Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukaemia (COMPLEMENT 1): a randomised, multicentre, open-label phase 3 trial

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Summary

Background Treatment for patients with chronic lymphocytic leukaemia who are elderly or who have comorbidities is challenging because fludarabine-based chemoimmunotherapies are mostly not suitable. Chlorambucil remains the standard of care in many countries. We aimed to investigate whether the addition of ofatumumab to chlorambucil could lead to better clinical outcomes than does treatment with chlorambucil alone, while also being tolerable for patients who have few treatment options.

Methods We carried out a randomised, open-label, phase 3 trial for treatment-naive patients with chronic lymphocytic leukaemia in 109 centres in 16 countries. We included patients who had active disease needing treatment, but in whom fludarabine-based treatment was not possible. We randomly assigned patients (1:1) to receive oral chlorambucil (10 mg/m²) on days 1–7 of a 28 day treatment course or to receive chlorambucil by this schedule plus intravenous ofatumumab (cycle 1: 300 mg on day 1 and 1000 mg on day 8; subsequent cycles: 1000 mg on day 1) for three to 12 cycles. Assignment was done with a randomisation list that was computer generated at GlaxoSmithKline, and was stratified, in a block size of two, by age, disease stage, and performance status. The primary endpoint was progression-free survival in the intention-to-treat population and assessment was done by an independent review committee that was masked to group assignment. The study is registered with ClinicalTrials.gov, number NCT00748189.

Findings We enrolled 447 patients, median age 69 years (range 35–92). Between Dec 22, 2008, and May 26, 2011, we randomly assigned 221 patients to chlorambucil plus ofatumumab and 226 patients to chlorambucil alone. Median progression-free survival was 22·4 months (95% CI 19·0–25·2) in the group assigned to chlorambucil plus ofatumumab compared with 13·1 months (10·6–13·8) in the group assigned to chlorambucil only (hazard ratio 0·57, 95% CI 0·45–0·72; p<0·0001). Grade 3 or greater adverse events were more common in the chlorambucil plus ofatumumab group (109 [50%] patients; *vs* 98 [43%] given chlorambucil alone), with neutropenia being the most common event (56 [26%] *vs* 32 [14%]). Grade 3 or greater infections had similar frequency in both groups. Grade 3 or greater infusion-related adverse events were reported in 22 (10%) patients given chlorambucil plus ofatumumab. Five (2%) patients died during treatment in each group.

Interpretation Addition of ofatumumab to chlorambucil led to clinically important improvements with a manageable side-effect profile in treatment-naive patients with chronic lymphocytic leukaemia who were elderly or had comorbidities. Chlorambucil plus ofatumumab is therefore an important treatment option for these patients who cannot tolerate more intensive therapy.

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Introduction

Treatment of patients with chronic lymphocytic leukaemia who are elderly or have comorbidities is challenging because these patients often cannot tolerate toxic chemotherapy and are therefore not suitable for purine-analogue-based therapies such as fludarabine, cyclophosphamide, and rituximab, the standard of care for young and healthy patients.[1] Alternative approaches have included reduced-doses of fludarabine, cyclophosphamide, and rituximab,[2,3] and bendamustine alone or in combination with rituximab.[4,5] Although these regimens are more tolerable and are effective alternatives, little data exists for use of these treatments in elderly patients and toxic effects are more pronounced than with chlorambucil. Therefore, chlorambucil is the standard of care for many patients with chronic lymphocytic leukaemia.[6,7]

Ofatumumab is a human monoclonal antibody that binds to a membrane-proximal epitope of CD20, distinct from the rituximab-binding site.[8] Ofatumumab induces cell lysis mainly through complement-dependent cytotoxicity, but also through antibody-dependent cellular cytotoxicity and antibody-dependent cellular

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See Online for appendix

For **protocol** see http://www.gsk-clinicalstudyregister.com/study/OMB110911

phagocytosis.[8–13] In clinical trials, ofatumumab monotherapy was active in patients with chronic lymphocytic leukaemia who were refractory to fludarabine and alemtuzumab, irrespective of previous rituximab, and in those with bulky disease.[14,15] The COMPLEMENT 1 study investigated the efficacy and safety of ofatumumab added to chlorambucil compared with chlorambucil monotherapy in patients with previously untreated chronic lymphocytic leukaemia for whom fludarabine-based treatment regimens were considered inappropriate for reasons such as advanced age or presence of a comorbidity.

Methods

Study design

We planned a prospective, randomised, open-label, phase 3 study of patients in 109 centres in 16 countries (appendix). A short version of the protocol is online. At participating centres, we enrolled untreated patients of any age who were diagnosed with chronic lymphocytic leukaemia, had active disease that needed treatment,[16] and for whom fludarabine-based therapy was considered inappropriate. We included only patients who had Eastern Cooperative Oncology Group (ECOG) performance status score 0–2. We excluded patients with chronic or active infections and those taking glucocorticoid drugs (>100 mg per day hydrocortisone, or equivalent for >7 days). The institutional review board or ethics committee of each participating institution approved the study protocol, and each patient provided written informed consent before enrolment.

Randomisation and masking

We randomly assigned (1:1) patients to chlorambucil alone or chlorambucil plus ofatumumab. Randomisation was stratified, in a block size of two, by age (<65 years *vs* ≥65 years), disease stage (Binet A *vs* Binet B *vs* Binet C), and ECOG performance status score (0–1 *vs* 2) with use of a randomisation list that was generated by a central computerised system, operated from GSK Research Triangle Park (NC, USA). No investigator was involved in the generation of the 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. A masked independent review committee assessed the primary efficacy endpoint. Crossover was not allowed between study groups. Patients who had disease progression could receive subsequent therapy according to local standard of care.

Procedures

Study site investigators confirmed the diagnosis of chronic lymphocytic leukaemia through centrally analysed immunophenotyping for CD5, CD19, CD20, CD23, CD79b, and kappa and lambda surface immunoglobulin light chain. Centralised laboratory analyses were: haematology laboratory tests; biochemistry laboratory tests; fluorescent in-situ hybridisation for deletions of 6q, 11q, 13q, 17p, and trisomy 12 (cutoff 20%); immunoglobulin heavy chain mutational status analysis as described by Ghia and colleagues[17] (cutoff 98% homology with immunogenetics database); and β_2-microglobulin. We measured ZAP70 T-cell and B-cell expression by flow cytometry (B-cell cutoff 120 molecules of equivalent soluble fluorochrome per cell; B-cell:T-cell ratio cutoff 0·14). We assessed minimal residual disease in peripheral blood and bone marrow by flow cytometry, as previously described.[18] We established number of comorbidities on the basis of affected, distinct organ system class. In addition, the investigator scored comorbidities with use of the cumulative illness rating scale (CIRS) for geriatrics.[19,20]

Oral chlorambucil was given at a dose of 10 mg/m² per day on days 1–7 of each 28 day cycle in both treatment groups.[21] Stepwise dose reduction for patients who developed chlorambucil-induced neutropenia or thrombocytopenia to 7·5 mg/m² and 5 mg/m² was recommended. Ofatumumab was given intravenously at a fixed dose of 300 mg on the first day of cycle one and 1000 mg on day 8 of cycle one. In subsequent cycles, 1000 mg of ofatumumab was given on day 1. Drugs were given every 28 days for a minimum of three cycles and for up to 12 cycles or until best response, with best response defined as a clinical response that did not improve with an additional three cycles of therapy. Drugs given before ofatumumab infusions included paracetamol, an antihistamine, and a glucocorticoid; the steroids could be reduced or omitted after cycle one if no severe infusion reaction occurred. Prophylaxis with anti-infective drugs, vaccines, allopurinol, antiemetic drugs, and use of granulocyte-colony stimulating factor was at the discretion of the local investigator.

Response to treatment and disease progression was assessed by the local investigator and by a blinded independent review committee according to the updated guidelines from the International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) National Cancer Institute (NCI) working group.[16] Response was assessed at least 2 months after completion of treatment and required a confirmatory bone marrow analysis for patients who had a clinical complete response. Investigators obtained CT scans for patients who had a complete response or partial response on clinical assessment. CT scans were also obtained at time of disease progression to assess validity for determination of disease progression. Investigators carried out post-treatment follow-up assessments on all patients every 3 months for up to 5 years. Minimal residual disease was assessed in bone marrow or, if not available, peripheral blood, 3 months after completion of treatment for patients with a complete response; and, if negative, assessment was repeated in peripheral blood every 3 months thereafter until positive. Assessment of

progression-free survival was based on the Institute of Cancer Research analysis of disease progression with use of blood counts and physical examination data.[16]

Outcomes

Our primary endpoint was progression-free survival—ie, time between randomisation and the date of disease progression or death from any cause. Our secondary endpoints were overall survival, time to progression, overall response rate, complete response rate, time to response, duration of response, time to next therapy, safety assessments, pharmacokinetics, pharmacogenetics, and quality of life. Here we report the primary endpoint, safety results, and results of major secondary efficacy endpoints. We documented non-haematological adverse events and graded according to the NCI Common Toxicity Criteria (version 3); we graded haematological events according to the updated IWCLL NCI working group guidelines.[16]

Statistical analysis

We calculated the planned sample size of 400 patients; (444 assuming a 10% drop out rate) to power the study to detect at least a 50% improvement in progression-free survival (hazard ratio [HR] of 0·67) with the addition of ofatumumab to chlorambucil. A minimum of 259 progression-free events were needed to detect the targeted difference with 90% power and a 5% two-sided α level.

For our analysis of endpoints, we summarised progression-free survival in Kaplan-Meier curves and compared treatment groups with a stratified log-rank test adjusted for randomisation stratification factors. Progression-free survival was censored for patients with two or more missing visits or start of alternative chronic lymphocytic leukaemia treatment before progression or death. We did secondary time-to-event endpoint analyses with Kaplan-Meier estimates. We compared response rates between the treatment groups with use of a Mantel-Haenszel test that was adjusted for stratification factors. For the demographic and efficacy analyses, we included all patients enrolled and grouped patients by treatment to which the patient was randomised to, irrespective of actual treatment received (intention-to-treat analysis set). We did safety assessments, including exposure, in the safety population (safety analysis set); patients were grouped by actual treatment received (figure 1). For sensitivity analyses, we assessed progression-free survival with CT scan, calculated investigator-assessed progression-free survival, and calculated event-free survival (appendix).

Role of the funding source

The trial was planned, initiated, and sponsored by GlaxoSmithKline and Genmab A/S with the intention to use the data for the approval of ofatumumab for front-line treatment of chronic lymphocytic leukaemia for regulatory agencies. The sponsor was responsible for data gathering and pharmacovigilance, shared safety data during the study with the corresponding author, contributed to the preparation and review of the report and to final approval of the report for submission of the publication. The sponsor and the authors were responsible for data analysis and interpretation. The corresponding author had full access to all the data in the study and all authors approved the manuscript for submission for publication. The corresponding author had final responsibility for the decision to submit for publication.

Results

Between Dec 22, 2008, and May 26, 2011, we randomly assigned 447 patients; 221 to chlorambucil plus ofatumumab and 226 to chlorambucil monotherapy (figure 1). Treatment groups were well balanced (table 1). Median age was 69 years (range 35–92), with 307 (69%) patients older than 65 years and 221 patients (49%) older than 70 years (table 1). Most (391 [87%]) patients reported at least one comorbidity; the most frequently affected organs classes were vascular (245 patients [55%]),

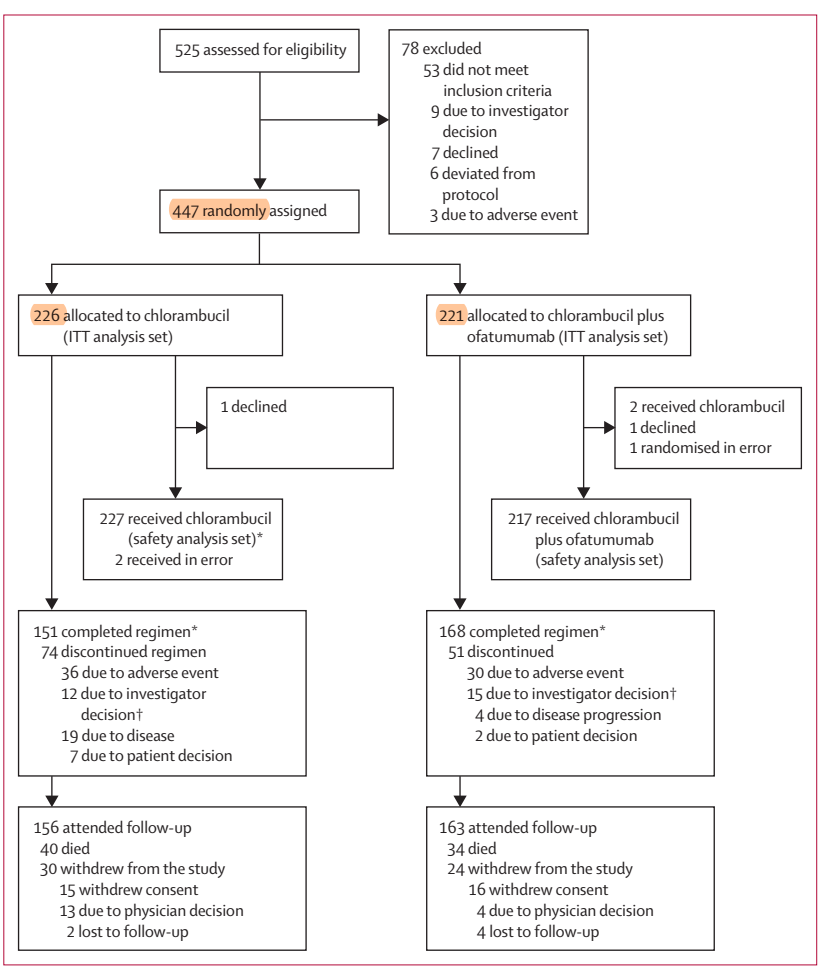

Figure 1: **Study profile**
ITT=intention to treat. *Includes death during treatment (n=5 for both groups). †Includes one patient who had protocol deviation.

metabolic (159 [36%]), musculoskeletal (128 [29%]), respiratory (110 [25%]), gastrointestinal (112 [25%]), and cardiac (95 [21%]). Overall, 389 (87%) patients were 65 years or older or had two or more comorbidities or a reduced creatinine clearance (<70 mL per min; table 1). Investigator-assessed unsuitability for fludarabine was mainly based on advanced age (174 patients [39%]), presence of comorbidities (85 [19%]), or advanced age plus comorbidities (64 [14%]). Patient's choice and medical decision were given as other reasons.

	Group assigned to chlorambucil (n=226)	Group assigned to chlorambucil plus ofatumumab (n=221)	All patients (n=447)
Median age (years)	70 (36–91)	69 (35–92)	69 (35–92)
<65 years	71 (31%)	69 (31%)	140 (31%)
≥65 years	155 (69%)	152 (69%)	307 (69%)
≥70 years	117 (52%)	104 (47%)	221 (49%)
≥75 years	63 (28%)	56 (25%)	119 (27%)
Men	140 (62%)	142 (64%)	282 (63%)
Binet stage			
A	70 (31%)	77 (35%)	147 (33%)
B	87 (38%)	74 (33%)	161 (36%)
C	69 (31%)	70 (32%)	139 (31%)
ECOG performance status			
0	84/224 (38%)	86/221 (39%)	170/445 (38%)
1	121/224 (54%)	118/221 (53%)	239/445 (54%)
2	19/224 (8%)	17/221 (8%)	36/445 (8%)
≥3	0	0	0
B symptoms	120 (53%)	118 (53%)	238 (53%)
≥2 comorbidities	159 (70%)	162 (73%)	321 (72%)
Creatinine clearance <70 mL per min	115 (51%)	99 (45%)	214 (48%)
Age ≥65 years or ≥2 comorbidities or creatinine clearance <70 mL per min	197 (87%)	192 (87%)	389 (87%)
CIRS-G	8 (4–19)	9 (4–21)	9 (4–21)
β_2-microglobulin >3500 mg/L	169/217 (78%)	153/214 (71%)	322/431 (75%)
Un-mutated IGHV	113/203 (56%)	114/201 (57%)	227/404 (56%)
Chromosomal abnormality			
17p deletion	17/216 (8%)	10/209 (5%)	27/425 (6%)
11q deletion (no 17p deletion)	24/216 (11%)	39/209 (19%)	63/425 (15%)
12q or 13q deletion or 6q deletion (no 17p or 11q deletion)	111/216 (51%)	119/209 (57%)	230/425 (54%)
ZAP70			
B-cell positive	110/213 (52%)	100/208 (48%)	210/421 (50%)
Positive B-cell:T-cell ratio	135/213 (63%)	137/208 (66%)	272/421 (65%)
B-cell positive and positive B-cell:T-cell ratio	80/213 (38%)	81/208 (39%)	161/421 (38%)
B-cell negative and negative B-cell:T-cell ratio	48/213 (23%)	52/208 (25%)	100/421 (24%)
B-cell positive or positive B-cell:T-cell ratio (intermediate)	85/213 (40%)	75/208 (36%)	160/421 (38%)

Data are median (range), n (%), or n/number assessed (%), unless otherwise stated. B-cell ZAP70-positive is defined as greater than 120 molecules of equivalent soluble fluorochrome per cell. B-cell:T-cell positive ratio is defined as a ratio of more than 0·14. ECOG=Eastern Cooperative Oncology Group. IGHV=immunoglobulin heavy chain. CIRS-G=Cumulative Illness Rating Scale for Geriatrics.

Table 1: **Baseline characteristics**

In the safety set, the mean number of treatment cycles was 6·4 (SD 2·38) in the ofatumumab group (median 6·0 cycles, range 1–12) and 6·0 (SD 2·71) in the chlorambucil group (median 6·0 cycles, range 1–12). Most patents received six or more cycles (177 [82%] of 217 patients in the ofatumumab group; 159 [70%] of 227 patients in the chlorambucil only group); with about two thirds of patients stopping treatment after six cycles. The median cumulative dose of chlorambucil was 763 mg (range 112–1694) in the ofatumumab group and 728 mg (range 98–1848) in the chlorambucil only. Chlorambucil dose reductions were made in a similar number of patients in both groups (41 [19%] of 217 patients given chlorambucil plus ofatumumab; 43 [19%] of 227 patients given chlorambucil only group), and the frequency of dose delays was also similar (155 (71%) of 217 *vs* 166 [73%] of 227). Taking into account the number of administered treatment cycles, most patients received 100% of the planned chlorambucil dose—185 [84%] of 221 patients given chlorambucil plus ofatumumab; 196 [87%] of 226 given chlorambucil only. For patients who received chlorambucil plus ofatumumab, the median cumulative dose of ofatumumab was 6300 mg (range 5–12 300 mg), with a median dose of 1300 mg (range 5–1300 mg) in the first cycle and a median of 1000 mg (range 131–1000 mg) for all subsequent cycles; with 191 [86%] of 221 patients receiving 100% of the planned total dose based on the number of cycles they received. Median duration of ofatumumab infusion (including incomplete infusion and protocol deviation when infusion was restarted the next day) was 5·2 h for the first infusion (range 1·6 to 29·5 h), 4·4 h (range 0·4–28·1 h) for the second infusion (cycle one; day 8) and 4·2–4·4 h (range 2·3–26·6 h) for all subsequent infusions.

Fewer patients in the group assigned to chlorambucil plus ofatumumab (64 [29%] of 221 patients) received salvage therapy than in the group assigned to chlorambucil alone (100 [44%] of 226). The most common salvage therapy was rituximab alone or in combination (38 [17%] of 221 patients assigned to chlorambucil plus ofatumumab; 69 [31%] of 226 assigned to chlorambucil).

Progression-free survival was significantly improved in the group assigned to chlorambucil plus ofatumumab (median 22·4 months [95% CI 19·0–25·2]) compared wih the group assigned to chlorambucil only (13·1 months [10·6–13·8]; HR 0·57 [95% CI 0·45–0·72], p<0·0001; figure 2A); thus, the study met its primary endpoint. Median progression-free survival was improved by 71%. Progression-free survival was longer with the addition of ofatumumab for most subgroups (figure 3).

Patients with older age showed similar improvement as did young patients in progression-free survival when assigned to chlorambucil plus ofatumumab (HR for patients aged <65 years 0·54 [95% CI 0·34–0·85]; aged ≥65 years 0·57 [0·43–0·76]; and aged ≥75 years 0·56 [0·35–0·89]; figure 3). Assignment to chlorambucil plus

ofatumumab resulted in a longer progression-free survival than did assignment to chlorambucil in patients with known risk factors (positive ZAP70, unmutated immunoglobulin heavy chain variable genes, β_2-microglobulin >3500 mg/mL, 11q deletion, and male sex; figure 3). Additionally, we recorded a numerical, albeit non-significant, improvement in patients with 17p deletion assigned to chlorambucil plus ofatumumab (HR 0·46, 95% CI 0·18–1·19). In the predefined sensitivity analysis that used CT scans to confirm progression, findings for progression-free survival were consistent with those for the primary endpoint (23·4 months for group assigned to chlorambucil plus ofatumumab; 14·5 months for group assigned to chlorambucil; HR 0·54, 95% CI 0·41–0·69; p<0·0001).

Patients assigned to chlorambucil plus ofatumumab had a significantly longer time to next therapy than did those assigned to chlorambucil only (median 39·8 months *vs* 24·7 months; HR 0·49, 95% CI 0·36–0·67; p<0·0001; appendix). With a median of 6 months of treatment in both groups, median treatment-free period was about 34 months with chlorambucil plus ofatumumab and 19 months with chlorambucil.

Overall response rate, based on the best overall response as assessed with IRC methods, was higher for patients assigned to chlorambucil plus ofatumumab compared with patients assigned to chlorambucil monotherapy (182 [82%] of 221 patients *vs* 155 [69%] of 226; odds ratio 2·16 [95% CI 1·36–3·42]; p=0·001), with a better complete response rate (32 [14%] of 221 patients *vs* 3 [1%] of 226; appendix). Overall response rates and complete response rates were higher for those assigned to chlorambucil plus ofatumumab than for those assigned to chlorambucil alone across all subgroups, irrespective of age, sex, disease stage, and prognostic factors (appendix).

Baseline flow cytometry analysis samples to confirm CD19-CD5-CD23 cell phenotype were available for 420 of the 447 patients (212 patients assigned to chlorambucil plus ofatumumab; 208 assigned to chlorambucil) and therefore we included these patients in the analysis for minimal residual disease, irrespective of whether follow-up samples were available. Post-treatment samples for minimal residual disease were available from 299 of these 420 patients (167 patients for chlorambucil plus ofatumumab, 132 for chlorambucil). Bone-marrow minimal residual disease assessments were done in patients only to confirm complete response at least 2 months after treatment and were available from 102 patients (66 for chlorambucil plus ofatumumab group, 36 for chlorambucil group). 3 months after the last treatment, 18 (8%) of 212 patients assigned to chlorambucil plus ofatumumab were negative for minimal residual disease, including four (2%) patients who achieved minimal residual disease negativity in bone marrow. By contrast, one (<1%) of 208 patients assigned to chlorambucil only had minimal residual disease negativity

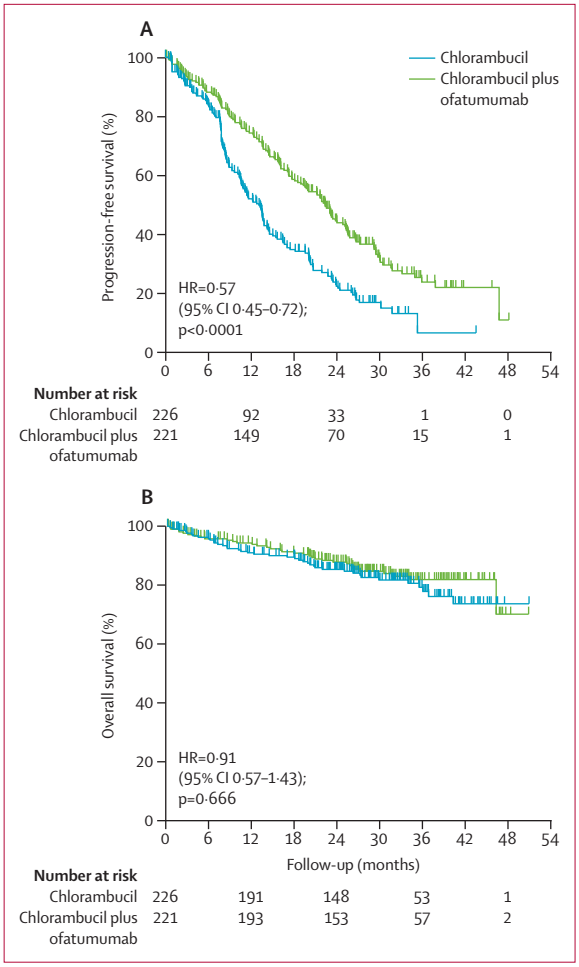

***Figure 2*: Progression-free survival (A) and overall survival (B) by treatment group**
Progression-free survival was defined as the time between randomisation and the date of disease progression or death from any cause; data were censored for patients with two or more missing visits or start of alternative treatment before progression or death. Overall survival was defined as time between randomisation and date of death; patients who had not died by the analysis data cutoff date were censored at their last contact date. HR=hazard ratio.

(none in bone marrow). Negativity for minimal residual disease in bone marrow at 3 months or peripheral blood at 6 months after treatment was documented in 17 (8%) of 212 patients assigned to chlorambucil plus ofatumumab compared with one (<1%) of 208 patients assigned to chlorambucil only. 12 (38%) of the 32 patients assigned to chlorambucil plus ofatumumab with an IRC-assessed complete response achieved minimal residual disease negativity compared with none of three patients assigned to chlorambucil. The median progression-free survival for any of the minimal residual disease negative groups was not reached.

With a median follow-up time of 28·9 months, the endpoint for overall survival was not reached in either treatment group, with 34 (15%) deaths in group assigned to chlorambucil plus ofatumumab (n=221) and 40 (18%)

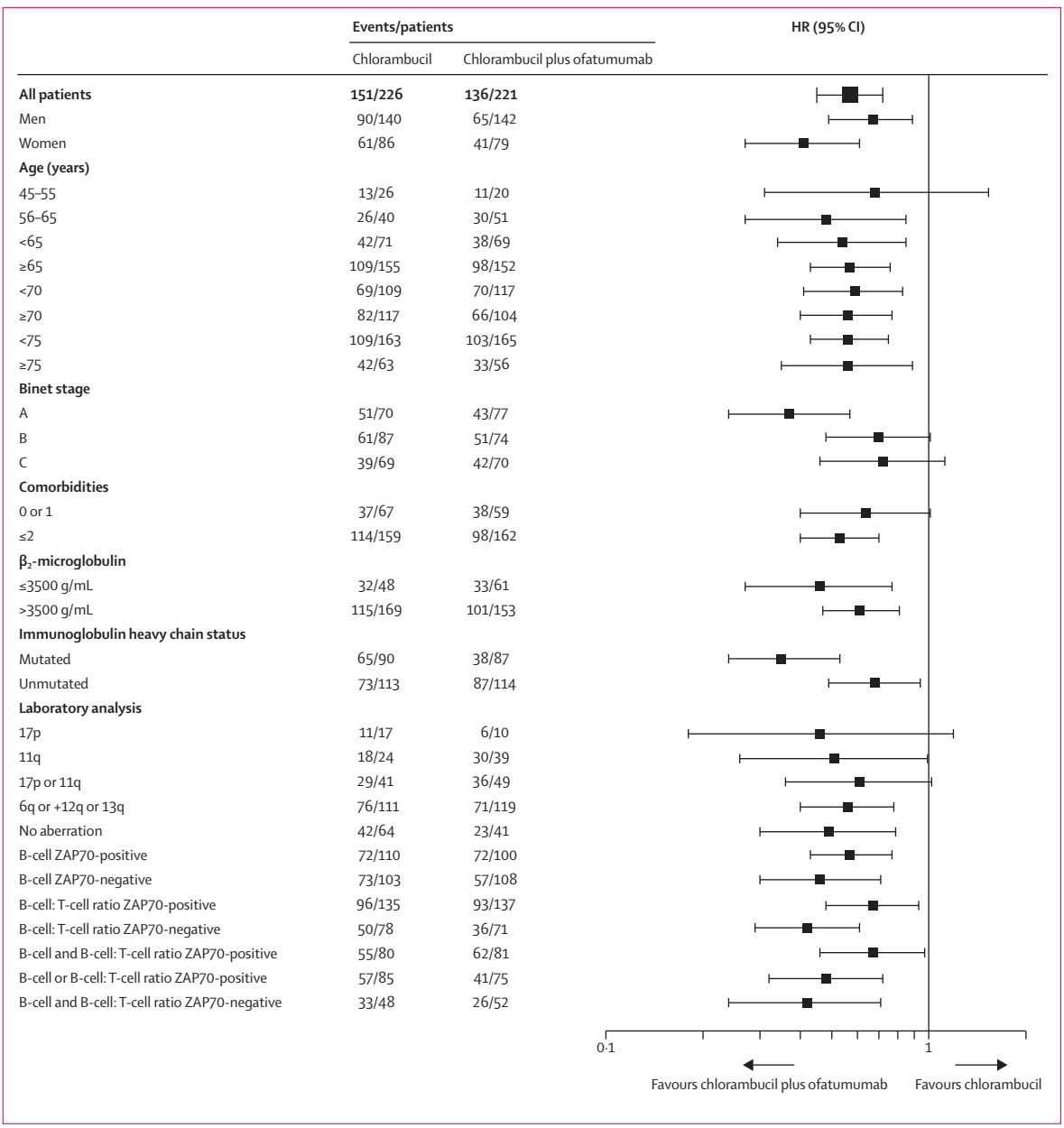

Figure 3: **Treatment effect on progression-free survival in prognostic subgroups**
HR=hazard ratio.

deaths in the group assigned to chlorambucil (n=226; HR 0·91 [95% CI 0·57–1·43], p=0·666; figure 2B). Survival after 2 years was 89% (196 of 221) for patients assigned to chlorambucil plus ofatumumab and 87% (196 of 226) for patients assigned to chlorambucil. 3 year survival was 85% (188 of 221) for the group assigned to chlorambucil plus ofatumumab and 83% (188 of 226) for the group assigned to chlorambucil.

More patients in the chlorambucil plus ofatumumab group had adverse events of any grade and adverse events of grade 3 or higher (table 2). The number of adverse events that led to treatment withdrawal was similar in both groups and frequency was similar for older patient groups compared with the total population (table 2). Neutropenia occurred more frequently in the group given chlorambucil plus ofatumumab, but did not result in a higher rate of infection; whereas thrombocytopenia and anaemia were more frequently reported in the group given chlorambucil alone (table 2). Fewer patients given chlorambucil plus ofatumumab received blood product transfusions (46 patients [21%] who received chlorambucil plus ofatumumab; 66 [29%] who received chlorambucil) but more patients received colony-stimulating factors (60 [28%] patients *vs* 51 [22%]). Administration of

	Group given chlorambucil				Group given chlorambucil plus ofatumumab			
	All patients (n=227)	≥65 years (n=156)	≥70 years (n=118)	≥75 years (n=64)	All patients (n=217)	≥65 years (n=148)	≥70 years (n=101)	≥75 years (n=53)
Adverse events								
Adverse events, any	197 (87%)	141 (90%)	108 (92%)	58 (91%)	204 (94%)	141 (95%)	95 (94%)	49 (92%)
Adverse events related to study treatment	148 (65%)	111 (71%)	88 (75%)	48 (75%)	182 (84%)	129 (87%)	88 (87%)	45 (85%)
Adverse events leading to withdrawal of treatment	29 (13%)	24 (15%)	17 (14%)	9 (14%)	28 (13%)	22 (15%)	18 (18%)	9 (17%)
Adverse events grade ≥3	98 (43%)	79 (51%)	59 (50%)	34 (53%)	109 (50%)	87 (59%)	63 (62%)	36 (68%)
Neutropenia								
Neutropenia, all grades	40 (18%)	27 (17%)	19 (16%)	9 (14%)	59 (27%)	46 (31%)	32 (32%)	15 (28%)
Neutropenia grade ≥3	32 (14%)	24 (15%)	18 (15%)	9 (14%)	56 (26%)	44 (30%)	30 (30%)	15 (28%)
Thrombocytopenia								
Thrombocytopenia, all grades	58 (26%)	44 (28%)	35 (30%)	20 (31%)	30 (14%)	24 (16%)	13 (13%)	6 (11%)
Thrombocytopenia, grade ≥3	22 (10%)	16 (10%)	14 (12%)	11 (17%)	10 (5%)	10 (7%)	6 (6%)	3 (7%)
Anaemia								
Anaemia, all grades	30 (13%)	20 (13%)	14 (12%)	9 (14%)	19 (9%)	15 (10%)	10 (10%)	8 (15%)
Anaemia, grade ≥3	12 (5%)	9 (6%)	7 (6%)	4 (6%)	10 (5%)	7 (5%)	2 (2%)	2 (4%)
Infections								
Infections, all grades	104 (46%)	79 (51%)	61 (52%)	31 (48%)	91 (42%)	66 (45%)	46 (46%)	29 (55%)
Infections, grade ≥3	27 (12%)	23 (15%)	18 (15%)	11 (17%)	20 (9%)	19 (13%)	17 (17%)	10 (19%)
Infusion-related reactions								
Infusion-related reactions, all grades	..	..	..	..	146 (67%)	103 (70%)	67 (66%)	34 (64%)
Infusion-related reactions, grade ≥3	..	..	..	..	22 (10%)	18 (12%)	14 (14%)	8 (15%)

Adverse events as reported by investigator. Reporting period from first dose to 60 days after last dose. Shown are all events with an incidence of 2% or higher of grade ≥3 in all patients. Infusion-related reactions were defined as events that occurred 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: **Incidence of adverse events for each group and by age**

erythropoietin (10 [5%] patients *vs* 14 [6%]) was similar. The most common infections were respiratory tract infections (58 [27%] patients *vs* 71 [31%]). Similar frequencies of sepsis (6 [3%] patients who received chlorambucil plus ofatumumab; 5 [2%] who received chlorambucil) and opportunistic infections (9 [4%] patients *vs* 12 [5%]) were reported in the two groups.

Infusion-related reactions were reported in 146 [67%] of 217 patients given chlorambucil plus ofatumumab and occurred predominantly in cycles one and two, with rash, nausea, and urticaria the most commonly reported events (table 2). Grade 3 and 4 infusion-related reactions were reported in 22 (10%) patients. Reactions led to drug withdrawal in seven (3%) patients and hospital admission in five (2%) patients. No fatal infusion-related reactions were reported. Baseline lymphocyte count was not associated with the incidence or severity of infusion reactions.

Deaths during treatment or within 60 days after the last dose occurred in eight (3%) patients given chlorambucil plus ofatumumab and seven patients (3%) given chlorambucil monotherapy. Causes of death were: pneumonia (n=1), sepsis (n=1), neutropenic sepsis (n=1), respiratory failure (n=1), respiratory failure and hypertension (n=1), cardiac failure (n=1), subdural haematoma (n=1), and disease progression (n=1) in the group given chlorambucil plus ofatumumab; and pneumonia (n=3), pneumococcal sepsis (n=1), cardiac failure (n=2), and sepsis (n=1) in the group given chlorambucil only. Ten deaths occurred during the treatment period (n=5 in each group), and five of these were thought to be related to study drug (three in patients given chlorambucil plus ofatumumab: two in patients given chlorambucil). Over the entire study period, chronic lymphocytic leukaemia caused nine (26%) of 34 deaths in the ofatumumab group and 17 (43%) of 40 deaths in the chlorambucil group.

Discussion

COMPLEMENT 1 is a phase 3 trial for the potential benefit of adding ofatumumab, a CD20 monoclonal antibody, to front-line chlorambucil chemotherapy in patients with chronic lymphocytic leukaemia who cannot tolerate fludarabine-based regimens. Addition of ofatumumab led to a significant benefit in progression-free survival in most subgroups of patients without a major increase in toxic effects.

Baseline disease characteristics of the patients enrolled into COMPLEMENT 1 were representative of untreated patients with chronic lymphocytic leukaemia who do not

Panel: Research in context

Systematic review

From Nov 13, 2007, to July 10, 2008, we searched PubMed with the search terms "CD20 monoclonal antibody", "clinical trial", and "chronic lymphoblastic leukemia", without date or language restrictions. Papers showed encouraging initial results with combination anti-CD20 monoclonal antibodies and chemotherapy (fludarabine with or without cyclophosphamide) compared with chemotherapy alone.[25,26] However, there had been little success with fludarabine-based chemoimmunotherapies for elderly patients with chronic lymphocytic leukaemia[6] and a systematic review of treatment options for elderly patients emphasised the need for special considerations and the absence of options for chemoimmunotherapy for this population.[27] Two phase 2 studies of combination chlorambucil and rituximab had been initiated[28,29] but in the absence of a large randomised phase 3 study, we designed this study with ofatumumab for further assessment of chemoimmunotherapy with chlorambucil, allowing for direct comparison to chlorambucil monotherapy.

Interpretation

Our data suggests that ofatumumab added to chlorambucil is an effective and well tolerated treatment for patients with previously untreated chronic lymphocytic leukaemia who cannot tolerate fludarabine-based therapy due to advanced age or presence of comorbidities. Together with the recently published data for obinutuzumab[22] or rituximab[22,28,29] added to chlorambucil, we view immunochemotherapy with anti-CD20 drugs and chlorambucil as an important treatment option for elderly patients with previously untreated chronic lymphocytic leukaemia.

receive fludarabine as first-line treatment in clinical practice. Most patients were age 65 years or older and had at least two comorbidities or reduced renal function. Although the median ages of patients in several other studies of a similar population have been higher than was the 69 years reported here,[6,22] eligibility in COMPLEMENT 1 was not restricted by age since treatment decisions should be driven by physiological considerations rather than chronological age.[1] Similarly, COMPLEMENT 1 did not restrict eligibility by a comorbidity scale such as CIRS. Several different comorbidity scales, including several CIRS scales, have been developed; however, none is uniformly used in clinical practice and none have been validated for oncology or haematology. COMPLEMENT 1 documented baseline comorbidity with the CIRS for geriatrics[19,20] but did not use this to decide eligibility, whereas the similar trial CLL 11 (discussed later) used the CIRS-modified scale[23] to establish eligibility. Therefore, comparison of the study populations with cumulative illness rating scale scores is not possible.

COMPLEMENT 1 trial met its primary endpoint—chlorambucil plus ofatumumab significantly improved progression-free survival compared with chlorambucil alone. HRs from predefined sensitivity analyses were similar to those from the primary analysis, showing robustness of data. Multivariable analysis showed that treatment with chlorambucil plus ofatumumab was an independent prognostic factor for progression-free survival, and significant improvements were shown in most subgroups. Median progression-free survival for patients aged 45–55 years was longer than that for any other subgroup in both treatment groups, but particularly in patients assigned to chlorambucil; the reason for this observation is unclear. Chlorambucil plus ofatumumab also prolonged time until next treatment for chronic lymphocytic leukaemia by 15 months. Replacement of lesion dimensions measured by palpation with dimensions determined by CT scan led to no significant difference in progression-free survival findings. Therefore, COMPLEMENT 1 supports previous retrospective findings that use of CT scans for the detection of progression or relapse in trials with chemotherapy is of little value.[24]

At the start of the study, no treatment had been shown to be superior to chlorambucil in elderly patients or those with a comorbidity with chronic lymphocytic leukaemia (panel).[25–29] Although Knauf and colleagues[5,29] reported that bendamustine was more effective than was chlorambucil, the median age in this study was lower than that of patients in COMPLEMENT 1 and patients' comorbidity burden was not reported.[5,30] In this population, two phase 2 studies showed the feasibility of addition of rituximab to chlorambucil, but did not directly compare with chlorambucil monotherapy.[28,29] More recently, the German Chronic Lymphocytic Leukaemia Study Group's trial CLL 11 (done in parallel with COMPLEMENT 1) has shown that a combination of the CD20 antibody drugs obinutuzumab or rituximab with chlorambucil resulted in better efficacy than with use of chlorambucil alone in less fit patients.[22] Chlorambucil monotherapy has been used as a comparator for several randomised studies and has shown varying results for median progression-free survival, ranging from 8 months to 20 months.[5,6,21,22,31,32] Several factors might account for these differences, including fitness and age of patients; different methods used by researchers to collect, process, and analyse data; and the regimen of chlorambucil dosing. In the absence of a standard chlorambucil regimen, investigators have used several different schedules, some with intermittent dosing (0·4–0·8 mg/kg on days 1 and 15, per cycle) whereas others have used a more intense dosing regimen (10 mg/m², day 1–7). We chose intermittent dosing for COMPLEMENT 1 on the basis of available data at the time of design that suggested that this regimen would provide the best benefit to risk ratio for the target population; however, other chlorambucil regimens have since shown successful combination with anti-CD20 antibodies.[22,29] In addition to differences in chlorambucil dosing, dosing of the anti-CD20 antibodies also differs between studies; in COMPLEMENT 1 the median cumulative antibody dose was 6300 mg (with 1300 mg in the first cycle), compared with CLL 11 in which patients received a median cumulative dose of obinutuzumab of 8000 mg (3000 mg in the first cycle) or a median cumulative dose of rituximab of 5106 mg (375 mg/m² in the first cycle).[22] Consequently, meaningful comparisons for the efficacy of the treatment group between individual studies is difficult because of differences in study populations, study conduct, and methodology dosing of the reference therapy and dosing of the anti-CD20 component.

The regimen of chlorambucil plus ofatumumab eradicated residual disease in some patients. Cross-study comparison of results for minimal residual disease poses a challenge due to differences in assessment timepoints, specimen (blood or marrow), analytical methods used, and differences in the patients who constitute the reference population in the denominator (all patients, all patients with residual disease samples, or those who achieve complete response). Although standardisation of the methodology for minimal residual disease has been done,[18,33] standardised criteria for selection of patients who should undergo assessment are needed to draw clear comparable conclusions about the efficacy of eradication of minimal residual disease. Here we report the eradication rate of minimal residual disease as the proportion of all analysable patients rather than as a proportion of patients with minimal residual disease samples available or selected for good response, and we used as the denominator all patients in whom minimal residual disease could be measured, even if subsequent response samples were not tested.

Over the study's median follow-up of 29 months, chlorambucil plus ofatumumab did not significantly improve survival compared with chlorambucil (figure 2B). By contrast, a survival advantage was shown for rituximab added to fludarabine and cyclophosphamide chemotherapy in fit patients in the German group CLL 8 trial (3 year overall subvival[34]) and for obinutuzumab (but not rituximab) added to chlorambucil in elderly patients and patients with comorbidities in the German group CLL 11 trial after about 3 years follow-up.[22] Although it is difficult to compare directly the results of these studies, and bearing in mind that overall survival data for both studies is still immature, there is no clear explanation why chlorambucil plus ofatumumab does not currently show a significant overall survival advantage compared with chlorambucil. However, although 3 year overall survival in the anti-CD20 plus chlorambucil groups are similar (85% in COMPLEMENT 1; about 70–80% in CLL 11), greater discrepancy exists between the 3 year overall survival for the chlorambucil groups (83% in COMPLEMENT 1; about 60–70% in CLL 11). Because the 3 year overall survival was so high in the group assigned to chlorambucil, longer follow-up might be needed to establish whether a survival advantage for chlorambucil plus ofatumumab will emerge in COMPLEMENT 1. Similarly, longer follow-up might also show an overall survival benefit for patients who had a negative status for minimal residual disease after being assigned chlorambucil plus ofatumumab, as was recently demonstrated in the CLL 8 study.[35]

Because of its favourable safety profile, chlorambucil monotherapy is a valid treatment choice for elderly patients with comorbidities. For this population especially, the addition of drugs to improve efficacy must not compromise tolerability. Findings from COMPLEMENT 1 show that addition of ofatumumab to chlorambucil has an acceptable safety profile and is well tolerated. Toxic effects attributable to chlorambucil are not exacerbated, as shown by the same number of chlorambucil dose reductions and similar numbers of treatment withdrawals due to adverse events in both groups (table 2). Furthermore, addition of ofatumumab to bendamustine was also recently shown to be a safe and efficacious combination for the treatment of patients with chronic lymphocytic leukaemia who were elderly or had comorbities.[36]

Intravenous administration of all monoclonal antibodies carries the risk of causing severe infusion-related reactions, which, although treatable, can be poorly tolerated by some patients, especially elderly patients or those with comorbidities. In COMPLEMENT 1, these reactions with ofatumumab were mostly mild and did not lead to more treatment withdrawals in this group than in that given chlorambucil. The addition of ofatumumab did result in a higher rate of neutropenia; however, this did not translate into a higher infection rate (table 2). Fewer patients in the group that received chlorambucil plus ofatumumab had thrombocytopenia and anaemia than in the one that received chlorambucil alone, suggesting ofatumumab could benefit myelosuppression due to chronic lymphocytic leukaemia.

One limitation of COMPLEMENT 1 is the absence of a rituximab plus chlorambucil comparison group, which would have addressed whether chlorambucil plus ofatumumab is better than chlorambucil plus rituximab. Efficacy results from recently published studies of chlorambucil plus rituximab in previously untreated, elderly patients with chronic lymphocytic leukaemia vary with overall response rates ranging from 65% to 84%[22,28,29] and median progression-free survival ranging from 16·3 months to 34·7 months.[22,28,29] Due to this variability and the aforementioned differences in study design, cross-trial comparison and interpretation of ofatumumab's efficacy relative to rituximab in combination with chlorambucil is difficult. Efficacy comparison of ofatumumab with obinutuzumab in combination with chlorambucil is even more difficult because of the immaturity of data in CLL11 and COMPLEMENT 1. For the same reasons, comparison of safety data for ofatumumab, rituximab, and obinutuzumab should be done cautiously. With the data currently available, incidence and severity of neutropenia and infections seem reasonably similar after all three anti-CD20 antibodies treatments when combined with chlorambucil whereas grade 3 or higher infusion-related-reactions seem to have occurred more regularly with obinutuzumab than with rituximab or ofatumumab.[22]

With the findings of COMPLEMENT 1 and CLL 11, clinical evidence from two randomised controlled studies clearly show that addition of an anti-CD20 antibody to chlorambucil results in a significant improved efficacy outcome compared with chlorambucil monotherapy. More research is warranted to establish whether and how ofatumumab and obinutuzumab differentiate from each other and from rituximab; to establish if one antibody is more suitable for a specific patient subgroup; and to explore which chlorambucil backbone regimen is the most complimentary to anti-CD20 antibody therapy.

Contributors

PH contributed in the design of the trial, recruitment of patients, monthly teleconferences throughout the trial as chief investigator, data collection, data analysis and interpretation, and writing the manuscript. TR contributed to data collection, data analysis, data interpretation, and writing the manuscript. AJ contributed in writing the manuscript. KGB recruited patients in the study from India. JK, SG, MD, and AS contributed to patient recruitment and data review. PP and ARP contributed to patient enrolment, data collection, and writing of the manuscript. EK contributed to patient recruitment, data collection, data interpretation, writing and approving of the last version of the manuscript. TB contributed to screening of patients for the study, patient enrolment (consenting, treating, and monitoring), reviewing data collection with the local clinical research coordinator, reviewing submitted data with clinical monitors, and provided some review of the manuscript. MM contributed to data collection, critical revision of the manuscript, and provided approval of the final version of the manuscript. IVG contributed to data analysis, data interpretation, and writing of the manuscript. As part of the sponsor study team, OW was responsible for aspects of the study design, study management, data collection, and data interpretation. As part of the study team, ID was responsible for aspects of the study design, study management, data collection, and data interpretation. JLC contributed to study design, data interpretation, and writing the manuscript. C-NC was the statistician for this study; she contributed to the design of the study, the writing of the protocol, the data analysis, the interpretation of the data and the writing of the manuscript. SL contributed to conception and design of the study, interpretation of the data for this publication, and critical review of the manuscript for important intellectual content. He had the opportunity to access the data (data tables, final study report, raw data if requested) reported in this manuscript. As GlaxoSmithKline investigation leader for this study (accountable for study conduct), AM contributed to the literature search, figure development, study design, data interpretation, and writing the manuscript. FO contributed to study design, data collection, data analysis and interpretation, writing and reviewing the manuscript.

Declaration of interests

PH's institution (Department of Haematology, St James's University Hospital, Leeds, UK) received payments from GlaxoSmithKline to cover the costs of recruitment for this study. He received personal fees for chairing a data safety monitoring board of an unrelated GlaxoSmithKline-sponsored trial and for attendance at an advisory board. TR reports grants from GlaxoSmithKline, during the conduct of this study. PP reports honoraria and research support from GlaxoSmithKline. EK reports support for the trial from GlaxoSmithKline, compensation for lectures and advisory board from Pfizer, compensation for advisory boards from Pharmacyclics, Janssen, and Gilead. AS reports personal fees from GlaxoSmithKline, Roche, Gilead, Celgene, and NAPP. ARP reports grants and non-financial support from GlaxoSmithKline, during the conduct of this study. Outside the submitted work, ARP reports grants and non-financial support from Celgene and Chugai; grants, personal fees and non-financial support from GlaxoSmithKline, Roche and Napp; grants from AstraZeneca. TB reports speaker and consultant personal fees from Celgene. MM received consultancy and honoraria personal fees from GlaxoSmithKline. IR, OW, IvG, JLC, C-NC, and AM are employees of and shares or stocks holders of GlaxoSmithKline. SL is an employee of Genmab A/S. AJ, KGB, JK, SG, MD, and FO declare no competing interests.

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