 300 mg during week 1 followed by 1000 mg during weeks 2–4. Treatment group B: in cycle 1, patients were administered ofatumumab 300 mg during week 1 followed by 2000 mg during weeks 2–5.

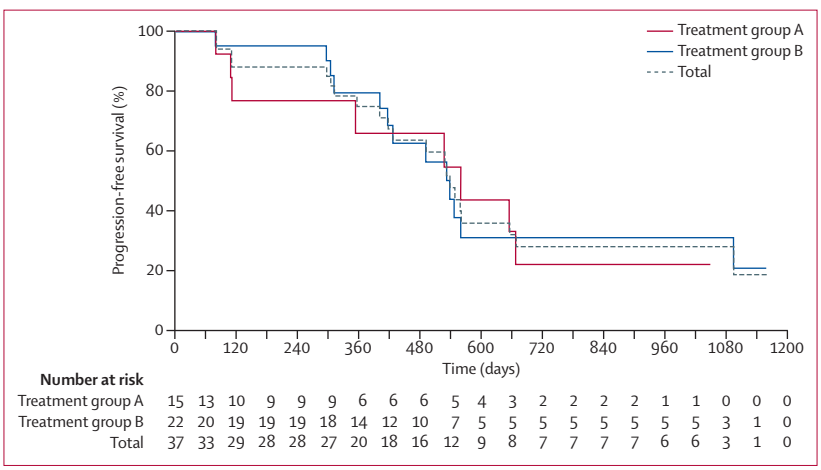

***Figure 3*: Progression-free survival**
Treatment group A: in cycle 1, patients were administered ofatumumab 300 mg during week 1 followed by 1000 mg during weeks 2–4. Treatment group B: in cycle 1, patients were administered ofatumumab 300 mg during week 1 followed by 2000 mg during weeks 2–5.

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report. All authors approved the manuscript for submission. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 17, 2009, and Feb 24, 2011, we enrolled and assigned 37 patients to treatment (15 in treatment group A and 22 in treatment group B; baseline characteristics in table 1). All 37 patients were included in the efficacy and safety analysis. 26 (70%) of 37 patients had a haemoglobin concentration of less than 110 g/L. 28 (76%) of 37 had been previously treated, with a median of three previous therapies (range 1–5), of whom 25 (89%) of 28 had received previous rituximab. Two patients (one in each group) discontinued cycle 1 early because of adverse events (one had haemolysis, the other had fluid overload), and one patient in treatment group B withdrew consent (figure 1). No data were obtained regarding plasmapheresis and symptomatic hyperviscosity before protocol enrolment.

All patients assessed for the primary endpoint were assessed for response, with a median duration follow-up of 405 days (IQR 142–743) for group A, 393 days (294–466) for group B. In patients who had a minor response or better, the median follow-up time was 743 days (670–799) for those in group A, and 414 days (345–484) for those in group B. In patients with a baseline IgM concentration of less than 4 g/dL, more than half responded to ofatumumab (table 2). 19 (51%, 95% CI 34·4–68·1) of 37 patients achieved an overall response after cycle 1 (table 3).

12 patients (32%, eight in treatment group A and four in treatment group B) entered the redosing cycle after cycle 1 (only patients with minor response or stable disease were eligible, and some patients chose not to receive retreatment). The median IgM concentration at the time of redosing was 3·2 g/dL (group A: 3·2 g/dL; group B: 4·0 g/dL). Ten patients (83%) had response assessments during the redosing cycle, three (25%) of whom improved in response status (one stable disease to minor response [time to redosing 216 days, no progression], one stable disease to partial response [time to redosing 183 days, time to progression 558 days], and one minor response to partial response [time to redosing 279 days, patient did not progress]). The remaining two patients (of 12 who entered redosing but who did not have response assessments) withdrew from the study and did not have visits with response assessments for the redosing period.

After cycle 1 and the redosing cycle, 22 (59%, 42·1–75·2) of 37 patients had achieved an overall response (table 3). 13 patients entered and received treatment cycle 2. The median IgM at the time of cycle 2 was 2·1 g/dL (group A: 1·7 g/dL; group B: 2·4 g/dL). Ten (77%) of 13 patients achieved an overall response after cycle 2 (group A: four [80%] of five, group B: six [75%] of eight), with six partial responses and four minor responses. Median time to response for the 13 patients in cycle 2 was 85 days (95% CI 78–153). Of these 13 patients, two had received redosing (group unknown).

The IgM concentrations at cycle 2 were 1·9 g/dL (value at nadir 1·0) and 1·7 g/dL (value at nadir 0·27). For all patients, the median change in IgM from baseline to nadir was –39·8% (figure 2, table 3). Median change was –44% in group A (n=15) and –39% in group B (n=22).

Of seven patients who had an enlarged spleen at baseline, five had a normal-sized spleen post-baseline, one spleen remained enlarged, and one patient did not have a post-baseline assessment of their spleen. One patient had an enlarged liver at baseline, which was normal post-baseline.

Median haemoglobin concentration was 98 g/L (range 53–132) at screening and increased to 115 g/L at month 3, 120 g/L at month 6, and 127 g/L at month 12. Of 26 patients who had a baseline haemoglobin

concentration less than 110 g/L, 14 (54%) had normal haemoglobin concentrations after a median 20·9 weeks (range 4–48; table 3). Of these 26 patients, 15 (58%) had a significant increase (≥30 g/L) in haemoglobin concentrations, including one patient who had an increase of at least 30 g/L but without normalisation of haemoglobin because of profound baseline anaemia. Of these 15 patients, ten achieved partial responses, two achieved minor responses, and three had stable disease.

Median progression-free survival for all patients was 536 days (95% CI 424–654; group A 558 days [353–666]; 18·3 months; group B 536 days [414–1093]; 17·6 months; figure 3). Overall survival at the data cutoff (date unknown) was 100% (37 of 37 patients); patients who discontinued the study early were not followed up. Median time to response for 22 responders was 78·5 days (95% CI 78–104; group A: 78 [72–269], group B: 81 [78–104]). Median duration of response was 449 days in group A (95% CI 275–not reached) and 455 days in group B (337–1016), with six (40%) of 15 patients, all in group B, continuing in remission at the time of analysis.

All 37 patients had at least one adverse event (36 [97%] of 37 in cycle 1; 11 [92%] of 12 in the redosing cycle, and nine [69%] of 13 in cycle 2). The most frequent adverse events were urticaria, pruritus, throat irritation, and flushing (table 4). 16 (43%) of 37 patients had adverse events of grade 3 or more (30 grade 3, one grade 4). The most common grade 3 or grade 4 adverse events, by preferred term, were infusion reactions (four [11%] of 37), chest pain (two [5%]), haemolysis (two [5%]), and neutropenia (two [5%]). 18 (49%) of 37 patients had infections; most were grade 1–2 upper respiratory infections. During cycle 1, one patient had a grade 3 urinary tract infection that resolved. Infusion-related reactions were defined as adverse events occurring from the beginning of an ofatumumab infusion to 24 h after the end of an infusion. 30 (81%) of 37 patients developed an infusion-related adverse event after the first infusion, and 21 (57%) of 37 developed an infusion-related adverse event after the second infusion. Most infusion-related reactions were grade 1 (table 4). No patients discontinued therapy because of infusion reactions.

	Treatment group A (1000 mg ofatumumab; n=15)			Treatment group B (2000 mg ofatumumab; n=22)			Total (n=37)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Urticaria	4 (27%)	0	0	9 (41%)	0	0	13 (35%)	0	0
Pruritus	5 (33%)	0	0	8 (36%)	0	0	13 (35%)	0	0
Throat irritation	7 (47%)	0	0	3 (14%)	0	0	10 (27%)	0	0
Flushing	6 (40%)	0	0	4 (18%)	0	0	10 (27%)	0	0
Rash	5 (33%)	1 (7%)	0	3 (14%)	0	0	8 (22%)	1 (3%)	0
Pyrexia	3 (20%)	0	0	5 (23%)	1 (5%)	0	8 (22%)	1 (3%)	0
Upper respiratory tract infection	7 (47%)	0	0	2 (9%)	0	0	9 (24%)	0	0
Headache	4 (27%)	1 (7%)	0	4 (18%)	0	0	8 (22%)	1 (3%)	0
Fatigue	4 (27%)	0	0	3 (14%)	1 (5%)	0	7 (19%)	1 (3%)	0
Oropharyngeal pain	2 (13%)	0	0	5 (23%)	0	0	7 (19%)	0	0
Insomnia	2 (13%)	0	0	4 (18%)	0	0	6 (16%)	0	0
Cough	4 (27%)	0	0	2 (9%)	0	0	6 (16%)	0	0
Ear pruritus	3 (20%)	0	0	3 (14%)	0	0	6 (16%)	0	0
Epistaxis	2 (13%)	1 (7%)	0	3 (14%)	0	0	5 (14%)	1 (3%)	0
Nasal congestion	3 (20%)	0	0	3 (14%)	0	0	6 (16%)	0	0
Chills	1 (7%)	0	0	5 (23%)	0	0	6 (16%)	0	0
Abdominal pain	3 (20%)	0	0	2 (9%)	0	0	5 (14%)	0	0
Diarrhoea	2 (13%)	0	0	3 (14%)	0	0	5 (14%)	0	0
Sinusitis	2 (13%)	0	0	3 (14%)	0	0	5 (14%)	0	0
Decreased appetite	3 (20%)	0	0	2 (9%)	0	0	5 (14%)	0	0
Muscle spasms	4 (27%)	0	0	1 (5%)	0	0	5 (14%)	0	0
Myalgia	1 (7%)	0	0	4 (18%)	0	0	5 (14%)	0	0
Infusion-related reactions*	2 (13%)	0	0	3 (14%)	0	0	5 (14%)	0	0
Constipation	2 (13%)	0	0	2 (9%)	0	0	4 (11%)	0	0
Urinary tract infection	3 (20%)	0	0	0	1 (5%)	0	3 (8%)	1 (3%)	0
Anaemia	0	0	1 (7%)	2 (9%)	0	0	2 (5%)	0	1 (3%)
Dizziness	1 (7%)	0	0	1 (5%)	1 (5%)	0	2 (5%)	1 (3%)	0
Back pain	1 (7%)	0	0	0	1 (5%)	0	1 (3%)	1 (3%)	0
Chest discomfort	1 (7%)	1 (7%)	0	0	0	0	1 (3%)	1 (3%)	0

(Table 4 continues on next page)

	Treatment group A (1000 mg ofatumumab; n=15)			Treatment group B (2000 mg ofatumumab; n=22)			Total (n=37)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
(Continued from previous page)									
Dyspnoea exertional	0	0	0	1 (5%)	1 (5%)	0	1 (3%)	1 (3%)	0
Paraesthesia	1 (7%)	0	0	3 (14%)	0	0	4 (11%)	0	0
Hyperglycaemia	1 (7%)	0	0	3 (14%)	0	0	4 (11%)	0	0
Arthralgia	1 (7%)	0	0	3 (14%)	0	0	4 (11%)	0	0
Haemolysis	0	1 (7%)	0	0	1 (5%)	0	0	2 (5%)	0
Neutropenia	0	1 (7%)	0	0	1 (5%)	0	0	2 (5%)	0
Chest pain	0	1 (7%)	0	2 (9%)	1 (5%)	0	2 (5%)	2 (5%)	0
Syncope	1 (7%)	0	0	0	1 (5%)	0	1 (3%)	1 (3%)	0
Abdominal discomfort	0	1 (7%)	0	0	0	0	0	1 (3%)	0
Blood creatinine increased	0	1 (7%)	0	0	0	0	0	1 (3%)	0
Cryoglobulinaemia	0	1 (7%)	0	0	0	0	0	1 (3%)	0
Febrile neutropenia	0	1 (7%)	0	0	0	0	0	1 (3%)	0
Fluid overload	0	0	0	0	1 (5%)	0	0	1 (3%)	0
Haemoglobin decreased	0	0	0	0	1 (5%)	0	0	1 (3%)	0
Haemolytic anaemia	0	0	0	0	1 (5%)	0	0	1 (3%)	0
Myocardial ischaemia	0	0	0	0	1 (5%)	0	0	1 (3%)	0
Protein total increased	0	0	0	0	1 (5%)	0	0	1 (3%)	0
Pulmonary oedema	0	0	0	0	1 (5%)	0	0	1 (3%)	0
Renal failure acute	0	1 (7%)	0	0	0	0	0	1 (3%)	0
Serum sickness	0	1 (7%)	0	0	0	0	0	1 (3%)	0
Small intestinal obstruction	0	0	0	0	1 (5%)	0	0	1 (3%)	0

Data are n (%) adverse events as reported by investigator occurring in at least 10% of patients (grade 1–2) or all patients (grades 3 or 4) by preferred term. Treatment group A=ofatumumab 300 mg during week 1 of the treatment cycle followed by 1000 mg during weeks 2–4. Treatment group B=ofatumumab 300 mg during week 1 of the treatment cycle followed by 2000 mg during weeks 2–5. *Reported as preferred term and does not reflect the study defined criteria for infusion-related reactions.

Table 4: **Adverse events**

Six (16%) of 37 patients had a haematological toxicity (two grade 1, three grade 3, one grade 4), four (11%) of 37 deemed drug-related. One patient (3%) of 37 had grade 3 neutropenia that was deemed drug-related. One (2%) of 37 patients had grade 3 Coombs-negative haemolysis, and one (2%) of 37 developed grade 3 Coombs-positive haemolysis. No adverse events due to other cytopenias were reported.

12 patients reported serious adverse events; haemolysis and pyrexia were the most common (each occurring in two [5%] of 37 patients). Three patients (8%) discontinued treatment because of adverse events (acute renal failure [n=1] and haemolysis [n=2]). No deaths had occurred by the end of this study.

Two (9%) of 22 responding patients, both in group B, met the protocol definition of an IgM flare. In these patients (baseline IgM: 4·34 and 1·14 g/dL, respectively), IgM concentration rose by 79% and 240%, peaking at day 42 and day 37, before achieving a response at day 356 and day 93, respectively. One of these patients was rituximab-naive, and the second had received previous rituximab treatment. In group A, geometric mean clearance and half-life values were 27·9 mL/h and 10·9 days, compared with 13·5 mL/h and 23·9 days, respectively in group B (table 5).

Discussion

Our findings suggest that ofatumumab is well tolerated, with significant clinical activity in untreated and relapsed Waldenström's macroglobulinaemia. As monotherapy, ofatumumab's activity in Waldenström's macroglobulinaemia is highly promising, especially in patients with a high tumour burden (IgM ≥4 g/dL), half of whom achieved an overall response. Published results of rituximab[11] in similar patients reported that 18% achieved an overall response. This finding can have a major clinical impact and warrants further assessment because the response rate and low risk of IgM flare extends potential non-chemotherapeutic treatment options for patients with high IgM concentrations for whom current practice typically requires chemotherapy to avoid IgM flares.

Improvement in haemoglobin concentrations is an important goal of treatment, as many patients with Waldenström's macroglobulinaemia have substantial anaemia, and baseline haemoglobin concentrations of 115 g/L or less correlate with a poor prognosis in these patients.[28] We noted that ofatumumab treatment improved haemoglobin concentrations, with some patients achieving a significant increase (≥30 g/L) in haemoglobin or resolution of anaemia. The prolonged

median time to normalisation of haemoglobin (20·9 weeks) and time to IgM response (11·2 weeks) in responders indicate the need to provide adequate time before determining whether a patient's disease has responded. Additionally, although 12 of 15 patients with a haemoglobin increase of at least 30 g/L achieved a minor response or partial response, the three remaining patients all had stable disease, indicating that patients might benefit even if the IgM concentration does not decrease by more than 25%.

On the basis of the safety profile of the 1000 mg dose in group A, the approval and safety data of the 2000 mg dose in chronic lymphocytic leukaemia, and lower expression of CD20 in Waldenström's macroglobulinaemia and the likely benefit of higher doses with lower CD20 expression, we revised the study to administer a higher dose of ofatumumab in group B. Although we could not make a statistical comparison between findings from group A and group B because of the small sample size and non-randomised treatment assignment, the higher dose seemed to improve clinical outcomes. Previous therapy correlated with a lower overall response in group A but did not affect the probability of response in group B. Similarly, previous rituximab exposure correlated with a lower overall response in group A but not in group B. Additionally, 17% of patients in group A with an IgM of at least 40 g/L achieved an overall response, compared with 83% in group B. These findings suggest that the 2000 mg dose of ofatumumab might be more effective in patients with Waldenström's macroglobulinaemia, and could negate adverse prognostic factors such as IgM of at least 40 g/L, previous therapy, and anaemia.

We could not draw any conclusions regarding the efficacy and tolerability of ofatumumab compared with rituximab because we did not obtain information on the outcome and tolerability of previous rituximab treatments, and because of the difficulties in comparing across two separate phase 2 studies. Similarly, we did not assess the effect of *FCGR3A* polymorphisms and *MYD88* and *CXCR4* mutations on response, preventing any conclusion regarding differences in mechanism of action between these two anti-CD20 monoclonal antibodies.

Patients in group A had higher ofatumumab clearance and shorter half-life values than patients in group B, although no statistical comparison was made. Since binding to B cells is a clearance mechanism for ofatumumab, these results suggest that the higher dosing regimen might have decreased the tumour cell burden more on average in group B, which is consistent with the clinical results. The pharmacokinetic parameter values in group B were similar to those in patients with chronic lymphocytic leukaemia; combined data from three clinical trials in patients with chronic lymphocytic leukaemia, geometric mean values of clearance and half-life were 12·9 mL/h and 15·6 days, respectively.[29]

	Treatment group A (1000 mg ofatumumab; n=15)		Treatment group B (2000 mg ofatumumab; n=22)	
	n	Geometric mean (between-patient coefficient of variation)	n	Geometric mean (between-patient coefficient of variation)
Clearance (mL/h)*	15	27·9 (132)	21	13·5 (122)
V_{ss} (L)*	15	10·0 (21)	21	10·7 (24)
$t_{½}$ (days)*	15	10·9 (103)	21	23·9 (103)
Cycle 1 (all values µg/mL)				
C_{max} dose 1	14	68·3 (67)	19	72·1 (50)
C_{max} dose 3	..	NE	19	465·0 (40)
C_{max} dose 4	13	259·0 (50)	..	NE
C_{max} dose 5		..	18	640·0 (42)
C_{trough} before dose 2	7	3·0 (1725)	12	8·0 (1084)
C_{trough} before dose 3	11	13·9 (5018)	19	121·0 (184)
C_{trough} before dose 4	13	23·4 (5252)	21	181·0 (252)
C_{trough} before dose 5	..	..	18	249·0 (230)
Redosing cycle 1 or cycle 2, depending upon the patient (all values µg/mL)				
C_{max} dose 1	9	53·2 (68)	11	64·8 (68)
C_{max} dose 3	8	554·0 (34)	12	577·0 (46)
C_{max} dose 5	10	528·0 (69)	12	803·0 (44)
C_{trough} before dose 2	7	8·1 (777)	10	20·4 (828)
C_{trough} before dose 3	8	144·0 (122)	12	169·0 (94)
C_{trough} before dose 4	11	225·0 (144)	12	310·0 (78)
C_{trough} before dose 5	11	279·0 (108)	12	384·0 (58)

Treatment group A=ofatumumab 300 mg during week 1 of the treatment cycle followed by 1000 mg during weeks 2–4. Treatment group B=ofatumumab 300 mg during week 1 of the treatment cycle followed by 2000 mg during weeks 2–5. V_{ss}=volume of distribution at steady state. $t_{½}$=elimination half-life. C_{max}=maximum observed concentration. ..=not available. NE=not evaluated. C_{trough}=plasma concentration before the start of the next infusion. *Based on post-hoc parameter estimates.

Table 5: **Summary of ofatumumab pharmacokinetic parameter values in patients with Waldenström's macroglobulinaemia**

Ten (77%) of 13 patients who responded to ofatumumab and subsequently had progressive disease responded to retreatment with ofatumumab (six partial responses, four minor responses), suggesting that patients with Waldenström's macroglobulinaemia who respond to ofatumumab might derive clinical benefit from retreatment at subsequent progression.

Ofatumumab was well tolerated in this study, and the adverse event profile was consistent with observations from other ofatumumab studies in B-cell non-Hodgkin lymphoma and chronic lymphocytic leukaemia. The most common adverse events were grade 1–2 infusion reactions and infections, none of which resulted in patient withdrawal. Three patients discontinued therapy due to serious adverse events; one patient, with a baseline IgM concentration of 6·6 g/dL, developed acute renal failure requiring plasmapheresis, and two patients experienced haemolysis. The incidence of IgM flare with ofatumumab (two [9%] of 22 patients) was lower than the 40–50% incidence reported for rituximab;[14,15] however, no direct comparisons can be made because of the

non-randomised nature of this study and the absence of a standardised definition across studies. Additionally, the frequency of IgM monitoring and previous exposure to rituximab might also be factors for difference in rituximab versus ofatumumab flare rates.

In this study, the median time to response for cycle 1 plus redosing cycle was 78·5 days; the median time to IgM nadir, or best response, was 298 days; and the median time to normalisation of haemoglobin was 20·9 weeks. These findings indicate that response to ofatumumab in Waldenström's macroglobulinaemia is a prolonged process, supporting the hypothesis that the therapy kills a compartment of malignant lymphocytes that probably differentiate into the IgM-secreting cells, which die at a standard rate.

In summary, ofatumumab monotherapy had significant clinical benefit with an acceptable toxicity profile in patients with Waldenström's macroglobulinaemia. A higher dose of ofatumumab might have contributed to a higher number of patients who had high serum IgM or previous rituximab-based therapy achieving a response. However, the small sample size and the use of the higher dosing regimen for the redosing cycle and cycle 2 in all patients preclude a definitive conclusion about the optimum ofatumumab dosing regimen in Waldenström's macroglobulinaemia. Additionally, because of short follow-up, data are not available regarding whether dosing might affect response duration or progression-free survival.

Immunotherapy offers the potential of clinical efficacy without the marrow toxicity of cytotoxic chemotherapy. Because Waldenström's macroglobulinaemia is an indolent lymphoma in which progression-free survival is the most clinically meaningful endpoint, longer follow-up with updated data will further support the durability of responses and the clinical efficacy of ofatumumab in Waldenström's macroglobulinaemia.

Contributors

RRF contributed to the conception and design of the study, patient enrolment, and reviewing and approving the manuscript for submission. HAE contributed to data interpretation and reviewing and approving the manuscript for submission. CGD contributed to data collection, data interpretation and analysis, and reviewing and approval of the manuscript for submission. CCH, MC, AC-K, and SRH contributed to patient enrolment and reviewing and approving the manuscript for submission. JPL contributed to data collection, interpretation, and analysis, and reviewing and approving the manuscript for submission. RA contributed to patient enrolment, reviewing data, and reviewing and approving the manuscript for submission. JS contributed to study design, data interpretation, and reviewing and approving the manuscript for submission. QML contributed to the study design, statistical analysis, data interpretation, and reviewing and approving the manuscript for submission. DS contributed to data interpretation and analysis, and reviewing and approving the manuscript for submission. RCJ and TSL contributed to the study design, data interpretation and analysis, and reviewing and approving the manuscript for submission. SL contributed to the study design, data interpretation, and reviewing and approving the manuscript for submission.

Declaration of interests

CGD, JS, QML, DS, RCJ, and TSL were employees of, and owned stock in, GlaxoSmithKline during the time of the study and initial publication development. CGD now works for Pfizer, JS now works for Incyte, and TSL now works for Janssen. SL is an employee of, and owns stock in, Genmab A/S. RRF served as a consultant and member of a speaker bureau for GlaxoSmithKline. JPL has served as a consultant for Novartis Pharmaceuticals. AC-K, SRH, CCH, RA, HAE, and MC declare no competing interests. As of March, 2015, ofatumumab is an asset of Novartis AG.

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References

1 Ghobrial IM, Gertz MA, Fonseca R. Waldenström macroglobulinaemia. *Lancet Oncol* 2003; **4:** 679–85.
2 Owen RG. Developing diagnostic criteria in Waldenstrom's macroglobulinemia. *Semin Oncol* 2003; **30:** 196–200.
3 Pangalis GA, Kyrtsonis MC, Kontopidou FN, et al. Differential diagnosis of Waldenström's macroglobulinemia and other B-cell disorders. *Clin Lymphoma* 2005; **5:** 235–40.
4 Leleu X, Soumerai J, Roccaro A, et al. Increased incidence of transformation and myelodysplasia/acute leukemia in patients with Waldenström macroglobulinemia treated with nucleoside analogs. *J Clin Oncol* 2009; **27:** 250–55.
5 Leleu X, Tamburini J, Roccaro A, et al. Balancing risk versus benefit in the treatment of Waldenström's macroglobulinemia patients with nucleoside analogue-based therapy. *Clin Lymphoma Myeloma* 2009; **9:** 71–73.
6 Treon SP. How I treat Waldenstrom macroglobulinemia. *Blood* 2009; **114:** 2375–85.
7 Treon SP, Soumerai JD, Branagan AR, et al. Thalidomide and rituximab in Waldenstrom macroglobulinemia. *Blood* 2008; **112:** 4452–57.
8 Gertz MA. Waldenström macroglobulinemia: 2012 update on diagnosis, risk stratification, and management. *Am J Hematol* 2012; **87:** 503–10.
9 Byrd JC, White CA, Link B, et al. Rituximab therapy in Waldenstrom's macroglobulinemia: preliminary evidence of clinical activity. *Ann Oncol* 1999; **10:** 1525–27.
10 Dimopoulos MA, Zervas C, Zomas A, et al. Treatment of Waldenström's macroglobulinemia with rituximab. *J Clin Oncol* 2002; **20:** 2327–33.
11 Dimopoulos MA, Alexanian R, Gika D, et al. Treatment of Waldenstrom's macroglobulinemia with rituximab: prognostic factors for response and progression. *Leuk Lymphoma* 2004; **45:** 2057–61.
12 Foran JM, Rohatiner AZ, Cunningham D, et al. European phase II study of rituximab (chimeric anti-CD20 monoclonal antibody) for patients with newly diagnosed mantle-cell lymphoma and previously treated mantle-cell lymphoma, immunocytoma, and small B-cell lymphocytic lymphoma. *J Clin Oncol* 2000; **18:** 317–24.
13 Gertz MA, Rue M, Blood E, Kaminer LS, Vesole DH, Greipp, PR. Multicenter phase 2 trial of rituximab for Waldenström macroglobulinemia (WM): an Eastern Cooperative Oncology Group Study (E3A98). *Leuk Lymphoma* 2004; **45:** 2047–55.
14 Ghobrial IM, Fonseca R, Greipp PR, et al. Initial immunoglobulin M 'flare' after rituximab therapy in patients diagnosed with Waldenström macroglobulinemia: an Eastern Cooperative Oncology Group Study. *Cancer* 2004; **101:** 2593–98.
15 Treon SP, Branagan AR, Hunter Z, Santos D, Tournhilac O, Anderson KC. Paradoxical increases in serum IgM and viscosity levels following rituximab in Waldenström's macroglobulinemia. *Ann Oncol* 2004; **15:** 1481–83.
16 Teeling JL, Mackus WJ, Wiegman LJ, et al. The biological activity of human CD20 monoclonal antibodies is linked to unique epitopes on CD20. *J Immunol* 2006; **177:** 362–71.
17 Pawluczkowycz AW, Beurskens FJ, Beum PV, et al. Binding of submaximal C1q promotes complement-dependent cytotoxicity (CDC) of B cells opsonized with anti-CD20 mAbs ofatumumab (OFA) or rituximab (RTX): considerably higher levels of CDC are induced by OFA than by RTX. *J Immunol* 2009; **183:** 749–58.

18 Teeling JL, French RR, Cragg MS, et al. Characterization of new human CD20 monoclonal antibodies with potent cytolytic activity against non-Hodgkin lymphomas. *Blood* 2004; **104:** 1793–800.

19 Wierda WG, Kipps TJ, Mayer J, et al. Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. *J Clin Oncol* 2010; **28:** 1749–55.

20 Österborg A, Jewell RC, Padmanabhan-Iyer S, et al. Ofatumumab monotherapy in fludarabine-refractory chronic lymphocytic leukemia: final results from a pivotal study. *Haematologica* 2015; **100:** e311–14.

21 Hillmen P, Robak T, Janssens A, et al. Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukaemia (COMPLEMENT 1): a randomised, multicentre, open-label phase 3 trial. *Lancet* 2015; **385:** 1873–83.

22 Czuczman MS, Kahanic S, Forero A, et al. Results of a phase II study of bendamustine and ofatumumab in untreated indolent B cell non-Hodgkin's lymphoma. *Ann Hematol* 2015; **94:** 633–41.

23 Gertz MA. Waldenström macroglobulinemia. *Hematology* 2012; **17** (suppl 1)**:** S112–116.

24 Gertz MA, Anagnostopoulos A, Anderson K, et al. Treatment recommendations in Waldenström's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenström's macroglobulinemia. *Semin Oncol* 2003; **30:** 121–26.

25 Kimby E, Treon SP, Anagnostopoulos A, et al. Update on recommendations for assessing response from the Third International Workshop on Waldenström's macroglobulinemia. *Clin Lymphoma Myeloma* 2006; **6:** 380–83.

26 Weber D, Treon SP, Emmanouilides C, et al. Uniform response criteria in Waldenström's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenström's macroglobulinemia. *Semin Oncol* 2003; **30:** 127–31.

27 Struemper H, Sale M, Patel BR, et al. Population pharmacokinetics of ofatumumab in patients with chronic lymphocytic leukemia, follicular lymphoma, and rheumatoid arthritis. *J Clin Pharmacol* 2014; **54:** 818–27.

28 Morel P, Duhamel A, Gobbi P, et al. International prognostic scoring system for Waldenström's macroglobulinemia. *Blood* 2009; **113:** 4163–70.

29 Arzerra (prescribing information. Novartis Pharmaceuticals Corporation. East Hanover, NJ; January 2016. http://www.pharma.us.novartis.com/product/pi/pdf/arzerra.pd (accessed Jan 12, 2016).