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

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Summary

Background Most patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma relapse after initial therapy. Bendamustine plus rituximab is often used in the relapsed or refractory setting. We assessed the efficacy and safety of adding ibrutinib, an oral covalent inhibitor of Bruton's tyrosine kinase (BTK), to bendamustine plus rituximab in patients with previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma.

Methods The HELIOS trial was an international, double-blind, placebo-controlled, phase 3 study in adult patients (≥18 years of age) who had active chronic lymphocytic leukaemia or small lymphocytic lymphoma with measurable lymph node disease (>1·5 cm) by CT scan, and had relapsed or refractory disease following one or more previous lines of systemic therapy consisting of at least two cycles of a chemotherapy-containing regimen, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and adequate bone marrow, liver, and kidney function. Patients with del(17p) were excluded because of known poor response to bendamustine plus rituximab. Patients who had received previous treatment with ibrutinib or other BTK inhibitors, refractory disease or relapse within 24 months with a previous bendamustine-containing regimen, or haemopoietic stem-cell transplant were also excluded. Patients were randomly assigned (1:1) by a web-based system to receive bendamustine plus rituximab given in cycles of 4 weeks' duration (bendamustine: 70 mg/m² intravenously on days 2–3 in cycle 1, and days 1–2 in cycles 2–6; rituximab: 375 mg/m² on day 1 of cycle 1, and 500 mg/m² on day 1 of cycles 2–6 for a maximum of six cycles) with either ibrutinib (420 mg daily orally) or placebo until disease progression or unacceptable toxicity. Patients were stratified according to whether they were refractory to purine analogues and by number of previous lines of therapy. The primary endpoint was independent review committee (IRC)-assessed progression-free survival. Crossover to ibrutinib was permitted for patients in the placebo group with IRC-confirmed disease progression. Analysis was by intention-to-treat and is continuing for further long-term follow-up. The trial is registered with ClinicalTrials.gov, number NCT01611090.

Findings Between Sept 19, 2012, and Jan 21, 2014, 578 eligible patients were randomly assigned to ibrutinib or placebo in combination with bendamustine plus rituximab (289 in each group). The primary endpoint was met at the preplanned interim analysis (March 10, 2015). At a median follow-up of 17 months (IQR 13·7–20·7), progression-free survival was significantly improved in the ibrutinib group compared with the placebo group (not reached in the ibrutinib group (95% CI not evaluable) *vs* 13·3 months (11·3–13·9) in the placebo group (hazard ratio [HR] 0·203, 95% CI 0·150–0·276; p<0·0001). IRC-assessed progression-free survival at 18 months was 79% (95% CI 73–83) in the ibrutinib group and 24% (18–31) in the placebo group (HR 0·203, 95% CI 0·150–0·276; p<0·0001). The most frequent all-grade adverse events were neutropenia and nausea. 222 (77%) of 287 patients in the ibrutinib group and 212 (74%) of 287 patients in the placebo group reported grade 3–4 events; the most common grade 3–4 adverse events in both groups were neutropenia (154 [54%] in the ibrutinib group *vs* 145 [51%] in the placebo group) and thrombocytopenia (43 [15%] in each group). A safety profile similar to that previously reported with ibrutinib and bendamustine plus rituximab individually was noted.

Interpretation In patients eligible for bendamustine plus rituximab, the addition of ibrutinib to this regimen results in significant improvements in outcome with no new safety signals identified from the combination and a manageable safety profile.

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See Online for appendix

Research in context

Evidence before this study

Chemoimmunotherapeutic regimens such as bendamustine plus rituximab, or fludarabine, cyclophosphamide, and rituximab, have shown efficacy in patients with relapsed chronic lymphocytic leukaemia, but their use is often limited by a patient's ability to tolerate them. These regimens formed the backbone of the phase 1b study that led to the development of the current study. We searched PubMed for articles published between Jan 1, 2006, and Aug 15, 2015, to identify new agents used to treat chronic lymphocytic leukaemia or small lymphocytic lymphoma; search terms were "CLL", "chronic lymphocytic leukaemia", "SLL", "small lymphocytic lymphoma", "novel therapy", "relapsed", and "refractory". Single-agent ibrutinib has been associated with a long progression-free survival in patients with relapsed or refractory chronic lymphocytic leukaemia or small lymphocytic lymphoma. In a 3-year follow-up of single-agent ibrutinib, the median progression-free survival had not been reached at 30 months, with an estimated 69% of relapsed or refractory patients remaining progression-free and 79% of patients alive. Additionally, in a randomised phase 3 study in patients not eligible for chemoimmunotherapy, ibrutinib significantly improved both progression-free survival and overall survival compared with ofatumumab, which has led to the National Comprehensive Cancer Network recommending ibrutinib as the preferred agent (category 1) in the relapsed setting. The combination of the phosphatidylinositol-3-kinase (PI3K) inhibitor idelalisib plus rituximab compared with placebo and rituximab has been shown to significantly improve progression-free survival, response rate, and overall survival in patients with relapsed chronic lymphocytic leukaemia who were less able to undergo chemotherapy.

Added value of this study

To our knowledge, this large, international trial is the first double-blind, placebo-controlled study of ibrutinib and the first phase 3 study to combine ibrutinib with chemoimmunotherapy for previously treated patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma. This trial is also the first phase 3 study of the newer targeted agents in combination with chemoimmunotherapy commonly used to treat chronic lymphocytic leukaemia. The addition of ibrutinib to bendamustine plus rituximab compared with placebo significantly improved progression-free survival and the proportion of patients achieving an overall response. The safety profile showed that there were no unexpected safety signals identified from the combination of ibrutinib with bendamustine plus rituximab. Our results suggest that ibrutinib in addition to bendamustine plus rituximab is better than the current standard of care with bendamustine plus rituximab in previously treated patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma.

Implications of all the available evidence

We have shown that ibrutinib has added benefit on top of standard-of-care chemoimmunotherapy in previously treated patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma. Ibrutinib can be given safely with bendamustine plus rituximab. Trials are underway to assess the efficacy and safety of ibrutinib as a single agent or in combination therapy in treatment-naive patients with chronic lymphocytic leukaemia.

The value of ibrutinib in relapsed or refractory chronic lymphocytic leukaemia or small lymphocytic lymphoma is supported by the results of this second phase 3 trial, although it remains uncertain if the use of chemoimmunotherapy combined with ibrutinib is better than single-agent ibrutinib. The previous large trial assessing ibrutinib monotherapy (RESONATE; NCT01578707) included a different patient population with more patients aged 65 years or older and a third of patients harbouring del(17p), thus impeding a cross-trial comparison of the outcomes achieved with bendamustine plus rituximab in combination with ibrutinib and single-agent ibrutinib.

Introduction

Chronic lymphocytic leukaemia and small lymphocytic lymphoma are incurable with conventional chemo-immunotherapy regimens, and almost all patients eventually relapse after initial therapy. The goal of treatment following relapse is to control the disease and provide durable progression-free survival, which may ultimately extend overall survival. Chemoimmunotherapy is the therapeutic standard for first-line treatment of patients without the high-risk genetic features del(17p) or *TP53* mutation.[1–3] However, before the advent of new agents targeting the B-cell receptor signalling pathway such as ibrutinib, no standard existed in the relapsed setting and one of the most commonly used regimens was bendamustine, an alkylating agent, in combination with the anti-CD20 antibody rituximab.[4,5] Phase 2 data with bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukaemia have shown that 59% of patients achieve an overall response and 9% achieve a complete response, with median progression-free survival of 15 months and median overall survival of 34 months.[6]

Ibrutinib is a first-in-class, once-daily, oral, covalent inhibitor of Bruton's tyrosine kinase (BTK). It binds covalently to a cysteine residue (Cys481) in the active site ATP-binding domain of BTK, which inhibits B-cell receptor signalling within the malignant B cell with downstream mitigation of cell growth and proliferation, survival, adhesion, and migration.[7–13]

Single-agent ibrutinib has been associated with unprecedented progression-free survival in patients with relapsed or refractory chronic lymphocytic leukaemia or small lymphocytic lymphoma in the phase 2 setting.[14] In a

3-year follow-up of single-agent ibrutinib, median progression-free survival had not been reached at 30 months, with an estimated 69% of relapsed or refractory patients remaining progression-free and 79% of patients alive.[15] Furthermore, in the randomised phase 3 RESONATE study in patients deemed ineligible for chemoimmunotherapy because of advanced age, comorbidities, impaired renal function, or presence of del(17p), ibrutinib significantly improved both progression-free survival and overall survival compared with ofatumumab.[16] As a consequence of these data, the National Comprehensive Cancer Network (NCCN) recommend ibrutinib as the preferred agent (category 1) in the relapsed setting.[5]

The addition of ibrutinib to bendamustine plus rituximab has been investigated in a phase 1b study to determine its safety and efficacy in patients with previously treated chronic lymphocytic leukaemia. Therapy was well tolerated and effective, with an overall response in 28 (93%) of 30 patients and 3-year progression-free survival of 70%.[17]

We assessed the efficacy and safety of ibrutinib versus placebo in combination with bendamustine plus rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia or small lymphocytic lymphoma.

Methods

Study design and participants

This phase 3, randomised, placebo-controlled, double-blind study was done at 133 sites in 21 countries in North America, Europe, Latin America, and Asia, enrolling patients between September, 2012, and January, 2014, (appendix p 22).

Eligible patients were aged 18 years or older, had a diagnosis of chronic lymphocytic leukaemia or small lymphocytic lymphoma requiring treatment according to International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria,[18] and had relapsed or refractory disease following one or more previous lines of systemic therapy consisting of at least two cycles of a chemotherapy-containing regimen. Other eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, measurable lymph node disease (>1·5 cm) by CT scan, an absolute neutrophil count of at least 1×10^9 cells per L, a platelet count of at least 50×10^9 cells per L, as well as adequate liver and kidney function.

Patients with del(17p) (defined as the presence of del[17p] in ≥20% of blood or bone marrow cells examined by fluorescence in situ hybridisation) were excluded because of known poor response to bendamustine plus rituximab.[6] Patients were also excluded if they had received previous treatment with ibrutinib or other BTK inhibitors, refractory disease or relapse within 24 months with a previous bendamustine-containing regimen, or haemopoietic stem-cell transplant. Additional exclusion criteria were central nervous system leukaemia or lymphoma or Richter's transformation; history of stroke, intracranial haemorrhage, or clinically significant cardiovascular disease within 6 months before randomisation; and a requirement for concurrent anticoagulation with warfarin or other vitamin K antagonists or strong CYP3A4 or CYP3A5 inhibitors.

An independent ethics committee or institutional review board approved the protocol at each site, and the study was done according to the principles of the Declaration of Helsinki and the guidelines for Good Clinical Practice. All patients provided written informed consent. An independent data monitoring committee assessed safety periodically and reviewed data from the protocol-specified interim analysis.

Randomisation and masking

Central randomisation was implemented in this study. Patients were randomly assigned to one of two treatment groups in a 1:1 ratio on the basis of a computer-generated randomisation schedule prepared by Bracket (Boston, MA, USA) before the study by an interactive web response system (IWRS). The randomisation was balanced by use of randomly permuted blocks with a block size of six and was stratified by purine analogue refractory status (yes [relapsed or failed to respond within 12 months] *vs* no) and number of previous lines of therapy (1 *vs* >1). The IWRS assigned a unique treatment code that dictated the treatment assignment and matching study drug kit for each patient. The investigators, patients, and study personnel were all blinded to the actual treatment assignment; capsules that were identical in appearance were provided.

Procedures

Patients were randomly assigned to receive either 420 mg daily oral ibrutinib (Pharmacyclics, Sunnyvale, CA, USA) or placebo in combination with bendamustine plus rituximab (maximum of six cycles). Ibrutinib or placebo were initiated in cycle 1 with bendamustine plus rituximab and were continued until disease progression or unacceptable toxicity. Bendamustine plus rituximab was given for a maximum of six cycles (one cycle was 28 days) (bendamustine: 70 mg/m² intravenously on days 2–3 in cycle 1, and days 1–2 in cycles 2–6; rituximab: 375 mg/m² on day 1 of cycle 1, and 500 mg/m² on day 1 of cycles 2–6). Patients could discontinue either rituximab or bendamustine or both drugs, if necessary, because of adverse events (appendix pp 2–3).

Assessment of tumour response and progression was in accordance with the iwCLL 2008 criteria.[18] CT scans were done at baseline and then every 12 weeks and were centrally reviewed and assessed by the independent review committee (IRC), including lymph node evaluation and volumetric assessment of spleen size. Minimal residual disease analysis was done by two approaches to account for the possible complication of anti-CD20 antibodies present with the concomitant use

of rituximab. First, minimal residual disease analysis was initially performed on bone marrow sampled at the time of assessment for complete response (ie, time of evaluation in which the investigator suspected the patient might have a complete response). Because of the long half-life of anti-CD20 monoclonal antibodies in peripheral blood, the initial sample of bone marrow was obtained to mitigate cross-reactivity. Subsequent analyses were done on peripheral blood every 12 weeks thereafter. Testing was performed by flow cytometry using an eight-colour panel of antibodies in keeping with the EuroFlow panel.[19] One of the markers used in the panel is CD20, and treatment with anti-CD20 antibodies may cause interference with this marker; however, CD20 is expected to be low to dim in this population of patients with relapsed chronic lymphocytic leukaemia. The panel also includes four other positive markers (including CD19 and CD5) and three negative markers to identify these cells.[19]

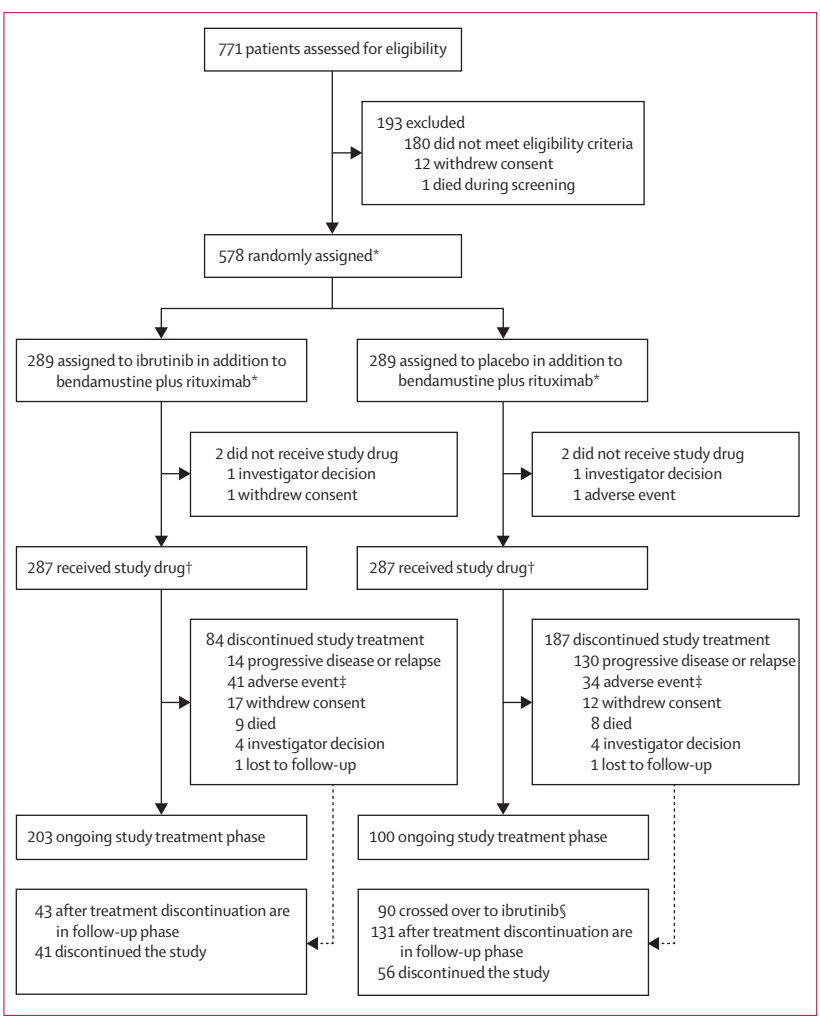

Figure 1: **Patient flow and disposition**
*All randomised patients were analysed as an intention-to-treat cohort. †All patients who received at least one dose of study drug were included in the safety analyses. ‡Some patients listed more than one adverse event for treatment discontinuation. §Individuals who crossed over can also be counted under the "post-treatment, before follow-up visit" category.

Patient-reported outcomes were a prespecified secondary endpoint and were collected using EORTC QLQ-C30, a general cancer assessment, EORTC QLQ-CLL 16, which is specific to symptoms or problems associated with chronic lymphocytic leukaemia, and the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale, specifically assessing aspects of fatigue. The patient-reported outcome questionnaires were collected at the beginning of clinic visits before procedures or physician interactions.

Outcomes

The primary endpoint was IRC-assessed progression-free survival, defined as the interval between the date of randomisation and the date of disease progression or death, whichever was reported first. A preplanned subgroup analysis of progression-free survival outcomes based on baseline patient and disease characteristics was also undertaken. Key secondary endpoints were overall survival, IRC-assessed overall response confirmed by at least two CT scans done every 12 weeks (overall response defined as complete response plus complete response with incomplete bone marrow recovery plus nodal partial response plus partial response), investigator-assessed progression-free survival and response, proportion of patients with a negative response for minimal residual disease (<1 chronic lymphocytic leukaemia cell per 10 000 leucocytes) confirmed by central laboratory assessment of peripheral blood or bone marrow aspirate, and safety. Other secondary endpoints included time to improvement in FACIT-Fatigue score, rate of sustained haemoglobin improvement, and rate of sustained platelet improvement. Analyses of progression-free survival and overall survival were adjusted for the stratification factors.

Statistical analysis

We calculated that about 580 patients (290 per treatment group) needed to be randomised to observe 342 progression-free survival events. The study was designed to detect a hazard ratio (HR) of 0·7 for the ibrutinib group compared with the placebo group (corresponding with an improvement of 43% in median progression-free survival from 15 months to 21·5 months), with 90% power at a one-sided significance level of 0·025 using a group sequential testing design. One interim analysis was planned after observing about 171 progression-free survival events (50% of the total planned events); the corresponding p value for early stopping for efficacy was 0·0015. Periodic safety review by the independent data monitoring committee was planned after about 120 patients were randomised and after 300 patients were randomised.

After a protocol amendment in early 2014, following the positive results of the phase 3 RESONATE study of ibrutinib versus ofatumumab,[16] crossover to ibrutinib

was permitted for eligible patients in the placebo group who had IRC-confirmed disease progression. To preserve the integrity of the data and minimise bias in the study, a separate designated team oversaw the crossover process for individual patients. The crossover was implemented after all patients had been enrolled in the study.

The distribution of time-to-event endpoints, including progression-free survival and overall survival, was estimated by the Kaplan-Meier method. All statistical tests were based on a two-sided alpha level of 0·05. Negative response for minimal residual disease was analysed by use of Fisher's exact test. To adjust for unequal lengths of study treatment duration among patients, and potentially between treatment groups, exposure-adjusted incidence was also used. The inverse probability of censoring weighting technique, a widely accepted statistical method for summarising the treatment difference by adjusting the crossover effect, creates a scenario of missing follow-up data by censoring the follow-up of each patient at the time of crossover (ie, weight=0 for time periods after crossover). For patients with similar characteristics that did not drop out or cross over, the inverse probability of censoring weighting method assigns larger weights to "re-create" the population that would have been observed without crossover. Consequently, the estimates of treatment benefit can be interpreted as the underlying treatment benefit if all patients stay on the assigned treatment until death provided that all the model assumptions are correct.[20]

All randomised patients were included in the efficacy analyses (intention-to-treat population). All randomised patients who received at least one dose of study drug were included in the safety analyses. SAS (version 9.2) software was used to generate statistical data. This trial is registered with ClinicalTrials.gov, number NCT01611090.

Role of the funding source

The study design was developed in a joint effort of the principal academic investigators and the funders of the study. The investigators collected the data and the sponsors confirmed the accuracy of the data and compiled them for summation and analysis. Final statistical analyses were performed by the biometrics group at Janssen Research & Development. This manuscript was written and approved by all the authors with editorial assistance from a professional medical writer funded by Janssen. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

Between Sept 19, 2012, and Jan 21, 2014, 578 patients were randomly assigned to ibrutinib or placebo in combination with bendamustine plus rituximab (289 in each group; figure 1). The number of patients with chronic lymphocytic leukaemia and small lymphocytic lymphoma was the same in both treatment groups (table 1). The groups were also well balanced with regard to age, sex, ECOG performance status, *IGHV* mutational status, whether or not patients were refractory to purine

	Ibrutinib, bendamustine, and rituximab (n=289)	Placebo, bendamustine, and rituximab (n=289)
Age (years)	64 (31–86)	63 (36–83)
Sex		
Male	193 (67%)	189 (65%)
Female	96 (33%)	100 (35%)
Diagnosis		
Chronic lymphocytic leukaemia	257 (89%)	257 (89%)
Small lymphocytic lymphoma	32 (11%)	32 (11%)
ECOG performance status		
0	125 (43%)	126 (44%)
1	164 (57%)	163 (56%)
Rai stage*	256	258
0–II	157 (61%)	139 (54%)
III–IV	99 (39%)	119 (46%)
Binet stage*	256	258
A	26 (10%)	23 (9%)
B	132 (52%)	119 (46%)
C	98 (38%)	116 (45%)
Bulky disease ≥5 cm	168 (58%)	156 (54%)
Del(11q)	87 (30%)	65 (22%)
IGHV status*	259	260
Mutated	49 (19%)	52 (20%)
Unmutated	210 (81%)	208 (80%)
ZAP70 expression*	271	276
Raised	204 (75%)	190 (69%)
Not raised	67 (25%)	86 (31%)
Purine analogue refractory	75 (26%)	74 (26%)
Previous lines of therapies	289	288
Mean (range)	2 (1–11)	2 (1–9)
1 previous line	140 (48%)	138 (48%)
2 previous lines	72 (25%)	78 (27%)
≥3 previous lines	77 (27%)	72 (25%)
Previous therapy		
Purine analogue	206 (71%)	209 (72%)
Alkylating agent	275 (95%)	275 (95%)
Anti-CD20	203 (70%)	200 (69%)
Common regimens used		
FCR	120 (42%)	109 (38%)
Other fludarabine-based combinations	92 (32%)	102 (35%)
Bendamustine plus rituximab	10 (3%)	9 (3%)
Chlorambucil plus anti-CD20 mAb	16 (6%)	15 (5%)
Time from progression or relapse since last line of treatment to randomisation (months)	2·9 (0–48)	2·6 (0–73)
Time from last treatment to randomisation (months)	24·0 (0·7–154·8)	20·9 (0·2–160·8)

Data are median (range), n (%), or n, unless otherwise stated. ECOG=Eastern Cooperative Oncology Group. FCR=fludarabine, cyclophosphamide, and rituximab. mAb=monoclonal antibody. *Staging criteria for patients with chronic lymphocytic leukaemia only, using diagnosis at study entry; not all samples were evaluable for biomarker data.

Table 1: **Baseline characteristics**

analogue treatment, and number and type of previous therapies (table 1). However, a higher proportion of patients in the placebo group had Rai stage III or IV disease, whereas the ibrutinib group had a higher proportion of patients with bulky disease and del(11q). Patients in both treatment groups had received a median of two previous therapies. Most patients had received previous treatment with purine analogues, alkylating agents, and anti-CD20 antibodies.

Six cycles of bendamustine plus rituximab were completed by 235 (81%) patients in the ibrutinib group and by 222 (77%) patients in the placebo group. Median exposure to the oral study drug was 14·7 months (IQR 11·7–19·1) in the ibrutinib group compared with 12·8 months (8·7–16·1) in the placebo group, with 210 patients (73%) and 160 (55%) patients receiving study drug treatment for 12 months or more, respectively (appendix p 4). Overall, 84 patients in the ibrutinib group and 187 patients in the placebo group discontinued treatment. An adverse event was the primary reason for discontinuation in 41 (14%) patients in the ibrutinib group and 34 (12%) patients in the placebo group. Progressive disease or relapse was the primary reason for discontinuation in 14 (5%) and 130 (45%) patients in the ibrutinib and placebo groups, respectively, and at the time of analysis, 90 patients from the placebo group had crossed over to ibrutinib after progression (figure 1).

On March 10, 2015, the independent data monitoring committee performed a formal interim analysis with 70% of the planned total number of events. The prespecified statistical boundary for early stopping was crossed ($p<0·0001$ for the primary endpoint, progression-free survival). The independent data monitoring committee recommended unblinding the study because of a favourable benefit-risk profile for the study, and the study was unblinded and the database was locked directly after this recommendation. At the interim analysis, the primary endpoint of the trial was met: after a median follow-up of 17 months (IQR 13·7–20·7). IRC-assessed progression-free survival was significantly longer in the ibrutinib group than in the placebo group (not reached [95% CI not evaluable] in the ibrutinib group *vs* 13·3 months [95% CI 11·3–13·9] in the placebo group; HR 0·203, 95% CI 0·150–0·276; $p<0·0001$; figure 2). There were 56 progression-free survival events in the ibrutinib group and 183 in the placebo group. At time of analysis, 90 (31%) of 289 patients in the placebo plus bendamustine plus rituximab group with IRC-confirmed progressive disease had crossed over to receive ibrutinib monotherapy (420 mg once daily). Follow-up is continuing for all patients; at the

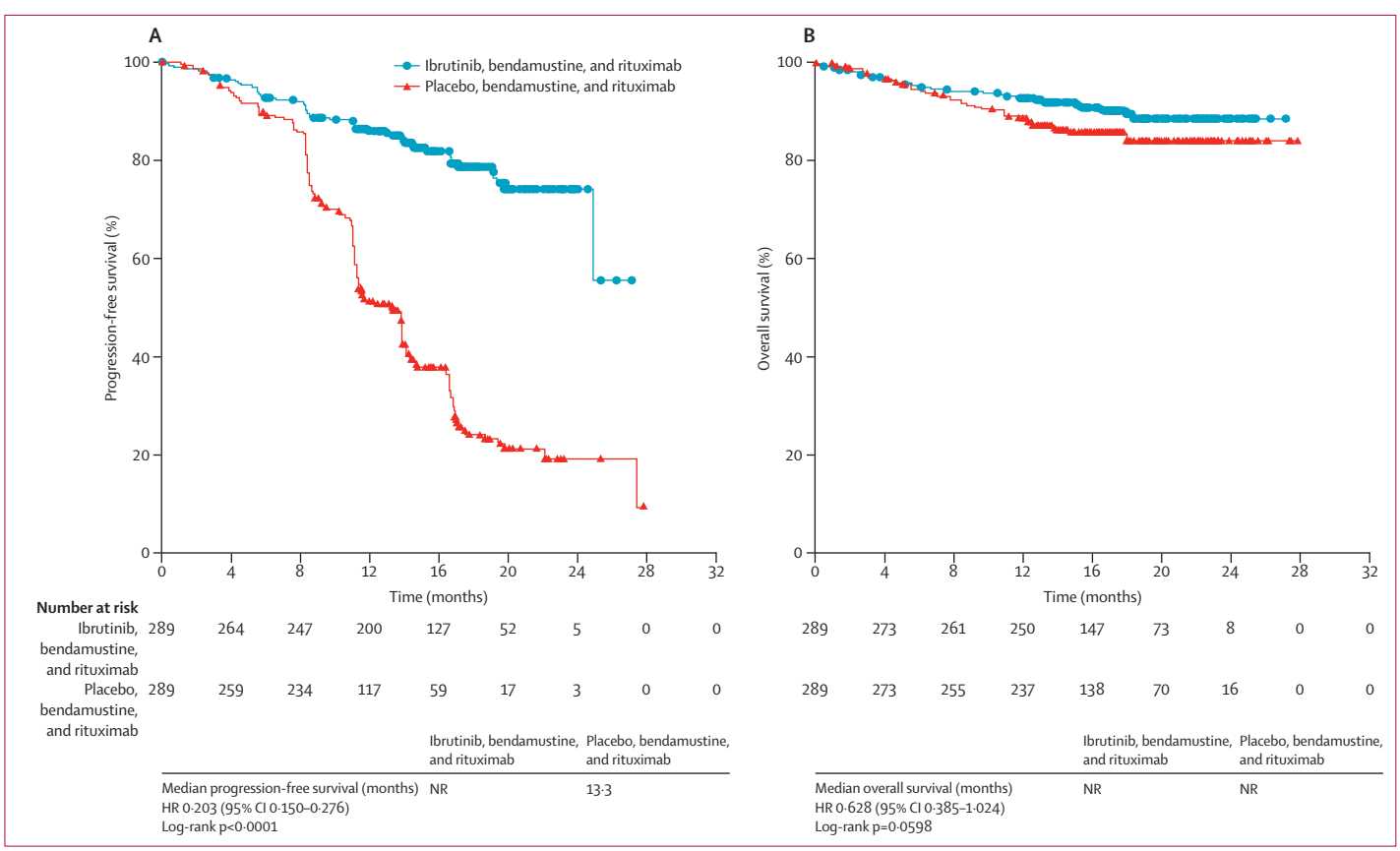

***Figure 2*: (A) Progression-free survival, as assessed by the IRC, and (B) overall survival**
IRC=independent review committee. HR=hazard ratio. NR=not reached.

time of analysis, 14 patients in the placebo group had received subsequent therapy other than ibrutinib following confirmed progressive disease.

IRC-assessed progression-free survival at 18 months was 79% (95% CI 73–83) in the ibrutinib group and 24% (18–31) in the placebo group (HR 0·203, 95% CI 0·150–0·276; p<0·0001). In planned analyses, the HR for IRC-assessed progression-free survival was consistently better in the ibrutinib group than in the placebo group across all subgroups, including those with adverse prognostic features (figure 3). Planned Kaplan-Meier analyses for IRC-assessed progression-free survival in subgroups based on refractory to purine analogues status (yes *vs* no), one versus more than one previous therapy, Rai stage, bulky disease status, and treatment-free interval from last therapy (≥36 months *vs* <36 months) are shown in the appendix (pp 17–18). Investigator-assessed progression-free survival outcomes were consistent with the IRC results (HR 0·201, 95% CI 0·145–0·278; p<0·0001; appendix p 19). Investigator-assessed median progression-free survival was not reached (95% CI not evaluable) in the ibrutinib group and 13·9 months (95% CI 13·8–14·5) in the placebo group.

Median overall survival was not reached in either group (figure 2), and there was no statistically significant difference in overall survival between patients treated with ibrutinib and those treated with placebo (HR 0·628, 95% CI 0·385–1·024; p=0·0598). However, 90 (31%) of 289 patients from the placebo group crossed over to receive ibrutinib after IRC-confirmed disease progression. A planned analysis for overall survival with adjustment for crossover using an inverse probability of censoring weighting method is shown in the appendix (p 20). When adjusting for crossover using this method, patients in the ibrutinib group had significantly longer overall survival than those in the placebo group (HR 0·577, 95% CI 0·348–0·957; p=0·033). Median overall survival was not reached (95% CI not evaluable) in either ibrutinib or placebo group.

The proportion of patients achieving an IRC-assessed overall response was significantly higher in the ibrutinib group than in the placebo group (239 [83%] *vs* 196 [68%]; risk ratio 1·22, 95% CI 1·11–1·34; p<0·0001). 30 (10%) patients achieved a complete response or complete response with incomplete bone marrow recovery in the ibrutinib group compared with eight (3%) patients in the placebo group (figure 4). Investigator-assessed overall responses were noted in 249 (86%) patients in the ibrutinib group compared with 199 (69%) patients in the placebo group, (p<0·0001), with 62 (21%) patients versus 17 (6%) patients achieving a complete response or complete response with incomplete bone marrow recovery, respectively (figure 4). This difference in complete response between investigator and IRC assessment is explained by an independent assessment of radiological scans including stringent evaluation of lymph node and volumetric assessment of spleen size used by the IRC. Although there was a difference in investigator-reported and IRC-reported results for response, the overall concordance in progressive disease assessment was 90% (261 patients) in the ibrutinib group and 85% (247 patients) in the placebo group.

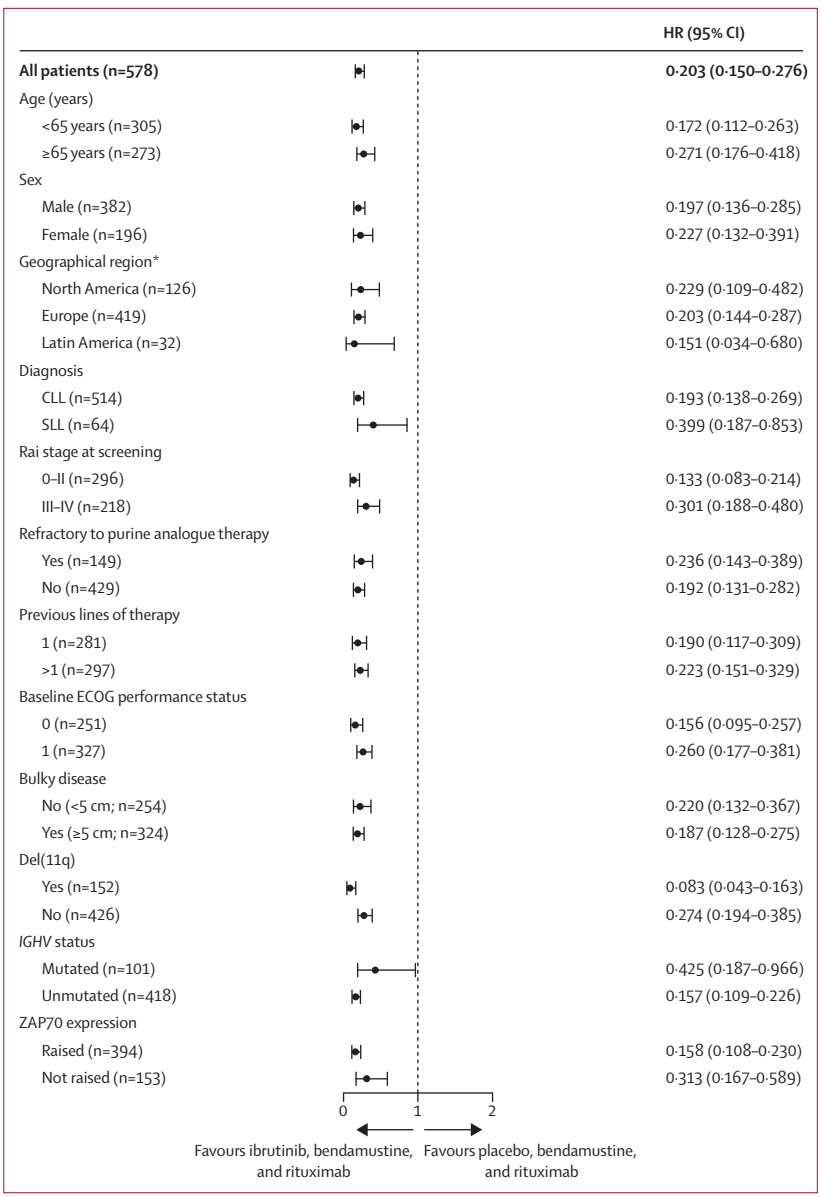

Figure 3: **Subgroup analysis of progression-free survival, as assessed by the IRC**
Numbers based on information available at randomisation, by stratification group. IRC=independent review committee. HR=hazard ratio. CLL=chronic lymphocytic leukaemia. SLL=small lymphocytic lymphoma. ECOG=Eastern Cooperative Oncology Group. *One patient from Asia not shown.

Minimal residual disease was assessed in patients with suspected clinical or radiographic complete response (120 [42%] patients in the ibrutinib group and 57 [20%] patients in the placebo group; figure 5). In the intention-to-treat population, the proportion of patients with minimal residual disease negative status (IRC assessed) was higher in the ibrutinib group than in the placebo group (37 [13%] *vs* 14 [5%]; p=0·0011).

Changes in haematological parameters during therapy were similar in both treatment groups. The absolute neutrophil count and platelet count fluctuated during the first six cycles and then showed a gradual increase. Haemoglobin concentrations decreased until cycle 2 in the ibrutinib group and cycle 3 in the placebo group, and then increased (appendix p 21). Mean and median neutrophil and haemoglobin values tended to be similar between groups or higher in the ibrutinib group, particularly during the first six cycles. Mean and median platelet counts fluctuated to a greater extent in the placebo group but generally tended to be higher than the ibrutinib group.

Four patients (two in each treatment group) from the intention-to-treat population did not receive oral study drug and so were excluded from the safety analysis group (figure 1). The overall proportion of patients with adverse events or grade 3–4 adverse events was similar between the two treatment groups (table 2; appendix pp 6–12); 222 (77%) of 287 patients in the ibrutinib group and 212 (74%) of 287 patients in the placebo group reported grade 3–4 events. Consistent with the known profile of the background bendamustine plus rituximab therapy, the most common all-grade adverse events were neutropenia and nausea (table 2). The most common grade 3–4 adverse events were neutropenia and thrombocytopenia. Diarrhoea was more frequent in the ibrutinib group than in the placebo group, but was predominantly grade 1. The frequency of grade 3 or worse diarrhoea was low and similar between groups.

Serious adverse events occurred in 150 (52%) patients in the ibrutinib group compared with 125 (44%) patients in the placebo group (appendix p 5). The number of deaths resulting from treatment-emergent adverse events was similar in both treatment groups (19 patients in the ibrutinib group and 18 patients in the placebo group). The number of deaths that occurred during the trial is reported in the appendix (p 13).

Transient cytopenias occurred, as expected with the background of bendamustine plus rituximab therapy.

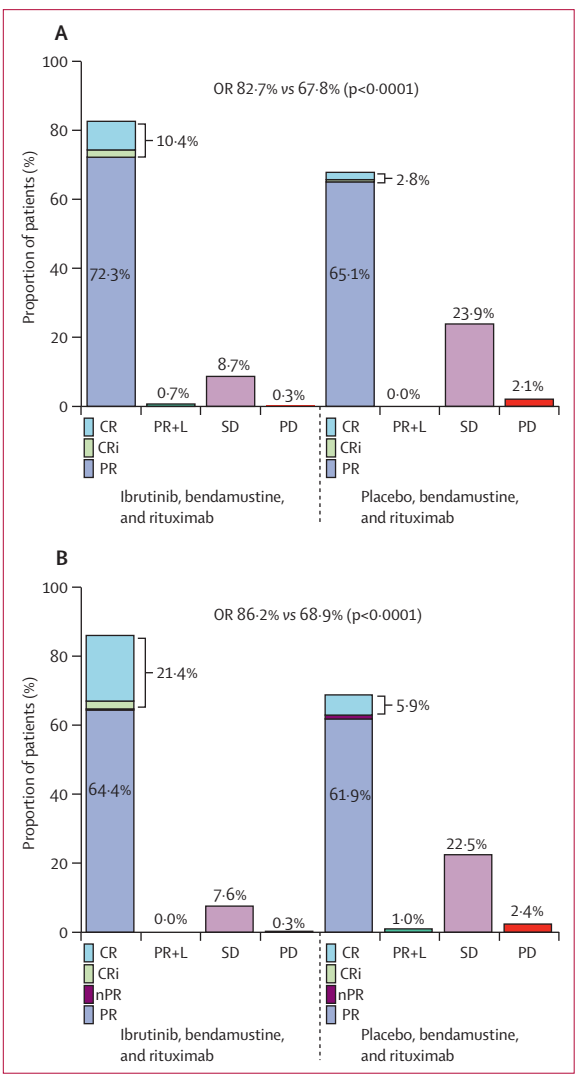

Figure 4: **Overall response, as assessed by (A) the IRC and (B) the investigator**
Intention-to-treat analysis (289 patients in each group). IRC=independent review committee. OR=overall response. CR=complete response. CRi=complete response with incomplete bone recovery. PR=partial response except for lymphocytosis. PR+L=partial response with lymphocytosis. SD=stable disease. PD=progressive disease. nPR=nodular partial response.

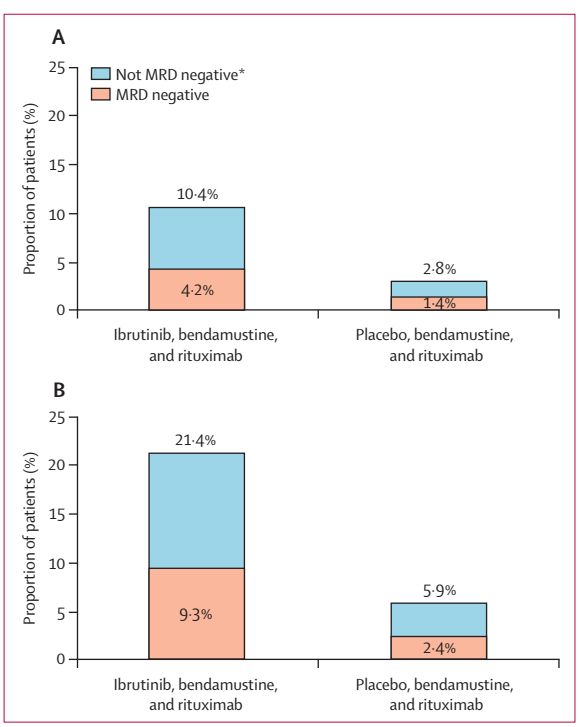

Figure 5: **Minimal residual disease analysis**
Patients with a negative response for minimal residual disease (MRD) among those with a complete response (CR) or complete response with incomplete bone marrow recovery (CRi), as assessed by (A) the independent review committee and (B) the investigator. MRD negative status, <1 chronic lymphocytic leukaemia cell per 10 000 leucocytes; 120 and 57 patients had MRD assessed in the ibrutinib and placebo groups, respectively. *Includes patients with missing MRD data.

	Ibrutinib, bendamustine, and rituximab (n=287)				Placebo, bendamustine, and rituximab (n=287)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Neutropenia	13 (5%)	52 (18%)	102 (36%)	0	12 (4%)	52 (18%)	93 (32%)	0
Nausea	104 (36%)	1 (<1%)	1 (<1%)	0	100 (35%)	1 (<1%)	0	0
Diarrhoea	96 (33%)	6 (2%)	0	0	63 (20%)	4 (1%)	0	0
Thrombocytopenia	45 (16%)	29 (10%)	14 (5%)	0	26 (9%)	28 (10%)	15 (5%)	0
Pyrexia	61 (21%)	10 (3%)	0	0	57 (20%)	5 (2%)	0	0
Anaemia	55 (19%)	10 (3%)	0	0	60 (21%)	22 (8%)	1 (<1%)	0
Fatigue	53 (18%)	9 (3%)	0	0	55 (19%)	10 (4%)	0	0
Cough	55 (19%)	0	0	0	68 (24%)	2 (<1%)	0	0
Constipation	52 (18%)	1 (<1%)	0	0	48 (17%)	2 (<1%)	0	0
Rash	49 (17%)	3 (1%)	0	0	29 (10%)	3 (1%)	0	0
Infusion-related reaction	44 (15%)	4 (1%)	0	0	58 (20%)	4 (1%)	1 (<1%)	0
Upper respiratory tract infection	40 (14%)	6 (2%)	0	0	49 (17%)	0	0	0
Headache	36 (13%)	5 (2%)	0	0	46 (16%)	0	0	0
Vomiting	37 (13%)	2 (<1%)	0	0	42 (15%)	3 (1%)	1 (<1%)	0
Bronchitis	30 (10%)	7 (2%)	0	0	19 (7%)	10 (4%)	0	0
Decreased appetite	34 (12%)	2 (<1%)	0	0	39 (14%)	1 (<1%)	1 (<1%)	0
Pneumonia	15 (5%)	16 (6%)	5 (2%)	0	15 (5%)	17 (6%)	3 (1%)	1 (<1%)
Oedema (peripheral)	33 (11%)	2 (<1%)	0	0	30 (11%)	3 (1%)	0	0
Abdominal pain	32 (11%)	2 (<1%)	0	0	22 (8%)	1 (<1%)	0	0
Febrile neutropenia	0	22 (8%)	12 (4%)	0	0	10 (4%)	13 (5%)	1 (<1%)
Muscle spasms	33 (11%)	1 (<1%)	0	0	14 (5%)	0	0	0
Arthralgia	28 (10%)	3 (1%)	0	0	26 (9%)	0	0	0
Chills	30 (10%)	1 (<1%)	0	0	31 (11%)	1 (<1%)	0	0
Back pain	28 (10%)	2 (<1%)	0	0	21 (7%)	0	0	0
Hyperuricaemia	22 (8%)	3 (1%)	4 (1%)	0	18 (6%)	0	0	0
Pruritus	29 (10%)	0	0	0	32 (11%)	1 (<1%)	0	0
Dyspnoea	13 (5%)	1 (<1%)	1 (<1%)	0	26 (9%)	4 (1%)	1 (<1%)	0

Data are n (%).

Table 2: **Treatment-emergent adverse events (>10% patients)**

Anaemia was reported in 65 (23%) patients in the ibrutinib group (grade 3–4 anaemia: ten [3%] patients) and 83 (29%) patients in the placebo group (grade 3–4 anaemia: 23 [8%]). However, patients with anaemia showed improvement over time (appendix p 21). Patients receiving ibrutinib required fewer transfusions than those receiving placebo (67 [23%] *vs* 82 [29%]), most of which were red blood cell transfusions. A similar proportion of patients in both groups required use of growth factors (155 [54%] in the ibrutinib group *vs* 148 [52%] in the placebo group).

The frequency of infections was similar between the ibrutinib and placebo groups (all-grade: 202 [70%] *vs* 201 [70%]; grade ≥3: 83 [29%] *vs* 72 [25%]). The exposure-adjusted incidence of infections was lower in the ibrutinib group than in the placebo group (10·3 *vs* 11·2 per 100 patient-months), with similar incidence of grade 3 or worse infections (2·4 per 100 patient-months in each group).

Major haemorrhage (grade ≥3 haemorrhage, central nervous system haemorrhage, or serious bleeding at any grade) was more frequent in the ibrutinib group than in the placebo group (table 3). In patients with major haemorrhage, six of 11 patients in the ibrutinib group and three of five patients in the placebo group were taking concomitant anticoagulant or antiplatelet treatment. The

	Ibrutinib, bendamustine, and rituximab (n=287)	Placebo, bendamustine, and rituximab (n=287)
Any grade bleeding	89 (31%)	42 (15%)
Grade 1–2 bleeding events		
Haematoma	23 (8%)	3 (1%)
Contusion	22 (8%)	9 (3%)
Epistaxis	17 (6%)	9 (3%)
Ecchymosis	9 (3%)	2 (1%)
Petechiae	8 (3%)	1 (<1%)
Major haemorrhage*	11 (4%)	5 (2%)

Data are n (%). *Major haemorrhage includes grade ≥3 haemorrhage, central nervous system haemorrhage, and serious bleeding events of any grade.

Table 3: **Bleeding-related events**

onset of major haemorrhage seemed independent of time (median 4·21 months [range 1·31–10·58] in the ibrutinib group *vs* 2·30 months [0·03–11·79] in the placebo group). Two patients in the ibrutinib group discontinued treatment because of major haemorrhage.

Two deaths caused by haemorrhagic events were seen in the ibrutinib group. One patient had a pre-existing 7·8 cm abdominal aortic aneurysm at baseline that ruptured shortly after starting treatment, and the other had postprocedural haemorrhage secondary to large intestine perforation that was deemed unrelated to ibrutinib.

Grade 1–2 bleeding events including haematoma, contusion, epistaxis, ecchymosis, and petechiae were more common in the ibrutinib group than in the placebo group (table 3).

Atrial fibrillation was reported in 21 (7%) patients in the ibrutinib group and seven (2%) patients in the placebo group. Most atrial fibrillation events were grade 1–2 and none were fatal. 25 patients in the ibrutinib group and 22 patients in the placebo group had a history of atrial fibrillation or atrial flutter. Of these patients, seven (28%) in the ibrutinib group and two (9%) in the placebo group developed atrial fibrillation or atrial flutter during the trial. Among patients with continuing cardiac comorbid disorders at study entry (including hypertension, atrial fibrillation, or abnormal heart rhythm), most did not develop an adverse event of atrial fibrillation or atrial flutter (58 [87%] of 67 in the ibrutinib group *vs* 64 [96%] of 67 in the placebo group).

The median time to onset of atrial fibrillation was 3·0 months (range 0·3–17·5) in the ibrutinib group and 2·4 months (0·6–18·9) in the placebo group. Only four (1%) of 289 patients in the ibrutinib group discontinued treatment because of atrial fibrillation. No dose reductions were performed because of atrial fibrillation, but seven (32%) of 22 patients with atrial fibrillation or atrial flutter in the ibrutinib group had treatment withheld and then restarted without further episodes of atrial fibrillation.

Eye disorders occurred in 66 (23%) patients in each group, with the most common being blurred vision (15 [5%] in the ibrutinib group *vs* 18 [6%] in the placebo group) and cataracts (ten [3%] *vs* three [1%]). The frequency of eye disorders of grade 3 or worse was low (four [1%] *vs* three [1%]).

Frequencies of other malignancies (mainly non-melanoma skin cancer) during treatment and follow-up were similar in both groups (24 [8%] in the ibrutinib group *vs* 23 [8%] in the placebo group). Non-skin cancers were reported in seven (2%) patients in the ibrutinib group compared with 14 (5%) in the placebo group. The occurrence of myelodysplastic syndrome was low and similar between groups (two patients in each group); no patients developed acute myeloid leukaemia. There were no transformations to a more aggressive histology in the ibrutinib group, whereas there were three in the placebo group.

Most patients did not need dose reductions of ibrutinib or placebo (243 [85%] and 261 [91%], respectively). In the ibrutinib group, one or two dose reductions were reported for 32 and 12 patients, respectively, compared with 16 and 10 patients in the placebo group, respectively. One patient in the ibrutinib group had a dose reduction because of concomitant CYP3A4 or CYP3A5 inhibitor use; all other dose reductions resulted from adverse events.

Patient-reported outcomes were gathered and fatigue data have been analysed. Of the 578 patients enrolled, 540 (93%) provided FACIT-Fatigue responses at baseline. Among those with the worst baseline fatigue, unadjusted results suggest apparent improvements in fatigue score over time for both treatment groups during the first six cycles of bendamustine plus rituximab therapy, and greater continued improvements in fatigue were subsequently seen in the ibrutinib group compared with the placebo group ($p<0·05$ at cycle 10).

Discussion

To our knowledge, this large, international trial is the first phase 3 study to combine any kinase inhibitor therapy with chemoimmunotherapy and the first double-blind, placebo-controlled study of ibrutinib. Our results show that the addition of ibrutinib to bendamustine plus rituximab led to significantly improved progression-free survival and the proportion of patients achieving an overall response, without unexpected or cumulative toxicities, in patients with relapsed or refractory chronic lymphocytic leukaemia or small lymphocytic lymphoma.

In this population of patients, with a large proportion having high-risk features such as unmutated *IGHV* status (81% of 519 patients), del(11q) (26%), and bulky disease (56%), the addition of ibrutinib to chemo-immunotherapy with bendamustine plus rituximab significantly improved outcomes compared with bendamustine plus rituximab alone, as evidenced by a statistically significant reduction in disease progression or death. The median time between previous treatment and study treatment was 24 months or less in both treatment groups, indicating a population with poor prognosis. The positive effects of ibrutinib in addition to bendamustine plus rituximab were seen across all subgroups of patients, including those with adverse prognostic factors such as those refractory to purine analogues, with Rai stage III or IV disease, and with bulky disease. The magnitude of benefit was notable in the subgroups of patients with unmutated *IGHV*, raised ZAP70 expression, and del(11q). Both unmutated *IGHV* and raised ZAP70 expression have long been associated with increased B-cell receptor signalling, which may therefore render these tumours susceptible to regimens containing B-cell receptor signalling inhibitors such as ibrutinib.[21] Progression-free survival outcomes were also consistent irrespective of whether the patient had received one or more than one previous line of therapy. No Richter's transformations were seen in the

ibrutinib group. This finding might be accounted for in part by the exclusion of patients with del(17p).

Patients with del(17p) were specifically excluded from this study because patients with del(17p) who were treated with bendamustine plus rituximab had a very poor outcome with a median progression-free survival of only 6·8 months.[22] These findings are reflected in guidelines in which bendamustine plus rituximab is not a recommended treatment for patients with relapsed or refractory chronic lymphocytic leukaemia who are positive for del(17p).[4,5]

The initial separation in progression-free survival curves between treatment groups was seen at 4 months. This finding supports the concomitant administration of ibrutinib and bendamustine plus rituximab, since the beneficial effects of ibrutinib were seen while patients were still receiving bendamustine plus rituximab therapy. The assessment of progression-free survival on the basis of whether a patient was treated after one previous therapy or more than one previous therapy showed that progression-free survival was longer for patients in the ibrutinib group after only one previous therapy. This result suggests that there might be a benefit of treating patients with chronic lymphocytic leukaemia with ibrutinib in addition to bendamustine plus rituximab earlier in their disease course rather than later.

The addition of ibrutinib also significantly improved the proportion of patients achieving an overall response compared with placebo, including the proportion of patients who achieved complete response or complete response with incomplete bone marrow recovery. The proportion of patients with a negative response for minimal residual disease also favoured treatment with ibrutinib in addition to bendamustine plus rituximab, suggesting that ibrutinib improves the depth of response. Because median follow-up was 17 months, the data are not sufficiently mature to demonstrate durability of minimal residual disease negativity. However, previous studies with ibrutinib have shown that response improves over time,[15] and the same was also seen in the phase 1b study of ibrutinib in addition to bendamustine plus rituximab where investigator-assessed complete response improved from 16·7% (similar to the investigator-assessed complete response rate in this study) at about 16 months' follow-up to 40% at 36 months' follow-up.[17] Hence, future follow-up in our study will be of interest.

In our study, median overall survival was not reached in either treatment group and there was no significant difference between the two groups. A potential contributing factor to this finding was that 90 (31%) of 289 patients from the placebo group crossed over to receive ibrutinib at the timepoint of progression. When adjusting for crossover using an inverse probability of censoring weighting method, survival benefit favouring the ibrutinib group was noted (HR 0·577; p=0·033). Overall survival data should be interpreted with some caution because most overall survival events have not yet occurred; long-term follow-up for overall survival is planned and is intended to be reported at a later date.

The results presented here are similar to those seen in a previous study of bendamustine plus rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia, in which median progression-free survival was 15·2 months after 24 months of follow-up, the proportion of patients achieving an overall response was 59%, and median overall survival was 33·9 months.[6] In that study, most patients only received four cycles of bendamustine plus rituximab, whereas most patients in our trial received the full six cycles of bendamustine plus rituximab. Median overall survival has not been reached in the placebo group in our study, but is likely to be longer than that previously reported because of patients crossing over to ibrutinib upon progressive disease.

Overall, the safety profile was consistent with the known individual profiles for ibrutinib and the combination of bendamustine plus rituximab. The frequency of all bleeding adverse events was higher in the group receiving ibrutinib in addition to bendamustine plus rituximab than it was in the group receiving placebo in addition to bendamustine plus rituximab, but these events were mostly grade 1 and 2 in nature. Overall, a low frequency of atrial fibrillation was seen in both treatment groups; however, a higher proportion was seen in the ibrutinib group. Both bleeding and atrial fibrillation adverse events are consistent with the single-agent ibrutinib safety profile, with these events being manageable and few patients discontinuing therapy. The placebo-controlled nature of this study allowed for a more robust review of various adverse events, including ocular disorders and second primary malignancies, both of which showed no overall difference between treatment groups. Of note, the frequency of non-skin cancers in the study was low, with fewer occurring in the ibrutinib group than in the placebo group. The occurrence of myelodysplastic syndrome was low and similar between both treatment groups and no patients developed acute myeloid leukaemia. There were no new unexpected safety signals, and thus these results indicate that ibrutinib can be safely combined with bendamustine plus rituximab, without cumulative toxicities.

One limitation to the interpretation of this study is that the study was not designed to evaluate ibrutinib as a single agent or ibrutinib plus rituximab compared with ibrutinib, bendamustine, and rituximab. While it seems clear that ibrutinib adds to the efficacy of bendamustine plus rituximab, the question remains if bendamustine plus rituximab is necessary to achieve good patient outcomes in this relapsed/refractory population. One of the difficulties in speculating about this is that the data from this trial have yet to fully mature. Because the median progression-free survival for ibrutinib, bendamustine, and rituximab has not yet been observed, the true effect of the addition of ibrutinib to bendamustine plus rituximab

is not yet fully evaluable. However, as data mature and follow-up continues, this should become clearer.

The results of this trial do demonstrate that ibrutinib has added benefit beyond the current standard-of-care chemoimmunotherapy in previously treated patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma. Ibrutinib can be administered safely with bendamustine plus rituximab and represents an alternative option to traditional chemoimmunotherapy.

Contributors

AC-K, PC, GF, RSS, SG, AP, AJ, HP, SR, OS, PP, MAP, MM, MS, SS, CP, AH, and MH were involved in the study conception and design, provision of study materials or patients, collection and assembly of data, data analysis and interpretation, manuscript writing, and manuscript approval. JM, M-SD, JL, AA, SR, NLB, DV, AG, AM, and CK were involved in provision of study materials or patients, collection and assembly of data, data analysis and interpretation, manuscript writing, and manuscript approval. SB was involved in study conception and design, data analysis and interpretation, manuscript writing, and manuscript approval. FD was involved in provision of study materials or patients, and manuscript approval.

Declaration of interests

AC-K declares that the Mayo Clinic received funds for this clinical trial. PC has received research grants and honoraria from Hoffmann-La Roche and Janssen-Cilag; a research grant from GlaxoSmithKline/Novartis; and grants and honoraria from Astellas, Gilead, and Mundipharma. FD has received an honorarium for an advisory board from Amgen and non-financial support from Janssen for travel and accommodation. GF has received fees from Janssen, Hoffmann-La Roche, Celgene, and Lundbeck. JM has received grants from Janssen and Roche. NLB has received fees for advisory boards from Gilead and Seattle Genetics. M-SD has received fees from Janssen and Roche. AA has received a grant from Janssen. SR has received fees from Janssen and Pharmacyclics. DV has received honoraria from Lundbeck, Celgene, and Genentech and research funding from Roche. PP has received honoraria from Janssen. AG has received fees for speaker bureaus and advisory boards from Johnson & Johnson/Pharmacyclics and Takeda, and consultancy and advisory board fees from Celgene. AM has received fees for speakers bureaus from Pharmacyclics, Celgene, and Genentech; research grants from Pharmacyclics, Gilead, TG Therapeutics, AbbVie, Celgene, and Acerta; and has served as an adviser for Pharmacyclics, Gilead, and AbbVie. MAP has received honoraria for speaking and consulting from Novartis and Janssen. CK has received a research grant to the Swedish CLL group. MM is an employee of Janssen R&D. MS and CP are employees of Johnson & Johnson and have stock ownership. SS is an employee of Johnson & Johnson. SB is an employee of Janssen R&D and has stock ownership with Janssen R&D, Pharmacyclics, and AbbVie. AH is an employee of Janssen and has stock ownership with Johnson & Johnson. All other authors declare that they have no competing interests.

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