First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial

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Summary

Background Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab is the standard therapy for physically fit patients with advanced chronic lymphocytic leukaemia. This international phase 3 study compared the efficacy and tolerance of the standard therapy with a potentially less toxic combination consisting of bendamustine and rituximab.

Methods Treatment-naive fit patients with chronic lymphocytic leukaemia (aged 33–81 years) without del(17p) were enrolled after undergoing a central screening process. Patients were randomly assigned (1:1) with a computer-generated randomisation list using randomly permuted blocks with a block size of eight and were stratified according to participating country and Binet stage. Patients were allocated to receive six cycles of intravenous fludarabine (25 mg/m² per day) and cyclophosphamide (250 mg/m² per day) for the first 3 days or to intravenous bendamustine (90 mg/m² per day) for the first 2 days of each cycle. Rituximab 375 mg/m² was given intravenously in both groups on day 0 of cycle 1 and subsequently was given at 500 mg/m² during the next five cycles on day 1. The primary endpoint was progression-free survival with the objective to assess non-inferiority of bendamustine and rituximab to the standard therapy. We aimed to show that the 2-year progression-free survival with bendamustine and rituximab was not 67·5% or less with a corresponding non-inferiority margin of 1·388 for the hazard ratio (HR) based on the 90·4% CI. The final analysis was done by intention to treat. The study is registered with ClinicalTrials.gov, number NCT 00769522.

Findings 688 patients were recruited between Oct 2, 2008, and July 11, 2011, of which 564 patients who met inclusion criteria were randomly assigned. 561 patients were included in the intention-to-treat population: 282 patients in the fludarabine, cyclophosphamide, and rituximab group and 279 in the bendamustine and rituximab group. After a median observation time of 37·1 months (IQR 31·0–45·5) median progression-free survival was 41·7 months (95% CI 34·9–45·3) with bendamustine and rituximab and 55·2 months (95% CI not evaluable) with fludarabine, cyclophosphamide, and rituximab (HR 1·643, 90·4% CI 1·308–2·064). As the upper limit of the 90·4% CI was greater than 1·388 the null hypothesis for the corresponding non-inferiority hypothesis was not rejected. Severe neutropenia and infections were more frequently observed with fludarabine, cyclophosphamide, and rituximab (235 [84%] of 279 *vs* 164 [59%] of 278, and 109 [39%] *vs* 69 [25%], respectively) during the study. The increased frequency of infectious complications with fludarabine, cyclophosphamide, and rituximab was more pronounced in patients older than 65 years.

Interpretation The combination of fludarabine, cyclophosphamide, and rituximab remains the standard front-line therapy in fit patients with chronic lymphocytic leukaemia, but bendamustine and rituximab is associated with less toxic effects.

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Introduction

Chronic lymphocytic leukaemia, the most common leukaemia in high-income countries, had been considered as incurable by conventional therapies.[1] In general, younger patients with chronic lymphocytic leukaemia have a reduced life expectancy.[1] The introduction of antibody-based chemoimmunotherapy has improved the outcome of younger patients by inducing long-lasting and possibly durable remissions with a median progression-free survival of up to 80 months in subgroups of patients.[2–4] Following the results of a phase 2 study by the MD Anderson Cancer Center[2] and a phase 3 study by the German CLL Group, the CLL8 study,[5] fludarabine, cyclophosphamide, and rituximab have become the

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Research in context

Evidence before this study

We searched PubMed between April 1, 2007, and Jan 31, 2008 for reports with the search terms "CLL", and "clinical trial" and "chemotherapy" and "antibody" without date or language restrictions. Publications showed promising results for chemoimmunotherapy regimens based on purine analogues with or without CD20 antibodies or with the CD52 antibody alemtuzumab. First data from the CLL8 study of the German CLL Study Group presented at the American Society of Hematology Meeting in December, 2007, showed the superiority of the fludarabine, cyclophosphamide, and rituximab regimen over chemotherapy alone. On the other hand, all purine analogue-based combinations were associated with toxic effects. First data from a phase 2 trial evaluating bendamustine and rituximab had favourable results with regard to toxic effects and good efficacy. In 2007, the National Institutes of Health registry for clinical trials listed no clinical trials with a head-to-head comparison of fludarabine, cyclophosphamide, and rituximab with bendamustine and rituximab in chronic lymphocytic leukaemia.

Added value of this study

The CLL10 study is the first trial directly comparing bendamustine-based chemoimmunotherapy with fludarabine and cyclophosphamide-based chemoimmunotherapy. The data confirm data from a meta-analysis suggesting the superiority of fludarabine and cyclophosphamide-based chemoimmunotherapy over bendamustine-based chemoimmunotherapy.

Implications of all the available evidence

In a head-to-head comparison bendamustine and rituximab is less effective than the standard therapy, but can be considered in patients older than 65 years with chronic lymphocytic leukaemia. Higher incidence of adverse events observed with fludarabine, cyclophosphamide, and rituximab in patients older than 65 years and good efficacy with bendamustine and rituximab in this group might support the use of bendamustine and rituximab in fit elderly patients. Moreover, our data show that immunosuppressive effects are long lasting with fludarabine and cyclophosphamide-based therapy. Prophylactic use of co-trimoxazole against *Pneumocystis jirovecii* pneumonia or virostatics against herpes virus infections in patients with previous infections should be considered in patients receiving front-line chemoimmunotherapy.

standard front-line therapy for physically fit patients with chronic lymphocytic leukaemia. However, this regimen is associated with substantial toxic effects, most importantly severe haematotoxicity in 56% of patients and severe infections in 25% of patients during treatment. A long-term follow-up of patients treated with fludarabine, cyclophosphamide, and rituximab showed prolonged neutropenia in 17–35% and an elevated risk of secondary neoplasia.[4,6,7]

The combination of the alkylating agent bendamustine and rituximab has shown promising results in a phase 2 study in front-line therapy of chronic lymphocytic leukaemia with overall responses in 103 (88%) of 117 patients and complete responses in 27 (23%) of 117 patients.[8] Event-free survival of 34 months and low incidence of severe neutropenia (20%) and infections (8%) led to the hypothesis that front-line treatment with bendamustine and rituximab might be similarly effective but less toxic compared with the standard treatment.

Therefore, the German CLL Study Group did an international phase 3 study to test the non-inferiority of bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in front-line therapy of fit patients with chronic lymphocytic leukaemia, but without del(17p).

Methods

Study design and participants

We did a randomised, open-label, phase 3, non-inferiority study in previously untreated fit patients aged 33–81 years with advanced chronic lymphocytic leukaemia who required treatment according to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria[9] and had an Eastern Cooperative Oncology Group (ECOG) status of 0–2.

Treatment-naive patients diagnosed with chronic lymphocytic leukaemia were registered for central screening, which was done by the German CLL Study Group central study office (Cologne, Germany) and included immunophenotyping for confirmation of the diagnosis, fluorescence-in-situ hybridisation (FISH) to determine del(17p) status, evaluation of the comorbidity burden, and renal function. Samples for central immunophenotyping and FISH were assessed at the reference laboratories (Department I for Internal Medicine, University Hospital, Cologne, Germany and the Department of Internal Medicine III, University of Ulm, Germany, respectively). Patients with del(17p) as detected by FISH were excluded. Patients had to have an advanced clinical stage (Binet C) or confirmed active disease requiring treatment.[9] Moreover, a low comorbidity burden as defined by a Cumulative Illness Rating Scale (CIRS)[10] score up to 6, a normal creatinine clearance of at least 70 mL/min, and an ECOG performance status of 0–2 were required for inclusion. Patients with impaired renal function due to an abdominal lymph node mass were eligible after central review. The main exclusion criteria were impaired renal function other than that caused by abdominal lymph node mass, CIRS score less than 6, previous therapy for chronic lymphocytic

leukaemia (except steroids), Richter transformation, detection of del(17p), and active secondary malignancy requiring treatment.

All patients provided written informed consent before central screening was begun. The study was done according to the Declaration of Helsinki.

Randomisation and masking

After the central screening process, eligible patients were randomly assigned (1:1) using a computer-generated randomisation list (Institute for Medical Statistics and Epidemiology, Technical University of Munich, Germany). The randomisation was balanced by the use of randomly permuted blocks with a block size of eight and was stratified according to participating country and Binet stage at pre-therapeutic staging (A *vs* B *vs* C). The assigned treatment group was provided to the German CLL Study Group central study office, and the screening result together with the confirmation of patient randomisation, and allocation to treatment were sent through the German CLL Study Group central study office to the investigators. Investigators and patients were not masked to the treatment assignment.

Procedures

Within the two-group parallel design of this investigator-initiated trial, six cycles of rituximab-based chemo-immunotherapy with fludarabine and cyclophosphamide were compared with six cycles of bendamustine and rituximab. The standard treatment consisted of six 28-day cycles of intravenous fludarabine (25 mg/m² per day) and cyclophosphamide (250 mg/m² per day) on the first 3 days of each cycle. The treatment with bendamustine (90 mg/m² per day) was given intravenously on the first 2 days of each of the six 28-day cycles. Rituximab 375 mg/m² was given to both groups intravenously on day 0 of cycle 1 and subsequently during the next five cycles rituximab 500 mg/m² was given on day 1 of each cycle. According to the protocol, prophylactic use of antibiotics or growth factors was not generally recommended. In cases of severe leukocytopenia with a duration of more than 7 days, prophylaxis for *Pneumocystis jirovecii* pneumonia with co-trimoxazole was recommended.

In patients whose blood counts had not recovered adequately within 28 days or still showed signs of an active infection, the next treatment was postponed and further cycles of therapy continued with a 25% dose reduction. After two dose reductions to a total dose reduction of 50%, treatment was stopped in case there was any further treatment delay due to adverse events.

Baseline disease assessment included physical examination, ECOG performance status, and imaging with CT scans or ultrasound. *IGHV* mutation status was analysed by DNA sequencing at the reference laboratory (Department of Internal Medicine III, University of Ulm, Ulm, Germany). During treatment, blood counts (leucocytes, haemoglobin, thrombocytes, and differential blood count of leucocytes) were measured on a weekly basis, and serum chemistry (creatinine, lactate dehydrogenase, bilirubin, AST, and ALT) at least once before the next treatment cycle.

Response to treatment was classified according to the IWCLL response criteria.[9] Radiographic imaging and blood counts were done at final restaging (ie, 3 months after the beginning of the last treatment cycle). Response and disease progression were assessed by the study investigators and confirmed by a central, investigator-independent medical review. Minimal residual disease status was examined centrally in the reference laboratory (Department of Internal Medicine II, University Hospital of Schleswig-Holstein, Campus Kiel, Kiel, Germany), as previously described.[11] For minimal residual disease status samples of peripheral blood were assessed by four-colour minimal residual disease status flow cytometry with a sensitivity of at least 10^{-4} at study entry, at interim staging, and for final staging in all patients. Infections of any grade and all severe adverse events were reported up to 5 years after treatment. Each adverse event was reported with severity rated in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) criteria (version 3) grades.

An interim assessment was done after three cycles of treatment. Patients who achieved a complete response, partial response, or stable disease, and in whom toxic effects were acceptable, continued treatment for three additional cycles. Patients with progressive disease stopped treatment and were treated outside the study protocol at the discretion of the treating physician. Patients with progressive disease were assessed as non-responders. An assessment of initial response was done 1 month (within 7 days) after the beginning of the last cycle of treatment. The results were confirmed 2 months later by final restaging, which had to be done in all patients receiving at least two treatment cycles. Subsequently, patients completed follow-up examination every 3 months for the first 2 years and every 6 months for the next 3 years. Thereafter, the disease status was assessed annually. Measurement for the presence of minimal residual disease cells in the bone marrow during final restaging was planned for all patients who achieved a clinical complete remission at the initial response assessment. For patients with clinical complete response at final restaging, a peripheral blood minimal residual disease status analysis at 12 and 18 months after final restaging was done.

Outcomes

The primary objective of this study was to show non-inferiority of bendamustine and rituximab compared with the standard treatment of fludarabine, cyclophosphamide, and rituximab with regard to a primary endpoint of progression-free survival, defined as time from randomisation until progression or death

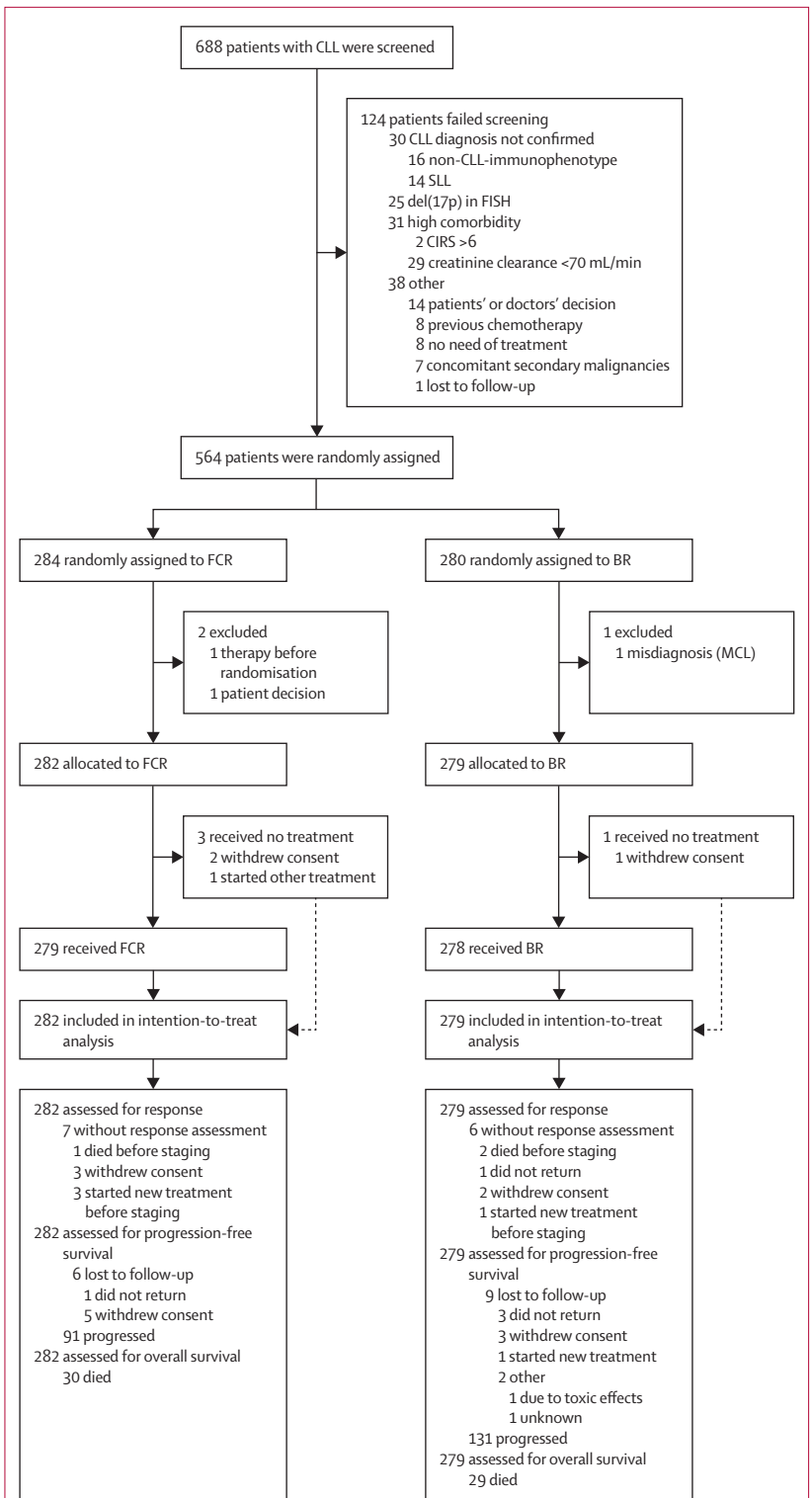

Figure 1: **Trial profile**
CLL=chronic lymphocytic leukaemia. SLL=small lymphocytic lymphoma. FISH=fluorescence in-situ hybridisation. CIRS=Cumulative Illness Rating Scale. GFR=glomerular filtration rate. FCR=fludarabine, cyclophosphamide, and rituximab. BR=bendamustine and rituximab.

from any cause. Progression was assessed by the site investigators and had a systematic investigator-independent medical review based on the IWCLL criteria (progression had to be centrally confirmed before being accepted).[9] Secondary endpoints were: overall survival (defined as time between randomisation until death from any cause); the proportion of patients who achieved an overall response (defined as proportion of patients having achieved a complete remission, complete remission with incomplete marrow recovery, or partial remission as response to study treatment with respect to the intention-to-treat population); minimal residual disease status assessment; the proportion of patients achieving a response in biologically defined risk groups (according to age, sex, Binet stage, *IGHV* status, and cytogenetic subgroup according to the hierarchical model); safety; event-free survival (defined as time from first study treatment to date of the beginning of a new treatment for any haematological maliganancy, disease progression, or death from any cause); duration of remission (defined as the time between date of first response until progression or death from any cause); and quality of life assessment using the EORTC-C30, including the fatigue module.

Statistical analysis

The primary endpoint of progression-free survival was used to calculate the sample size of the study. The non-inferiority hypothesis of bendamustine and rituximab compared with fludarabine, cyclophosphamide, and rituximab was tested by assessing whether the 90·4% CI of the hazard ratio (HR) excluded a predefined non-inferiority margin including the adjustment for one interim analysis using the O'Brien and Fleming method. Based on results from the CLL8 trial[5] and the fludarabine, cyclophosphamide, and rituximab trial of the MD Anderson Cancer Center[2] it was assumed that treatment with fludarabine, cyclophosphamide, and rituximab would lead to a 75·0% progression-free survival at 2 years. We aimed to show that the 2-year progression-free survival with bendamustine and rituximab was not 67·5% or less with a corresponding non-inferiority margin of 1·388 for the HR. 198 progression-free survival events were required to have 80% power (alpha was 0·048, one sided). 511 patients needed to be enrolled with these assumptions. Due to an expected drop-out rate of 10%, we aimed to recruit 550 patients. The interim analysis was done after two-thirds (ie, 132) of the required progression-free survival events. For the primary endpoint analysis the HR including the 90·4% CI was calculated with a multivariable Cox regression analysis under the assumption of proportional hazards adjusted for the stratification factors Binet stage and country. In a second step, a Cox proportional-hazards model with both stepwise forward and backward selection procedures was applied to progression-free survival, including treatment, country, Binet stage, and other prognostic factors, such as

age, sex, total CIRS score, presence of B-symptoms, ECOG status, *IGHV* mutation status, cytogenetics, serum thymidine kinase, and β_2-microglobulin. For factors found to be independent, HRs including 95% CIs were shown. Factors included in the multivariable model were obtained from univariate analyses. Further sensitivity analyses were not done for the primary endpoint analysis.

Time-to-event endpoints including 95% CIs were estimated according to the Kaplan-Meier method and survival curves were compared using two-sided non-stratified log-rank tests. For comparison of the treatment groups, Fisher's exact test or Pearson's χ^2 test (categorical variables) or Wilcoxon rank-sum test (continuous variables) were used. Exploratory post hoc subgroup analyses for progression-free survival and response were done considering the factors age, Binet stage, cytogenetic categories, *IGHV* mutation status, and sex. Methods included two-sided non-stratified log-rank tests and the calculation of HRs including 95% CIs. Additionally, the interaction with study treatment was explored for each factor; a term for the interaction between the factor and the study treatment was included in a Cox regression model. Post hoc matched paired analysis was done for *IGHV* mutation status and progression-free survvial (appendix).

All statistical tests were two-sided and a p value of less than 0·05 was considered significant. Adjustments for multiple comparisons were not considered for analysing secondary endpoints and exploratory subgroup analyses.

All analyses were done in the intention-to-treat population. The results of minimal residual disease status at follow-up were calculated based on the intention-to-treat population and based on those patients for whom a sample at follow-up month 12 and month 18 was available.

Safety analyses were restricted to patients from the intention-to-treat population who received at least one dose of one component of the study treatment. A data and safety monitoring board reviewed the data regularly once randomisation was opened. Analyses regarding quality of life were not part of this analysis and will be done and presented later. Analyses were done using SPSS version 21. The study is registered at ClinicalTrials.gov, number NCT 00769522.

Role of funding source

Roche and Mundipharma funded the study, and the German Ministery for Education and Research financed a subproject related to detailed analysis of infections. The funders had no involvement in the design, data collection, data analysis, data interpretation, or writing of the report. The study sponsor was the University of Cologne; the representative of the sponsor for this study was the German CLL Study Group. The the German CLL Study Group was responsible for study design, data collection, data cleaning, and medical review. The corresponding author was responsible for data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data and the final responsibility to submit for publication.

Results

688 patients with previously untreated but advanced chronic lymphocytic leukaemia were recruited between Oct 2, 2008, and July 11, 2011 from 158 sites, including university hospitals, community hospitals, and private

	Fludarabine, cyclophosphamide, and rituximab (n=282)	Bendamustine and rituximab (n=279)
Age (years)	62·1 (55·0–67·0)	61·0 (54·0–69·0)
>65 years	86 (30%)	108 (39%)
>70 years	28 (10%)	51 (18%)
Sex		
Male	201 (71%)	207 (74%)
Female	81 (29%)	72 (26%)
Median time from diagnosis to study entry (months)	21·6 (4·0–52·6)	24·6 (6·2–50·1)
Binet stage		
A	63 (22%)	62 (22%)
B	105 (37%)	107 (38%)
C	114 (41%)	110 (39%)
Rai stage		
0	7/221 (3%)	11/224 (5%)
I	29/221 (13%)	32/224 (14%)
II	86/221 (39%)	84/224 (37%)
III	44/221 (20%)	34/224 (15%)
IV	55/221 (25%)	65/224 (29%)
ECOG performance status		
0	180/281 (64%)	177/276 (64%)
1	95/281 (34%)	98/276 (36%)
2	6/281 (2%)	1/276 (<1%)
B-symptoms present	116 (41%)	113 (41%)
Median CIRS	2·0 (1·0–3·0)	2·0 (0–3·0)
Total CIRS ≤3	240 (85%)	234 (84%)
Number of involved CIRS categories ≤1	163 (58%)	149 (53%)
Median creatinine clearance (mL/min)	87·0 (71·7–106·9)	86·4 (72·6–101·6)
Thymidine kinase >10 U/L	198/272 (73%)	196/270 (73%)
β_2-microglobulin >3·5 mg/L	84/272 (31%)	103/270 (38%)
Cytogenetic abnormalities		
del(11q)	68 (24%)	63 (23%)
12q+	33 (12%)	32 (11%)
del(13q)	155 (55%)	147 (53%)
Unmutated *IGHV*	152/275 (55%)	183/270 (68%)

Data are median (IQR) or n (%). Rai stage and ECOG were not assessed in all patients; serum samples for thymidine kinase and β_2-microglobulin were not centrally evaluated in all patients because they were not mandatory for inclusion or exclusion; *IGHV* status could technically not be assessed in 16 patients; CIRS was evaluable in all patients. ECOG=Eastern Cooperative Oncology Group. CIRS=Cumulative Illness Rating Scale.

Table 1: **Baseline characteristics of the eligible patients**

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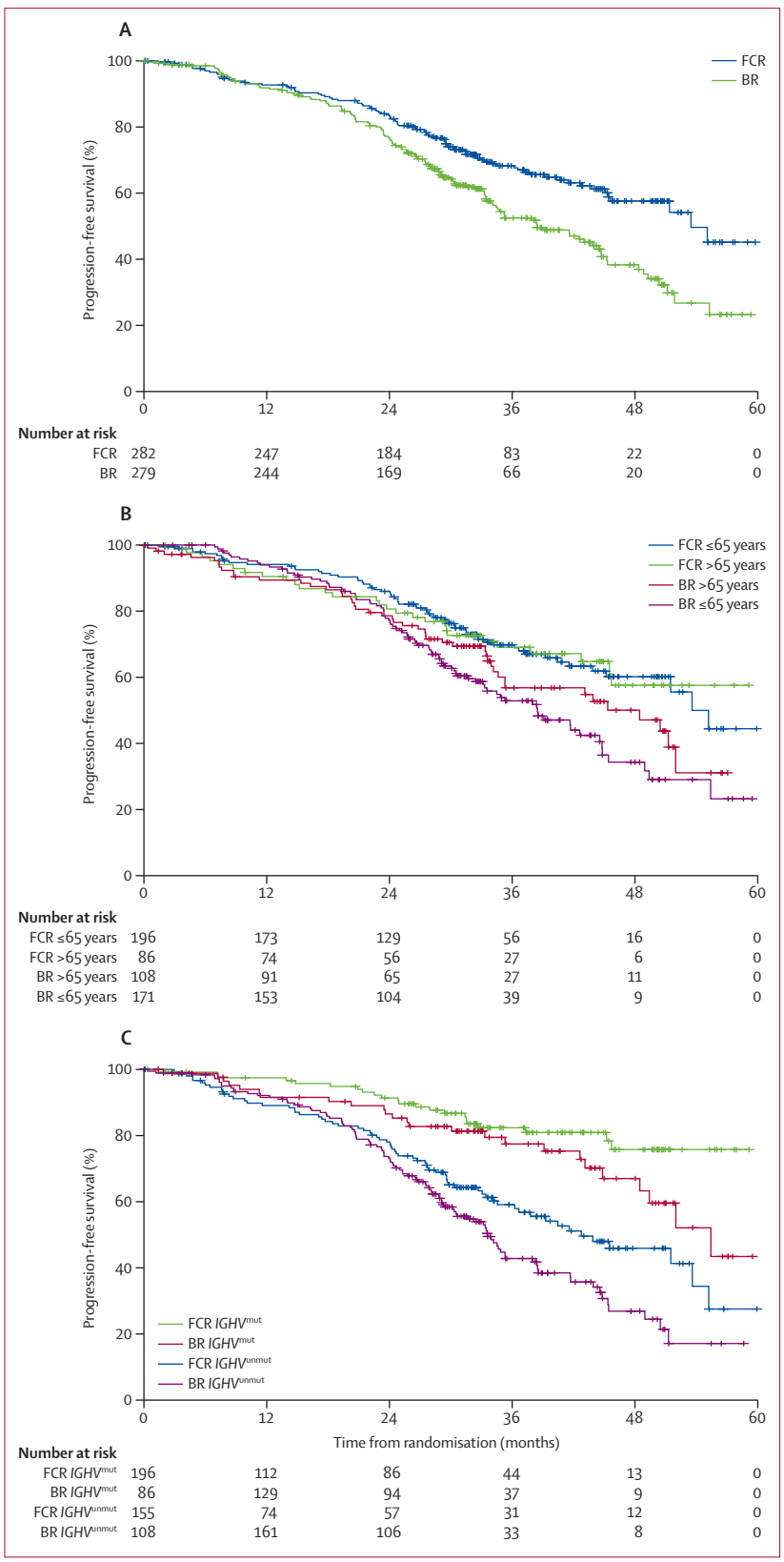

Figure 2: **Progression-free survival**
Progression-free survival according to treatment group (A), treatment group and age group (B), and treatment group and *IGHV* mutational status (C). FCR=fludarabine, cyclophosphamide, and rituximab. BR=bendamustine and rituximab. *IGHV*^{mut}=mutated *IGHV*. *IGHV*^{unmut}=unmutated *IGHV*.

oncology practices in five countries (Germany, Austria, Switzerland, Denmark, and Czech Republic), participated in the trial (appendix). After central screening, 124 patients were not eligible for trial participation. 564 patients (aged 33–81 years) who met the inclusion criteria were randomly assigned to the treatment groups (figure 1). Three patients were excluded immediately after allocation due to major violation of the inclusion and exclusion criteria resulting in 282 patients included in the fludarabine, cyclophosphamide, and rituximab group and 279 in the bendamustine and rituximab group (the intention-to-treat population; figure 1). Both treatment groups were well balanced with respect to disease stage, median age, sex, time from initial diagnosis, physical fitness (CIRS, ECOG status), creatinine clearance, presence of B-symptoms, serum concentration of β_2-microglobulin and thymidine kinase, and genomic aberrations according to the hierarchical model and detected by FISH (table 1). However, there was an imbalance in the distribution of patients with unmutated *IGHV* status with a higher proportion in the bendamustine and rituximab group. Moreover, the proportion of patients older than 70 years was higher in the bendamustine and rituximab group than the fludarabine, cyclophosphamide, and rituximab group. Among female patients there was an imbalance in the distribuation of del(11q) between both groups (triple combination, 21 [26%] of 81 had del(11q), double combination, 11 [15%] of 72). The median follow-up for the fludarabine, cyclophosphamide, and rituximab group was 37·4 months (IQR 31·7–46·4) and for the bendamustine and rituximab group was 36·0 months (30·6–44·7) (for all patients 37·1 months [IQR 31·0–45·5]).

The median number of treatment cycles was six (triple combination IQR 5–6, double combination 6–6) for both groups (mean number for fludarabine, cyclophosphamide, and rituximab 5·27 [SD 1·33], for bendamustine and rituximab 5·41 [1·35]; p=0·02). 83 (29%) of 282 patients in the fludarabine, cyclophosphamide, and rituximab group compared with 54 (19%) of 279 patients in the bendamustine and rituximab group received less than the planned six cycles of treatment (p=0·005). In patients aged 65 years or younger the proportion receiving less than six treatment cycles was 48 (24%) of 196 with the triple combination and 28 (16%) of 171 with bendamustine and rituximab (p=0·06). By contrast, the proportion of patients older than 65 years not receiving all planned treatment cycles was significantly higher in the triple combination therapy group (37 [43%] of 86 *vs* 26 [24%] of 108; p=0·013). Early treatment discontinuations within the first three cycles occurred in 37 (13%) patients in the fludarabine,

cyclophosphamide, and rituximab group and 32 (11%) patients in the bendamustine and rituximab group (p=0·552). Reasons for early treatment discontinuation in the triple combination group were toxic effects in 26 patients, progressive disease in two patients, patient decision for six patients, and three patients went off study before start of treatment, and in the double combination group, toxic effects in 24 patients, progressive disease in two patients, patient decision for four patients, one patient achieved a complete response, and one patient went off study before start of treatment.

For any of the three drugs a dose reduction of more than 10% was done during at least one treatment cycle in 148 (52%) of 282 patients of the fludarabine, cyclophosphamide, and rituximab group and in 145 (52%) of 279 patients of the bendamustine and rituximab group (p=0·904). No significant difference for dose reduction was observed between the two age groups. Of the patients aged 65 years or younger, 108 (55%) received at least one cycle of a dose-reduced fludarabine, cyclophosphamide, and rituximab regimen and 85 (50%) at least one cycle of a dose-reduced bendamustine and rituximab regimen (p=0·302). In patients older than 65 years, bendamustine and rituximab was dose reduced in 60 (56%) patients and fludarabine, cyclophosphamide, and rituximab in 40 (47%; p=0·211). Overall, a significantly higher proportion of treatment cycles with bendamustine and rituximab were dose reduced by more than 10% (423 [28%] of 1510 cycles) than with fludarabine, cyclophosphamide, and rituximab (363 [24%] of 1487 cycles; p=0·025). No differences in dose reductions were observed between male and female patients in the fludarabine, cyclophosphamide, and rituximab group (41 [51%] of 81 female patients and 107 [53%] of 201 male patients; p=0·69) or the bendamustine and rituximab groups (34 [47%] of 72 female patients and 111 (54%) of 207 male patients; p=0·35).

Progression-free survival was significantly shorter for bendamustine and rituximab in comparison with fludarabine, cyclophosphamide, and rituximab (median 41·7 months [95% CI 34·9–45·3] *vs* 55·2 months [not evaluable], HR 1·643 [90·4% CI 1·308–2·064] p=0·0003; figure 2). As the upper limit of the 90·4% CI was greater than 1·388 the null hypothesis for the corresponding non-inferiority hypothesis was not rejected. Treatment with bendamustine and rituximab, elevated serum thymidine kinase, del(11q), and unmutated *IGHV* status were independently associated with a higher risk of progression in multivariate analysis (table 2). The results of the univariate analysis are in the appendix.

In younger patients (≤65 years) median progression-free survival was significantly longer with the triple combination (53·6 months [95% CI not evaluable]) than with the double combination (38·5 months [33·1–44·8], p=0·0004; figures 2, 3). There was no significant difference in progression-free survival in elderly (>65 years) patients in the fludarabine, cyclophosphamide, and rituximab treated group compared with the bendamustine and rituximab group (median not reached [95% CI not evaluable] *vs* 48·5 months [34·6–52·0]; p=0·172; figure 2). There was no significant interaction between study treatment and age (p=0·413). Post-hoc assessment of progression-free survival according to *IGHV* status showed a median time to progression of 42·7 months (95% CI 36·2–55·2) in the fludarabine, cyclophosphamide, and rituximab therapy group versus 33·6 months (30·3–38·4) in the bendamustine and rituximab group for patients with unmutated *IGHV* status (p=0·017; figures 2, 3). For patients with a mutated *IGHV* status median progression-free survival was not reached (95% CI not evaluable) with fludarabine, cyclophosphamide, and rituximab treatment versus 55·4 months (not evaluable) with bendamustine and rituximab treatment (p=0·089; figures 2, 3). A significant

	Hazard ratio (95% CI)	p value
Treatment with bendamustine and rituximab	1·680 (1·270–2·222)	0·0003
Serum thymidine kinase >10 U/L	1·581 (1·104–2·265)	0·012
del(11q)	1·878 (1·391–2·536)	<0·0001
IGHV unmutated	1·937 (1·357–2·763)	0·000269

524 patients with 210 progression-free survival events.

Table 2: **Multivariable analysis of the effects of various prognostic variables on progression-free survival**

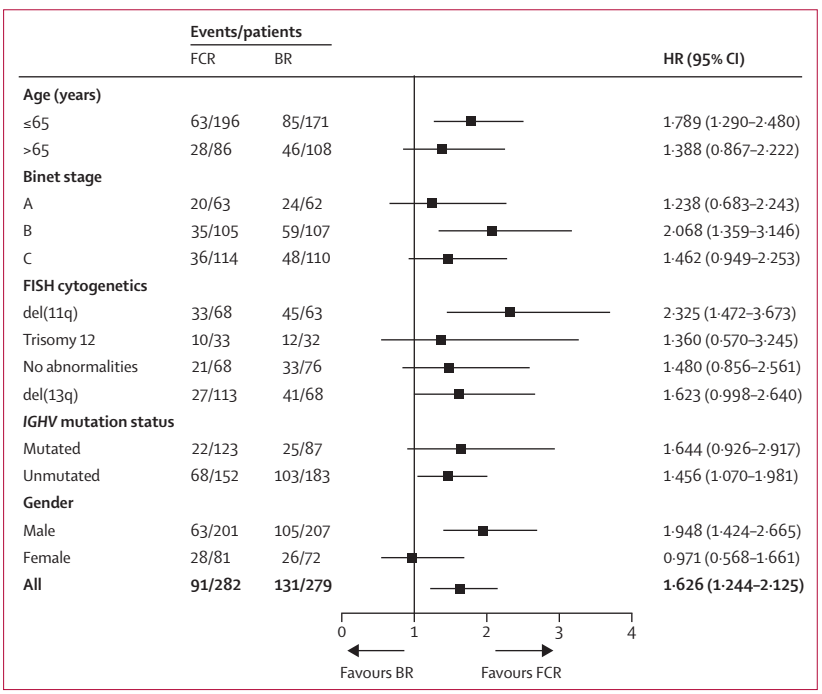

Figure 3: **Forest plot showing progression-free survival of subgroups for fludarabine, cyclophosphamide, and rituximab versus bendamustine and rituximab**

FISH=fluorescence in-situ hybridisation. FCR=fludarabine, cyclophosphamide, and rituximab. BR=bendamustine and rituximab.

	Fludarabine, cyclophosphamide, and rituximab	Bendamustine and rituximab	p value
All (n=561)			
Complete response	112/282 (40%)	86/279 (31%)	0·034
Overall response	269/282 (95%)	267/279 (96%)	1·0
Binet stage A (n=125)			
Complete response	30/63 (48%)	23/62 (37%)	0·234
Overall response	61/63 (97%)	61/62 (98%)	0·568
Binet stage B (n=212)			
Complete response	44/105 (42%)	35/107 (33%)	0·166
Overall response	104/105 (99%)	103/107 (96%)	0·181
Binet stage C (n=224)			
Complete response	38/114 (33%)	28/110 (25%)	0·196
Overall response	104/114 (91%)	103/110 (94%)	0·496
Male (n=408)			
Complete response	75/201 (37%)	61/207 (29%)	0·093
Overall response	192/201 (96%)	195/207 (94%)	0·546
Female (n=153)			
Complete response	37/81 (46%)	25/72 (35%)	0·168
Overall response	77/81 (95%)	72/72 (100%)	0·056
Age ≤65 years (n=367)			
Complete response	81/196 (41%)	51/171 (30%)	0·022
Overall response	186/196 (95%)	168/171 (98%)	0·096
Age >65 years (n=194)			
Complete response	31/86 (36%)	35/108 (32%)	0·648
Overall response	83/86 (97%)	99/108 (92%)	0·164
del(11q) (n=131)			
Complete response	26/68 (38%)	12/63 (19%)	0·016
Overall response	67/68 (99%)	57/63 (90%)	0·055
Trisomy 12* (n=65)			
Complete response	16/33 (48%)	11/32 (34%)	0·248
Overall response	32/33 (97%)	32/32 (100%)	1·0
No abnormalities according to the hierarchical model (n=144)			
Complete response	30/68 (44%)	27/76 (36%)	0·293
Overall response	64/68 (94%)	74/76 (97%)	0·422
del(13q)† (n=220)			
Complete response	40/113 (35%)	36/107 (34%)	0·785
Overall response	106/113 (94%)	104/107 (97%)	0·334
***IGHV* mutated (n=210)**			
Complete response	48/123 (39%)	24/87 (28%)	0·085
Overall response	117/123 (95%)	84/87 (97%)	0·739
***IGHV* unmutated (n=335)**			
Complete response	60/152 (39%)	60/183 (33%)	0·204
Overall response	145/152 (95%)	174/183 (95%)	1·0

Data are n/N (%). *Not including del(11q). †Not including del(11q) or trisomy 12.

***Table 3*: Response to treatment overall and in post-hoc analysis of subgroups**

interaction between study treatment and the *IGHV* mutation status was not found (p=0·881). In a post-hoc analysis there was no significant difference between progression-free survival for the fludarabine, cyclophosphamide, and rituximab group versus the bendamustine and rituximab group in patients with Binet stage A or C (Binet A 55·2 months [95% CI not evaluable] *vs* 43·1 months [not evaluable], p=0·481; Binet C 53·6 months [not evaluable] *vs* 44·6 months [38·0–51·3], p=0·083; figure 3), but it was significantly different for patients with Binet stage B only (not reached [95% CI not evaluable] *vs* 33·3 months [27·8–44·8], HR 2·068 [95% CI 1·359–3·146], p=0·001; figure 3). The interaction between study treatment and Binet stage was not significant (p=0·272). Post-hoc analysis according to the pre-therapeutic lymph node size showed a greater benefit for the triple combination for patients with lymph nodes more than 5 cm diameter than for patients with no lymph nodes or lymph nodes less than 5 cm diameter (3 year progression-free survival 57·5% [95% CI 43·1–71·9] for the triple combination group *vs* 31·4% [19·0–43·8] for the double combination group; HR 1·751 [95% CI 1·048–2·924]; p=0·0323; appendix). Post-hoc subgroup analysis according to sex showed no difference in progression-free survival between treatment groups for women (figure 3). In female patients median progression-free survival was 51·5 months (95% CI not evaluable) with the triple combination therapy and 52·0 months (not evaluable) with the bendamustine and rituximab therapy (p=0·916), by contrast with male patients, in whom progression-free survival was not reached (95% CI not evaluable) versus 35·3 months (33·5–42·6, p<0·0001; figure 3, appendix). Moreover, there was a significant interaction between study treatment and sex (p=0·034). Post-hoc anlaysis showed that fludarabine, cyclophosphamide, and rituximab treatment resulted in a significantly longer progression-free survival in the genetic subgroup of patients with del(11q) (37·8 months [95% CI 31·5–45·5] *vs* 25·3 months [23·5–30·3], p=0·0002; figure 3). In all other genetic subgroups the difference in progression-free survival was not significant and did not have any interactions with study treatment (figure 3, appendix). Due to the imbalance in *IGHV* status between treatment groups, a post-hoc *IGHV*-matched pair analysis was done: 201 patients from the fludarabine, cyclophosphamide, and rituximab group were matched to 197 patients from the bendamustine and rituximab group by *IGHV* status. Progression-free survival in the matched pair bendamustine and rituximab group was 43·1 months (95% CI 35·3–48·5) and not reached yet in the fludarabine, cyclophosphamide, and rituximab group (95% CI not evaluable; HR=1·565 [95% CI 1·141–2·148]; p=0·005; appendix).

A higher proportion of patients assigned to fludarabine, cyclophosphamide, and rituximab than bendamustine and rituximab achieved a complete response (p=0·034; table 3). The difference in complete responses between groups was not significant among most prognostic subgroups, with the exception of patients with del(11q) (table 3). Minimal residual disease in peripheral blood at final restaging was evaluated in 185 (66%) of 282 patients

receiving fludarabine, cyclophosphamide, and rituximab and in 170 (61%) of 279 patients receiving bendamustine and rituximab. Significantly more patients treated with the triple combination had negative minimal residual disease (137 [49%, 74% referring to available samples only]) in comparison with patients treated with bendamustine and rituximab (107 [38%, 63% referring to available samples only]; p=0·041, and p=0·029 for available samples, respectively). Bone marrow samples were evaluated in 129 (46%) patients after fludarabine, cyclophosphamide, and rituximab treatment and 98 (35%) patients after bendamustine and rituximab treatment. Negative minimal residual disease in bone marrow was achieved in 75 patients (27%, 58% referring to available samples only) after fludarabine, cyclophosphamide, and rituximab and 31 patients (11%, 32% referring to available samples only; both comparisons p<0·0001) after bendamustine and rituximab. During follow-up at month 12, 80 patients (67 patients at month 18) after fludarabine, cyclophosphamide, and rituximab therapy and 78 patients (59 patients at month 18) after bendamustine and rituximab therapy were assessed for minimal residual disease in peripheral blood. Minimal residual disease was not detected in a significantly higher proportion of patients treated with fludarabine, cyclophosphamide, and rituximab compared with those treated with bendamustine and rituximab after 12 months (referring to available samples 47 [59%] *vs* 20 [26%], p<0·0001; referring to all patients 17% *vs* 7%, p=0·0001) and after 18 months (37 [55%] *vs* 16 [27%], p=0·002; 13% *vs* 6%, p=0·005, respectively).

No difference in overall survival was observed between treatment groups. After 3 years, 91% (95% CI 87·0–94·2) of the patients treated with fludarabine, cyclophosphamide, and rituximab and 92% [88·7–95·6] of those treated with bendamustine and rituximab were still alive (HR 1·034 [95% CI 0·620–1·724], p=0·897; figure 4). 30 patients assigned to triple combination therapy and 29 patients assigned to bendamustine and rituximab therapy had died as of January, 2014. In most patients, chronic lymphocytic leukaemia was the cause of death (ten [33%] of 30 with fludarabine, cyclophosphamide, and rituximab and 12 [41%] of 29 with bendamustine and rituximab). Secondary cancers (seven [23%] with fludarabine, cyclophosphamide, and rituximab and five [17%] with bendamustine and rituximab) were the second most frequent cause followed by death due to other diseases, such as cardiovascular diseases (five [17%] with fludarabine, cyclophosphamide, and rituximab and seven [24%] with bendamustine and rituximab). Other causes of death included: in the fludarabine, cyclophosphamide, and rituximab group, one liver failure due to cirrhosis, one death due to graft-versus-host disease, one death due to intra-abdominal bleeding with anticoagulants, one death with no autopsy performed; and in the bendamustine and rituximab group, one lung embolism. Due to the low number of deaths, subgroup analyses were not done.

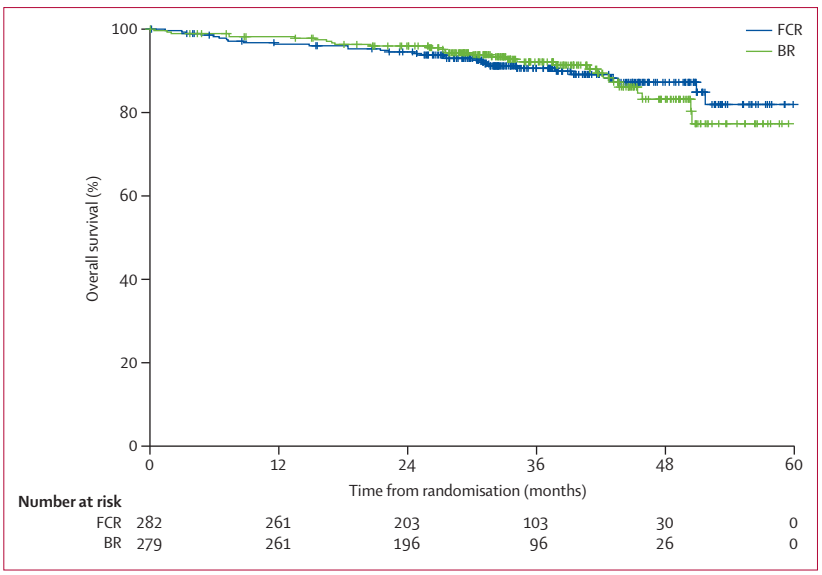

Figure 4: **Overall survival according to treatment group**
FCR=fludarabine, cyclophosphamide, and rituximab. BR=bendamustine and rituximab.

Event-free survival analysis and duration of response data are shown in the appendix. Duration of response was significantly longer with the triple combination than with the double combination (52·7 months [95% CI not evaluable] *vs* 38·9 months [34·2–43·6]; HR 1·657 [95% CI 1·256–2·185]; p=0·001). Median event-free survival was 55·2 months (95% CI not evaluable) with the triple combination and 38·5 months (32·4–44·6) with bendamustine and rituximab (HR 1·626 [95% CI 1·255–2·108]; p=0·001). As of data cutoff, 12 (4%) patients in the fludarabine, cyclophosphamide, and rituximab group and 18 (6%) patients in the bendamustine and rituximab group only have received treatment for relapse (appendix). Four patients from each group had an allogeneic stem cell transplant.

All 557 patients who received at least one dose of study treatment were included in the safety analysis. Severe, CTCAE grade 3 and 4, adverse events occurred more frequently in the fludarabine, cyclophosphamide, and rituximab group compared with the bendamustine and rituximab group (table 4). Neutropenia, leukocytopenia, thrombocytopenia, and the incidence of severe infections were more frequent with the triple combination therapy. Among those patients with an identified pathogen, severe viral infections occurred more often with the triple combination than with the double combination (table 4). General and severe infections occurred more frequently after termination of the triple combination therapy than after the double combination therapy (235 [84%] of 279 *vs* 164 [59%] of 278, and 109 [39%] *vs* 69 [25%]; table 4). However, during the first three cycles and cycles 4–6 the incidence of infections including CTCAE grade 3 and 4 between treatment

	Fludarabine, cyclophosphamide, and rituximab				Bendamustine and rituximab			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Adverse events per patient including all patients*								
Patients with adverse events	11 (4%)	56 (20%)	192 (69%)	13 (5%)	22 (8%)	104 (37%)	116 (42%)	14 (5%)
Haematological toxic effects	3 (1%)	60 (21%)	193 (69%)	0	4 (1%)	79 (28%)	109 (39%)	0
Neutropenia	2 (1%)	63 (23%)	172 (62%)	0	1 (<1%)	66 (24%)	98 (35%)	0
Leukocytopenia	2 (1%)	116 (42%)	109 (39%)	0	1 (<1%)	104 (37%)	31 (11%)	0
Thrombocytopenia	9 (3%)	37 (13%)	23 (8%)	0	10 (4%)	29 (10%)	11 (4%)	0
Anaemia	3 (1%)	28 (10%)	10 (4%)	0	2 (1%)	24 (9%)	5 (2%)	0
Infections total	103 (37%)	97 (35%)	8 (3%)	6 (2%)	114 (41%)	61 (22%)	6 (2%)	7 (2%)
Bacterial infection	6 (2%)	5 (2%)	0	0	5 (2%)	5 (2%)	1 (<1%)	0
Fungal infection	6 (2%)	2 (1%)	1 (<1%)	0	5 (2%)	0	0	0
Viral infection	50 (18%)	22 (8%)	1 (<1%)	1 (<1%)	41 (15%)	9 (3%)	0	1 (<1%)
Unspecified pathogen	116 (42%)	67 (24%)	2 (1%)	2 (1%)	123 (44%)	38 (14%)	4 (1%)	1 (<1%)
Pneumonia	12 (4%)	29 (10%)	4 (1%)	1 (<1%)	13 (5%)	22 (8%)	0	2 (1%)
Sepsis	0	6 (2%)	1 (<1%)	2 (1%)	0	1 (<1%)	1 (< 1%)	3 (1%)
Secondary neoplasia	1 (<1%)	7 (2%)†	9 (3%)‡	4 (1%)§	2 (1%)	6 (2%)¶	3 (1%)‖	3 (1%)**
Allergic conditions	8 (3%)	12 (4%)	3 (1%)	0	12 (4%)	21 (8%)	6 (2%)	0
Cardiac and pulmonary disorders	11 (4%)	19 (7%)	5 (2%)	2 (1%)	12 (4%)	16 (6%)	4 (1%)	4 (1%)
Gastrointestinal disorders	20 (7%)	19 (7%)	2 (1%)	1 (<1%)	15 (5%)	16 (6%)	2 (1%)	0
Neurological and psychiatric disorders	12 (4%)	10 (4%)	2 (1%)	0	13 (5%)	8 (3%)	3 (1%)	0
Skin reactions	28 (8%)	8 (3%)	0	0	25 (9%)	9 (3%)	1 (<1%)	0
Pyrexia	16 (6%)	1 (<1%)	0	0	15 (5%)	6 (2%)	0	0
Renal disorders	3 (1%)	7 (3%)	2 (1%)	0	3 (1%)	2 (1%)	0	0
Fatigue	6 (2%)	2 (1%)	0	0	3 (1%)	2 (1%)	0	0
Arthritis and arthralgia	7 (2%)	0	1 (<1%)	0	7 (2%)	1 (1%)	1 (<1%)	0
Trauma and orthopaedic problems	5 (2%)	7 (2%)	0	0	6 (2%)	8 (3%)	0	0
Laboratory abnormalities	5 (2%)	7 (2%)	0	0	6 (2%)	8 (3%)	0	0
Urticaria	1 (<1%)	0	0	0	2 (1%)	3 (2%)	0	0
Other	25 (9%)	12 (4%)††	0	0	18 (6%)‡‡	16 (6%)§§	2 (1%)	0
Adverse events per patient including only patients ≤65 years¶¶								
Patients with adverse events	7 (4%)	42 (22%)	133 (69%)	3 (2%)	6 (3%)	60 (35%)	75 (44%)	2 (1%)
Haematological toxic effects	3 (2%)	44 (23%)	129 (67%)	0	1 (1%)	45 (26%)	66 (39%)	0
Neutropenia	2 (1%)	44 (23%)	115 (60%)	0	0	36 (21%)	53 (37%)	0
Leukocytopenia	1 (<1%)	77 (40%)	75 (39%)	0	0	62 (36%)	18 (11%)	0
Thrombocytopenia	9 (5%)	20 (10%)	14 (7%)	0	6 (3%)	13 (8%)	4 (2%)	0
Anaemia	2 (1%)	20 (10%)	6 (3%)	0	0	12 (7%)	3 (2%)	0
Infections total	77 (40%)	60 (31%)	7 (4%)	3 (2%)	69 (40%)	43 (25%)	3 (2%)	1 (1%)
Bacterial infection	4 (2%)	3 (2%)	0	0	4 (2%)	1 (1%)	1 (1%)	0
Fungal infection	4 (2%)	1 (<1%)	1 (<1%)	0	4 (2%)	0	0	0
Viral infection	38 (20%)	11 (6%)	1 (<1%)	1 (<1%)	26 (15%)	8 (5%)	0	1 (1%)
Unspecified pathogen	91 (47%)	41 (21%)	2 (1%)	0	77 (45%)	27 (16%)	2 (1%)	0
Pneumonia	8 (4%)	20 (10%)	2 (1%)	1 (<1%)	7 (4%)	15 (9%)	0	0
Sepsis	0	0	1 (<1%)	1 (<1%)	0	1 (<1%)	0	0
Secondary neoplasia	0	4 (2%)	4 (2%)	1 (<1%)	0	4 (3%)	2 (1%)	1 (1%)
Allergic conditions	8 (4%)	9 (5%)	2 (1%)	0	9 (5%)	12 (7%)	3 (2%)	0
Cardiac and pulmonary disorders	8 (4%)	11 (6%)	3 (2%)	1 (<1%)	4 (2%)	10 (6%)	3 (2%)	1 (1%)
Gastrointestinal disorders	15 (8%)	17 (9%)	0	0	10 (6%)	12 (7%)	1 (1%)	0
Neurological and psychiatric disorders	7 (4%)	6 (3%)	2 (1%)	0	4 (2%)	4 (2%)	3 (2%)	0
Skin reactions	18 (9%)	6 (3%)	0	0	14 (8%)	6 (3%)	1 (1%)	0
Pyrexia	9 (5%)	1 (<1%)	0	0	11 (6%)	3 (2%)	0	0

(Table 4 continues on next page)

	Fludarabine, cyclophosphamide, and rituximab				Bendamustine and rituximab			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Renal disorders	3 (2%)	5 (3%)	0	0	1 (1%)	0	0	0
Fatigue	5 (3%)	0	0	0	2 (1%)	1 (1%)	0	0
Arthritis and arthralgia	5 (3%)	0	1 (<1%)	0	4 (2%)	2 (1%)	0	0
Trauma and orthopaedic problems	5 (3%)	3 (2%)	0	0	4 (2%)	5 (3%)	0	0
Laboratory abnormalities	2 (1%)	0	0	0	2 (1%)	1 (1%)	0	0
Urticaria	1 (<1%)	0	0	0	1 (<1%)	3 (2%)	0	0
Other	19 (10%)	8 (4%)	0	0	8 (5%)	9 (5%)	1 (1%)	0
Adverse events per patient including only patients >65 years||||								
Patients with adverse events	2 (2%)	14 (16%)	61 (71%)	6 (7%)	9 (8%)	41 (38%)	44 (41%)	5 (5%)
Haematological toxic effects	0	16 (19%)	64 (74%)	0	3 (3%)	34 (32%)	43 (40%)	0
Neutropenia	0	19 (22%)	57 (66%)	0	1 (1%)	30 (28%)	35 (33%)	0
Leukocytopenia	1 (1%)	39 (45%)	34 (39%)	0	1 (1%)	42 (39%)	13 (12%)	0
Thrombocytopenia	0	17 (20%)	9 (11%)	0	4 (4%)	16 (15%)	7 (6%)	0
Anaemia	1 (1%)	8 (9%)	4 (5%)	0	2 (2%)	12 (11%)	2 (2%)	0
Infections total	26 (30%)	37 (43%)	1 (1%)	3 (3%)	45 (42%)	18 (17%)	3 (3%)	6 (6%)
Bacterial infection	2 (2%)	2 (2%)	0	0	1 (1%)	4 (4%)	0	0
Fungal infection	2 (2%)	1 (1%)	0	0	1 (1%)	0	0	0
Viral infection	12 (14%)	11 (13%)	0	0	15 (14%)	1 (1%)	0	0
Unspecified pathogen	25 (29%)	26 (30%)	0	2 (2%)	46 (43%)	11 (10%)	2 (2%)	1 (1%)
Pneumonia	4 (5%)	9 (10%)	2 (2%)	0	6 (6%)	7 (6%)	0	2 (2%)
Sepsis	0	6 (7%)	0	1 (1%)	0	0	1 (1%)	3 (3%)
Secondary neoplasia	1 (1%)	3 (3%)	5 (6%)	3 (3%)	2 (2%)	2 (2%)	1 (1%)	2 (2%)
Allergic conditions	0	3 (3%)	1 (1%)	0	3 (3%)	9 (8%)	3 (3%)	0
Cardiac and pulmonary disorders	3 (3%)	8 (9%)	2 (2%)	1 (1%)	8 (7%)	6 (6%)	1 (1%)	3 (3%)
Gastrointestinal disorders	5 (6%)	2 (2%)	2 (2%)	1 (1%)	5 (5%)	4 (4%)	1 (1%)	0
Neurological and psychiatric disorders	5 (6%)	4 (5%)	0	0	9 (8%)	4 (4%)	0	0
Skin reactions	5 (6%)	2 (2%)	0	0	11 (10%)	3 (3%)	0	0
Pyrexia	7 (8%)	0	0	0	4 (4%)	3 (3%)	0	0
Renal disorders	0	2 (2%)	2 (2%)	0	2 (2%)	2 (2%)	0	0
Fatigue	1 (1%)	2 (2%)	0	0	1 (1%)	1 (1%)	0	0
Arthritis and arthralgia	2 (2%)	0	0	0	3 (3%)	0	1 (1%)	0
Trauma and orthopaedic problems	0	4 (5%)	0	0	2 (2%)	3 (3%)	1 (1%)	0
Laboratory abnormalities	0	0	1 (1%)	0	0	1 (2%)	0	0
Other	6 (7%)	4 (5%)	2 (2%)	0	11 (10%)	7 (7%)	1 (1%)	0

*Fludarabine, cyclophosphamide, and rituximab group (n=279), bendamustine and rituximab group (n=278). †Including four patients with basalioma and one each with squamous cell carcinoma, myelodysplastic syndrome, melanoma, and thyroid carcinoma (one patient had squamous cell carcinoma and thyroid carcinoma). ‡Including two patients each with breast cancer, myelodysplastic syndrome, and colon cancer and one patient each with renal cancer, oesophageal cancer, and carcinoma of unknown primary origin. §Including two patients with secondary acute myeloid leukaemia and one patient each with colon cancer and carcinoma of unknown primary origin. ¶Including two patients each with basalioma and squamous cell carcinoma and one patient each with colon carcinoma and prostate cancer. ||Including one patient each with bladder cancer, glioblastoma, and acute myeloid leukaemia. **Including one patient each with melanoma, lung cancer, and head and neck cancer. ††Including two patients with osteoporosis and one patient each with autoimmune disorder, back pain, epistaxis, arterial stenosis, alcohol-induced hepatitis, hiccups, hyperglycaemia, immunoglobulin substitution, iron overload, retinal detachment, petechial and soft tissue injury. ‡‡Including one patient each with back pain, prostate hyperplasia, prostate calcification, dystonia, glaucoma, hyperglycaemia, hysterectomy, immunoglobulin substitution, intravenous catheter management, leukoplakia, perianal abscess, thyroidectomy, thrombosis, and testicular pain. §§One patient with aortic aneurysm. ¶¶Fludarabine, cyclophosphamide, and rituximab group (n=193), bendamustine and rituximab group (n=171). ||||Fludarabine, cyclophosphamide, and rituximab group (n=86), bendamustine and rituximab group (n=107).

Table 4: **Incidence of adverse events during the whole study period**

groups was similar. Six patients treated with fludarabine, cyclophosphamide, and rituximab developed myelodysplastic syndrome or secondary acute myeloid leukaemia in comparison with one patient treated with bendamustine and rituximab. 64 (23%) of the patients treated with fludarabine, cyclophosphamide, and rituximab discontinued the study treatment due to toxic effects as compared with 37 (13%) of the patients treated with bendamustine and rituximab (p=0·003). Serious adverse events are listed in table 4.

Data regarding the routine use of granulocyte-colony stimulating factor (G-CSF) were not available for all patients because the administration of G-CSF was documented only in cases of infection. Neutropenia including severe neutropenia occurred more often during treatment with the triple combination therapy than with the double combination therapy and during the first follow-up time until 5 months after the end of therapy (appendix).

In patients older than 65 years adverse events occurred significantly more frequently in the triple combination therapy group (table 4). In these patients, fludarabine, cyclophosphamide, and rituximab was associated with a higher incidence of neutropenia, leukocytopenia, infections, and secondary neoplasias than was bendamustine and rituximab (table 4). In the group of younger patients aged up to 65 years the incidence of severe neutropenia, leukocytopenia, and thrombocytopenia was increased with fludarabine, cyclophosphamide, and rituximab treatment compared with bendamustine and rituximab.

19 (3%) deaths in 564 patients were related to treatment, 13 (5%) in the fludarabine, cyclophosphamide, and rituximab group and six (2%) in the bendamustine and rituximab group. Seven of 13 patients in the fludarabine, cyclophosphamide, and rituximab group died because of treatment-related infections (sepsis [n=3], pneumonia [n=2], colitis [n=1], hepatitis B [n=1]) and all six patients in the bendamustine and rituximab group (sepsis [n=2], pneumonia [n=3], progressive multifocal leukoencephalopathy [n=1]). Three patients assigned to fludarabine, cyclophosphamide, and rituximab died because of secondary neoplasias, one patient because of secondary myelodysplastic syndrome, and two because of secondary acute myeloid leukaemia. Three more patients in this group died for unknown causes during or after treatment. These deaths were considered as possibly related to treatment.

Discussion

This phase 3 study investigating the non-inferiority of chemoimmunotherapy with bendamustine and rituximab compared with the standard front-line therapy of fludarabine, cyclophosphamide, and rituximab regimen for patients with chronic lymphocytic leukaemia with a low comorbidity burden found that bendamustine and rituximab resulted in significantly shorter progression-free survival, and lower proportions of patients achieving complete remission and minimal residual disease negativity. This result, clearly favouring the standard triple combination treatment, was somewhat surprising because previous studies showed promising results with bendamustine and rituximab treatment for chronic lymphocytic leukaemia regarding response quality and duration of response.[8,12] Although more patients assigned to bendamustine and rituximab completed six cycles of treatment and toxic effects were lower, this did not translate into a similar depth of response when compared with fludarabine, cyclophosphamide, and rituximab.

The imbalance in *IGHV* status between both treatment groups might favour fludarabine, cyclophosphamide, and rituximab. Therefore, an *IGHV*-matched analysis was done (appendix) and confirmed the longer progression-free survival with the triple combination therapy. Moreover, there was no significant interaction between the treatment and the *IGHV* mutation status regarding progression-free survival. This corroborates the finding that bendamustine and rituximab therapy is significantly less effective than the standard triple combination therapy.

However, no difference in overall survival was observed between both groups at the time of data cutoff, most likely because the number of deaths is very low, but patients receiving second-line treatment regimens might also have an effect. Because of the small numbers of patients receiving treatment for relapse, and the high risk profile of these mostly early relapses followed by allogeneic stem-cell transplantation, it is difficult to draw any conclusions on the effect of relapse treatment yet.

Similar to the CLL8 study, the treatment effect on progression-free survival in the CLL10 study was different in the different Binet stages.[5] The difference in progression-free survival was largest in Binet stage B patients and in patients with lymph nodes greater than 5 cm diameter. The greater efficacy of fludarabine, cyclophosphamide, and rituximab in patients with del(11q) shows that bendamustine-based chemo-immunotherapy is not adequate in patients with chronic lymphocytic leukaemia and large lymph nodes. Patients with del(17p) were excluded by screening and treated in a separate protocol. Data regarding the prognostic effect of specific mutations (eg, *TP53*, *NOTCH1*) will be published separately.

In elderly patients the difference in progression-free survival between both groups was not significant after a median observation of 3 years. However, this might change with a longer observation time. Additionally, no significant interaction between treatment and age was observed. Surprisingly, elderly patients treated with bendamustine and rituximab had a longer progression-free survival than younger patients treated with bendamustine and rituximab (appendix). However, no differences in pharmacokinetics of bendamustine in different age groups have been observed in previous studies.[13] Remarkably, a numerical age cutoff at the age of 65 years differentiated efficacy and toxic effects better than various cutoffs using the CIRS, including severity and number of involved organ systems, in all subgroup analyses regarding efficacy and toxicity. The efficacy and good tolerability of bendamustine and rituximab in front-line therapy for elderly patients with chronic lymphocytic leukaemia has previously been shown.[8,14] A phase 3 study comparing bendamustine and rituximab

with chlorambucil and rituximab in elderly patients with chronic lymphocytic leukaemia (MaBLe study[12]) showed a median progression-free survival of 39·6 months with bendamustine and rituximab. The shorter progression-free survival in comparison with the 48·5 months (95% CI 34·6–52·0) median progression-free survival of the elderly patients here can possibly be explained by the selection of very fit patients. However, although exploratory subgroup analyses have to be interpreted cautiously, our data, in addition to previously published data and the so far unpublished data of the MaBLe study, suggest that bendamustine and rituximab might be an alternative treatment regimen in elderly fit patients, who are at high risk for toxic effects with standard therapy.

In female patients progression-free survival did not differ between both groups. However, we observed a small imbalance in female patients carrying del(11q) in their leukaemia cells between both groups. 11 (15%) of 72 patients in the bendamustine and rituximab group had del(11q) versus 21 (26%) of 81 in the triple combination group, thus favouring the double combination group regarding progression-free survival in female patients. A significant interaction between sex and treatment was observed. No differences in adherence to treatment were observed between female and male patients in both treatment groups. Previously published pharmacokinetic data for bendamustine in lymphoma patients showed no differences between sexes.[13] However, the known slower rituximab clearance in elderly female patients[15] could result in a better efficacy of bendamustine and rituximab.

The toxic effect profile was better with bendamustine and rituximab. Fludarabine, cyclophosphamide, and rituximab therapy was associated with more toxic effects in comparison with the bendamustine and rituximab therapy predominantly in elderly patients, although all included patients were physically fit. Several studies have evaluated dose-reduced fludarabine, cyclophosphamide, and rituximab in elderly patients with chronic lymphocytic leukaemia.[16–19] Progression-free survival in these studies with dose-reduced fludarabine, cyclophosphamide, and rituximab was shorter in comparison with study results with a full-dose regimen, either because of early treatment stops[19] or because of lower efficacy.[18] The bendamustine and rituximab regimen used here compares favourably with other studies using dose-reduced fludarabine, cyclophosphamide, and rituximab,[17–19] although more fit elderly patients might have been included in the CLL10 study.

A significant number of severe infections in the triple combination therapy group occurred after the end of treatment until 5 months after treatment. Long-lasting cytopenias have also been reported before with fludarabine, cyclophosphamide, and rituximab therapy,[4] yielding a higher post-treatment infection rate. Secondary malignancies after the triple combination therapy are of great concern, because a 2·38 times increased risk of secondary malignancies in comparison with the normal population has been reported.[7] The incidence rate of secondary malignancies in the fludarabine, cyclophosphamide, and rituximab group was higher than that in the bendamustine and rituximab group, particularly in patients older than 65 years. With longer follow-up this difference might become significant for the whole group of patients treated with the standard triple combination therapy.

Several strategies to increase the efficacy of fludarabine, cyclophosphamide, and rituximab or bendamustine and rituximab are being investigated. One such strategy substitutes rituximab with obinutuzumab. The superiority of obinutuzumab over rituximab when combined with chlorambucil has been shown in a head-to-head comparison.[20] A phase 1b study evaluating bendamustine or fludarabine and cyclophosphamide in combination with obinutuzumab in treatment-naive chronic lymphocytic leukaemia showed an acceptable toxic effect profile.[21] Infusion-related reactions during the first administration appeared to be more frequent than with rituximab. Because of the limited number of patients, it is difficult to draw conclusions regarding efficacy, but so far overall response and proportions of patients achieving complete remission do not seem to be superior over the rituximab-based chemoimmunotherapy regimen.

In 2014, the BTK inhibitor ibrutinib[22] and the PI3K inhibitor idelalisib,[23] two kinase inhibitors, were approved for treating relapsed or very high-risk untreated patients with chronic lymphocytic leukaemia. Two phase 3 studies in relapsed chronic lymphocytic leukaemia evaluated either ibrutinib or idelalisib versus placebo in combination with bendamustine plus rituximab.[24,25] Both studies showed a benefit not only in progression-free survival but also in overall survival with the addition of the kinase inhibitor to bendamustine and rituximab.[24,25] These very promising combinations including chemo-immunotherapy, kinase inhibitors, and BCL2 inhibitors are now being investigated in front-line therapy.

Our results confirm a previously published meta-analysis[26] and show that fludarabine, cyclophosphamide, and rituximab remains the standard first-line therapy in fit patients with chronic lymphocytic leukaemia without del(17p) for better disease control, but yields higher adverse events incidence in comparison with bendamustine and rituximab.[3,4] The data confirm previous results of the CLL8 study that a higher rate of minimal residual disease negativity translates into longer progression-free survival. Long-term follow-up data of the fludarabine, cyclophosphamide, and rituximab regimen suggest that patients with mutated *IGVH* status can achieve very long-lasting remissions beyond 10 years and could possibly be cured.[3,4] However, the question is if high minimal residual disease negativity rates are still needed for long-term disease control in the era of new targeted treatment options, in which excellent disease

control can be achieved with persistent lymphocytosis.[27] Similarly, it remains to be investigated whether chemoimmunotherapy can be replaced by chemotherapy-free combinations including BCL2 or kinase inhibitors.

Contributors

BE, MH, RB, KF, A-MF, C-MW, SS, HD, MKn, and SB designed the study. BE and MH cochaired the study. BE, KF, A-MF, GKo, and CM were responsible for the conduct of the study. EL, HK, MKi, MS, RS, UV-K, GKö, CP, MG, TB, and MT were responsible for country-specific issues and supported the study. SS, HD, K-AK, MKn, and SB did the central laboratory tests. JB, BE, MH, RB, A-MF, GKo, and CM analysed the study data. BE and MH drafted the report and all authors revised the report for important intellectual content.

Declaration of interests

BE received honoraria and research funding from Roche and Mundipharma for educational presentations and declared advisory board membership for Roche and Mundipharma. A-MF received grants from Hoffman-La Roche, Mundipharma, and Celgene. CM reports travel grants from Mundipharma. MKi received grants and honoraria from Roche for advisory board, travel, and speaker's bureau. MG received honoraria from Celgene, Gilead, GlaxoSmithKline, Janssen, Mundipharma, and Roche. MG receives support for congress visits from Celgene, Janssen, and Roche. MT received grants and personal fees from Roche, Celgene, and Janssen, and personal fees from Takeda, Gilead, and Amgen, outside the submitted work. WK received grants from Hoffmann-La Roche, Novartis, Celgene, and Takeda Millenium. K-AK received personal fees from Roche and Mundipharma. SS received honoraria for consultant or advisory board membership and research funding from Mundipharma and Hoffmann-La Roche. SB received travel expenses from Roche, honoraria from Roche and AbbVie, and research funding from Roche, AbbVie, Celgene, and Mundipharma. C-MW received grants and personal fees from Hoffmann-La Roche, Mundipharma, and Servier, personal fees from Janssen-Cilag, Novartis, Gilead, Morphosys, and AbbVie, outside the submitted work. MH received grants and personal fees from Roche. JB, RB, GKo, EL, HK, MS, U-VK, GKö, CP, TB, KF, HD, and MKn declare no competing interests.

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References

1 Parikh SA, Rabe KG, Kay NE, et al. Chronic lymphocytic leukemia in young (</= 55 years) patients: a comprehensive analysis of prognostic factors and outcomes. *Haematologica* 2014; **99:** 140–47.

2 Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. *J Clin Oncol* 2005; **23:** 4079–88.

3 Thompson PA, Tam CS, O'Brien SM, et al. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia. *Blood* 2016; **127:** 303–09.

4 Fischer K, Bahlo J, Fink AM, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. *Blood* 2016; **127:** 208–15.

5 Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukemia: a randomised, open-label, phase III trial. *Lancet* 2010; **376:** 1164–74.

6 Strati P, Wierda W, Burger J, et al. Myelosuppression after frontline fludarabine, cyclophosphamide, and rituximab in patients with chronic lymphocytic leukemia: analysis of persistent and new-onset cytopenia. *Cancer* 2013; **119:** 3805–11.

7 Benjamini O, Jain P, Trinh L, et al. Second cancers in patients with chronic lymphocytic leukemia who received frontline fludarabine, cyclophosphamide and rituximab therapy: distribution and clinical outcomes. *Leuk Lymphoma* 2015: **56:** 1643–50.

8 Fischer K, Cramer P, Busch R, et al. Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. *J Clin Oncol* 2012; **30:** 3209–16.

9 Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood* 2008; **111:** 5446–56.

10 Extermann M, Overcash J, Lyman GH, Parr J, Balducci L. Comorbidity and functional status are independent in older cancer patients. *J Clin Oncol* 1998; **16:** 1582–87.

11 Bottcher S, Ritgen M, Fischer K, et al. Minimal residual disease quantification is an independent predictor of progression-free and overall survival in chronic lymphocytic leukemia: a multivariate analysis from the randomized GCLLSG CLL8 trial. *J Clin Oncol* 2012; **30:** 980–08.

12 Michallet A-S, Aktan M, Schuh A, et al. Rituximab in combination with bendamustine or chlorambucil for the treatment of chronic lymphocytic leukaemia: primary results from the randomised phase IIIb MaBLe study. *Leuk Lymphoma* 2015; **56** (suppl 1)**:** abstract 88.

13 Owen JS, Melhem M, Passarell JA, D'Andrea D, Darwish M, Kahl B. Bendamustine pharmacokinetic profile and exposure-response relationships in patients with indolent non-Hodgkin's lymphoma. *Cancer Chemother Pharmacol* 2010; **66:** 1039–49.

14 Laurenti L, Innocenti I, Autore F, et al. Bendamustine in combination with rituximab for elderly patients with previously untreated B-cell chronic lymphocytic leukemia: a retrospective analysis of real-life practice in Italian hematology departments. *Leuk Res* 2015; **39:** 1066–70.

15 Pfreundschuh M, Muller C, Zeynalova S, et al. Suboptimal dosing of rituximab in male and female patients with DLBCL. *Blood* 2014; **123:** 640–46.

16 Foon KA, Mehta D, Lentzsch S, et al. Long-term results of chemoimmunotherapy with low-dose fludarabine, cyclophosphamide and high-dose rituximab as initial treatment for patients with chronic lymphocytic leukemia. *Blood* 2012; **119:** 3184–85.

17 Dartigeas C, Van Den Neste E, Berthou C, et al. Evaluating abbreviated induction with fludarabine, cyclophosphamide, and dose-dense rituximab in elderly patients with chronic lymphocytic leukemia. *Leuk Lymphoma* 2015; **28:** 1–7.

18 Smolej L, Brychtova Y, Doubek M, et al. Low-dose FCR is a safe and effective treatment option for elderly/comorbid patients with chronic lymphocytic leukemia/small lymphocytic lymphoma. Updated results of Project Q-Lite By Czech CLL Study Group. *Blood* 2014; **124:** abstract 4670.

19 Mulligan S, Gill D, Turner P, et al. A randomised dose de-escalation study of oral fludarabine, ± oral cyclophosphamide and intravenous rituximab as first-line therapy of fit patients with chronic lymphocytic leukaemia (CLL) aged ≥65 years: final analysis of response and toxicity. *Blood* 2014; **124:** abstract 3325.

20 Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med* 2014; **370:** 1101–10.

21 Brown JR, O'Brien S, Kingsley CD, et al. Obinutuzumab plus fludarabine/cyclophosphamide or bendamustine in the initial therapy of CLL patients: the phase 1b GALTON trial. *Blood* 2015; **125:** 2779–85.

22 Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med* 2013; **369:** 32–42.

23 Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med* 2014; **370:** 997–1007.

24 Chanan-Khan A, Cramer P, Demirkan F, et al. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. *Lancet Oncol* 2016; **17:** 200–11.

25 Zelenetz A, Robak T, Coiffier B, et al. Idelalisib plus bendamustine and rituximab (BR) is superior to BR alone in patients with relapsed/refractory chronic lymphocytic leukemia: results of a phase 3 randomized double-blind placebo-controlled study. *Blood* 2015; **126:** LBA5.

26 Ladyzynski P, Molik M, Foltynski P. A network meta-analysis of progression free survival and overall survival in first-line treatment of chronic lymphocytic leukemia. *Cancer Treat Rev* 2015; **41:** 77–93.

27 Woyach JA, Smucker K, Smith LL, et al. Prolonged lymphocytosis during ibrutinib therapy is associated with distinct molecular characteristics and does not indicate a suboptimal response to therapy. *Blood* 2014; **123:** 1810–17.