Ofatumumab maintenance versus observation in relapsed chronic lymphocytic leukaemia (PROLONG): an open-label, multicentre, randomised phase 3 study

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Lancet Oncol 2015; 16: 1370–79

Published Online September 14, 2015 http://dx.doi.org/10.1016/S1470-2045(15)00143-6

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Summary

Background Ofatumumab is a human anti-CD20 monoclonal antibody that has proven efficacy as monotherapy in refractory chronic lymphocytic leukaemia. We assessed the efficacy and safety of ofatumumab maintenance treatment versus observation for patients in remission after re-induction treatment for relapsed chronic lymphocytic leukaemia.

Methods This open-label, multicentre, randomised phase 3 study enrolled patients aged 18 years or older from 130 centres in 24 countries who had chronic lymphocytic leukaemia in complete or partial remission after second-line or third-line treatment. Eligible patients had a WHO performance status of 0–2, had a response assessment within the previous 3 months, did not have refractory disease, autoimmune haemolytic anaemia requiring treatment, chronic or active infection requiring treatment, and had not previously received maintenance treatment or autologous or allogeneic stem-cell transplant. Using a randomisation list generated by a central computerised system and an interactive voice recognition system, we randomly assigned (1:1) patients to receive ofatumumab (300 mg followed by 1000 mg 1 week later and every 8 weeks for up to 2 years) or undergo observation. Randomisation was stratified by number and type of previous treatment and remission status after induction treatment (block size of four). Treatment assignment was open label. The primary endpoint was investigator-assessed progression-free survival in the intention-to-treat population. We report the results of a prespecified interim analysis after two-thirds of the planned study events (disease progression or death) had happened. This trial is closed to accrual but follow-up is ongoing. This trial is registered with ClinicalTrials.gov, number NCT00802737.

Findings Between May 6, 2010, and June 19, 2014, we enrolled 474 patients: 238 patients were randomly assigned to receive ofatumumab maintenance treatment and 236 to undergo observation. One (<1%) patient in the ofatumumab group did not receive the allocated intervention (withdrawal of consent). The median follow-up was 19·1 months (IQR 10·3–28·8). Progression-free survival was improved in patients assigned to the ofatumumab group (29·4 months, 95% CI 26·2–34·2) compared with those assigned to observation (15·2 months, 11·8–18·8; hazard ratio 0·50, 95% CI 0·38–0·66; p<0·0001). The most common grade 3 or higher adverse events up to 60 days after last treatment were neutropenia (56 [24%] of 237 patients in the ofatumumab group *vs* 23 [10%] of 237 in the observation group) and infections (31 [13%] *vs* 20 [8%]). 20 (8%) of 237 patients in the ofatumumab group and three (1%) of 237 patients in the observation group had adverse events that led to permanent discontinuation of treatment. Up to 60 days after last treatment, two deaths related to adverse events occurred in the ofatumumab treatment group and five deaths related to adverse events occurred in the observation group; no deaths were attributed to the study drug.

Interpretation These data are important for the development of optimum maintenance strategies in patients with relapsed chronic lymphocytic leukaemia, notably in the present era of targeted drugs, many of which are to be used until progression.

Funding GlaxoSmithKline and Genmab.

Introduction

Although many treatments have become available in the past few years that effectively induce remission and improve progression-free survival, allogeneic stem-cell transplantation is still the only potentially curative treatment for chronic lymphocytic leukaemia.[1] Because allogeneic stem-cell transplantation is feasible in only a few patients with chronic lymphocytic leukaemia, prolonged progression-free survival and overall survival are the fundamental treatment goals for most patients.

Chronic lymphocytic leukaemia and follicular lymphoma are different diseases, yet they show similarities in their clinical behaviour, such as a long natural course, decreasing remission duration upon successive treatments, and incurability. In follicular lymphoma, maintenance treatment with the chimeric anti-CD20 monoclonal antibody rituximab has been shown to result in a significant and clinically relevant improvement in progression-free survival, both after first-line remission induction treatment[2] and after relapse.[3,4] As a corollary, maintenance treatment might also be beneficial in chronic

Research in context

Evidence before this study

When the study protocol was developed in 2009, little data for the efficacy and safety of maintenance treatment in chronic lymphocytic leukaemia existed. We searched PubMed without restrictions of time of publication using the terms "CLL AND maintenance" and "CLL AND consolidation", without time or language restrictions. We identified two studies, both in previously untreated patients: consolidation (4 months) and maintenance (12 months) with rituximab was assessed in a phase 2 trial, and consolidation (3 months) with alemtuzumab was tested in a phase 3 study. The phase 3 study was stopped prematurely because of severe infections.

Added value of this study

This study is the first large, randomised, phase 3 study of maintenance treatment in a population of patients with relapsed chronic lymphocytic leukaemia in remission after re-induction treatment. We show that 2 years of maintenance treatment with ofatumumab, a human anti-CD20 monoclonal antibody, prolonged progression-free survival and time to next treatment. Ofatumumab was well tolerated and did not cause unexpected toxicities. Importantly, we show that ofatumumab maintenance did not increase the risk of transformation.

Implications of all the available evidence

Our data are timely in the present era of novel treatment modalities for chronic lymphocytic leukaemia, notably the BTK and PI3K inhibitors. At present, continued treatment with these kinase inhibitors until relapse is recommended—ie, they are used as a prolonged maintenance treatment. Our data for the efficacy and safety of ofatumumab maintenance treatment are important for the determination of the optimum maintenance strategies in relapsed chronic lymphocytic leukaemia.

lymphocytic leukaemia. In mostly small, phase 2 trials, consolidation or maintenance treatment with lenalidomide,[5,6] rituximab,[7–10] or alemtuzumab[11,12] for varying durations has been feasible. Results of a randomised phase 3 trial with 201 patients showed that maintenance treatment with rituximab for 2 years improved progression-free survival and overall survival only in the patients carrying chromosomal deletion 11q (del[11q]) or deletion 17p (del[17p]) who are at high risk of disease progression.[13]

Ofatumumab is a human type I CD20 (IgG1-κ) monoclonal antibody, with potent in-vitro, complement-dependent cytotoxicity even in rituximab-refractory cells,[14,15] a higher antibody-dependent cytotoxicity than rituximab,[16] and in-vivo efficacy in rituximab-refractory chronic lymphocytic leukaemia.[17] The aim of this study was to compare ofatumumab maintenance treatment with observation for patients in remission after re-induction treatment for relapsed chronic lymphocytic leukaemia. Here we present the prespecified interim efficacy and toxicity analysis.

Methods

Study design and patients

PROLONG was an open-label, randomised, phase 3 study done at 130 centres in 24 countries worldwide (appendix). Eligible patients were aged 18 years or older with a diagnosis of chronic lymphocytic leukaemia in second or third complete or partial remission based on the International Workshop on Chronic Lymphocytic Leukaemia's (IWCLL) updated National Cancer Institute-sponsored working group (NCI-WG) criteria[18] and a WHO performance status of 0–2. Patients were eligible for enrolment if it was 3 months or less since their last response assessment, which, according to IWCLL guidelines, should be done 2 months after last treatment. We excluded patients who had refractory disease, active autoimmune haemolytic anaemia requiring treatment, or chronic or active infection requiring treatment, and those who had previously received maintenance therapy or autologous or allogeneic stem-cell transplant. Other exclusion criteria were: absolute neutrophil count less than $1{\cdot}0\times10^9$ cells per L; platelet count less than 50×10^9 platelets per L; creatinine more than 1·5 times the upper limit of normal (ULN); total bilirubin, alanine aminotransferase, and aspartate aminotransferase more than 2·5 times the ULN.

The study protocol was approved by an ethics review board at each participating centre. The study was done in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guideline for Good Clinical Practice. Written informed consent was provided by all patients.

Randomisation and masking

Patients were randomly assigned (1:1) to receive ofatumumab or undergo observation. Randomisation was done with a randomisation list generated by a central computerised system operated from GlaxoSmithKline (Research Triangle Park, NC, USA). We stratified the randomisation, in a block size of four, by clinical response at entry (complete remission or partial remission), number of previous induction treatments (two or three), and type of the most recent previous treatment (chemo-immunotherapy, only alkylating monotherapy, or other treatment). No investigator was involved in the generation of the randomisation lists. Investigators enrolled patients and then received centrally allocated randomisation codes through an interactive voice recognition system. Investigators and patients were not masked to the study treatment. Crossover was not allowed between study groups.

See Online for appendix

Procedures

Within 1 week of treatment assignment, patients in the ofatumumab group received a first dose of 300 mg ofatumumab intravenously. The following week, the dose of ofatumumab was increased to 1000 mg intravenously, and this dose was given at 8 week intervals for up to 2 years. Between 30 min and 2 h before ofatumumab infusion start, patients received premedication with acetaminophen (1000 mg oral), antihistamine (diphenhydramine 50 mg intravenous or oral [or equivalent acccording to local policies]), and a glucocorticoid (prednisolone 50 mg intravenous [or equivalent]). Dose reductions were not allowed, but interruptions or delays in treatment because of adverse events were permitted. Treatment continued until a patient had disease progression or withdrew from study treatment because of unacceptable side-effects, withdrew consent, or left the study for other reasons. Patients who were withdrawn prematurely from study treatment were included in the analysis, irrespective of treatment duration.

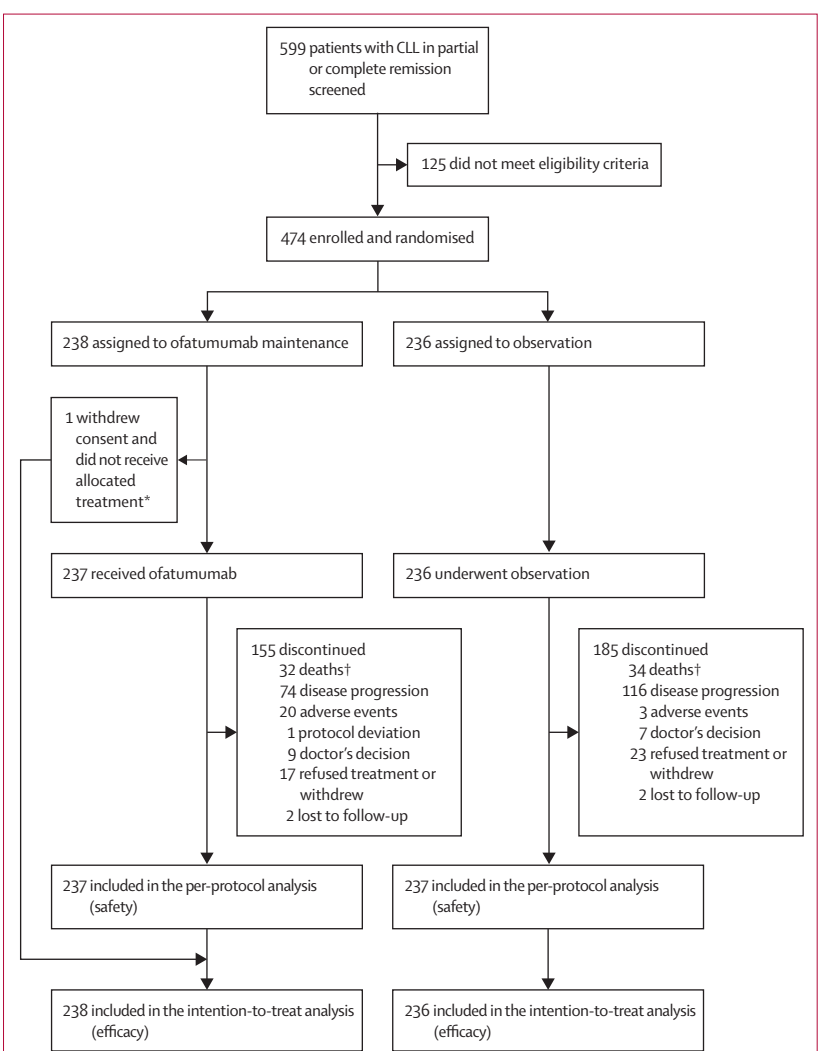

Figure 1: **Trial profile**
*One patient did not receive allocated treatment and was included in the intention-to-treat analysis of the ofatumumab group and the per-protocol analysis of the observation group. †Death at any time, ie, death during treatment or observation phase and follow-up.

We did physical examinations and laboratory tests (haematology [haemoglobin, haematocrit, reticulocytes, platelets, leucocytes, and white blood cell differential (neutrophils, eosinophils, basophils, lymphocytes and monocytes, prolymphocytes)] and biochemistry [sodium, potassium, chloride, bicarbonate, calcium, blood urea nitrogen, creatinine, uric acid, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactic acid dehydrogenase, albumin, glucose, and haptoglobulin]) for patients in both study groups every 8 weeks during the first 2 years of the study and then every 3 months during follow-up (maximum 3 days before next treatment). In both study groups, CT scans were done at enrolment, once a year during the study, at the end of the first 2 years of the study, and on clinical relapse. We analysed minimal residual disease by four-colour flow cytometry as described by Rawstron.[19] The absence of minimal residual disease was defined as less than one malignant B cell per 10 000 leucocytes. We analysed cytogenetic aberrations in malignant cells by fluorescence in-situ hybridisation using standard probes for chromosomes 17p, 11q, 13q, 6q, and 12. A cutoff value of 12% for positivity was used. Patient-reported outcomes were measured using the European Organisation for Research and Treatment of Cancer's (EORTC) core quality-of-life questionnaires (QLQ-C30 and QLQ-CLL16), which were administered to all patients during study visits and follow-up until progression. We assessed global health status or health-related quality of life (QLQ-C30) and a B-symptom index that included fatigue, night sweats, temperature changes, and weight loss using relevant questions from QLQ-C30 and QLQ-CLL16.[20] Adverse events were measured using the National Cancer Institute common terminology criteria for adverse events version 4.0. β-2 microglobulin (β2M) and serum immunoglobulin concentrations and IgHV mutation status were measured within 14 days before start treatment, by standard techniques.

Outcomes

Because overall survival from chronic lymphocytic leukaemia is affected by the availability of effective salvage treatments upon relapse, the primary endpoint of this study was progression-free survival as assessed by the investigator, defined as the time from randomisation to the earliest date of disease progression or death due to any cause. For patients who did not have disease progression or die, progression-free survival was censored at the time of last follow-up. Progression-free survival was also censored for patients who received new anticancer treatment before disease progression and for patients with two or more missing visits. Secondary

endpoints were overall survival, time to next treatment, progression-free survival after next-line therapy (defined as the time from randomisation until progression or death after next-line therapy), safety, and quality of life. Clinical response was defined and assessed according to the IWCLL updated NCI-WG guidelines.[18]

Statistical analysis

The planned sample size for the study was 478 patients (requiring an enrolment of 532 patients assuming 10% dropouts) to detect at least a 40% improvement in progression-free survival (hazard ratio [HR] 0·71) with ofatumumab maintenance treatment compared with observation, assuming a median progression-free survival of 28 months in the observation group and targeting a median progression-free survival of 39·2 months in the ofatumumab group, with 80% power and a two-sided α error of 0·05. We estimated that at least 280 patients had to have disease progression or death to detect the targeted difference in progression-free survival.

This prespecified interim analysis of progression-free survival was done when two-thirds of the 280 patients had disease progression or died (ie, 187 events). The analysis was done by an independent data monitoring committee using a conservative significance level of 0·001. On the basis of the outcome of this interim analysis, the independent data monitoring committee recommended to close the study for further accrual.

All efficacy analyses were done in the randomised (intention-to-treat) population. Safety analyses included all patients who were randomly assigned to treatment, grouped based on the actual treatment received (per protocol). We used the log-rank test (adjusted for the stratification factors) to analyse progression-free survival, overall survival, time to next treatment, and progression-free survival after next-line therapy. Kaplan-Meier curves were generated to graphically show the differences between the survival distributions of the treatment groups. All p values are two-sided. At each post-baseline timepoint, changes in patient-reported outcome scores were calculated by subtracting the baseline score. Change from baseline scores over time were analysed with a repeated measures analysis of covariance model where the model was a mixed model using PROC MIXED in SAS and included terms for baseline score, stratification factors, age group, binet stage at screening, baseline score by time interaction, and treatment by time interaction. Using 50% SD for the baseline B-symptom index score, a preliminary minimally important difference of 5·6 points was assumed to be clinically meaningful.[21]

Post-hoc analyses were completed to compare the prevalence of grade 3 or higher neutropenia and grade 3 or higher infection up to 60 days after last treatment between treatment groups. The comparisons were done using the Cochran-Mantel-Haenszel test, adjusting for stratification factors. We used SAS version 9.3 for all statistical analyses.

This study is registered at ClinicalTrials.gov, number NCT00802737, and at the WHO International Clinical Trial Registry Platform, number U111111480253.

Role of funding source

GlaxoSmithKline provided the drug and worked with the HOVON-Nordic CLL group in the development of

	Ofatumumab (n=238)	Observation (n=236)
Age (years)*		
Median	64·0 (33–86)	65·0 (39–87)
<70	168 (71%)	162 (69%)
≥70	70 (29%)	74 (31%)
≥75	40 (17%)	35 (15%)
Sex		
Female	77 (32%)	77 (33%)
Male	161 (68%)	159 (67%)
Median time since diagnosis (years)	6·0 (1–22)	5·0 (1–22)
Response to last CLL treatment		
Complete remission	45 (19%)	46 (19%)
Partial remission	193 (81%)	189 (80%)
Missing	0 (0%)	1 (<1%)
Baseline minimal residual disease		
Negative	31 (13%)	41 (17%)
Positive	137 (58%)	107 (45%)
Missing	70 (29%)	88 (37%)
Number of previous treatments		
2	168 (71%)	166 (70%)
3	66 (28%)	62 (26%)
Other	4 (2%)	8 (3%)
Type of last previous treatment		
Chemoimmunotherapy	191 (80%)	189 (80%)
BR	46 (24%)	47 (25%)
FCR	100 (52%)	103 (54%)
FR	4 (2%)	5 (3%)
Other	28 (15%)	23 (12%)
RCVP	13 (7%)	11 (6%)
Alkylating monotherapy	14 (6%)	9 (4%)
Other	33 (14%)	38 (16%)
Baseline cytogenetics†		
Deletion 11q	15 (6%)	12 (5%)
Deletion 17p	7 (3%)	4 (2%)
Deletion 6q or 12q trisomy or deletion 13q	44 (18%)	16 (7%)
No aberration	150 (63%)	171 (72%)
Missing	22 (9%)	33 (14%)
IgHV mutational status		
Mutated	47 (20%)	66 (28%)
Not mutated	129 (54%)	108 (46%)
Not available or missing	62 (26%)	62 (26%)

Data are n (%) or median (range). CLL=chronic lymphocytic leukaemia. BR=bendamustine plus rituximab. FCR=fludarabine, cyclophosphamide, plus rituximab. FR=fludarabine plus rituximab. RCVP=rituximab, cyclophosphamide, vincristine, and prednisolone. IgHV=immunoglobulin heavy chain variable region genes. *Age was calculated from birth date to screening date in years. †12% cutoff (ie, at least 12% of chromosome interphases should have the specific chromosomal abnormality for the patient to be scored as having deletion 11q, deletion 17p, etc).

Table 1: **Baseline demographics and clinical characteristics**

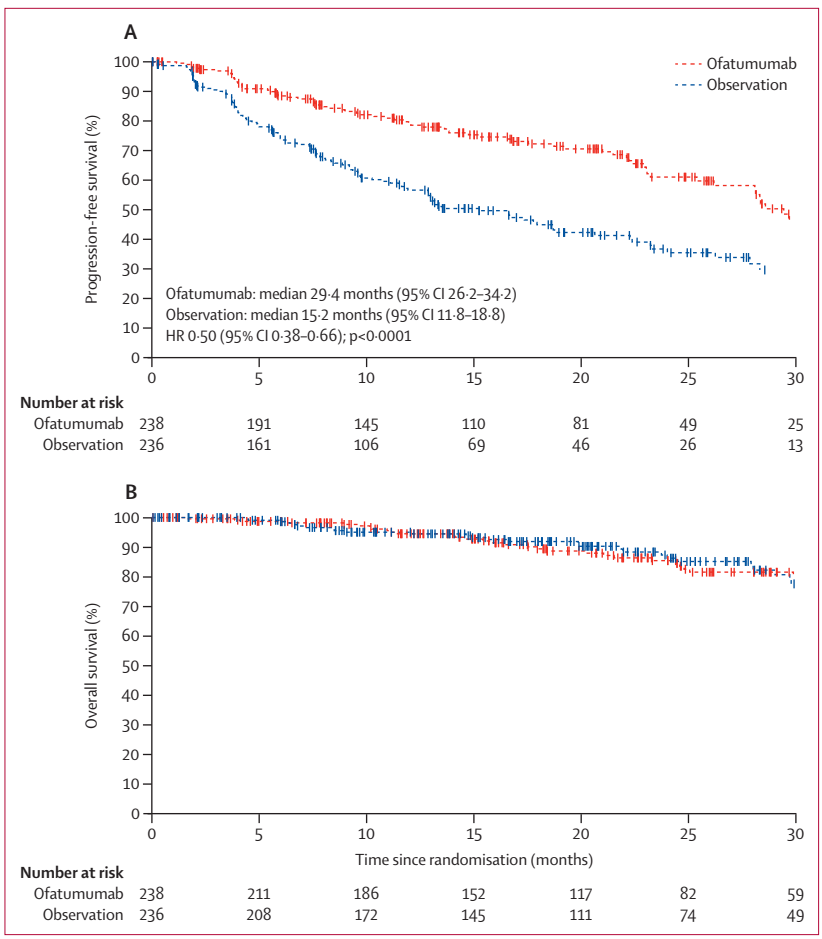

Figure 2: **Kaplan-Meier estimates of progression-free survival (A) and overall survival (B) assessed in the intention-to-treat population**

the study design and interpretation of the data. GlaxoSmithKline was also responsible for data collection and analysis, but had no role in the writing of the report. Graphic support was provided by PharmaWrite (Princeton, NJ, USA) and funded by GlaxoSmithKline. VW and CG had access to the raw data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Between May 6, 2010, and June 19, 2014, 559 patients were screened and 474 patients were enrolled: 238 patients were assigned to the ofatumumab maintenance group and 236 patients were assigned to the observation group (figure 1). Baseline demographics and clinical characteristics were generally well balanced between the groups (table 1). Type of previous treatment was also well balanced between the treatment groups (table 1). 380 (80%) of patients had received chemoimmunotherapy as their most recent previous treatment, and 23 (5%) patients had received alkylating monotherapy as the most recent previous treatment; therefore, the proportion of patients who might have had only alkylators in any treatment line is 5% at most (table 1).

One patient in the ofatumumab group did not receive the allocated intervention (withdrawal of consent) and was not included in the safety analysis of the ofatumumab group but was included in the safety analysis of the observation group. At the time of the prespecified interim analysis (IDMC meeting July 29, 2014), 66 (14%) of 474 patients had died, and disease progression was observed in 190 (40%) patients (figure 1).

At the time of data cutoff on June 16, 2014, median follow-up was 19·1 months (IQR 10·3–28·8). 59 (25%) of 238 patients in the ofatumumab group had received all 13 cycles of ofatumumab and 205 (86%) patients had received all assigned treatment doses. 24 (10%) patients had received between 80% and 100% of the assigned treatment doses and eight (3%) patients had received less than 80% of the expected total dose due to treatment delays and interruptions associated with adverse events, mostly infusion-related reactions, neutropenia, and infections. 78 events were recorded in the ofatumumab group (74 progression and four deaths), whereas 120 events were recorded in the observation group (116 progression and four deaths).

Investigator-assessed progression-free survival by physical examination was longer in the ofatumumab maintenance group than in the observation group (median 29·4 months [95% CI 26·2–34·2] *vs* 15·2 months [11·8–18·8]; HR 0·50 [95% CI 0·38–0·66]; p<0·0001; figure 2). The independent review committee (Parexel International, Waltham, MA, USA) found similar estimates (median 30·4 months [95% CI 25·3–35·6] in the ofatumumab group *vs* 14·8 months [11·3–21·2] in the observation group; HR 0·55 [95% CI 0·42–0·72]; p<0·0001). Results of investigator-assessed progression by CT scan showed marginally shorter progression-free survival in both groups (median 23·7 months [95% CI 22·8–28·9] in the ofatumumab group *vs* 13·5 months [11·4–21·2] in the observation group; HR 0·66 [95% CI 0·50–0·87]; p=0·002) than when assessed by palpated measurements of lymph nodes and organs. There was no difference in overall survival between the groups (HR 0·85 [0·52–1·37] p=0·4877; figure 2). Progression-free survival in all subgroups was consistent with the overall results and did not depend on baseline demographic characteristics (age, sex), remission status at study entry, previous treatments, baseline minimal residual disease, cytogenetic abnormalities, β2M concentration, or mutational status of the immunoglobulin heavy chain variable region genes (figure 3).

Patients who received ofatumumab maintenance treatment had a longer time to next treatment (median 38·0 months [95% CI 28·3–not reached]) than patients in the observation group (median 31·1 months [21·6–not

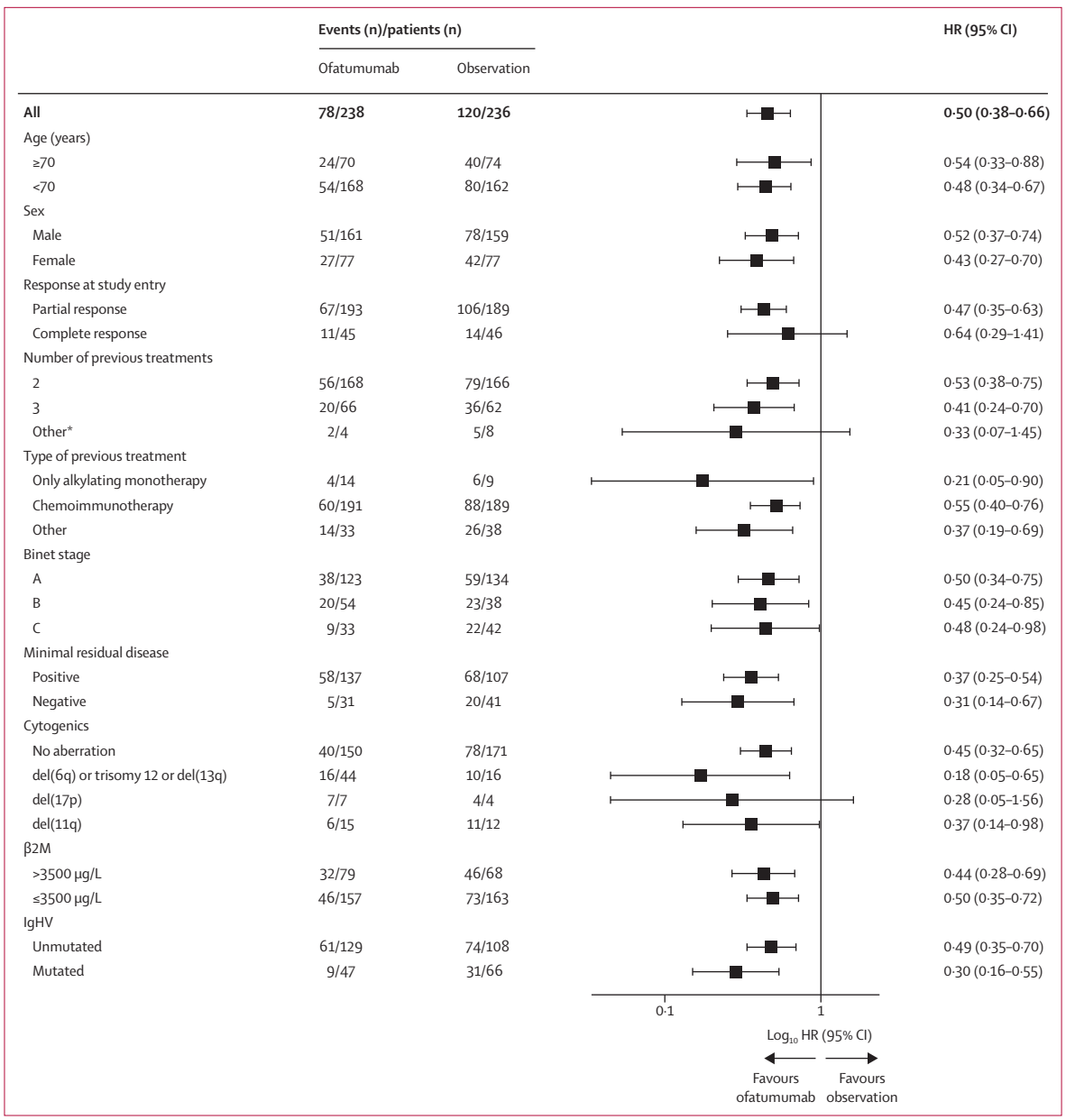

***Figure 3*: Subgroup analysis of progression-free survival**
β2M=β2-microglobulin. IgHV=mutational status of the immunoglobulin heavy chain variable region genes. HR=hazard ratio. *One patient (observation) received one previous treatment; ten patients (three ofatumumab, seven observation) received four previous treatments, and one patient (ofatumumab) received five previous treatments.

reached]; HR 0·66 [95% CI 0·47–0·92]; p=0·011; figure 4). Progression-free survival after next treatment did not differ between patients in each group (HR 1·00 [0·48–2·07]; p=0·9977; figure 4). Patients who did not progress or die after next-line treatment were censored at their last date of contact. The types of next-line treatment given to patients were comparable between study groups, with the exception of the use of next-line ofatumumab for one (2%) of 61 patients in the ofatumumab group who received next-line treatment versus 14 (17%) of 81 patients in the observation group who received next-line treatment (appendix).

Both the total number of adverse events and the number of grade 3 or higher adverse events were higher in the ofatumumab group than in the observation group (table 2). Post-hoc analyses showed an increased incidence of grade 3 or higher neutropenia in the ofatumumab group compared with the observation group (table 2; p=0.0001). Prolonged and severe neutropenia, defined as grade 3 or 4 neutropenia occurring during the treatment

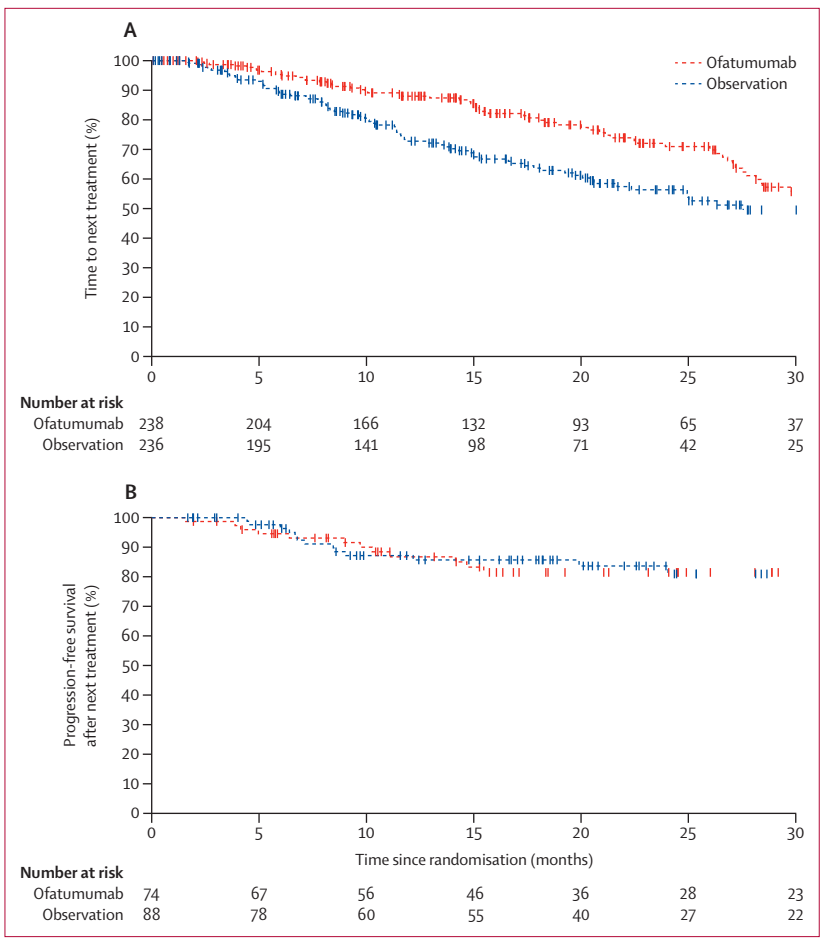

***Figure 4*: Kaplan-Meier estimates of time to next treatment (A) and progression-free survival after next treatment (B)**

period and not resolved at least 42 days after the last dosing date, was more prevalent in the ofatumumab group (13 [5%] of 237 patients) than in the observation group (five [2%] of 237 patients). The increase in both incidence and duration of severe neutropenia probably contributed to the observed increase in grade 3 or higher infections (31 [13%] of 237 patients in the ofatumumab group *vs* 20 [8%] of 237 patients in the observation group; p=0·11; table 2). Growth factor support (G-CSF) was used in 42 (18%) patients in the ofatumumab maintenance group and in 17 (7%) patients in the observation group. Serum immunoglobulin concentrations, which were lower than normal in both study groups at study entry, did not change during treatment with ofatumumab (data not shown); by contrast, serum concentrations of IgM but not that of IgG and IgA, increased during follow-up (data not shown). Peripheral blood B cells started to recover 3 months after the end of ofatumumab maintenance treatment but had not yet reached normal levels by the end of follow-up (data not shown). Adverse events that led to permanent discontinuation of treatment were reported in 20 (8%) patients in the ofatumumab group and in three (1%) patients in the observation group. During the period between the first dose and 60 days after last dose, two (1%) patients in the ofatumumab group died due to adverse events (one sepsis and one bowel obstruction), and five (2%) patients in the observation group died due to adverse events (one progressive disease, one pneumonia, one cardiac arrest, one fall, one subdural haematoma in setting of supratherapeutic INR and sepsis); no deaths were attributed to the study drug. 31 (47%) of the 66 deaths were due to progressive disease. We detected no Richter transformations in the ofatumumab group and two Richter transformations in the observation group.

We found no clinically relevant differences in health-related quality of life between the groups at any timepoint during treatment. With the EORTC QLQ-C30 (global health status domain), we detected a mean reduction from baseline to end of treatment of 0·2 points (SD 38·5) in the ofatumumab group and a mean reduction of 1·9 points (38·5) in the observation group. With respect to the B-symptom index, a repeated measures analysis of all timepoints showed that patients in the ofatumumab group had no change in symptoms from baseline to end of 2 years of treatment (mean points change 0·01 [27·7]), whereas patients in the observation group reported a worsening of symptoms (mean points change 2·8 [26·2]; p=0·002). When patients were asked about worry for future health in the QLQ-CLL16 questionnaire, patients who had been treated with ofatumumab were less worried than patients in the observation group (four point difference, p=0·06).

Discussion

Our data indicate that ofatumumab maintenance treatment improved both progression-free survival and time to next treatment in patients with relapsed chronic lymphocytic leukaemia who are in partial or complete remission after re-induction treatment. Ofatumumab was well tolerated when given intravenously once every 8 weeks at a dose of 1000 mg and did not cause unexpected toxic effects. The progression-free survival benefit was independent of baseline demographic characteristics, remission status at study entry, prior treatments, cytogenetic abnormalities, and mutational status of the immunoglobulin heavy chain variable region genes. Furthermore, ofatumumab maintenance did not increase the risk of Richter transformation and did not negatively affect health-related quality of life.

The results from the cytogenetic subgroups have to be interpreted with caution because of the low number of patients, notably in the del(17p) and del(11q) subgroups. Moreover, a subset of patients without cytogenetic abnormalities undoubtedly will have chromosomal aberrations because most patients were in partial remission or complete remission at study entry, and numbers of circulating malignant cells might have been too low to detect rare cytogenetically abnormal clones.

	Ofatumumab (n=237)				Observation (n=237)			
	Grade 1/2	Grade 3	Grade 4	Grade 5	Grade 1/2	Grade 3	Grade 4	Grade 5
Neutropenia	10 (4%)	33 (14%)	23 (10%)	0	4 (2%)	13 (5%)	10 (4%)	0
Cough	48 (20%)	2 (1%)	0	0	22 (9%)	0 (0%)	0	0
Upper respiratory tract infection	42 (18%)	3 (1%)	0	0	22 (9%)	1 (<1%)	0	0
Pyrexia	33 (14%)	4 (2%)	0	0	22 (9%)	2 (1%)	0	1 (<1%)
Pneumonia	9 (4%)	11 (5%)	5 (2%)	1 (<1%)	5 (2%)	9 (4%)	1 (<1%)	3 (1%)
Fatigue	27 (11%)	0 (0%)	0	0	16 (7%)	0	0	0
Diarrhoea	32 (14%)	1 (<1%)	0	0	9 (4%)	0	0	0
Infusion-related reaction*	36 (15%)	3 (1%)	0	0	0	0	0	0
Bronchitis	19 (8%)	2 (1%)	0	0	15 (6%)	1 (<1%)	0	0
Thrombocytopenia	15 (6%)	2 (1%)	2 (1%)	0	7 (3%)	5 (2%)	5 (2%)	0 (0%)
Rash	22 (9%)	1 (<1%)	0	0	10 (4%)	0	0	0
Sinusitis	17 (7%)	2 (1%)	0	0	11 (5%)	0	0	0
Arthralgia	16 (7%)	1 (<1%)	0	0	11 (5%)	1 (<1%)	0	0
Pruritus	20 (8%)	1 (<1%)	0	0	7 (3%)	0	0	0
Respiratory tract infection	11 (5%)	1 (<1%)	0	0	13 (5%)	0	1 (<1%)	1 (<1%)
Headache	20 (8%)	1 (<1%)	0	0	5 (2%)	0 (0%)	0	0
Herpes zoster	10 (4%)	3 (1%)	0	0	7 (3%)	1 (<1%)	0	0
Back pain	11 (5%)	1 (<1%)	0	0	8 (3%)	0 (0%)	0	0
Urinary tract infection	8 (3%)	1 (<1%)	0	0	7 (3%)	1 (<1%)	1 (<1%)	0 (0%)
Insomnia	12 (5%)	1 (<1%)	0	0	5 (2%)	0	0	0
Dyspnoea	9 (4%)	1 (<1%)	0	0	5 (2%)	0	0	1 (<1%)
Asthenia	6 (3%)	1 (<1%)	0	0	9 (4%)	0	0	0
Hypertension	7 (3%)	3 (1%)	0	0	5 (2%)	0	0	0
Febrile neutropenia	2 (1%)	5 (2%)	3 (1%)	0	0	3 (1%)	1 (<1%)	0
Hypogammaglobulinaemia	9 (4%)	2 (1%)	0	0	0	2 (1%)	0	0
ALT increased	7 (3%)	1 (<1%)	0	0	2 (1%)	0	0	0
Decreased appetite	7 (3%)	1 (<1%)	0	0	1 (<1%)	0	0	0
Weight decreased	2 (1%)	1 (<1%)	0	0	5 (2%)	0	0	0

Data are n (%), as reported by investigator. Reporting period was from first dose to 60 days after last dose. ALT=alanine aminotransferase. *Infusion-related reactions were defined as events occurring during infusion or within 24 h after completion of infusion and included chills, dyspnoea, flushing, hypotension, nausea, pain, pruritus, pyrexia, rash, and urticaria.

***Table 2*: Treatment-related adverse events occurring in at least 2% of patients (any grade) by preferred term**

Unfortunately, cytogenetic data before last re-induction treatment before study entry were not available. Because the percentage of missing data of the mutational status of the immunoglobulin heavy chain variable region genes was comparable in both study groups and many patients could still be analysed, we find it valid to conclude that progression-free survival benefit of ofatumumab maintenance treatment is independent of the mutational status of these genes.

Although there is no way to know or address any selection bias by the individual investigators or institutions, we find it reasonable to assume that younger, high-risk patients with chronic lymphocytic leukaemia (del[17p] or fludarabine refractory, or both) will not have been considered for participation in our study because they are candidates for other treatment modalities, notably allogeneic stem-cell-transplantation or kinase inhibitors.

Two other randomised phase 3 trials of anti-CD20 antibody maintenance treatment have been reported.[13,22] A Chinese trial[13] included 201 patients with chronic lymphocytic leukaemia who had been newly diagnosed or previously treated. These patients were treated with rituximab maintenance for 2 years (first year 375 mg/m² monthly, second year 375 mg/m² every 3 months) after induction treatment with fludarabine, cyclophosphamide, plus rituxmab. Rituximab maintenance treatment was found to improve progression-free survival and overall survival only in high-risk patients (del[11q], del[17p]). The discrepancy with our results might partly be explained by a difference in the proportion of patients in complete remission at the start of maintenance treatment (71% in the Chinese study[13] *vs* 19% in our study), the difference in the maintenance schedule, and the fact the former study included an unknown number of previously untreated patients. The interim analysis of a European trial of rituximab maintenance treatment in 263 patients with chronic lymphocytic leukaemia (81% after first-line

treatment and 19% after second-line treatment), showed a progression-free survival at 17·3 months of 85·1% in the rituximab group versus 75·5% in the observation group (p=0·007).[22] Thus, in addition to our study these data support the beneficial clinical effect of maintenance treatment with an anti-CD20 monoclonal antibody in chronic lymphocytic leukaemia. With only 19·1 months of median follow-up and the availability of effective salvage treatments on relapse, the absence of an effect of ofatumumab maintenance on overall survival is not unexpected.

Remarkably, the interval between progression and next treatment in our trial seems to be longer in the observation group than in the ofatumumab maintenance group (figure 2 and figure 4). Although a more rapid disease progression in the ofatumumab group cannot be excluded, a possible difference in the biology of the relapse is not supported by the observed similar progression-free survival after next treatment in both study groups (figure 4). In chronic lymphocytic leukaemia, like in all indolent B-cell malignancies, progression per se is not an indication for next treatment, which might explain the prolonged time to next treatment compared with progression-free survival. Because time to next treatment is sensitive to subjectivity, the investigators, in consultation with their patients, could possibly have had a lower threshold for treatment of progression during or after maintenance treatment than for progression after a period of observation. However, we do not have data to support or reject this interpretation.

The observed increase in grade 3 or higher neutropenia in the ofatumumab maintenance group compared with the observation group was also seen in studies with rituximab maintenance treatment in follicular lymphoma,[4] although the incidence was higher in our study. The high incidence of grade 3 or higher neutropenia is probably due to the baseline prevalence of neutropenia in patients with chronic lymphocytic leukaemia. Infusion-related adverse events were rare.

We have data of B-cell depletion and circulating B-cell counts at different treatment timepoints (baseline, cycle 2 week 9, cycle 2 week 17, etc) but have yet to analyse these data and compare with associated pharmacokinetic data. Results of pharmacokinetics and pharmacodynamics analyses in patients exposed to ofatumumab in relation to number of circulating B cells and clinical endpoints will be the topic of another report.

The clinical benefit of ofatumumab maintenance treatment will probably be important for relapsed patients with chronic lymphocytic leukaemia, notably if the required treatment does not negatively affect quality of life. However this benefit has to be weighed against the costs and toxicity of ofatumumab. We found a rapid decline in progression-free survival and time to next treatment after discontinuation of ofatumumab treatment, suggesting that longer maintenance might increase the clinical benefit. Longer follow-up of all patients, to see whether differences increase or decrease with time, is warranted. The same holds for the interpretation of the overall survival data.

Our data of ofatumumab maintenance are very timely in the present era of novel treatment modalities, notably the BTK and PI3K inhibitors. Although data on long-term safety are limited, continued treatment with these kinase inhibitors until relapse is recommended (ie, using the kinase inhibitors as prolonged maintenance therapy). The emergence of resistant clones with mutations in BTK or the downstream effector PLCγ after 2 years of continuous treatment with a BTK inhibitor[23,24] and Richter transformation[25] have been described. Our data on the progression-free survival and safety of ofatumumab maintenance treatment are important for the future discussions on the optimum maintenance strategies in relapsed chronic lymphocytic leukaemia.

Contributors

MHJvO was responsible for the study design, protocol writing, data analysis, data interpretation, and manuscript writing. KK was responsible for data collection, and manuscript review. LS was responsible for patient enrolment, manuscript review and editing, and approval of the final version of the manuscript. MP was responsible for patient enrolment, discussion of protocol, and review of the manuscript. FO was responsible for the study design, data collection, data interpretation, and manuscript writing and revision. SG was responsible for study conception and design, data interpretation, and critical review of intellectual content. M-DL was responsible for patient enrolment and critically reviewed the manuscript. IG made a substantial contribution to data analysis and interpretation, literature search, and critical review of manuscript content; JP was responsible for literature search, study design, data collection, data analysis, data interpretation, and manuscript writing. VW was responsible for data analyses, and review and revision of the manuscript. SM was responsible for data analysis, data interpretation, and manuscript writing. SL was responsible for conception and design of study, interpretation of data, and critical revision of intellectual content of manuscript. CG was responsible for study conception and design, submission of patient data, data interpretation, and critical review of all aspects of the manuscript and its revision.

Declaration of interests

MHJvO has served on advisory boards of Roche, GlaxoSmithKline, and AbbVie. LS has served on advisory boards and received travel grants and honoraria from GlaxoSmithKline, Roche, Janssen, Gilead, and Sanofi. MP has received research grants from GlaxoSmithKline. CG has served on advisory boards of and received personal fees from Roche, Celgene, GSK, Novartis, and Janssen. IG, JP, VW, and SM are employed by and have an ownership stake in GlaxoSmithKline. SL is employed by and has an ownership stake in Genmab. SG, KK, M-DL, and FO declare no competing interests.

Acknowledgments

This study was a collaboration of GlaxoSmithKline and Genmab with the Dutch-Belgian Cooperative Trial Group for Hematology-Oncology (HOVON) and the Nordic CLL Study Group. We thank the patients and the investigators in the PROLONG study (appendix) for their participation.

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