Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial

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Summary

Background Both single-agent ibrutinib and chlorambucil plus obinutuzumab have shown superior efficacy to chlorambucil monotherapy and are standard first-line treatments in chronic lymphocytic leukaemia. We compared the efficacy of the combination of ibrutinib plus obinutuzumab with chlorambucil plus obinutuzumab in first-line chronic lymphocytic leukaemia or small lymphocytic lymphoma.

Methods iLLUMINATE is a multicentre, randomised, open-label, phase 3 trial done at 74 academic and community hospitals in Australia, Canada, Israel, New Zealand, Russia, Turkey, the EU, and the USA in patients with previously untreated chronic lymphocytic leukaemia or small lymphocytic lymphoma, either aged 65 years or older or younger than 65 years with coexisting conditions. Patients were randomly assigned (1:1) using a blocked randomisation schedule, stratified by Eastern Cooperative Oncology Group performance status and cytogenetics, to receive ibrutinib plus obinutuzumab (oral ibrutinib [420 mg once daily continuously] combined with intravenous obinutuzumab [100 mg on day 1, 900 mg on day 2, 1000 mg on day 8, and 1000 mg on day 15 of cycle 1 and on day 1 of subsequent 28-day cycles, for a total of six cycles]) or chlorambucil plus obinutuzumab (oral chlorambucil [0·5 mg/kg bodyweight on days 1 and 15 of each 28-day cycle for six cycles] combined with the same obinutuzumab regimen). Allocation concealment was achieved using an interactive web response system. Patients and investigators were not masked to treatment assignment. The primary endpoint was progression-free survival assessed by a masked independent review committee in the intention-to-treat population. Safety was assessed in all patients who received at least one dose of study treatment. This study is registered with ClinicalTrials.gov (NCT02264574), and patient enrolment is complete.

Findings Between Oct 6, 2014, and Oct 12, 2015, 229 patients were enrolled and randomly assigned to receive ibrutinib plus obinutuzumab (n=113) or chlorambucil plus obinutuzumab (n=116). After a median follow-up of 31·3 months (IQR 29·4–33·2), median progression-free survival was significantly longer in the ibrutinib plus obinutuzumab group (median not reached [95% CI 33·6–non-estimable]) than in the chlorambucil plus obinutuzumab group (19·0 months [15·1–22·1]; hazard ratio 0·23; 95% CI 0·15–0·37; p<0·0001). Estimated 30-month progression-free survival was 79% (95% CI 70–85) in the ibrutinib plus obinutuzumab group and 31% (23–40) in the chlorambucil plus obinutuzumab group. The most common grade 3 or 4 adverse events in both groups were neutropenia and thrombocytopenia. Serious adverse events occurred in 65 (58%) of 113 patients treated with ibrutinib plus obinutuzumab and 40 (35%) of 115 patients treated with chlorambucil plus obinutuzumab. Ibrutinib or chlorambucil treatment-related deaths were reported in one (1%) of 113 patients in the ibrutinib plus obinutuzumab group (sudden death) and one (1%) of 115 patients in the chlorambucil plus obinutuzumab group (neuroendocrine carcinoma of the skin).

Interpretation Ibrutinib plus obinutuzumab is an efficacious and safe chemotherapy-free combination treatment in previously untreated patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma independent of high-risk features and provides an alternative first-line treatment option for these patients.

Funding Pharmacyclics LLC, an AbbVie Company, and Janssen Research and Development.

Introduction

Treatment of chronic lymphocytic leukaemia has dramatically evolved with the introduction of B-cell receptor signalling inhibitors. Ibrutinib, a first-in-class, once-daily oral inhibitor of tyrosine-protein kinase BTK (also known as Bruton tyrosine kinase), has shown substantial single-drug efficacy in chronic lymphocytic leukaemia and provides a chemotherapy-free treatment option for

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Research in context

Evidence before this study

We searched PubMed up to Aug 8, 2018, for articles using the search terms "chronic lymphocytic leukemia" AND "ibrutinib" AND (["chemotherapy" OR "fludarabine" OR "chlorambucil" OR "cyclophosphamide" OR "bendamustine"] AND ["anti-CD20 monoclonal antibody" OR "rituximab" OR "ofatumumab" OR "obinutuzumab"]) with no restrictions on language or publication date. We found that combinations of ibrutinib with anti-CD20 antibodies (rituximab or ofatumumab) have been assessed in phase 2 studies and show rapid and durable remissions. No randomised studies have directly compared an ibrutinib-based regimen with chemoimmunotherapy in first-line chronic lymphocytic leukaemia.

Added value of this study

To our knowledge, the iLLUMINATE study is the first prospective study to compare a novel, non-chemotherapy ibrutinib-based regimen with a standard chemoimmunotherapy regimen in the first-line treatment of patients with chronic lymphocytic leukaemia, including in patients with high-risk genomic features (eg, del17p or *TP53* mutation). Our results show superior progression-free survival outcomes with ibrutinib plus obinutuzumab compared with chlorambucil plus obinutuzumab. A progression-free survival benefit was observed in patients with high-risk disease features (del17p, *TP53* mutation, del11q, or unmutated *IGHV*). Given that most patients in this study had non-del17p high-risk chronic lymphocytic leukaemia, the results also confirm the superior efficacy of an ibrutinib-based regimen in these other high-risk patient groups in addition to patients with a del17p or *TP53* mutation. To our knowledge, results from this study are the first to suggest that patients with del11q or unmutated *IGHV* status will have better outcomes with a non-chemoimmunotherapy regimen than with chemoimmunotherapy.

Implications of all the available evidence

Our results suggest that ibrutinib plus obinutuzumab, a chemotherapy-free option, is more efficacious than a standard chemoimmunotherapy regimen for first-line treatment of patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma, including patients with high-risk disease features.

this common leukaemia.[1–3] In the phase 3 RESONATE-2 study,[1] ibrutinib showed superior progression-free survival, overall survival, and overall response compared with chlorambucil in previously untreated older patients (aged ≥65 years) with chronic lymphocytic leukaemia or small lymphocytic lymphoma. Among older patients or those with comorbidities, recommended first-line treatment includes single-agent ibrutinib or the combination of chlorambucil with anti-CD20 therapy.[1,4–7] The efficacy of chlorambucil plus obinutuzumab in previously untreated patients with comorbidities was demonstrated by improved progression-free survival and overall survival compared with chlorambucil plus rituximab or chlorambucil alone in the CLL11 study.[5,8]

The updated 2018 International Workshop on Chronic Lymphocytic Leukaemia (iwCLL) guidelines[9] emphasise the importance of cytogenetic testing with fluorescence in-situ hybridisation (FISH) to identify chromosomal aberrations (eg, del17p or del11q) and testing for tumour protein p53 (*TP53*) and immunoglobulin heavy-chain variable region gene (*IGHV*) mutation status to aid initial treatment decisions, because these high-risk features confer unfavourable outcomes with chemoimmunotherapy.[10–14] Despite advances in chronic lymphocytic leukaemia therapy, optimal care for patients with common high-risk genomic features is not clearly defined because no published data are available from prospective, randomised controlled trials that assessed standard chemotherapy-based treatments versus novel therapies,[10,11] including chemotherapy-free regimens. Ibrutinib has shown high activity in patients with del17p or *TP53* mutations, with estimated 24-month progression-free survival of 63–82% (including in relapsed or refractory patients).[3,15–18] Although data on first-line treatment of patients with del17p or *TP53* mutation are few, a single-centre study reported 5-year progression-free survival of 74% in 34 previously untreated patients,[19] which is substantially better than previously reported progression-free survival outcomes with the first-line chemoimmunotherapy, fludarabine–cyclophosphamide–rituximab.[13] Additionally, patients with del11q chronic lymphocytic leukaemia have shorter progression-free survival with chemoimmunotherapy than those without the deletion,[13,14] whereas outcomes with ibrutinib were similar between patients with or without del11q.[1,3,15,17,20] Unmutated *IGHV* is associated with enhanced B-cell receptor signalling[21–23] and confers shorter progression-free survival and overall survival with chemoimmunotherapy than in patients with mutated *IGHV*.[10,12–14] By contrast, ibrutinib, a B-cell receptor inhibitor, has shown similar survival outcomes irrespective of *IGHV* mutation status.[1,3,15,17,20] In the iLLUMINATE study, we investigated the addition of obinutuzumab to ibrutinib versus chlorambucil plus obinutuzumab (a standard regimen widely recommended in international guidelines[4,7]) for first-line treatment of chronic lymphocytic leukaemia, with the aim of prospectively confirming the superiority of the chemotherapy-free regimen ibrutinib plus obinutuzumab over the chlorambucil plus obinutuzumab regimen in patients with high-risk genomic features.

Methods

Study design and participants

iLLUMINATE was a multicentre, randomised, open-label, phase 3 trial done at 74 academic and community hospitals

in Australia, Canada, Israel, New Zealand, Russia, Turkey, the EU, and the USA (appendix pp 2–3).

Eligible patients were aged at least 18 years, had untreated, active chronic lymphocytic leukaemia or small lymphocytic lymphoma requiring treatment per iwCLL criteria,[24] and were considered unsuitable for fludarabine-based chemoimmunotherapy because they were aged 65 years or older or younger than 65 years with at least one of the following coexisting conditions: cumulative illness rating scale score greater than 6, creatinine clearance of less than 70 mL/min, presence of del17p confirmed by FISH, or *TP53* mutation. Additional eligibility criteria were Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, measurable lymph node disease (>1·5 cm longest diameter) by CT scan, adequate haematological function (absolute neutrophil count ≥1×10^9 cells per L, platelet count >50×10^9 per L), adequate hepatic and renal function, and creatinine clearance of at least 30 mL per min.

The study was done in accordance with International Conference on Harmonisation Guideline for Good Clinical Practice and the principles of the Declaration of Helsinki. The protocol was approved by institutional review boards or independent ethics committees of all participating institutions. All patients provided written, informed consent.

Randomisation and masking

Patients were randomly assigned (1:1) to receive ibrutinib plus obinutuzumab or chlorambucil plus obinutuzumab. A blocked randomisation schedule was generated for each of the two geographic regions (North America and the rest of the world); within each scheme, randomisation was stratified by ECOG performance status (0–1 *vs* 2) and cytogenetics (del17p with or without del11q *vs* del11q without del17p *vs* neither del11q nor del17p). Patients and investigators were not masked to treatment assignment. Randomisation was controlled centrally via an interactive web response system to prevent knowledge of the next assignment in the sequence. Progression and response were assessed by an independent review committee (IRC) whose members were unaware of the treatment assignments and unaware of the investigator's assessment of response. Access to efficacy data was limited to the sponsor's staff overseeing the conduct of the study or analysing and summarising data so that no person had the ability to make an aggregated summary by treatment group before database lock.

Procedures

Treatment with ibrutinib plus obinutuzumab comprised oral ibrutinib (420 mg once daily) given until disease progression or unacceptable toxicity in combination with intravenous obinutuzumab (100 mg on day 1, 900 mg on day 2, 1000 mg on day 8, and 1000 mg on day 15 of cycle 1, then 1000 mg on day 1 of each 28-day cycle for cycles 2–6). Treatment with chlorambucil plus obinutuzumab comprised oral chlorambucil (0·5 mg/kg bodyweight on days 1 and 15 of each 28-day cycle) for six cycles in combination with the obinutuzumab regimen as in the ibrutinib plus obinutuzumab group. All patients received standard premedication for obinutuzumab-related infusion-related reactions, comprising intravenous corticosteroids, oral analgesics or antipyretics, and an antihistamine. To assess any effect of ibrutinib on the incidence of infusion-related reactions, oral study drug (ibrutinib or chlorambucil) was administered before obinutuzumab. Patients in the chlorambucil plus obinutuzumab group could receive next-line single-agent ibrutinib in crossover after IRC-confirmed disease progression. Treatment with ibrutinib or chlorambucil could be withheld for unmanageable, potentially study drug-related adverse events of grade 3 or worse; treatment with obinutuzumab could be withheld for unmanageable, potentially obinutuzumab-related toxicity meriting dose delay in the investigator's opinion. Dose modifications of ibrutinib and chlorambucil were allowed for management of adverse events (appendix p 5). Patients were withdrawn from the study in the case of consent withdrawal, loss to follow-up, or death.

See Online for appendix

CT scans were performed and assessed by local radiologists at baseline, every four treatment cycles from cycle 5 to cycle 33, and every six cycles thereafter until confirmed disease progression. CT scans were assessed and reviewed by independent central radiologists as part of an IRC for establishing response and progression.

Safety was assessed by adverse events, laboratory measurements, and clinical evaluation across the entire treatment-emergent adverse event period. This period included the time from the first dose until 30 days after the last dose of study medication or initiation of subsequent antineoplastic therapy, whichever occurred first. Non-haematological adverse events were graded using National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Haematological adverse events were assessed using iwCLL criteria.[24]

Blood samples were collected during screening and analysed centrally to examine pretreatment prognostic factors. For all patients, baseline peripheral blood samples were tested at a central laboratory for cytogenetic profiles using FISH probes to detect abnormalities in chromosomes 13q, 12, 11q, and 17p (Vysis CLL FISH Probe kit; Abbott Molecular; Des Plaines, IL, USA), and genomic profiling for mutational status of *IGHV* and other genes known to be involved in chronic lymphocytic leukaemia prognosis (eg, *TP53*). *TP53* mutations (defined as ≥10% variant allele frequency) were detected by next-generation sequencing methods. Existing locally assessed FISH and *TP53* results from the 180 days before randomisation confirming the status of del17p, del11q and *TP53* were considered adequate for eligibility and stratification purposes only. FISH cytogenetics and *TP53* mutation status by central laboratory assessment were used for all data analyses.

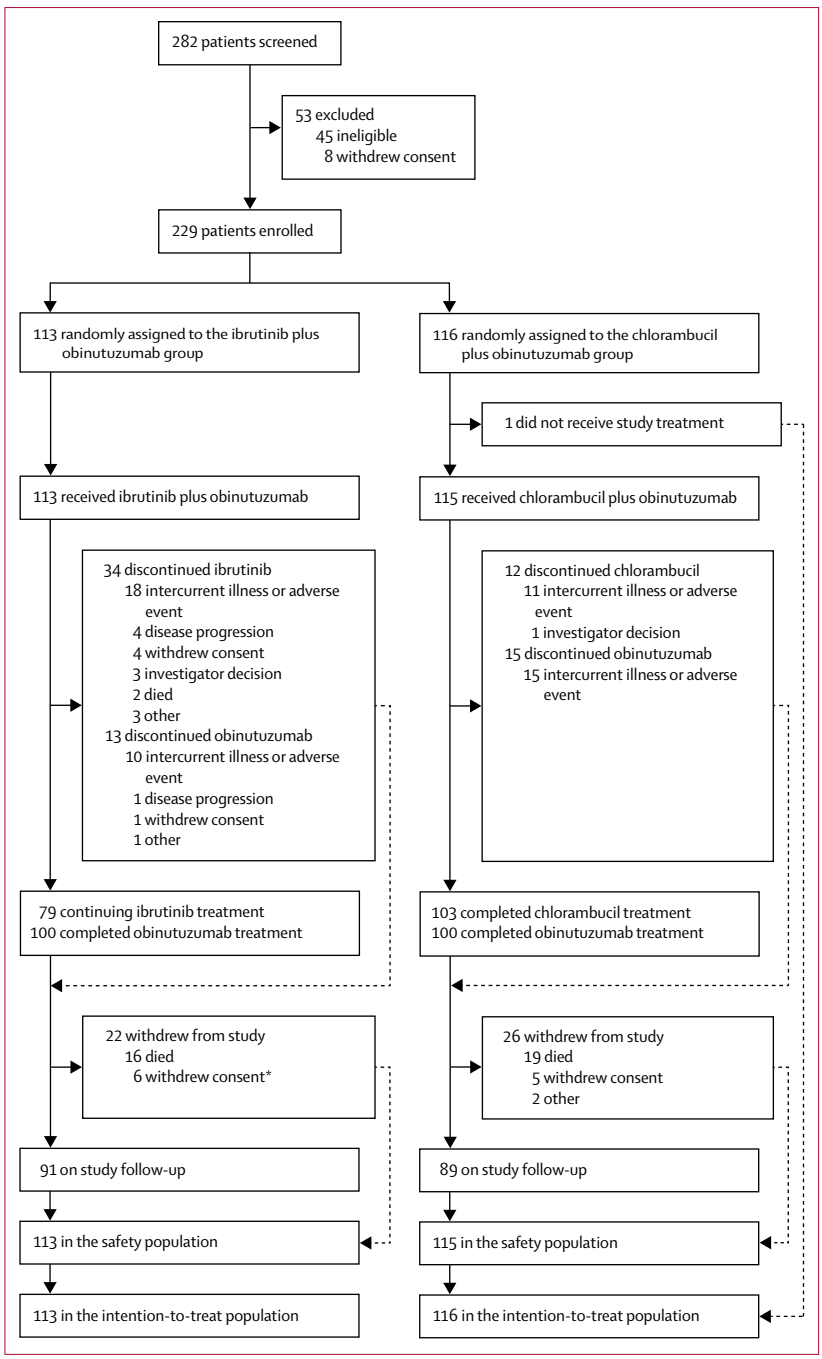


Figure 1: **Patient flow and disposition**
*One patient who discontinued because of withdrawal of consent subsequently died, resulting in a total of 17 deaths in the ibrutinib plus obinutuzumab group.

Outcomes

The primary endpoint was IRC-assessed progression-free survival, defined as time from randomisation until confirmed disease progression[24] or death from any cause. Secondary endpoints were progression-free survival in the high-risk population (del17p or *TP53* mutation, del11q, or unmutated *IGHV*, as described by Byrd and colleagues[10]), overall response (defined as patients who achieved a complete response, complete response with incomplete bone marrow recovery [CRi], nodular partial response [nPR], or partial response), proportion of patients with undetectable minimal residual disease (MRD; defined as <1 chronic lymphocytic leukaemia cell per 10 000 leucocytes as measured by flow cytometry at a central laboratory), proportion of patients with sustained haemoglobin or platelet improvement, overall survival, infusion-related reactions, and safety (appendix pp 4–5). Patient-reported outcome by EQ-5D-5L was also a secondary endpoint, but the results are not included in this report and will not be published. The primary analysis was to be done after a prespecified number of progression or death events have occurred. The analysis of secondary endpoints was to be done at the time of the primary analysis.

Statistical analysis

Assuming a median progression-free survival duration of 27 months for patients in the chlorambucil plus obinutuzumab group, 94 events of disease progression or death would provide 80% power to detect a hazard ratio (HR) of 0·55 with a two-sided statistical significance level of 5%. With an estimated accrual rate of 18 patients per month, approximately 212 eligible patients were to be enrolled to observe 94 events of disease progression or death over approximately 36 months. To preserve the studywise type I error rate, tests of primary and secondary endpoints were performed at the two-sided significance level of 0·05 based on a serial gatekeeping testing procedure prespecified in the statistical analysis plan in the following sequential hierarchy: (1) progression-free survival by IRC, (2) progression-free survival by IRC in the high-risk population, (3) sustained haemoglobin improvement, (4) undetectable MRD, (5) overall response by IRC, (6) overall survival, (7) infusion-related reactions, and (8) sustained platelet improvement. For IRC-assessed endpoints (progression-free survival and overall response), sensitivity analyses were done using investigator assessments. Time-to-event endpoints were estimated using the Kaplan-Meier method; HRs were calculated using Cox proportional hazards modelling, and treatment groups were compared using the log-rank test. Sustained haemoglobin improvement, sustained platelet improvement, undetectable MRD, overall response, and infusion-related reactions were compared between treatment groups using the χ^2 test. Prespecified subgroup analyses of efficacy outcomes by baseline characteristics, including by high-risk features, were also done. Analyses were performed using SAS (version 9.4). Efficacy was analysed in the intention-to-treat population according to randomly assigned treatment group. Safety was analysed according to actual treatment received in all patients who received at least one dose of any study medication. Safety data were reviewed regularly throughout the study by an independent data monitoring

committee. This study is registered with ClinicalTrials.gov, number NCT02264574.

Role of the funding source

The funders of the study were involved in study design, data interpretation, and writing and review of the manuscript and they confirmed accuracy of data and compiled them for analysis. The funders had no role in data collection. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Oct 6, 2014, and Oct 12, 2015, 282 patients were screened and 229 eligible patients were randomly assigned to receive ibrutinib plus obinutuzumab (n=113) or chlorambucil plus obinutuzumab (n=116; figure 1). Median age was 71 years (IQR 66–76), and 148 (65%) of 229 patients had high-risk disease features of del17p, *TP53* mutation, del11q, or unmutated *IGHV* (table 1; appendix p 13). One patient assigned to the chlorambucil plus obinutuzumab group did not receive any study medication and was excluded from the safety population (figure 1).

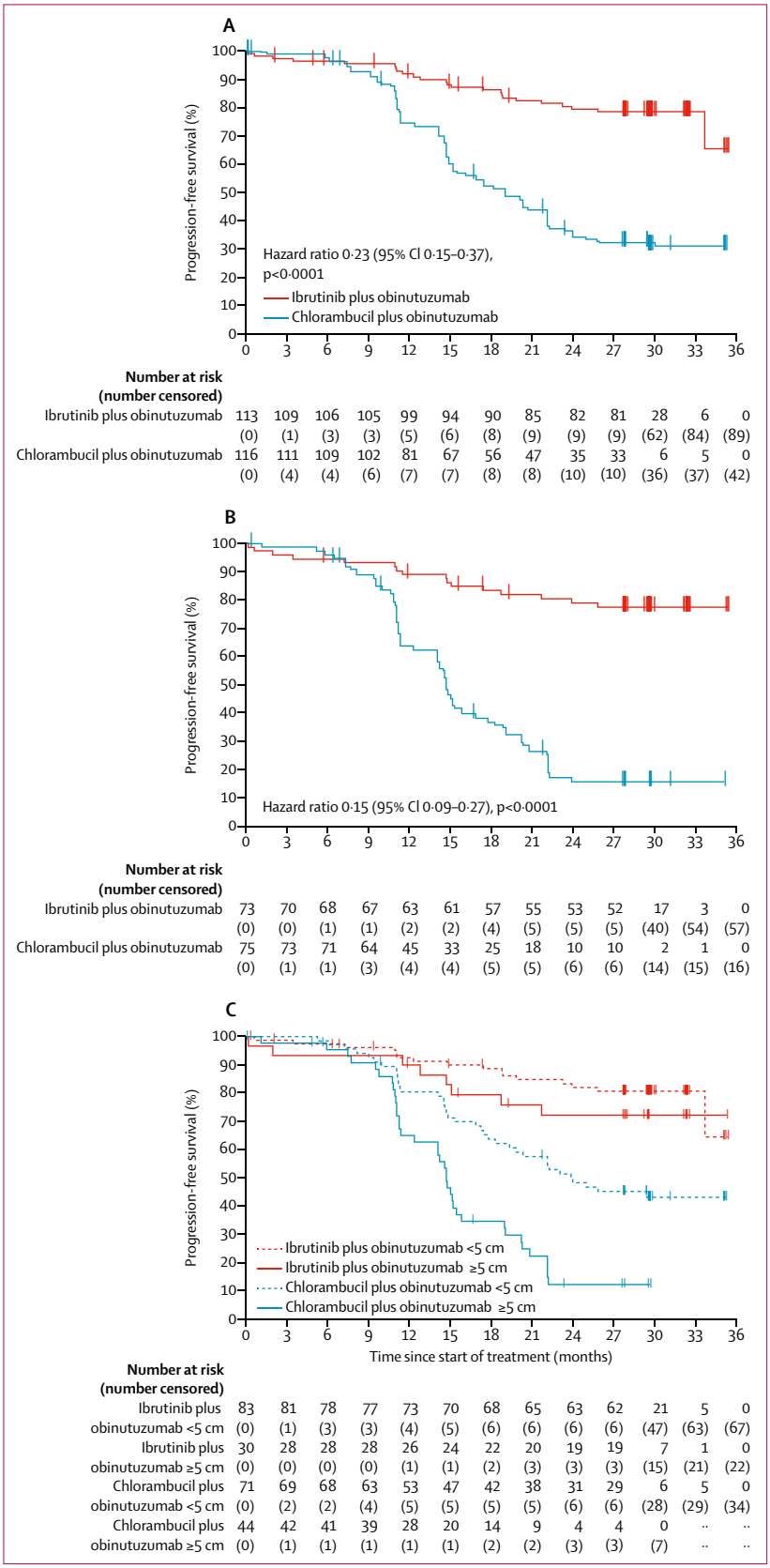
Median follow-up was 31·3 months (IQR 29·4–33·2). In the ibrutinib plus obinutuzumab group, treatment with ibrutinib was ongoing in 79 (70%) of 113 patients, and 100 (88%) of 113 patients completed six cycles of obinutuzumab. In the chlorambucil plus obinutuzumab group, 103 (89%) of 116 patients completed six cycles of chlorambucil and 100 (86%) of 116 patients completed six cycles of obinutuzumab (figure 1; appendix p 14). Of 116 patients initially randomly assigned to chlorambucil plus obinutuzumab treatment, 46 (40%) received single-agent ibrutinib as second-line therapy.

At the time of analysis on March 26, 2018, progression-free survival had been achieved by 89 (79%) of 113 patients in the ibrutinib plus obinutuzumab group and 42 (36%) of 116 patients in the chlorambucil plus obinutuzumab group (figure 2A). The ibrutinib plus obinutuzumab group had significantly longer progression-free survival than the chlorambucil plus obinutuzumab group (median not reached [95% CI 33·6–non-estimable; NE] in the ibrutinub plus obinutuzumab group *vs* 19·0 months [15·1–22·1] in the chlorambucil plus obinutuzumab group), with an HR of 0·23 (95% CI 0·15–0·37; p<0·0001) as assessed by an IRC. The estimated progression-free survival at 30 months was 79% (95% CI 70–85) in the ibrutinub plus obinutuzumab group and 31% (23–40) in the chlorambucil plus obinutuzumab group. Sensitivity analysis of investigator-assessed progression-free survival also showed improved progression-free survival with ibrutinib plus obinutuzumab (median not reached [95% CI 33·6–NE] *vs* 21·9 months [95% CI 18·4–26·7]; HR 0·26; 95% CI 0·16–0·42; p<0·0001). Patients in the ibrutinib plus obinutuzumab group had significantly better progression-free survival than the chlorambucil plus obinutuzumab group in all but one of the subgroups analysed (figure 3), including in patients with del17p (median not reached [95% CI 14·7–NE] in the ibrutinib plus obinutuzumab group *vs* 11·3 months [9·5–15·3] in the chlorambucil plus obinutuzumab group), del11q (median not reached [17·4–NE] *vs* 15·2 months [14·1–20·8]), unmutated *IGHV* (median not reached [NE–NE] *vs* 14·6 months [11·1–15·1];

	Ibrutinib plus obinutuzumab group (n=113)	Chlorambucil plus obinutuzumab group (n=116)
Age		
Median, years	70 (66–75)	72 (66–77)
65 years or older	91 (81%)	92 (79%)
Sex		
Female	46 (41%)	37 (32%)
Male	67 (59%)	79 (68%)
Ethnicity		
White	109 (96%)	111 (96%)
Black or African–American	2 (2%)	2 (2%)
Asian	1 (1%)	2 (2%)
Native Hawaiian or other Pacific Islander	1 (1%)	1 (1%)
ECOG performance status		
0	57 (50%)	53 (46%)
1	52 (46%)	56 (48%)
2	4 (4%)	7 (6%)
Diagnosis		
Chronic lymphocytic leukaemia	107 (95%)	107 (92%)
Small lymphocytic lymphoma	6 (5%)	9 (8%)
Rai stage III or IV	60 (53%)	59 (51%)
Bulky disease of at least 5 cm	30 (27%)	44 (38%)
High-risk features		
Del17p, *TP53* mutation, del11q, or unmutated *IGHV*	73 (65%)	75 (65%)
Del17p or *TP53* mutation	18 (16%)	23 (20%)
Del17p	14 (12%)	18 (16%)
TP53 mutation*	13/112 (12%)	16/110 (15%)
Del11q†	13 (12%)	22 (19%)
Unmutated *IGHV*	66/107 (62%)	57/107 (53%)
Cytopenia at baseline		
Any cytopenia	63 (56%)	62 (53%)
Haemoglobin 11 g/dL or less	51 (45%)	50 (43%)
Platelet count 100×10^9 per L or less	28 (25%)	22 (19%)
Absolute neutrophil count $1·5 \times 10^9$ cells per L or less	7 (6%)	4 (3%)
Median absolute lymphocyte count, $\times 10^9$ cells per L	59·7 (28·4–118·8)	48·9 (14·4–101·3)
Cumulative illness rating scale for geriatrics score		
Median	4·0 (2·0–7·0)	4·0 (2·0–7·0)
Greater than 6	37 (33%)	36 (31%)
Creatinine clearance		
Median, mL/min	72·0 (61·2–94·2)	69·6 (55·8–89·4)
Less than 60 mL/min	26 (23%)	38 (33%)
Median time from initial diagnosis, months	29·6 (10·5–55·6)	36·5 (11·8–71·7)

Data are median (IQR), n (%), or n/N (%). ECOG=Eastern Cooperative Oncology Group. *Irrespective of del17p (four of 112 patients in the ibrutinib-obinutuzumab group and five of 110 patients in the chlorambucil-obinutuzumab group had *TP53* mutations in the absence of del17p); †Without del17p (hierarchical categories according to Dohner classification).

Table 1: **Baseline characteristics**



appendix p 7), and bulky disease of at least 5 cm (median not reached [NE–NE] *vs* 14·7 months [11·3–15·8]; figure 2C). Progression in the form of Richter's transformation occurred in none of the 113 patients in the ibrutinib plus obinutuzumab group and in two (2%) of 116 patients in the chlorambucil plus obinutuzumab group.

In the high-risk population (patients with del17p, del11q, TP53 mutations, or unmutated IGHV), median progression-free survival was not reached (95% CI NE–NE) for ibrutinib plus obinutuzumab (n=73) versus 14·7 months (12·4–16·9) for chlorambucil plus obinutuzumab (n=75), with an HR of 0·15 (95% CI 0·09–0·27; p<0·0001; figure 2B). At 30 months, 77% (95% CI 66–86) of patients in the ibrutinib plus obinutuzumab group were estimated to be progression free versus 16% (8–25) in the chlorambucil plus obinutuzumab group. In a post-hoc analysis excluding patients with del17p, ibrutinib plus obinutuzumab was associated with a lower risk of progression or death than was chlorambucil plus obinutuzumab (appendix p 11).

A greater proportion of patients achieved an overall response in the ibrutinib plus obinutuzumab group (100 [88%] of 113 patients) than in the chlorambucil plus obinutuzumab group (85 [73%] of 116 patients); similarly, a higher proportion of patients achieved a complete response (including CRi) in the ibrutinib plus obinutuzumab group (22 [19%] of 113 patients) than in the chlorambucil plus obinutuzumab group (nine [8%] of 116 patients) as assessed by IRC (figure 4A). Median duration of response per IRC was not reached in the ibrutinib plus obinutuzumab group (95% CI 29·7–NE) and was 18·1 months (15·2–NE) in the chlorambucil plus obinutuzumab group. Overall response and complete response (including CRi) by investigator assessment were also achieved by a greater proportion of patients in the ibrutinib plus obinutuzumab group (overall response 103 [91%] of 113 patients and complete response 46 [41%] of 113 patients) than in the chlorambucil plus obinutuzumab group (overall response 94 [81%] of 116 patients and complete response 19 [16%] of 116 patients; figure 4B).

Overall, 39 (35%) of 113 patients treated with ibrutinib plus obinutuzumab had undetectable MRD in bone marrow or peripheral blood compared with 29 (25%) of 116 patients treated with chlorambucil plus obinutuzumab (appendix p 15). In the ibrutinib plus obinutuzumab group, 23 (20%) of 113 patients had undetectable MRD in bone marrow and 34 (30%) of 113 patients had undetectable

Figure 2: **Progression-free survival**
Progression-free survival as assessed by the IRC in the ITT population (A), in the high-risk population of patients with del17p, del11q, *TP53* mutations, or unmutated *IGHV* (B), and according to bulky disease status (C). Bulky disease was defined as longest diameter of 5 cm or greater of target lymph nodes at screening per the IRC assessment. IRC=independent review committee. ITT=intention-to-treat.

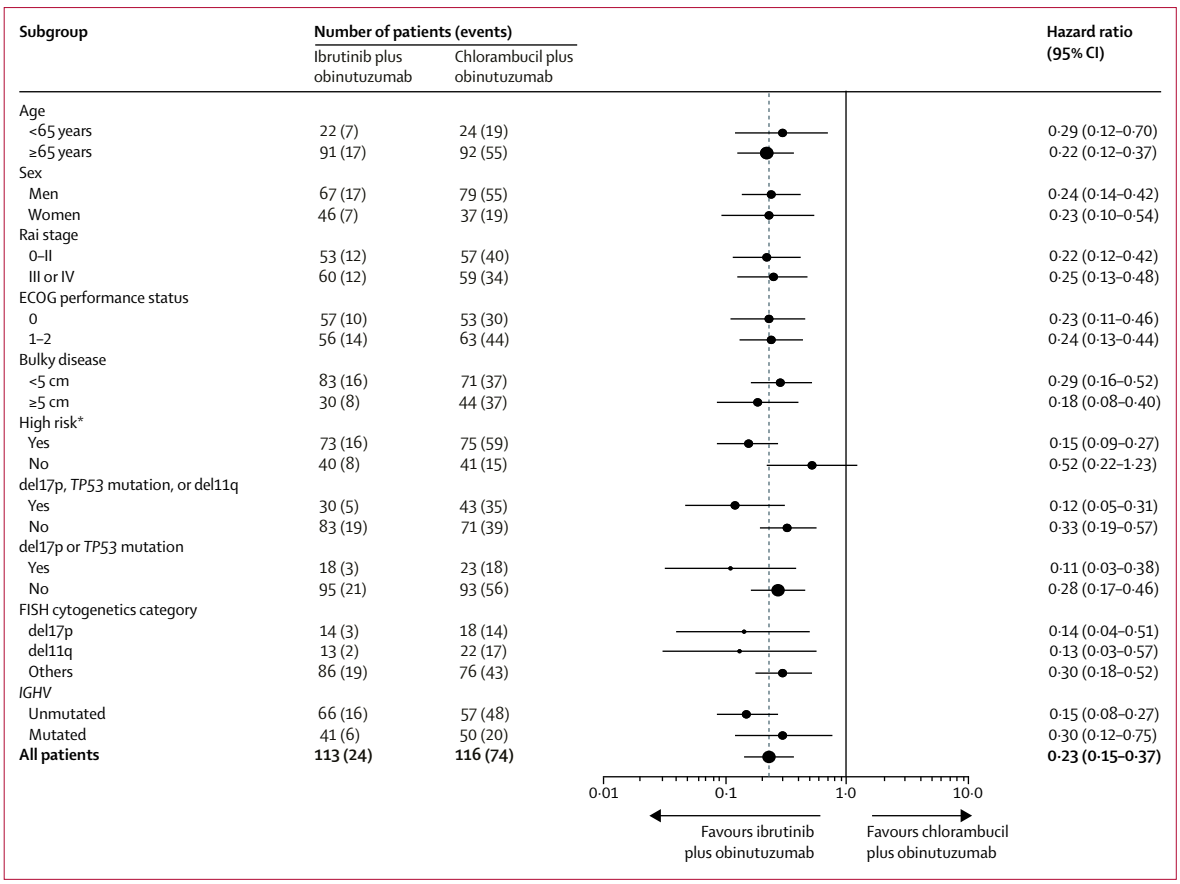


Figure 3: **Subgroup analyses of progression-free survival**
Forest plot of hazard ratios for disease progression or death across patient subgroups. Circle sizes are proportional to the sample size of the subgroup and error bars show 95% CIs. ECOG=Eastern Cooperative Oncology Group. FISH=fluorescence in-situ hybridisation. *Presence of del17p, *TP53* mutation, del11q, or unmutated *IGHV*.

MRD in peripheral blood (appendix p 15). In the chlorambucil plus obinutuzumab group, 20 (17%) of 116 patients had undetectable MRD in bone marrow and 23 (20%) of 116 patients had undetectable MRD in blood. 81 (72%) patients in the ibrutinib plus obinutuzumab group and 51 (44%) patients in the chlorambucil plus obinutuzumab group had both peripheral blood and bone marrow samples collected. There was overall concordance (ie, the same MRD results in both the bone marrow and peripheral blood samples) in 65 (80%) of 81 patients in the ibrutinib plus obinutuzumab group and 39 (76%) of 51 patients in the chlorambucil plus obinutuzumab group (appendix p 16). All cases of undetectable MRD in the bone marrow were in patients with complete (including CRi) or partial (including nPR) response by both IRC and investigator assessment. All but one of the patients with undetectable MRD in peripheral blood were responders by both IRC and investigator assessment. The 39 patients with undetectable MRD in the ibrutinib plus obinutuzumab group included 24 patients with investigator-assessed complete response or CRi and 14 patients with partial response or nPR; one other patient had undetectable MRD. The 29 patients with undetectable MRD in the chlorambucil plus obinutuzumab group included 15 patients with complete response or CRi and 14 patients with partial response or nPR.

In the high-risk population, IRC-assessed overall response was achieved by 66 (90%) of 73 patients in the ibrutinib plus obinutuzumab group and 51 (68%) of 75 patients in the chlorambucil plus obinutuzumab group and complete response was achieved by ten (14%) of 73 patients and three (4%) of 75 patients. Median duration of response was not reached (95% CI NE–NE) in the ibrutinib plus obinutuzumab group and was 11·8 months (10·4–15·9) in the chlorambucil plus obinutuzumab group. In the high-risk population, undetectable MRD was achieved in 20 (27%) of 73 patients with ibrutinib plus obinutuzumab and 11 (15%) of 75 patients with chlorambucil plus obinutuzumab. In the non-high-risk population, IRC-assessed overall response was achieved by 34 (85%) of 40 patients in the ibrutinib plus obinutuzumab group and 34 (83%) of 41 patients in the chlorambucil plus obinutuzumab group and complete response was achieved by 12 (30%) of 40 patients and six (15%) of 41 patients.

No difference between treatment groups was observed in the proportion of patients with sustained improvement

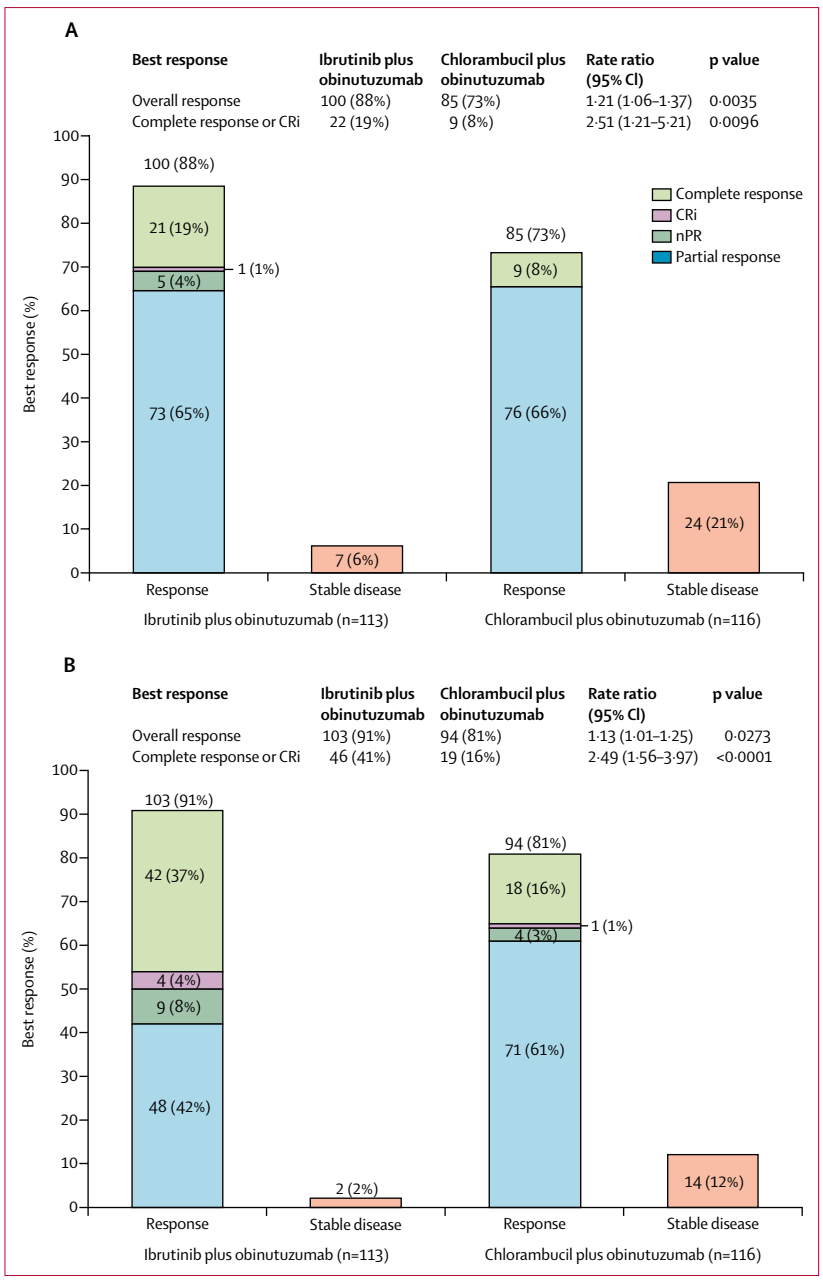


Figure 4: **Best overall response ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab**
Best overall response as assessed by independent review committee (A) and by the investigator (B). No patients had a best overall response of progressive disease in either group by independent review committee assessments. CRi=complete response with incomplete bone marrow recovery. nPR=nodular partial response.

in haemoglobin concentrations (appendix p 8). Sustained improvement in platelet counts was more frequent for the ibrutinib plus obinutuzumab group than the chlorambucil plus obinutuzumab group for both the entire study period (33 [29%] of 113 patients *vs* 16 [14%] of 116 patients) and during the first 6 months (17 [15%] of 113 patients *vs* seven [6%] of 116 patients; appendix p 9).

At the time of analysis, 17 (15%) of 113 patients in the ibrutinib plus obinutuzumab group and 19 (16%) of 116 patients in the chlorambucil plus obinutuzumab group had died (appendix p 22). Median overall survival was not reached in either group (HR 0·92; 95% CI 0·48–1·77); and overall survival at 30 months was 86% (95% CI 77–91) in the ibrutinib plus obinutuzumab group and 85% (77–90) in the chlorambucil plus obinutuzumab group (appendix p 10). Death due to progressive disease occurred in two patients in the ibrutinib plus obinutuzumab group and three patients in the chlorambucil plus obinutuzumab group.

Over a median follow-up of 31·3 months (IQR 29·4–33·2), four (4%) of 113 patients in the ibrutinib plus obinutuzumab group had initiated subsequent treatment compared with 51 (44%) of 116 patients in the chlorambucil plus obinutuzumab group. Median time to next treatment was not reached in either group. Ibrutinib plus obinutuzumab reduced the risk of needing second-line therapy versus chlorambucil plus obinutuzumab (HR 0·06; 95% CI 0·02–0·18; appendix p 12).

The median duration of exposure to ibrutinib was 29·3 months (IQR 23·0–32·2) in the ibrutinib plus obinutuzumab group; median duration of exposure to chlorambucil was 5·1 months (5·1–5·3) in the chlorambucil plus obinutuzumab group (appendix p 14). Grade 1–2 adverse events occurring in at least 10% of patients and all grade 3 or worse adverse events are in the appendix (pp 17–21). Infusion-related reactions of any grade occurred less frequently in the ibrutinib plus obinutuzumab group than in the chlorambucil plus obinutuzumab group (28 [25%] of 113 patients *vs* 67 [58%] of 115 patients; table 2) and grade 3 or worse or serious infusion-related reactions were also lower (three [3%] of 113 patients *vs* ten [9%] of 115 patients). In the ibrutinib plus obinutuzumab group, infusion-related reactions led to interruption of obinutuzumab in seven (6%) of 113 patients, and no patient discontinued obinutuzumab; in the chlorambucil plus obinutuzumab group, infusion-related reactions led to interruptions of obinutuzumab in 35 (30%) of 115 patients and permanent discontinuation in seven (6%) of 115 patients.

Over a median 29·3 months (IQR 23·0–32·2) of therapy, any treatment-emergent adverse events (regardless of attribution to study treatment) leading to discontinuation of ibrutinib occurred in 18 (16%) of 113 patients; treatment-related adverse events leading to discontinuation occurred in ten (9%) of 113 patients, and thrombocytopenia (in two patients) was the only adverse event leading to discontinuation in more than one patient. Over a median 5·1 months (5·1–5·3) of therapy, any treatment-emergent adverse events leading to discontinuation of chlorambucil occurred in 11 (9%) of 115 patients; treatment-related adverse events leading to discontinuation occurred in five (4%) of 115 patients, with none leading to discontinuation in more than one patient. Any treatment-emergent adverse events leading to discontinuation of obinutuzumab occurred in ten (9%) of 113 patients in the ibrutinib plus obintuzumab group

	Ibrutinib plus obinutuzumab group (n=113)			Chlorambucil plus obinutuzumab group (n=115)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
TEAE period*						
All	25 (22%)	49 (43%)	28 (25%)	29 (25%)	49 (43%)	31 (27%)
Neutropenia	8 (7%)	20 (18%)	21 (19%)	20 (17%)	32 (28%)	21 (18%)
Thrombocytopenia	19 (17%)	17 (15%)	4 (4%)	17 (15%)	6 (5%)	6 (5%)
Diarrhoea	35 (31%)	3 (3%)	0	12 (10%)	0	0
Cough	29 (26%)	1 (1%)	0	14 (12%)	0	0
Infusion-related reaction	26 (23%)	2 (2%)	0	58 (50%)	6 (5%)	3 (3%)
Arthralgia	24 (21%)	1 (1%)	0	12 (10%)	0	0
Pyrexia	20 (18%)	2 (2%)	0	29 (25%)	1 (1%)	0
Fatigue	20 (18%)	0	0	17 (15%)	2 (2%)	0
Back pain	20 (18%)	0	0	11 (10%)	1 (1%)	0
Anaemia	15 (13%)	4 (4%)	0	20 (17%)	9 (8%)	0
Hypertension	15 (13%)	4 (4%)	0	1 (1%)	3 (3%)	1 (1%)
Constipation	18 (16%)	0	0	13 (11%)	1 (1%)	0
Rash maculopapular	15 (13%)	2 (2%)	0	2 (2%)	0	0
Upper respiratory tract infection	15 (13%)	1 (1%)	0	7 (6%)	0	0
Pneumonia	7 (6%)	7 (6%)	1 (1%)	3 (3%)	3 (3%)	1 (1%)
Muscle spasms	15 (13%)	0	0	7 (6%)	0	0
Hyperuricaemia	14 (12%)	0	1 (1%)	0	0	0
Nausea	14 (12%)	0	0	35 (30%)	0	0
Oedema peripheral	14 (12%)	0	0	8 (7%)	0	0
Atrial fibrillation	8 (7%)	6 (5%)	0	0	0	0
Urinary tract infection	10 (9%)	3 (3%)	0	7 (6%)	1 (1%)	0
Insomnia	13 (12%)	0	0	5 (4%)	0	0
Nasopharyngitis	13 (12%)	0	0	4 (3%)	0	0
Conjunctivitis	12 (11%)	0	0	2 (2%)	0	0
Asthenia	11 (10%)	0	0	17 (15%)	0	0
Dyspnoea	9 (8%)	1 (1%)	1 (1%)	15 (13%)	1 (1%)	0
Vomiting	11 (10%)	0	0	14 (12%)	0	0
Headache	9 (8%)	0	0	12 (10%)	1 (1%)	0
Febrile neutropenia	1 (1%)	2 (2%)	3 (3%)	1 (1%)	6 (5%)	1 (1%)
Hyperglycaemia	4 (4%)	2 (2%)	0	3 (3%)	4 (3%)	0
Neutrophil count decreased	1 (1%)	4 (4%)	0	1 (1%)	0	0
Leukopenia	3 (3%)	1 (1%)	0	0	2 (2%)	1 (1%)
Hepatic function abnormal	0	2 (2%)	1 (1%)	0	1 (1%)	0
Acute coronary syndrome	0	3 (3%)	0	0	0	0
Tumour lysis syndrome†	1 (1%)	0	0	4 (3%)	3 (3%)	0
First 6 months						
All	47 (42%)	37 (33%)	19 (17%)	30 (26%)	49 (43%)	30 (26%)
Neutropenia	10 (9%)	15 (13%)	17 (15%)	20 (17%)	32 (28%)	21 (18%)
Thrombocytopenia	18 (16%)	16 (14%)	4 (4%)	17 (15%)	6 (5%)	6 (5%)
Diarrhoea	30 (27%)	0	0	12 (10%)	0	0
Infusion-related reaction	26 (23%)	2 (2%)	0	58 (50%)	6 (5%)	3 (3%)
Cough	18 (16%)	0	0	13 (11%)	0	0
Pyrexia	15 (13%)	1 (1%)	0	29 (25%)	1 (1%)	0
Anaemia	12 (11%)	3 (3%)	0	20 (17%)	9 (8%)	0
Rash maculopapular	12 (11%)	2 (2%)	0	2 (2%)	0	0
Fatigue	13 (12%)	0	0	17 (15%)	2 (2%)	0
Back pain	13 (12%)	0	0	11 (10%)	1 (1%)	0
Constipation	12 (11%)	0	0	13 (11%)	1 (1%)	0
Arthralgia	11 (10%)	0	0	12 (10%)	0	0

(Table 2 continues on next page)

	Ibrutinib plus obinutuzumab group (n=113)			Chlorambucil plus obinutuzumab group (n=115)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
(Continued from previous page)						
Nausea	10 (9%)	0	0	35 (30%)	0	0
Dyspnoea	7 (6%)	1 (1%)	1 (1%)	15 (13%)	1 (1%)	0
Asthenia	8 (7%)	0	0	17 (15%)	0	0
Vomiting	8 (7%)	0	0	14 (12%)	0	0
Hypertension	7 (6%)	1 (1%)	0	1 (1%)	3 (3%)	1 (1%)
Pneumonia	2 (2%)	3 (3%)	1 (1%)	3 (3%)	2 (2%)	1 (1%)
Atrial fibrillation	3 (3%)	3 (3%)	0	0	0	0
Febrile neutropenia	1 (1%)	1 (1%)	2 (2%)	1 (1%)	6 (5%)	1 (1%)
Hyperglycaemia	3 (3%)	1 (1%)	0	3 (3%)	4 (3%)	0
Neutrophil count decreased	1 (1%)	3 (3%)	0	1 (1%)	0	0
Leukopenia	2 (2%)	0	0	0	2 (2%)	1 (1%)
Tumour lysis syndrome†	1 (1%)	0	0	4 (3%)	3 (3%)	0

Data are n (%). Adverse events of grade 1–2 occurring in at least 10% of patients and grade 3 or worse occurring in at least 2% of patients are shown. Ten (9%) patients in the ibrutinib plus obinutuzumab group had grade 5 adverse events, of which five were in the first 6 months. Three (3%) patients had grade 5 events in the chlorambucil plus obinutuzumab group, all occurring in the first 6 months. Tables of all adverse events are in the appendix (pp 17–21). TEAE=treatment-emergent adverse event. *The TEAE period was the time from the first dose until 30 days after the last dose of study medication or initiation of subsequent antineoplastic therapy, whichever occurred first. †Tumour lysis syndrome was assessed per Common Terminology Criteria for Adverse Events and did not delineate clinical versus laboratory cases.

Table 2: **Summary of adverse events**

and in 15 (13%) of 115 patients in the chlorambucil plus obintuzumab group. Treatment-related adverse events leading to obinutuzumab discontinuation occurred in five (4%) of 113 patients in the ibrutinib plus obinutuzumab group (with thrombocytopenia in two patients) and in 13 (11%) of 115 patients in the chlorambucil plus obinutuzumab group (with infusion-related reaction in seven and neutropenia in three patients). Dose reductions because of adverse events were required in 17 (15%) of 113 patients in the ibrutinib plus obinutuzumab group and 14 (12%) of 115 patients in the chlorambucil plus obinutuzumab group (appendix p 23).

Although the safety reporting period was longer for the ibrutinib plus obinutuzumab group than for the chlorambucil plus obinutuzumab group, the numbers of grade 3 or 4 adverse events were similar between groups (77 [68%] of 113 patients in the ibrutinib plus obinutuzumab group *vs* 80 [70%] of 115 patients in the chlorambucil plus obinutuzumab group; table 2). The most common grade 3 or 4 adverse events were neutropenia, thrombocytopenia, pneumonia, and atrial fibrillation in the ibrutinib plus obinutuzumab group, and neutropenia, thrombocytopenia, infusion-related reactions, anaemia, and febrile neutropenia in the chlorambucil plus obinutuzumab group (table 2). In the ibrutinib plus obinutuzumab group, ibrutinib-related serious adverse events occurred in 30 (27%) of 113 patients, most commonly pneumonia (n=5), atrial fibrillation (n=5), and febrile neutropenia (n=4), and obinutuzumab-related serious adverse events occurred in 17 (15%) of 113 patients, most commonly febrile neutropenia (n=3) and thrombocytopenia (n=3). In the chlorambucil plus obinutuzumab group, chlorambucil-related serious adverse events occurred in 21 (18%) of 115 patients, most commonly febrile neutropenia (n=7) and tumour lysis syndrome (n=4), and obinutuzumab-related serious adverse events occurred in 27 (23%) of 115 patients, most commonly infusion-related reactions (n=8), febrile neutropenia (n=7), tumour lysis syndrome (n=5), and pyrexia (n=4). Overall, serious adverse events occurred in 65 (58%) of 113 patients treated with ibrutinib plus obinutuzumab and 40 (35%) of 115 patients treated with chlorambucil plus obinutuzumab (appendix p 24). Deaths due to adverse events occurred in ten (9%) of 113 patients in the ibrutinib plus obinutuzumab group over the median 2·5 years of treatment and in three (3%) of 115 patients in the chlorambucil plus obinutuzumab group over the median 5 months of treatment (appendix p 22). Deaths due to adverse events were considered at least possibly related to ibrutinib or chlorambucil treatment in one (1%) of 113 patients in the ibrutinib plus obinutuzumab group (sudden death) and one (1%) of 115 patients in the chlorambucil plus obinutuzumab group (neuroendocrine carcinoma of the skin).

Discussion

In this study we showed that ibrutinib plus obinutuzumab treatment conferred a reduction in the risk of progression or death versus chlorambucil plus obinutuzumab treatment in previously untreated patients with chronic lymphocytic leukaemia, as per IRC assessment. We obtained similar results with investigator-assessed progression-free survival and consistent progression-free survival benefits across most patient subgroups.

The progression-free survival benefit in the ibrutinib plus obinutuzumab group was particularly notable in patients considered to be in the high-risk group, which consisted of patients with del17p or *TP53* mutation,

del11q, or unmutated *IGHV*. The 30-month progression-free survival with ibrutinib plus obinutuzumab in this high-risk population was similar to that in the overall population.

To our knowledge, the iLLUMINATE study is the first prospective, head-to-head clinical trial comparing first-line chemoimmunotherapy with a chemotherapy-free regimen in patients with chronic lymphocytic leukaemia, including patients with del17p or *TP53* mutation. Also, at the time this study was designed, ibrutinib was not approved in the EU and other regions for the first-line treatment of patients with del17p chronic lymphocytic leukaemia unless the patient was unsuitable for chemo-immunotherapy. This study also confirms ibrutinib's superior efficacy in high-risk groups in addition to patients with del17p or *TP53* mutation, because most patients in our study had non-del17p high-risk chronic lymphocytic leukaemia (ie, unmutated *IGHV* or del11q). Progression-free survival with ibrutinib plus obinutuzumab in subgroups with del11q or unmutated *IGHV* appears favourable to 3-year progression-free survival reported with first-line bendamustine–rituximab or fludarabine–cyclophosphamide–rituximab from the CLL10 study[14] in patients with del11q (3-year progression-free survival 14–64%) or unmutated *IGHV* (43–59%) chronic lymphocytic leukaemia, despite the younger, more physically fit population treated with these more intensive regimens (bendamustine–rituximab and fludarabine–cyclophosphamide–rituximab). Results from our prospective analysis of high-risk patients in iLLUMINATE confirm results of previous reports that these high-risk genomic features identify a population at risk of poorer outcomes with chemoimmunotherapy.[10–12] Furthermore, these results are in line with findings from a previous integrated analysis of three randomised trials of ibrutinib in patients with chronic lymphocytic leukaemia, in which del11q and *IGHV* status had less relevance for outcomes with ibrutinib-based regimens than with other regimens (ofatumumab, chlorambucil, and bendamustine–rituximab).[17] To our knowledge, results from our study prospectively show for the first time that patients with unmutated *IGHV* status or del11q will fare better with a non-chemoimmunotherapy regimen than with a chemotherapy-containing regimen.

Notably, in iLLUMINATE the IRC-assessed progression-free survival with chlorambucil plus obinutuzumab (median 19·0 months) was shorter than that reported for chlorambucil plus obinutuzumab in the CLL11 study (median 28·9 months).[5] The shorter progression-free survival in this group in our study compared with the CLL11 study can be attributed to several factors. The chlorambucil plus obinutuzumab regimen in our study was the same as for CLL11; our study included an IRC that used iwCLL criteria to assess regularly scheduled CT scans as surveillance for progression. This probably led to earlier detection of progressive disease than in CLL11, in which radiographic imaging scans were only obtained when the treating physician suspected progression based on clinical examination.[5] Additionally, owing to the inclusion criteria, iLLUMINATE enrolled a higher proportion of patients with high-risk features than the CLL11 study, including del17p (16% in our study *vs* 7% in the CLL11 study), which would also be expected to result in a shorter median progression-free survival.

Chemoimmunotherapy, a mainstay of first-line treatment, is typically administered over six cycles and permits treatment breaks, which can be considered advantageous over continuously administered drugs such as ibrutinib. However, our study shows that time to progression or relapse with chlorambucil plus obinutuzumab is short, and patients treated with first-line chlorambucil plus obinutuzumab needed second-line therapy more frequently and rapidly than those who received ibrutinib plus obinutuzumab. With a median follow-up of 31·3 months, 4% of patients on ibrutinib plus obinutuzumab and 44% on chlorambucil plus obinutuzumab received subsequent treatment. The time to next treatment with chlorambucil plus obinutuzumab in iLLUMINATE appears shorter than that reported in the CLL11 study (median 42·7 months)[8] and was also probably affected by the higher proportion of patients with high-risk features in our study. Comparison of time to next treatment data between the two studies would potentially be confounded by several other factors, including but not limited to differences in the follow-up duration (with median time to next treatment not yet reached in either group in iLLUMINATE) and differences in availability of next-line treatment options, including ibrutinib.

The frequency and depth of responses were greater in the ibrutinib plus obinutuzumab group than the chlorambucil plus obinutuzumab group, as assessed by both IRC and investigator, with almost a third of assessed patients achieving undetectable MRD levels with ibrutinib plus obinutuzumab. Additional follow-up in the iLLUMINATE study is required to establish whether undetectable MRD translates into improved response duration or survival outcomes. The investigator-assessed complete response of 41% in the ibrutinib plus obinutuzumab group was higher than the 16% in the chlorambucil plus obinutuzumab group. With similar follow-up duration in previous studies, investigator-assessed complete response with single-agent ibrutinib is approximately 20%.[20,25] This suggests that the addition of obinutuzumab to ibrutinib improves the proportion of patients achieving a response. However, single-agent ibrutinib still achieves long progression-free survival intervals independent of complete response and remains a standard of care for first-line chronic lymphocytic leukaemia. Ibrutinib and obinutuzumab in combination provides another option for patients, particularly in patients with high-risk or bulky disease who might benefit from this combination, as shown by the longer progression-free survival compared with chlorambucil plus obinutuzumab in our study.

Although not directly addressed in this study, understanding which patients might benefit from the combination of ibrutinib with obinutuzumab over single-agent ibrutinib is of interest. In terms of progression-free survival, ibrutinib as monotherapy affords outstanding disease control in most patients when taken continuously; in RESONATE-2,[20] 89% of patients remained progression free at 24 months with only 3% of patients discontinuing treatment because of progressive disease after 3 years of follow-up. In a randomised, phase 2 study in patients with relapsed or high-risk chronic lymphocytic leukaemia, the combination of ibrutinib with rituximab provided more rapid and deeper remissions (ie, more patients with undetectable MRD and lower levels of residual cells in bone marrow) than single-agent ibrutinib, but at 2 years, progression-free survival was not different between the treatment groups.[26] Given that the study included only a small number of previously untreated patients, it is unclear whether these observations would apply to the first-line setting in which faster response might be a desirable goal, particularly in patients with high-risk chronic lymphocytic leukaemia.[26] Nevertheless, it is possible that in addition to achieving deeper responses more quickly, a long-term progression-free survival benefit might be obtained in combination with an anti-CD20 antibody such as obinutuzumab, which showed clear superiority over rituximab in the CLL11 study.[5] For patients who need to discontinue ibrutinib before progression, achieving a complete response might provide longer time to progression than other responses if treatment is discontinued. Given the small number of progression events in the ibrutinib plus obinutuzumab group of iLLUMINATE, we could not analyse time to progression by response category. Similarly, the immature progression-free survival data from the RESONATE-2 ibrutinib group (median progression-free survival not yet reached) and important differences in patient populations (RESONATE-2 excluded del17p patients) limit direct comparisons to the ibrutinib plus obinutuzumab regimen used in our study. The ongoing Alliance 041202 study (NCT01886872) that directly compares ibrutinib with ibrutinib–rituximab in the first-line chronic lymphocytic leukaemia setting will provide additional information. Stopping treatment after achieving a response with undetectable MRD levels or after a fixed duration of an ibrutinib-based regimen is under investigation in the ongoing CAPTIVATE study (NCT02910583).

In our study, no difference in overall survival was observed between the ibrutinib plus obinutuzumab and chlorambucil plus obinutuzumab groups, with death in only 15–16% of patients in each group, most because of causes other than chronic lymphocytic leukaemia progression. Over the longer treatment period in the ibrutinib plus obinutuzumab group versus the chlorambucil plus obinutuzumab group (median 29·3 months *vs* 5·1 months), more fatal adverse events were reported in the ibrutinib plus obinutuzumab group. This study was not powered to assess an overall survival benefit for first-line therapy, and crossover to single-agent ibrutinib upon progression (which occurred in 40% of patients in the chlorambucil plus obinutuzumab group) precludes naive comparison of overall survival between treatment groups.

Although this was a randomised, controlled trial with blinded efficacy assessments (by IRC), several limitations exist, including the inability to mask patients and investigators to study treatments and the small sample size designed to show a substantial efficacy benefit for progression-free survival (target HR of 0·55), which might have limited power for other endpoints. Another potential limitation is that data later became available from the CLL10[14] phase 3 study suggesting that the bendamustine–rituximab combination might have been a better comparator group in older patients (aged >65 years); however, this information was not available until after the initiation of iLLUMINATE. Additionally, the absence of a single-agent ibrutinib group in our study to allow for a head-to-head comparison with ibrutinib plus obinutuzumab limits interpretation of the study.

Overall safety findings were consistent with the known safety profiles of the individual drugs, with no new safety signals identified. Most adverse events in the ibrutinib plus obinutuzumab group occurred during the first 6 months of treatment. Compared with single-agent ibrutinib, cytopenia was more frequent in the ibrutinib plus obinutuzumab group as were infusion-related reactions, which are one of the most frequent and severe adverse events reported with anti-CD20 therapies. Consistent with another report of ibrutinib combined with anti-CD20 therapy,[27] infusion-related reactions of any grade were much less frequent in the ibrutinib plus obinutuzumab group (25%) than in the chlorambucil plus obinutuzumab group (58%) including serious events. No patients treated with ibrutinib plus obinutuzumab discontinued obinutuzumab because of infusion-related reactions, whereas 6% of patients in the chlorambucil plus obinutuzumab group had this reason for discontinuation. The mechanism underlying the reduced incidence and severity of infusion-related reactions with ibrutinib in combination with anti-CD20 therapy is unknown, but might be related to ibrutinib-mediated inhibition of cytokine release associated with obinutuzumab use.[28,29] Ibrutinib was discontinued because of treatment-emergent adverse events in 18 (16%) of 113 patients after a median follow-up duration of 31·3 months, which is similar to the rate of discontinuations for adverse events with single-agent ibrutinib after a median follow-up duration of 29 months in the RESONATE-2 study.[20] This observation lends support to the similar tolerability of ibrutinib when administered in combination with obinutuzumab.

In conclusion, the results from iLLUMINATE show that ibrutinib plus obinutuzumab is an effective chemotherapy-free treatment option for previously untreated patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma, including in patients with high-risk disease.

The ibrutinib plus obinutuzumab regimen had an acceptable safety profile and was tolerated by most patients for up to 3 years. Furthermore, patients given this regimen had better progression-free survival outcomes than those who had the standard chlorambucil plus obinutuzumab combination regimen recommended in consensus treatment guidelines, regardless of risk factors.

Contributors

CM, RG, FD, AT, BA, LL, MS, OS, JN, DB-Y, VS, DG, JGG, and IWF collected data. As members of the steering committee, CM, DG, JGG, and IWF provided clinical and scientific input on the study design and protocol. All authors had full access to the data output and interpreted the data. CZ and FC performed statistical analyses. CM, DFJ, and LS collaboratively wrote the first draft of the manuscript. All authors critically reviewed the manuscript and participated in the revision of the manuscript.

Declaration of interests

CM reports consulting or advisory roles with Janssen, AbbVie, and Pharmacyclics LLC. RG reports honoraria from Celgene, Roche, Merck, and AstraZeneca; consulting or advisory roles at Celgene, Roche, Bristol-Myers Squibb (BMS), and Takeda; research funding from Celgene, Roche, Novartis, and BMS; and travel, accommodations, or expenses from Roche, Amgen, and Janssen. FD reports consulting or advisory roles with Janssen, AbbVie, and Amgen; research funding from Janssen, AbbVie, and Amgen; and travel, accommodations, or expenses from Janssen and AbbVie. AT reports consulting or advisory roles with Janssen, Gilead, and AbbVie; and speakers' bureau compensation from Janssen. MS reports honoraria from Roche/Genentech, Janssen, and Gilead; consulting or advisory roles with Roche/Genentech; and research funding from Roche/Genentech, Janssen, and Gilead. JN reports consulting or advisory roles with Amgen, Takeda, Roche, Celgene, and Pfizer. VS reports employment at ECO-SAFETY Medical Center; stock or other ownership with AbbVie, Juno, Portola Pharmaceuticals, Kite, Beigene, Aptose Biosciences, Esperion Therapeutics, Ignyta, Editas Medicine, Intellia Therapeutics, Crispr Therapeutics, Loxo Oncology, and TG Therapeutics; travel, accommodations, or expenses from Merck Sharp & Dohme and AbbVie; and honoraria from Janssen, AbbVie, and Astellas. DG reports speakers' bureau compensation from Janssen; and travel, accommodations, or expenses from Janssen. JGG reports honoraria payments from and consulting or advisory roles at Pharmacyclics LLC and Janssen; and research funding from Janssen. EH reports employment at Pharmacyclics LLC; stock or other ownership with AbbVie. C-JL reports employment at and travel, accommodations, or expenses from Pharmacyclics LLC; and stock or other ownership with AbbVie. CZ reports employment at Pharmacyclics LLC; and stock or other ownership with AbbVie. FC reports employment, a leadership role or compensation, and travel, accommodations, or expenses at Pharmacyclics LLC; and stock or other ownership with AbbVie. DFJ reports employment at Pharmacyclics LLC; stock or other ownership with AbbVie; and patents, royalties, or other intellectual property with AbbVie. LS reports employment at Pharmacyclics LLC; and stock or other ownership at AbbVie. IWF reports research funding from Agios, ArQule, Beigene, Calithera, Celgene, Constellation, Curis, Forma, Forty Seven, Genentech, Gilead, Incyte, Infinity, Janssen, KITE, Merck, Novartis, Pfizer, Pharmacyclics LLC, Portola, Seattle Genetics, Takeda, TG Therapeutics, Trillium, and Verastem. All other authors declare no competing interests.

Data sharing

Individual participant data from this clinical study are not available; Pharmacyclics LLC, an AbbVie Company, is currently developing a data sharing plan.

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