Ibrutinib and rituximab versus fludarabine, cyclophosphamide, and rituximab for patients with previously untreated chronic lymphocytic leukaemia (FLAIR): interim analysis of a multicentre, open-label, randomised, phase 3 trial

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Summary

Background The approval of Bruton tyrosine kinase (BTK) inhibitors in patients with previously untreated chronic lymphocytic leukaemia (CLL) was based on trials which compared ibrutinib with alkylating agents in patients considered unfit for fludarabine, cyclophosphamide, and rituximab, the most effective chemoimmunotherapy in CLL. We aimed to assess whether ibrutinib and rituximab is superior to fludarabine, cyclophosphamide, and rituximab in terms of progression-free survival.

Methods This study is an interim analysis of FLAIR, which is an open-label, randomised, controlled, phase 3 trial in patients with previously untreated CLL done at 101 UK National Health Service hospitals. Eligible patients were between 18 and 75 years of age with a WHO performance status of 2 or less and disease status requiring treatment according to International Workshop on CLL criteria. Patients with greater than 20% of their CLL cells having the chromosome 17p deletion were excluded. Patients were randomly assigned (1:1) by means of minimisation (Binet stage, age, sex, and centre) with a random element in a web-based system to ibrutinib and rituximab (ibrutinib administered orally at 420 mg/day for up to 6 years; rituximab administered intravenously at 375 mg/m² on day 1 of cycle 1 and at 500 mg/m² on day 1 of cycles 2–6 of a 28-day cycle) or fludarabine, cyclophosphamide, and rituximab (fludarabine 24 mg/m² per day orally on day 1–5, cyclophosphamide 150 mg/m² per day orally on days 1–5; rituximab as above for up to 6 cycles). The primary endpoint was progression-free survival, analysed by intention to treat. Safety analysis was per protocol. This study is registered with ISRCTN, ISRCTN01844152, and EudraCT, 2013-001944-76, and recruiting is complete.

Findings Between Sept 19, 2014, and July 19, 2018, of 1924 patients assessed for eligibility, 771 were randomly assigned with median age 62 years (IQR 56–67), 565 (73%) were male, 206 (27%) were female and 507 (66%) had a WHO performance status of 0. 385 patients were assigned to fludarabine, cyclophosphamide, and rituximab and 386 patients to ibrutinib and rituximab. After a median follow-up of 53 months (IQR 41–61) and at prespecified interim analysis, median progression-free survival was not reached (NR) with ibrutinib and rituximab and was 67 months (95% CI 63–NR) with fludarabine, cyclophosphamide, and rituximab (hazard ratio 0·44 [95% CI 0·32–0·60]; p<0·0001). The most common grade 3 or 4 adverse event was leukopenia (203 [54%] patients in the fludarabine, cyclophosphamide, and rituximab group and 55 [14%] patients in the ibrutinib and rituximab group. Serious adverse events were reported in 205 (53%) of 384 patients receiving ibrutinib and rituximab compared with 203 (54%) of 378 patients receiving fludarabine, cyclophosphamide, and rituximab. Two deaths in the fludarabine, cyclophosphamide, and rituximab group and three deaths in the ibrutinib and rituximab group were deemed to be probably related to treatment. There were eight sudden unexplained or cardiac deaths in the ibrutinib and rituximab group and two in the fludarabine, cyclophosphamide, and rituximab group.

Interpretation Front line treatment with ibrutinib and rituximab significantly improved progression-free survival compared with fludarabine, cyclophosphamide, and rituximab but did not improve overall survival. A small number of sudden unexplained or cardiac deaths in the ibrutinib and rituximab group were observed largely among patients with existing hypertension or history of cardiac disorder.

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Research in context

Evidence before this study

A search of PubMed for clinical trial reports published between Jan 1, 2010 and Dec 1, 2021, by means of the terms "ibrutinib" and "chronic lymphocytic leuk(a)emia" or "CLL" and "chemo(-)immunotherapy" identified six randomised phase 3 studies of ibrutinib (monotherapy or in combination with bendamustine or rituximab, or both) in patients with CLL, four published on patients who were previously untreated. These studies showed the superiority of ibrutinib regimens as compared with chemoimmunotherapy in terms of progression-free survival.

Added value of this study

To the best of our knowledge, the FLAIR trial recruited more patients with previously untreated CLL from UK National Health Service hospitals than any previous interventional study and, because of this, patients treated were broadly representative of the real world. We observed a significant benefit of ibrutinib plus rituximab on progression-free survival. This was maintained in patients with CLL with unmutated IGHV. We confirmed the increased risk of sudden unexplained death or cardiac death with ibrutinib and rituximab treatment compared with fludarabine, cyclophosphamide, and rituximab treatment. This risk was increased in those participants receiving treatment for hypertension or a cardiac disorder at trial entry.

Implications of all the available evidence

The results of the FLAIR trial contribute to a body of evidence that suggests that the use of ibrutinib-based regimens should be considered for patients with previously untreated CLL, especially those with *IGHV* unmutated CLL. With the addition of these new data from the FLAIR trial, a meta-analysis of all published trials of ibrutinib treatment compared with chemoimmunotherapy, including 2877 patients, confirmed the progression-free survival benefit of ibrutinib-based regimens in this setting (hazard ratio 0·31 [95% CI 0·22–0·42]). Future studies examining combinations of targeted therapies are needed to further improve outcomes for CLL patients with mutated *IGHV*. Ibrutinib treatment selection for previously untreated patients with CLL should be considered carefully in the light of the small number of sudden unexplained cardiac deaths observed in the trial. In patients already receiving treatment for hypertension or other cardiac conditions a formal cardiac assessment should be done before initiating ibrutinib; in patients with clinically significant cardiac comorbidity alternative class therapies are considered. A similar meta-analysis of the incidence of sudden unexplained cardiac deaths per 100 person-years suggested FLAIR was consistent with other published studies (incidence per 100 person-years 0·62 [95% CI 0·40–0·96]).

Introduction

Chronic lymphocytic leukaemia (CLL) is one of the most common haematological malignancies affecting approximately 6·0 per 100 000 of the population.[1] Until recently the standard treatment for CLL was chemo-immunotherapy with the most effective being the combination of fludarabine and cyclophosphamide plus rituximab for patients considered suitable for intensive therapy. The development of therapy targeting kinases associated with the B-cell receptor pathway, most effectively with the Bruton tyrosine kinase (BTK) inhibitor ibrutinib, has revolutionised the outlook for patients with CLL, improved progression-free survival and in some studies, improved overall survival.[2–6] The approval of BTK inhibitors, has been based on trials in which ibrutinib was given until disease progression, shifting the paradigm of treatment from fixed duration to continuous therapy. Also the trials leading to the approval of BTK inhibitors in previously untreated CLL were phase 3 trials in which the comparator was either chlorambucil alone or in combination with obinutuzumab rather than fludarabine, cyclophosphamide, and rituximab.[7] When FLAIR was designed in 2014 it was thought that the addition of rituximab to ibrutinib would lead to improved efficacy. However, since then randomised trials have shown that the addition of rituximab to ibrutinib confers no improvement in depth of remission or progression-free survival compared with ibrutinib alone.[8,9] Therefore, although in FLAIR, rituximab was added to ibrutinib, this is not necessary and the outcomes can be considered to be similar to ibrutinib monotherapy. Thus, it is crucial to do large phase 3 trials to study the long-term outcomes of therapies in CLL compared with standard chemo-immunotherapy, and in key biological disease subsets. The use of BTK inhibitors has been reported to be associated with several toxicities, including both cardiac arrhythmias (mostly atrial fibrillation and ventricular arrhythmias) and hypertension. Previous reports have indicated that these complications continue to occur after prolonged treatment with ibrutinib.[10] In addition, previous phase 3 trials have reported small numbers of ventricular tachyarrhythmias and sudden unexplained deaths.[11]

The National Cancer Research Institute (NCRI) FLAIR trial compared efficacy and toxicity of ibrutinib and rituximab with fludarabine, cyclophosphamide, and rituximab in previously untreated patients with CLL fit for combination chemoimmunotherapy and requiring treatment. In this report, we describe the initial outcomes of FLAIR following the first formal interim analysis of the primary endpoint (progression-free survival) overall and in risk-stratified subsets by *IGHV* mutation status and analyse the cardiovascular risk associated with prolonged ibrutinib use.

Methods

Study design and participants

Assessment of Ibrutinib-containing Regimens (FLAIR) is an open-label, randomised, controlled, phase 3 trial in patients with previously untreated CLL. The trial recruited from 101 National Health Service (NHS) hospitals in

England, Wales, Scotland, and Northern Ireland (appendix pp 3, 4). There were three major amendments to the standard risk pathway trial design involving addition or removal of possible allocated treatment group and an amendment to add a high-risk pathway.[12] This article reports the results of an interim analysis of the original randomisation question comparing ibrutinib and rituximab with fludarabine, cyclophosphamide, and rituximab. Results of the amended trial questions will be presented subsequently.

Inclusion criteria were treatment naive CLL–small lymphocytic lymphoma (SLL), considered fit to receive fludarabine, cyclophosphamide, and rituximab, between 18 and 75 years of age with a WHO performance status of 2 or less and disease status requiring treatment according to International Workshop on CLL (IWCLL) criteria. Patients with progressive Stage A CLL, defined as those with active disease requiring therapy by IWCLL criteria but still defined as Binet stage A, were eligible.[13] Within 14 days before randomisation, alanine aminotransferase or aspartate aminotransferase had to be no more than 3 times the upper limit of normal (ULN; ULN=40 international units/L) and total bilirubin had to be no more than 1·5 times the upper limit of normal (ULN=21 μmoles/L; unless bilirubin rise was due to Gilbert's syndrome or of non-hepatic origin) to be eligible. Key exclusion criteria were Richter's transformation, CNS involvement, symptomatic cardiac disease, and unwillingness to use pregnancy prevention (if indicated). Patients with greater than 20% of their CLL cells having the deletion of chromosome 17p detected on FISH were also excluded from FLAIR as fludarabine, cyclophosphamide, and rituximab was considered inappropriate, but all other patients considered fit for fludarabine, cyclophosphamide, and rituximab or ibrutinib were eligible. Symptomatic cardiac failure, unstable angina not controlled by current therapy, respiratory impairment and other severe, concurrent diseases or mental disorders that could interfere with the ability to participate were also exclusion criteria. Detailed inclusion and exclusion criteria are included in the study protocol, in the appendix (p 32). All participants provided written informed consent.

This study was approved by the national ethics review board (National Research Ethics Service, London, UK), institutional review boards of the participating centres, and the competent regulatory authority (Medicines and Healthcare Products Regulatory Agency, London, UK), and was done according to the Declaration of Helsinki and the principles of Good Clinical Practice as espoused in the Medicines for Human Use (Clinical Trials) Regulations.

Randomisation and masking

Participants were randomly assigned (1:1) to treatment with either fludarabine, cyclophosphamide, and rituximab or ibrutinib and rituximab. A computer-generated minimisation algorithm with a random element was used to avoid chance imbalances in three variables established at trial entry: Binet stage (stage A progressive or B *vs* C), age (≤65 years *vs* >65 years), sex (male *vs* female), and centre (appendix p 5).

See **Online** for appendix

Randomisations were done at the Clinical Trials Research Unit at the University of Leeds by authorised members of staff with a centralised automated 24-h telephone system according to a validated minimisation algorithm developed under the supervision of DRH. Because of the nature of the intervention, the study was open-label, and the allocated treatment was not masked from study investigators or patients. The funders remained masked to treatment results until data cutoff.

Procedures

Sex and ethnicity were collected from electronic medical records where possible, and self-report otherwise. Patients were free to refuse to disclose this information.

Fludarabine, cyclophosphamide, and rituximab was repeated every 28 days for a total of six cycles in the absence of disease progression or toxicity requiring cessation. Fludarabine was administered orally at a dose of 24 mg/m² and cyclophosphamide was administered orally at a dose of 150 mg/m² per day for the first 5 days of each cycle. Rituximab was administered intravenously at 375 mg/m² on day 1 of cycle 1 and 500 mg/m² on day 1 in cycles 2–6. Ibrutinib was administered orally at 420 mg/day on the rituximab schedule with the fludarabine, cyclophosphamide, and rituximab regimen and then ibrutinib was delivered for either 6 years, until the measurable residual disease stopping rules were reached, until toxicity requiring cessation, or until disease progression, whichever was earliest. Dose reductions and delays were permitted for toxicity and renal function. The detailed dose reduction schedules are shown in the protocol in the appendix and prophylaxis with granulocyte colony-stimulating factor was recommended for patients who had neutropenia.

FISH analysis (Cytocell, Cambridge UK) and *IGHV* mutation status (Sigma-Genosys, Haverhill, UK) were done at baseline and measurable residual disease was assessed in the peripheral blood and bone marrow by highly sensitive multiparameter flow cytometry (Becton Dickinson, Franklin Lanes, NJ; Miltenyi Biotec, Bergisch Gladbach, Germany; IQ Products, Groningen, Netherlands) with a detection limit of one CLL cell in 100 000 leukocytes (0·001%, 1×10^{-5}) in a central laboratory (Haematological Malignancy Diagnostic Service, Leeds, UK). Measurable residual disease was categorised as detectable measurable residual disease if CLL cells represented at least 0·01% of total blood or bone marrow leukocytes or undetectable-measurable residual disease if CLL cells represented less than 0·01% of total blood or bone marrow leukocytes. The first assessment in both groups was 9 months post-randomisation (peripheral blood and bone marrow)

followed by peripheral blood assessment at 12 months, then every 6 months thereafter in the ibrutinib group. Measurable residual disease was assessed in the fludarabine, cyclophosphamide, and rituximab group every 12 months. The hierarchy of cytogenetic abnormalities was assessed in all patients.[14] Progression-free survival outcomes for various cytogenetic aberrations were analysed.

The measurable residual disease stopping rules were based on a stopping algorithm. Starting at the 12-month assessment, patients had measurable residual disease measured in peripheral blood every 6 months. Once an undetectable measurable residual disease result was obtained, the time from randomisation to this first undetectable measurable residual disease result was calculated, and treatment continued for that same duration before being stopped. Sustained undetectable measurable residual disease to confirm stopping was checked with a peripheral blood test 3 months following the first instance of undetectable measurable residual disease and a bone marrow aspirate and peripheral blood test 6 months later.

Adverse events were assessed at the start of each treatment cycle and were graded according to the US National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Adverse events were collected from randomisation until 30 days after the last dose of treatment. Serious adverse events were reported for all patients from the date of randomisation until 30 days after the last dose of treatment except in the case of serious adverse reactions (serious adverse events with a suspected relationship to an investigational medicinal product), which were collected for the duration of the trial.

Response assessments according to IWCLL criteria were done at 9 months post-randomisation (3 months after the end of treatment with fludarabine, cyclophosphamide, and rituximab, or rituximab [for patients randomly assigned to receive ibrutinib and rituximab]) and then every 6 months from 12 months post-randomisation until 7 years post-randomisation or progressive disease, whichever occurred first. A CT-scan (thorax, abdomen, and pelvis) was done at trial entry, at 9 months post-randomisation and at stopping and restarting treatment with ibrutinib. Response and progression were assessed by local investigators according to IWCLL criteria. All patients ended 6 monthly follow-up at progressive disease if this was sooner. Post-progression follow-up is annual for survival status.

Outcomes

The primary endpoint of the trial was progression-free survival, defined as the time from randomisation to progressive disease or death (from any cause). Patients without an event were censored at the time of last follow-up.

Secondary endpoints were overall survival, defined as the time from randomisation to death from any cause or last follow-up. Additional secondary endpoints were measurable residual disease assessments including the proportion with undetectable measurable residual disease at 9 months post-randomisation and longitudinally (measurable residual disease response over time), pattern of measurable residual disease relapse and retreatment, response to therapy according to IWCLL criteria at 9 months post-randomisation and longitudinally including proportion with complete response, partial response, and overall response, safety, and toxicity, health-related quality of life assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) and Quality of Life Questionnaire—Chronic Lymphocytic Leukemia 16 (EORTC QLQ-CLL16) and cost-effectiveness assessed by means of the Short-Form 12 and EQ-5D to produce quality adjusted life years. The pattern of measurable residual disease relapse and retreatment will be reported at final analysis when the number of measurable residual disease relapses is greater. Health-related quality of life and cost-effectiveness are the subject of separate reports in preparation.

Statistical analysis

The data cutoff date for this analysis was May 24, 2021. The hypothesis being tested was that ibrutinib and rituximab treatment improved progression-free survival compared with fludarabine, cyclophosphamide, and rituximab in patients with previously untreated CLL. The trial was designed to show a 1·5-year increase in median progression-free survival in the ibrutinib and rituximab group (median 6 years) compared with the fludarabine, cyclophosphamide, and rituximab group (median 4·5 years, hazard ratio [HR] 0·75) when a total of 379 progression-free survival events had been observed. This calculation[15] assumed the time-to-event was exponentially distributed and that recruitment would last 4 years with a further 4 years of follow-up, a two-sided 5% significance level, and 80% power. A minimum recruitment target of 748 patients randomly assigned (1:1) to ibrutinib and rituximab or fludarabine, cyclophosphamide, and rituximab was specified, allowing for 5% dropout. These assumptions and estimated outcomes with fludarabine, cyclophosphamide, and rituximab were based on results from the German CLL8 trial.[16] A formal interim analysis was prespecified in the study protocol for the primary endpoint, progression-free survival. This was prespecified to occur when at least 50% of required progression-free survival events had been observed (191 events) or 101 events had been observed in the fludarabine, cyclophosphamide, and rituximab group, whichever was earlier. To ensure that an overall significance level of 5% was maintained, the O'Brien

and Fleming alpha-spending function was used with prespecified bounds of 0·5% for interim and 4·8% for final analysis.[17] The interim analysis was completed and presented to the data monitoring and ethics committee on July 1, 2021, and the recommendation was made to report the interim analysis. The trial steering committee accepted the recommendation on July 7, 2021.

Efficacy analyses were done by intention to treat, including all patients randomly assigned to either ibrutinib and rituximab or fludarabine, cyclophosphamide, and rituximab. The safety population included all patients who received at least one dose of study treatment. For the primary endpoint, we estimated summaries of time to event per treatment group using the Kaplan-Meier method with corresponding 95% CIs estimated using the Hall-Wellner method. We made comparisons between the allocated groups using the Cox proportional hazards model adjusted for the minimisation factors, excluding centre, to estimate HRs and 95% CIs. Centre was not included in the model owing to the large number of recruiting centres and therefore dummy variables in the model which would lead to unstable estimates. Overall survival was analysed in the same manner. The proportional hazards assumptions were assessed by plotting the hazards over time for each treatment group and by use of the Kolmogorov-Type supremum test described by Lin and colleagues.[18] None of the model terms showed significant evidence of violation of the assumption. Subgroup analysis for progression-free survival and overall survival was prespecified for the minimisation factors (excluding centre), *IGVH* mutation status, hierarchical model of chromosomal abnormalities,[14] FISH abnormalities (17p deletion, *ATM* deletion, trisomy 12, 13q14 deletion), next generation sequencing (data in preparation), creatinine clearance and granulocyte colony stimulating factor use. Subgroup analysis for overall survival has not as yet been done owing to the small number of deaths on study. We did a likelihood ratio test for heterogeneity of treatment effect using Cox models identical to those used for the main analysis, with the inclusion of terms for the subgroup in question and the appropriate interaction terms. The reported test for heterogeneity for subgroup analysis corresponds to a one degree of freedom test for two category subgroups and a two degrees of freedom test for three category subgroups, etc. The number and proportion of patients in each measurable residual disease and response category was summarised descriptively and exact 95% CIs calculated by means of the Clopper-Pearson method. Binary logistic regression models were fitted to assess the effect of treatment on the odds of attaining undetectable measurable residual disease in the bone marrow and peripheral blood at any point in the trial, adjusting for the minimisation factors, excluding centre. Similar analysis was done for achieving overall response and complete response at 9 months post-randomisation. The Hosmer-Lemeshow test was used to examine the fit of the logistic regression models. Time to undetectable measurable residual disease was estimated by means of the Kaplan-Meier method. Post-hoc exploratory analyses considered the effect of ibrutinib and rituximab on progression-free survival within key subgroups.

The use of second line and subsequent treatment for patients after disease progression was a potential source of bias in the comparison of overall survival. Post-hoc exploratory analysis considered rank-preserving structural failure time models relating the observed overall survival to the counterfactual estimate without treatment with ibrutinib.[19–21]

We summarised toxicity, in terms of adverse events, descriptively. On the basis of an imbalance noted at the time of interim analysis, the following exploratory analyses were done in a post-hoc manner. All deaths occurring on study were reviewed by the chief investigator and another clinical trial management group member

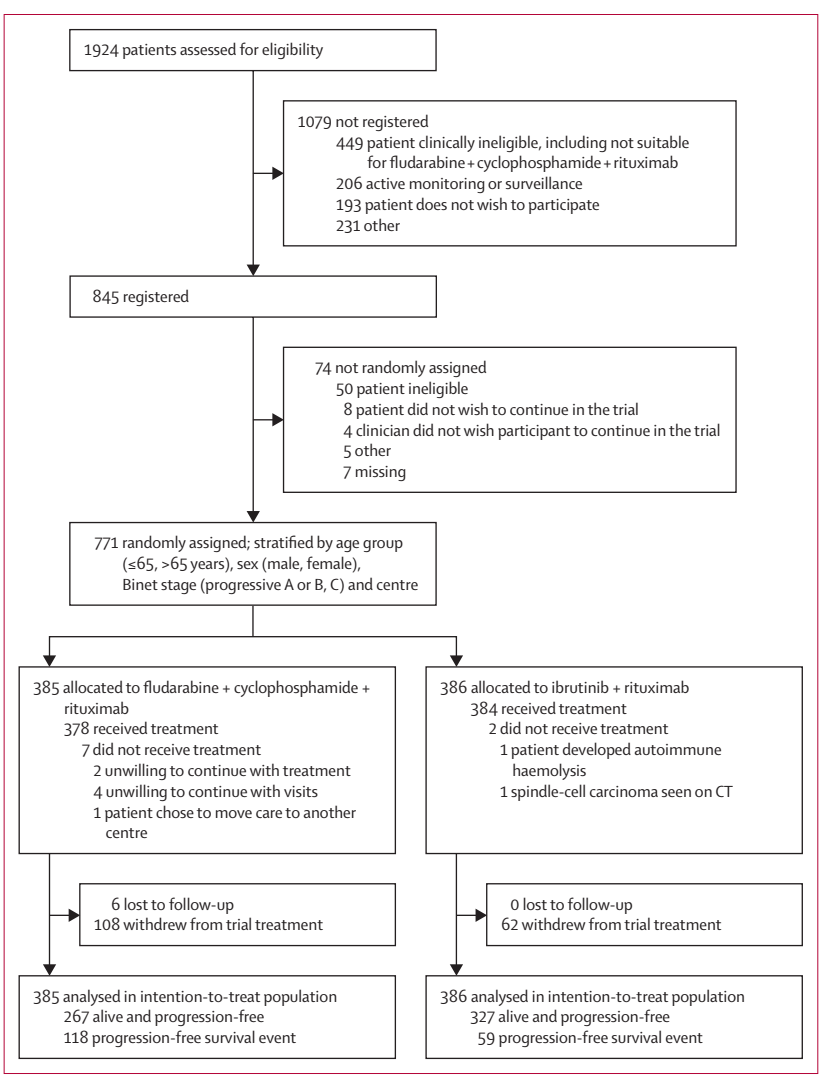

Figure 1: **Trial profile**

	Ibrutinib and rituximab group (n=386)	Fludarabine, cyclophosphamide, and rituximab group (n=385)	Total (n=771)
Age, years			
median (IQR)	63 (55–67)	62 (56–67)	62 (56–67)
≤65 years	254 (66%)	258 (67%)	512 (66%)
>65 years	132 (34%)	127 (33%)	259 (34%)
Sex			
Male	283 (73%)	282 (73%)	565 (73%)
Female	103 (27%)	103 (27%)	206 (27%)
Ethnicity			
White	364 (94%)	365 (95%)	729 (95%)
Mixed—White and Asian	1 (<1%)	0	1 (<1%)
Other mixed background	1 (<1%)	0	1 (<1%)
Asian—Indian	0	4 (1%)	4 (1%)
Asian—Pakistani	0	1 (<1%)	1 (<1%)
Other Asian background	0	1 (<1%)	1 (<1%)
Black—Caribbean	3 (1%)	2 (1%)	5 (1%)
Black—African	1 (<1%)	2 (1%)	3 (<1%)
Other Black background	0	1 (<1%)	1 (<1%)
Other ethnic group	2 (1%)	2 (1%)	4 (1%)
Not stated	14 (4%)	7 (2%)	21 (3%)
Binet stage			
Progressive A or B	208 (54%)	215 (56%)	423 (55%)
C	178 (46%)	170 (44%)	348 (45%)
WHO performance status			
0	244 (63%)	263 (68%)	507 (66%)
1	129 (33%)	115 (30%)	244 (32%)
2	12 (3%)	6 (2%)	18 (2.3%)
Missing	1 (<1%)	1 (<1%)	2 (<1%)
IGHV status			
Mutated	148 (38%)	146 (38%)	294 (38%)
Unmutated	194 (50%)	194 (50%)	388 (50%)
Subset 2: mutated	15 (4%)	13 (3%)	28 (4%)
Subset 2: unmutated	11 (3%)	7 (2%)	18 (2%)
Not done	0	1 (<1%)	1 (<1%)
Failed	14 (4%)	16 (4%)	30 (4%)
Unproductive†	4 (1%)	8 (2%)	12 (2%)
Hierarchy			
TP53 deletion	2 (1%)	1 (<1%)	3 (<1%)*
ATM deletion	56 (15%)	63 (16%)	119 (15%)
Trisomy 12	46 (12%)	49 (13%)	95 (12%)
Normal karyotype	117 (30%)	112 (29%)	229 (30%)
13q deletion	139 (36%)	131 (34%)	270 (35%)
Failed	4 (1%)	1 (<1%)	5 (1%)
Incomplete	22 (6%)	28 (7%)	50 (7%)

(Table 1 continues on next page)

masked to treatment allocation. We identified sudden unexplained death or cardiac death as one of a sudden death with no obvious cause or a sudden death with a cardiac cause with the exception of myocardial infarction. The number of sudden unexplained or cardiac deaths was summarised and the relative risk and corresponding 95% CIs were estimated. The association between risk factors and sudden unexplained or cardiac death was tested with the Fisher's exact test and by means of Poisson regression including an offset applied to the linear predictor to account for duration of exposure to trial treatment. Cumulative incidence function curves were estimated by non-parametric maximum likelihood estimation.[22] Fine and Gray competing risks regression[23] was used to compare the hazard of sudden unexplained death or sudden cardiac death by treatment, adjusting for the minimisation factors with unrelated or other death specified as a competing risk. Similar analysis was done by means of Poisson regression. Person-years were calculated as the sum over all patients receiving at least one dose of study treatment of the time in years from randomisation to death or last date known to be alive. Incidence rates were calculated with the number of events per person as the numerator and the number of person-years on trial as the denominator. CIs for incidence rate were calculated by means of normal approximations to the Poisson distribution. Post-hoc analyses were undertaken to synthesise progression-free survival HRs and incidence rates from identified phase 3 trials of ibrutinib in random effects meta-analysis. A normal-normal model was used for hazard ratios and a Poisson-normal model for incidence rates due to the sparsity of the data (few events occurring during follow-up time).

All reported p values are two-sided and considered significant at an overall significance level of 5%. We used SAS (version 9.4), Stata–IC (version 16), and R (version 4.0.1) for statistical analyses.

This study is registered with ISRCTN, ISRCTN01844152 and EudraCT, 2013-001944-76.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of 1924 patients assessed for eligibility, 771 were randomly assigned (figure 1) between Sept 19, 2014, and July 19, 2018. 385 patients were assigned to receive fludarabine, cyclophosphamide, and rituximab, and 386 patients were assigned to receive ibrutinib and rituximab. Patient and disease characteristics were well balanced between groups (table 1). Median age was 62 years (IQR 56–67), 565 (73%) were male, 206 (27%) were female and 507 (66%) were WHO performance status of 0. Six patients (1%) of 771 had a 17p deletion (three [1%] of 385 in the fludarabine, cyclophosphamide, and rituximab group and three [1%] of 386 in the ibrutinib and rituximab group). One patient in each group had greater than 20% 17p deletion on assessment at the central laboratory. One (<1%) patient in the fludarabine, cyclophosphamide, and rituximab group had 9·5% of lymphocytes with a *TP53* deletion

and two (1%) patients in the ibrutinib and rituximab group had 59·7% and 87·4% of lymphocytes with a *TP53* deletion, respectively.

For the primary analysis, 59 (15%) of 386 patients in the ibrutinib and rituximab group and 118 (31%) of 385 patients in the fludarabine, cyclophosphamide, and rituximab group had disease progression or died. No patients were excluded from this analysis. After a median follow-up of 53 months (IQR 41–61), median progression-free survival was was not reached with ibrutinib and rituximab and was 67 months (95% CI 63–NR) with fludarabine, cyclophosphamide, and rituximab (HR 0·44 [0·32–0·60]; p <0·0001; figure 2A). Annual progression-free survival estimates are given in the appendix (p 14). 4-year progression-free survival was 85·6% (95% CI 81·3–89·0) in the ibrutinib and rituximab group and 73·0% (67·7–77·5) in the fludarabine, cyclophosphamide, and rituximab group.

In subgroup analyses, the benefit of ibrutinib and rituximab on progression-free survival was seen across most subgroups (figure 3) and there was no significant heterogeneity within the subgroups. The progression-free survival was significantly better with ibrutinib and rituximab compared with fludarabine, cyclophosphamide, and rituximab in patients with *IGHV* unmutated-CLL (HR 0·41 [95% CI 0·28–0·61]; p<0·0001), but was not significantly different for patients with *IGHV* mutated-CLL (HR 0·64 [0·35–1·16]; p=0·15: appendix p 8) or subset 2 (HR 0·30 [0·05–1·63]; p=0·19; appendix p 8). Similarly, the progression-free survival was significantly better with ibrutinib and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with *ATM* deletion (HR 0·29 [95% CI 0·14–0·69]; p=0·0010) or normal karyotype (HR 0·38 0·20–0·69]; p=0·0010; appendix pp 9–10), but was not significantly different for trisomy 12 (HR 0·47 [0·18–1·24]; p=0·13; appendix p 9) or 13q deletion (HR 0·62 [0·36–1·08]; p=0·093; appendix pp 9–11).

31 (8%) of 386 patients died in the ibrutinib and rituximab group and 29 (8%) of 385 patients died in the fludarabine, cyclophosphamide, and rituximab group. Median overall survival was not reached with ibrutinib and rituximab or fludarabine, cyclophosphamide, and rituximab. Annual overall survival estimates are given in the appendix (p 14). The 4-year overall survival was 92·1% (95% Cl 88·6–94·5) in the ibrutinib and rituximab group and 93·5% (90·1–95·7) in the fludarabine, cyclophosphamide, and rituximab group. No difference was observed between ibrutinib and rituximab and fludarabine, cyclophosphamide, and rituximab for overall survival (HR 1·01 [95% CI 0·61–1·68]; p=0·96; figure 2B).

At 9 months post-randomisation, 15 (3·9%; 95% CI 2·19–6·33) of 386 patients had attained undetectable measurable residual disease in bone marrow in the ibrutinib and rituximab group versus 213 (55·3%; 50·20–60·36) of 385 patients in the fludarabine, cyclophosphamide, and rituximab group (appendix p 14). The cumulative incidence of measurable residual disease negativity in peripheral blood continued to increase throughout treatment in the ibrutinib and rituximab group but this did not occur in the fludarabine, cyclophosphamide, and rituxumab group (appendix p 12, 14). 177 (46%) of 385 patients in the fludarabine, cyclophosphamide, and rituximab group and 14 (4%) of 386 patients in the ibrutinib and rituximab group had undetectable measurable residual disease in bone marrow at any time during the trial. Similarly, 290 (75%) of 385 patients in the fludarabine, cyclophosphamide, and rituximab group and 38 (10%) of 386 patients in the ibrutinib and rituximab group had undetectable measurable residual disease in the peripheral blood at any time during the trial. The odds ratios for ibrutinib and rituximab versus fludarabine, cyclophosphamide, and rituximab from logistic regression models adjusted for minimisation factors age group, sex, and Binet stage were 0·04 (95% CI 0·02–0·07; p<0·0001) in bone marrow and 0·04 (0·02–0·05; p<0·0001) in peripheral blood. There was a lack of fit (p=0·0090) for the bone marrow logistic regression model. This was expected because of the small number of participants with an undetectable measurable residual disease result in bone marrow. However, the peripheral blood logistic regression model was deemed to fit the data well (p=0·69).

Median time to first undetectable measurable residual disease in bone marrow was 9·1 months (95% CI 8·6–10·4) for the fludarabine, cyclophosphamide, and rituximab group and was not reached for the ibrutinib and rituximab group (figure 4A). Similarly, median time to first undetectable measurable residual disease in peripheral blood was 8·3 months (95% CI 8·1–8·4]

	Ibrutinib and rituximab group (n=386)	Fludarabine, cyclophosphamide, and rituximab group (n=385)	Total (n=771)
(Continued from previous page)			
Haematology			
Haemoglobin <110 (males only), g/L	104 (37%)	93 (33%)	197 (35%)
Haemoglobin <100 (females only), g/L	33 (32%)	35 (34%)	68 (33%)
Platelets <100, ×10⁹/L	99 (26%)	98 (26%)	197 (26%)
Median ALC lymphocytes, ×10⁹/L	79·3 (0·8– 581)	82·2 (0·4–511)	81·4 (0·4– 581)
Median creatinine clearance, mL/min	78·6 (30·0–211)	77·8 (30·7–194)	78·0 (30·0–211)
Duration of CLL before study entry, months	23·7 (0·0–219)	24·7 (0·0–162)	24·1 (0·0–219)

Data are median (IQR), n (%), or n (95% CI). ALC=absolute lymphocyte count. CLL=chronic lymphocytic leukaemia. *There are three additional participants with *TP53* deletion which was in <20% of CLL cells. †IGHV-IGHD-IGHJ gene rearrangements can be rendered unproductive if they carry pseudogenes; out-of-frame variable, diversity, and joining junctions; stop codons; or indels leading to frameshifts within the coding part of the sequence. ‡Results for some cytogentic aberration not available. Hierarchy of cytogenetic abnormalities was established by Leeds Haematological Malignancy Diagnostic Service (HMDS, Leeds, UK) and owing to low-level deletion, these participants were not deemed by HMDS to have a *TP53* deletion prognostic marker for progression-free survival.

Table 1: **Baseline characteristics**

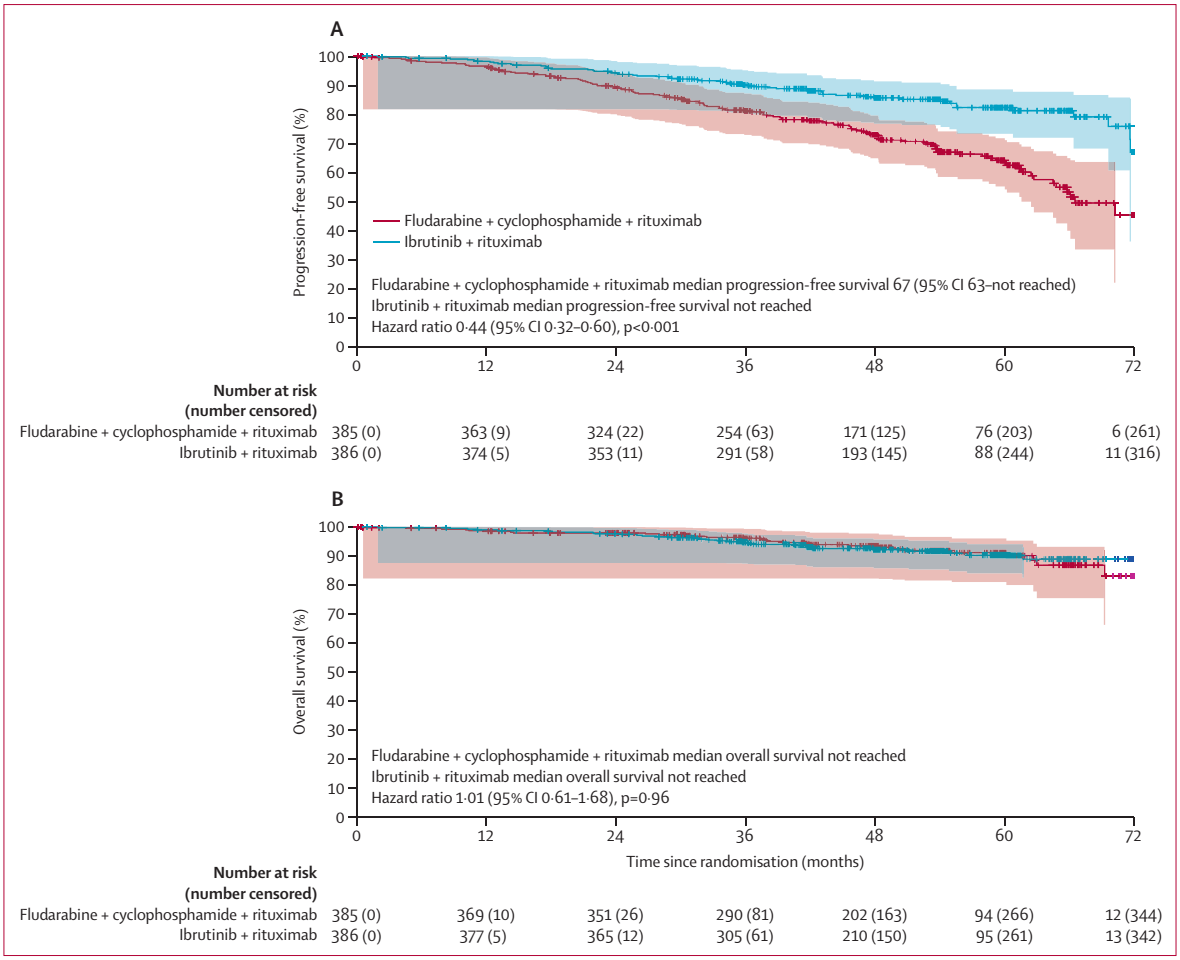

Figure 2: **(A) Progression-free survival by allocated treatment, (B) overall survival by allocated treatment**
Shaded lines represent 95% CIs.

for participants randomly assigned to fludarabine, cyclophosphamide, and rituximab and was not reached for participants randomly assigned to ibrutinib and rituximab (figure 4B).

At 9 months post-randomisation, 233 (61%; 95% CI 55·4–65·4) of 385 patients had attained complete response in the fludarabine, cyclophosphamide, and rituximab group and 81 (21%; 95% CI 17·0–25·4) of 386 patients had attained complete response in the ibrutinib and rituximab group (appendix p 15). The adjusted odds ratio estimate for the achievement of complete response in the ibrutinib and rituximab group compared with the fludarabine, cyclophosphamide, and rituximab group was 0·17 (95% CI 0·12–0·24; p<0·0001). Similarly, at 9 months post-randomisation, 339 (88%; 95% CI 84·4–91·1) of 385 patients in the fludarabine, cyclophosphamide, and rituximab group and 352 (91%; 87·9–93·8) of 386 patients in the ibrutinib and rituximab group achieved an overall response (appendix p 15). The adjusted odds ratio estimate for the achievement of overall response in the ibrutinib and rituximab group compared with the fludarabine, cyclophosphamide, and rituximab group was 1·41 (95% CI 0·88–2·25; p=0·15). Partial remission with lymphocytosis was achieved by no patients in the fludarabine, cyclophosphamide, and rituximab group and 60 patients (16%) in the ibrutinib and rituximab group (appendix p 15).

Similar results are seen when considering the proportion of participants who have achieved an overall response as assessed by investigator at any time during the trial; 93·0% (95% CI 90·0–95·3) of patients in the fludarabine, cyclophosphamide, and rituximab group achieved an objective response rate compared with 95·6% (93·0–97·4) of patients in the ibrutinib and rituximab group (appendix p 15).[9]

In subgroup analyses, the effect of ibrutinib and rituximab on complete response at 9 months was similar in patients with *IGHV* unmutated-CLL (fludarabine, cyclophosphamide, and rituximab 110 [57%] of 193 [95% CI 50–64] and ibrutinib and rituximab 41 (21%) of 194 [16–28]) and patients with *IGHV* mutated-CLL (fludarabine, cyclophosphamide, and rituximab 91 [62%]

	Fludarabine + cyclophosphamide + rituximab, n (events)	Fludarabine + cyclophosphamide + rituximab, 3-year progression-free survival (95% CI)	Ibrutinib + rituximab, n (events)	Ibrutinib + rituximab, 3-year progression-free survival (95% CI)	Hazard ratio (95% CI)	$p_{heterogeneity}$
Sex						0·53
Male	282 (94)	78·2% (72·7–82·8)	283 (50)	89·1% (84·7–92·2)	0·46 (0·32–0·64)	
Female	103 (24)	88·9% (80·9–93·7)	103 (9)	92·8% (85·5–96·5)	0·35 (0·16–0·76)	
Age group						0·069
≤65 years	259 (79)	81·6% (76·1–85·9)	255 (31)	92·6% (88·5–95·3)	0·35 (0·23–0·52)	
>65 years	126 (39)	80·2% (71·7–86·4)	131 (28)	85·0% (77·5–90·2)	0·64 (0·39–1·04)	
Binet stage						0·12
Progressive A or B	217 (69)	82·8% (76·8–87·3)	218 (41)	88·0% (82·8–91·7)	0·52 (0·36–0·77)	
C	168 (49)	79·0% (71·7–84·6)	168 (18)	92·6% (87·4–95·8)	0·31 (0·18–0·54)	
Hierarchical model of chromosomal abnormalities						0·53
TP53 deletion	1 (1)	100·0%	2 (1)	50·0% (0·6–91·0)		
ATM deletion	63 (28)	66·8% (52·8–77·5)	56 (10)	92·7% (81·7–97·2)	0·28 (0·13–0·61)	
Trisomy 12	49 (14)	83·2% (69·2–91·2)	46 (6)	88·3% (74·1–95·0)	0·47 (0·18–1·24)	
Normal karyotype	112 (33)	84·9% (76·5–90·4)	117 (16)	91·2% (84·3–95·2)	0·38 (0·20–0·69)	
13q deletion	131 (31)	85·2% (77·6–90·4)	139 (22)	88·8% (82·1–93·1)	0·62 (0·36–1·08)	
Undetermined	29 (11)	74·1% (53·1–86·7)	26 (4)	91·6% (70·4–97·8)	0·23 (0·07–0·76)	
IGHV* risk						
Undetermined	25 (8)	78·1% (55·1–90·3)	18	100·0%		
Unmutated	194 (77)	74·2% (67·1–79·9)	194 (38)	87·8% (82·1–91·7)	0·41 (0·28–0·61)	
Subset 2	20 (6)	84·4% (58·9–94·7)	26 (2)	91·8% (71·1–97·9)	0·30 (0·05–1·63)	
Mutated	146 (27)	90·5% (84·2–94·4)	148 (19)	91·6% (85·6–95·1)	0·64 (0·35–1·16)	
TP53* deletion						
Yes	3 (2)	66·7% (5·4–94·5)	3 (1)	66·7% (5·4–94·5)		
No	381 (116)	81·2% (76·7–84·9)	379 (56)	90·4% (86·9–93·0)	0·43 (0·31–0·59)	
Undetermined	1		4 (2)	75·0% (12·8–96·1)		
ATM* deletion						
Yes	67 (30)	67·3% (53·9–77·6)	59 (11)	93·1% (82·6–97·3)	0·29 (0·14–0·61)	
No	314 (88)	83·8% (79·0–87·5)	321 (45)	90·0% (86·0–92·8)	0·45 (0·31–0·64)	
Undetermined	4	100·0%	6 (3)	66·7% (19·5–90·4)		
Trisomy 12						0·21
Yes	55 (15)	85·1% (72·3–92·2)	53 (8)	86·0% (72·8–93·1)	0·59 (0·25–1·41)	
No	299 (89)	81·6% (76·5–85·7)	304 (47)	90·1% (86·1–93·0)	0·46 (0·32–0·66)	
Undetermined	31 (14)	69·9% (50·1–83·1)	29 (4)	96·2% (75·7–99·4)	0·14 (0·04–0·46)	
13q14 deletion						0·21
Yes	192 (51)	82·3% (75·7–87·2)	190 (31)	88·0% (82·4–92·0)	0·56 (0·36–0·87)	
No	162 (54)	81·2% (74·1–86·6)	171 (24)	91·4% (85·9–94·8)	0·35 (0·21–0·57)	
Undetermined	31 (13)	73·9% (54·5–86·0)	25 (4)	95·7% (72·9–99·4)	0·19 (0·06–0·63)	
Granulocyte colony-simulating factor						0·092
Yes	236 (70)	81·0% (75·2–85·5)	66 (4)	96·9% (88·3–99·2)	0·19 (0·07–0·53)	
No	149 (48)	81·4% (73·7–87·0)	320 (55)	88·7% (84·6–91·7)	0·47 (0·32–0·69)	
Creatinine clearance						0·46
≤60 mL/min	69 (16)	82·9% (71·3–90·2)	59 (9)	89·6% (78·2–95·2)	0·58 (0·26–1·31)	
>60 mL/min	316 (102)	80·7% (75·7–84·8)	327 (50)	90·1% (86·2–93·0)	0·41 (0·30–0·58)	
Overall	**385 (118)**	**81·1% (76·7–84·8)**	**386 (59)**	**90·0% (86·5–92·7)**	**0·44 (0·32–0·60)**	

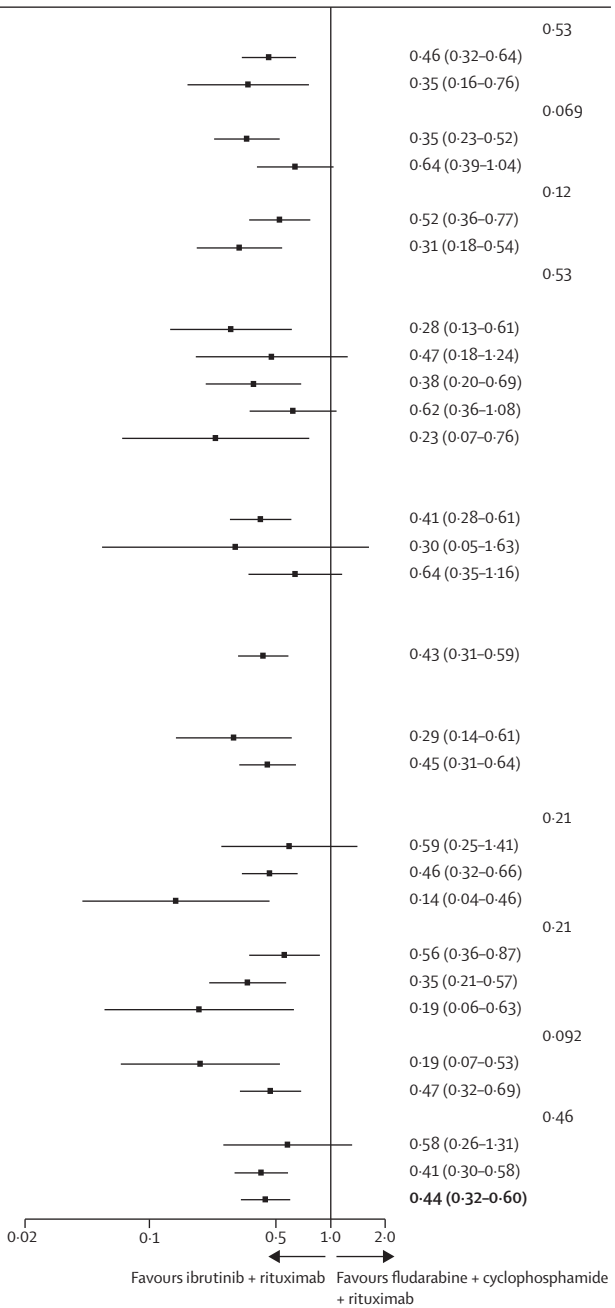

Figure 3: **Progression-free survival subgroup analysis**
*Likelihood ratio test for heterogeneity inestimable.

of 147 [54–70] and ibrutinib and rituximab 27 [18%] of 148 [12–25]). Similarly, the effect of ibrutinib and rituximab on overall response at 9 months was similar in patients with *IGHV* unmutated-CLL (fludarabine, cyclophosphamide, and rituximab 167 [87%] of 193 [95% CI 80·89–91·01%] and ibrutinib and rituximab 176 [91%] of 194 [85·73–94·41]) and patients with *IGHV* M-CLL (fludarabine, cyclophosphamide, and rituximab 130 [88%] of 147 [82·13–93·12] and ibrutinib and rituximab 134 (91%) of 148 [84·64–94·73]).

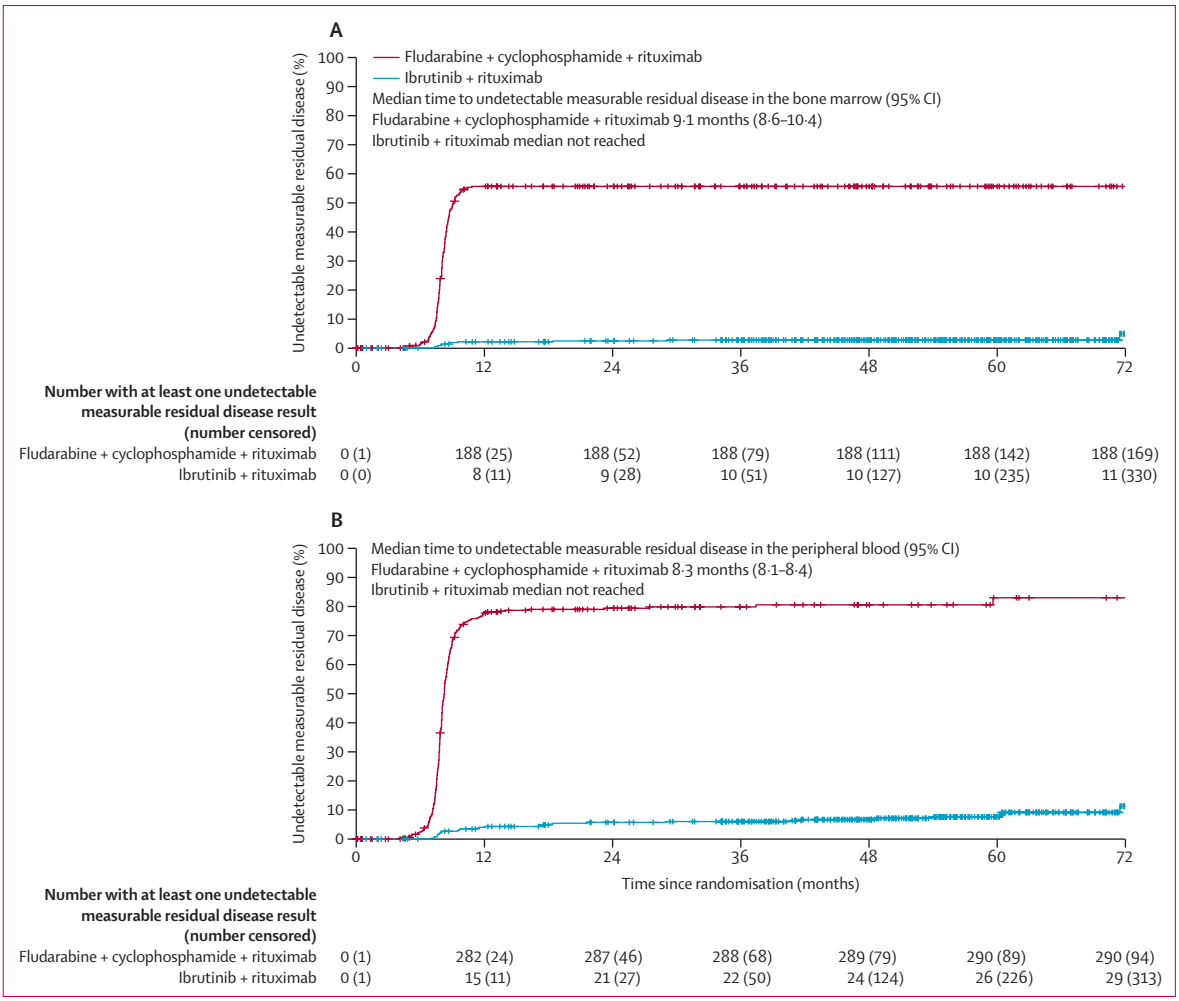

Figure 4: **(A) Time to first undetectable measurable residual disease in the bone marrow by allocated treatment. (B) Time to first undetectable measurable residual disease in the peripheral blood by allocated treatment**

The most common cause of death was non-haematological malignancies (appendix p 15). Of the patients allocated to fludarabine, cyclophosphamide, and rituximab, two (7%) of 29 deaths were deemed to be probably related to treatment and three (10%) of the 30 deaths of those receiving ibrutinib and rituximab treatment were deemed to be probably related to treatment (treatment-related myelodysplastic syndrome–acute myeloid leukaemia [n=2], acute cardiac failure and ischaemic heart disease [n=1], retroperitoneal haemorrhage ([n=1], infection [n=1]). To date, seven patients in the fludarabine, cyclophosphamide, and rituximab group have developed a myelodysplastic syndrome or acute myeloid leukaemia as compared with one patient in the ibrutinib and rituximab group. Four patients developed Richter's transformation in the fludarabine, cyclophosphamide, and rituximab group and three patients in the ibrutinib and rituximab group (appendix p 17). The 4-year cumulative incidence of other diagnosed cancers was higher in the fludarabine, cyclophosphamide, and rituximab group than the ibrutinib and rituximab group (17·3% [95% CI 13·0–21·6] *vs* 7·4% [4·7–10·1]; HR 0·46 [95% CI 0·3–0·7], appendix p 17). The overall incidence of other diagnosed cancers per 100 patient-years was 5·0 (95% CI 4·8–5·3) in the fludarabine, cyclophosphamide, and rituximab group and 2·3 (2·2–2·5) in the ibrutinib and rituximab group.

In the fludarabine, cyclophosphamide, and rituximab group, 11 patients (of 378 treated, 3%) died of all cause infections as compared with four patients (of 384 treated, 1%) in the ibrutinib and rituximab group. Of these, three patients in each group died of COVID-19 (appendix p 15). Five patients died before the rollout of COVID-19 vaccines in the UK and one patient was eligible to have received only a first vaccine dose.

There were two (1%) sudden unexplained or cardiac deaths in the fludarabine, cyclophosphamide, and rituximab group and eight (2%) sudden unexplained or cardiac deaths in the ibrutinib and rituximab group

(appendix p 13). The incidence of sudden unexplained or cardiac deaths per 100 person-years was higher in the ibrutinib and rituximab group compared with the fludarabine, cyclophosphamide, and rituximab group; 0·5 (95% CI 0·3–1·0) versus 0·1 (0·0–0·5). This post-hoc estimate is like those observed in other reported studies that use ibrutinib regimens (appendix p 7). Post-mortem details were available for three patients in the study (appendix p 16). The corresponding adjusted HR from the Fine-Gray regression was 3·8 (95% CI 0·8–17·7; p=0·092) whereby the other deaths, including those attributed to CLL, were specified as a competing risk. In the ibrutinib and rituximab group the relative risk of a sudden unexplained death or cardiac death for those who were on medication at study entry for hypertension or a cardiac disorder compared with those who were not was 18·1 (95% CI 2·3–145·5; p<0·0001). The relative risk for those who reported use of an ACE inhibitor, specifically, at study entry was 17·9 (3·7–86·7; p<0·0001) compared with those who did not. When considering other classes of anti-hypertensive drugs there was similar significant elevated risk in the ibrutinib and rituximab group for β blockers and there was not an elevated risk for angiotensin receptor blockers, calcium channel blockers, and diuretics compared with those in the ibrutinib and rituximab group who were not receiving treatment for hypertension or a cardiac disorder at trial entry (appendix p 18). Similar analysis was done for emergent cardiac disorder, hypertension, or treatments for hypertension at date of data-lock or event with similar findings (data not shown). There were no sudden unexplained deaths or cardiac deaths in the fludarabine, cyclophosphamide, and rituximab group among patients who were on medication at study entry for hypertension or a cardiac disorder, or among patients who reported receiving an ACE inhibitor at study entry and as such, the relative risks for ibrutinib and rituximab compared with fludarabine, cyclophosphamide, and rituximab in these populations were not estimable (appendix p 18). An exploratory analysis on the effect of potential risk factors (pre-exisiting cardiac disorders, hypertension, or treatments for hypertension) on serious cardiac adverse events were not significant (appendix pp 5, 19–20).

279 patients (74%) in the fludarabine, cyclophosphamide, and rituximab group received six cycles of fludarabine, cyclophosphamide, and rituximab and 373 patients (97%) in the ibrutinib and rituximab group received six cycles of rituximab. Dose modifications consisting of reductions, delays, and omissions were applied to 275 patients (75%) allocated to fludarabine, cyclophosphamide, and rituximab and 189 patients (49%) allocated to ibrutinib and rituximab (appendix pp 21–23). Dose modifications were applied to 174 patients (45%) up to 12 months post-randomisation and 109 patients (28%) 12–24 months post-randomisation allocated to ibrutinib and rituximab treatment, to 95 patients (28%) in the fludarabine, cyclophosphamide, and rituximab group and 63 patients (16%) in the ibrutinib and rituximab group withdrew from trial treatment appendix (p 24).

In the fludarabine, cyclophosphamide, and rituximab group, 47 patients received targeted therapies (BCL-2 inhibitor, BTK inhibitor) after progression or withdrawal from trial treatment (appendix p 24). Of the 39 patients who switched to receive BTK inhibitors, 34 patients switched to receive ibrutinib treatment after progression. In the ibrutinib and rituximab group, eight patients received targeted therapies. Rank-preserving structural failure time methods did not show whether the allocated treatment effect on overall survival was affected by treatment switching (appendix p 5).

Adverse events were assessed in the 762 patients who completed at least one dose of study therapy. The most common grade 3 or 4 adverse events occurring within 1 year of randomisation were a decrease in white blood cells (203 [54%] patients in the fludarabine, cyclophosphamide, and rituximab group, 55 [14%] patients in the ibrutinib and rituximab group) and anaemia (54 [14%] patients in the fludarabine, cyclophosphamide, and rituximab group, 13 [3%] patients in the ibrutinib and rituximab group; table 2). Common adverse events of any grade were fatigue (198 patients [52%] in the fludarabine, cyclophosphamide, and rituximab group, 166 [43%] in the ibrutinib and rituximab group) and white blood cell decreased (244 [64%] patients in the fludarabine, cyclophosphamide, and rituximab group, 80 [21%] patients in the ibrutinib and rituximab group). Bruising or bleeding occurred in four (1%) patients in the fludarabine, cyclophosphamide, and rituximab group and 104 (27%) in the ibrutinib and rituximab group (table 2). Major haemorrhage occurred in one patient (<1%) in the fludarabine, cyclophosphamide, and rituximab group and four (1%) patients in the ibrutinib and rituximab group. Intracranial haemorrhage occurred in no patients in the fludarabine, cyclophosphamide, and rituximab group and two patients (1%) in the ibrutinib and rituximab group. In the fludarabine, cyclophosphamide, and rituximab group, eight hypertension adverse events occurred in two (1%) patients, and in the ibrutinib and rituximab group, 122 adverse events occurred in 51 patients (12%). The number of hypertension adverse events reported that were grade 3 or higher was one (13%) in the fludarabine, cyclophosphamide, and rituximab group and 14 (12%) in the ibrutinib and rituximab group. In the fludarabine, cyclophosphamide, and rituximab group, 11 atrial fibrillation or arrythmia adverse events occurred in seven patients (2%), and in the ibrutinib and rituximab group, 85 adverse events occurred in 47 patients (12%). The number of atrial fibrillation or arrythmia adverse events reported that were grade 3 or higher was one (10%) in the fludarabine, cyclophosphamide, and rituximab group and six (7%) in the ibrutinib and rituximab group. In the fludarabine, cyclophosphamide, and rituximab group, 15 febrile neutropenia adverse events occurred in 15 patients (4%), and in the ibrutinib and rituximab group,

	Fludarabine, cyclophosphamide, and rituximab group (n=378)				Ibrutinib and rituximab group (n=384)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Abdominal pain	4 (1%)	1 (<1%)	0	0	6 (2%)	1 (<1%)	0	0
Abdominal pain–bloating	39 (10%)	4 (1%)	0	0	55 (14%)	9 (2%)	0	0
Abnormal liver function tests	4 (1%)	0	0	0	0	1 (<1%)	0	0
Acute coronary syndrome	0	1 (<1%)	0	0	1 (<1%)	1 (<1%)	0	0
Adenoviral hepatitis	0	1 (<1%)	0	0	0	0	0	0
Adenovirus test positive	0	0	0	0	0	1 (<1%)	0	0
Administration site discomfort	0	0	0	0	0	1 (<1%)	0	0
Adverse drug reaction	1 (<1%)	1 (<1%)	0	0	0	0	0	0
Alanine aminotransferase increased	8 (2%)	2 (1%)	0	0	10 (3%)	2 (1%)	0	0
Alkaline phosphatase increased	7 (2%)	1 (<1%)	0	0	7 (2%)	0	0	0
Amnesia–memory impairment	1 (<1%)	0	1 (<1%)	0	3 (1%)	0	0	0
Anal pain	0	0	0	0	0	1 (<1%)	0	0
Anaemia	104 (28%)	43 (11%)	11 (3%)	0	79 (21%)	10 (3%)	3 (1%)	0
Anxiety	8 (2%)	0	0	0	8 (2%)	1 (<1%)	0	0
Aortic dissection	0	0	0	0	0	0	1 (<1%)	0
Aplasia pure red cell	0	1 (<1%)	0	0	0	0	0	0
Appendicitis	0	0	0	0	0	1 (<1%)	0	0
Arthralgia–arthritis	21 (6%)	0	0	0	67 (17%)	0	0	0
Arthritis	7 (2%)	0	0	0	18 (5%)	1 (<1%)	0	0
Ascites	0	1 (<1%)	0	0	0	0	0	0
Aspartate aminotransferase increased	2 (1%)	0	0	0	1 (<1%)	1 (<1%)	0	0
Atelectasis	0	1 (<1%)	0	0	0	0	0	0
Atrial fibrillation–arrythmia		1 (<1%)	0	0	16 (4%)	2 (1%)	0	0
Autoimmune haemolytic anaemia	0	1 (<1%)	0	0	0	0	0	0
Back pain	20 (5%)	1 (<1%)	0	0	18 (5%)	2 (1%)	0	0
Bladder infection	0	0	0	0	1 (<1%)	1 (<1%)	0	0
Blood bilirubin increased	9 (2%)	0	1 (<1%)	0	5 (1%)	0	0	0
Bronchiectasis	0	1 (<1%)	0	0	0	0	0	0
Bruising–bleeding	4 (1%)	0	0	0	102 (27%)	2 (1%)	0	0
Bullous dermatitis	1 (<1%)	0	0	0	3 (1%)	1 (<1%)	0	0
Campylobacter gastroenteritis	0	0	0	0	0	1 (<1%)	0	0
Cardiorespiratory arrest	0	0	0	0	0	0	0	1 (<1%)
Chest pain	3 (1%)	0	0	0	9 (2%)	1 (<1%)	0	0
Chest wall pain	0	0	0	0	0	1 (<1%)	0	0
Chills	20 (5%)	0	0	0	13 (3%)	2 (1%)	0	0
Cholecystitis	1 (<1%)	1 (<1%)	0	0	1 (<1%)	1 (<1%)	0	0
Confusion	1 (<1%)	0	1 (<1%)	0	1 (<1%)	0	1 (<1%)	0
Conjunctival cyst	0	0	0	0	0	1 (<1%)	0	0
Constipation	111 (29%)	0	0	0	34 (9%)	0	1 (<1%)	0
Cough	97 (26%)	6 (2%)	1 (<1%)	0	101 (26%)	1 (<1%)	0	0
Cystitis–urinary symptoms	32 (9%)	0	0	0	20 (5%)	1 (<1%)	0	0
Cytopenia	0	1 (<1%)	0	0	0	0	0	0
Dehydration	1 (<1%)	2 (1%)	0	0	0	0	0	0
Dental caries	2 (1%)	1 (<1%)	0	0	0	0	0	0
Diarrhoea	71 (19%)	8 (2%)	0	0	134 (35%)	7 (2%)	0	0
Dizziness–hypotension	21 (6%)	9 (2%)	0	0	23 (6%)	0	0	0
Dyspepsia	12 (3.2%)	1 (<1%)	0	0	41 (11%)	0	0	0
Dyspnoea	42 (11%)	6 (2%)	1 (<1%)	0	35 (9%)	6 (2%)	0	0
Enteritis	0	0	0	0	0	1 (<1%)	0	0
Enterocolitis infectious	1 (<1%)	0	0	0	0	1 (<1%)	0	0

(Table 2 continues on next page)

	Fludarabine, cyclophosphamide, and rituximab group (n=378)				Ibrutinib and rituximab group (n=384)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Escherichia infection	0	0	0	0	0	1 (<1%)	0	0
Fatigue	185 (49%)	13 (3%)	0	0	163 (42%)	3 (1%)	0	0
Febrile convulsion	0	1 (<1%)	0	0	0	0	0	0
Febrile neutropenia	0	14 (4%)	1 (<1%)	0	0	2 (1%)	0	0
Fever	103 (27%)	34 (9%)	1 (<1%)	0	52 (14%)	5 (1%)	0	0
Flu-like symptoms	9 (2%)	4 (1%)	0	0	11 (3%)	1 (<1%)	0	0
Fungal infection	1 (<1%)	0	0	0	0	1 (<1%)	0	0
Gamma-glutamyltransferase increased	2 (1%)	1 (<1%)	0	0	2 (1%)	0	0	0
Giant cell arteritis	0	0	0	0	0	1 (<1%)	0	0
Haemolysis–haemolytic anaemia	3 (1%)	6 (2%)	0	0	1 (<1%)	1 (<1%)	0	0
Haemorrhage	2 (1%)	0	0	0	12 (3%)	0	1 (<1%)	0
Haemorrhage urinary tract	0	0	0	0	0	1 (<1%)	0	0
Haptoglobin decreased	0	1 (<1%)	0	0	0	0	0	0
Headache	52 (14%)	2 (1%)	0	0	58 (15%)	4 (1%)	0	0
Hearing impaired	1 (<1%)	0	0	0	2 (1%)	1 (<1%)	0	0
Haematuria	1 (<1%)	0	0	0	4 (1%)	2 (1%)	0	0
Haemolysis	0	1 (<1%)	0	0	0	0	0	0
Hip fracture	0	1 (<1%)	0	0	0	1 (<1%)	0	0
Hospitalisation	0	1 (<1%)	0	0	0	0	0	0
Hyperglycaemia	1 (<1%)	1 (<1%)	0	0	0	0	0	0
Hyperkalaemia	0	1 (<1%)	0	0	1 (<1%)	0	0	0
Hypertension	1 (<1%)	1 (<1%)	0	0	11 (3%)	6 (2%)	0	0
Hypokalemia	2 (1%)	1 (<1%)	0	0	7 (2%)	2 (1%)	0	0
Hyponatraemia	1 (<1%)	1 (<1%)	0	0	1 (<1%)	2 (1%)	0	0
Hypotension	1 (<1%)	3 (1%)	0	0	2 (1%)	0	1 (<1%)	0
Hypoxia	4 (1%)	0	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
Implantable cardiac monitor insertion	0	0	0	0	0	1 (<1%)	0	0
Infections	2 (1%)	4 (1%)	0	0	8 (2%)	3 (1%)	0	0
Infections and infestations—other	3 (1%)	8 (2%)	0	0	7 (2%)	6 (2%)	0	0
Infusion related reaction	111 (29%)	18 (5%)	2 (1%)	0	46 (12%)	3 (1%)	1 (<1%)	0
Insomnia	13 (3%)	1 (<1%)	0	0	18 (5%)	1 (<1%)	0	0
Intestinal infarction	0	0	0	0	0	0	0	1 (<1%)
Intestinal obstruction	0	0	0	0	0	0	1 (<1%)	0
Investigations—other, specify	5 (1%)	1 (<1%)	0	0	3 (1%)	0	0	0
Left ventricular systolic dysfunction	0	0	0	0	0	1 (<1%)	0	0
Leukocytosis	1 (<1%)	0	0	0	0	4 (1%)	0	0
Liver function test increased	0	1 (<1%)	0	0	1 (<1%)	0	0	0
Lower respiratory tract infection	0	0	0	0	2 (1%)	1 (<1%)	0	0
Lung infection	9 (2%)	11 (3%)	1 (<1%)	0	12 (3%)	4 (1%)	2 (1%)	0
Lymphocyte count decreased	3 (1%)	6 (2%)	7 (2%)	0	1 (<1%)	1 (<1%)	0	0
Lymphocyte count increased	0	0	0	0	1 (<1%)	2 (1%)	0	0
Malaise	10 (3%)	1 (<1%)	0	0	7 (2%)	1 (<1%)	0	0
Meningitis	0	0	0	0	0	1 (<1%)	0	0
Metastatic squamous cell carcinoma	0	0	0	0	0	1 (<1%)	0	0
Mouth ulcers	24 (6%)	0	0	0	66 (17%)	1 (<1%)	0	0
Mucositis/thrush	22 (6%)	1 (<1%)	1 (<1%)	0	25 (7%)	3 (1%)	0	0
Myalgia	5 (1%)	0	0	0	13 (3%)	2 (1%)	0	0
Nausea	224 (59%)	4 (1%)	0	0	68 (18%)	1 (<1%)	0	0

(Table 2 continues on next page)

	Fludarabine, cyclophosphamide, and rituximab group (n=378)				Ibrutinib and rituximab group (n=384)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Neuralgia	3 (1%)	0	0	0	1 (<1%)	1 (<1%)	0	0
Neutrophil count decreased	1 (<1%)	0	1 (<1%)	0	1 (<1%)	0	0	0
Non-specific pain	23 (6%)	2 (1%)	0	0	41 (11%)	2 (1%)	0	0
Oesophageal obstruction	0	0	0	0	0	1 (<1%)	0	0
Oropharyngeal pain	0	0	0	0	0	1 (<1%)	0	0
Other	21 (6%)	6 (2%)	0	1 (<1%)	45 (12%)	5 (1%)	1 (<1%)	0
Pain	4 (1%)	1 (<1%)	0	0	7 (2%)	0	0	0
Palpitations	6 (2%)	0	0	0	19 (5%)	1 (<1%)	0	0
Pelvic mass	0	0	0	0	0	1 (<1%)	0	0
Pericardial effusion	0	0	0	0	0	1 (<1%)	0	0
Peripheral motor neuropathy	3 (1%)	1 (<1%)	0	0	7 (2%)	0	0	0
Pharyngitis	0	0	0	0	1 (<1%)	1 (<1%)	0	0
Platelet count decreased	108 (29%)	27 (7%)	6 (2%)	0	70 (18%)	6 (2%)	5 (1%)	0
Pleural effusion	1 (<1%)	0	0	0	1 (<1%)	2 (1%)	0	0
Pleuritic pain	1 (<1%)	0	0	0	2 (1%)	1 (<1%)	0	0
Pneumocystis jirovecii pneumonia	0	0	0	0	0	1 (<1%)	0	0
Pneumonia cryptococcal	0	0	0	0	0	1 (<1%)	0	0
Pneumonitis	0	0	0	0	0	0	1 (<1%)	0
Portal hypertension	0	1 (<1%)	0	0	0	0	0	0
Pruritus	26 (7%)	1 (<1%)	0	0	14 (4%)	1 (<1%)	0	0
Pseudomonas test positive	0	1 (<1%)	0	0	0	0	0	0
Pulmonary embolism	0	2 (1%)	0	0	0	0	0	0
Rash	111 (29%)	12 (3%)	1 (<1%)	0	116 (30%)	9 (2%)	1 (<1%)	0
Rash maculo-papular	3 (1%)	0	0	0	2 (1%)	1 (<1%)	0	0
Renal colic	0	0	0	0	0	2 (1%)	0	0
Sepsis	2 (1%)	28 (7%)	17 (5%)	0	1 (<1%)	5 (1%)	2 (1%)	0
Sinus tachycardia	6 (2%)	1 (<1%)	0	0	0	0	0	0
Skin infections	9 (2%)	3 (1%)	0	0	28 (7%)	4 (1%)	0	0
Soft tissue inflammation	1 (<1%)	0	0	0	0	1 (<1%)	0	0
Sore throat	16 (4%)	1 (<1%)	0	0	33 (9%)	0	0	0
Surgery	0	0	0	0	0	1 (<1%)	0	0
Syncope	1 (<1%)	2 (1%)	0	0	2 (1%)	2 (1%)	0	0
Taste alteration–loss of appetite	44 (12%)	0	0	0	26 (7%)	0	0	0
Thromboembolic event	1 (<1%)	1 (<1%)	0	0	0	0	0	0
Transaminitis	1 (<1%)	1 (<1%)	0	0	1 (<1%)	0	0	0
Tumour lysis syndrome	0	1 (<1%)	0	0	0	0	0	0
Typhlitis	0	1 (<1%)	0	0	0	0	0	0
Upper gastrointestinal haemorrhage	0	1 (<1%)	0	0	0	0	0	0
Upper respiratory infection	64 (17%)	10 (3%)	0	0	83 (22%)	10 (3%)	0	0
Urinary tract discomfort	0	0	0	0	0	1 (<1%)	0	0
Urinary tract infection	6 (2%)	0	0	0	10 (3%)	5 (1%)	0	0
Vasovagal reaction	1 (<1%)	2 (1%)	0	0	1 (<1%)	0	0	0
Vitreous haemorrhage	0	0	0	0	0	1 (<1%)	0	0
Vomiting	103 (27%)	7 (2%)	0	0	31 (8%)	5 (1%)	0	0
Weight gain	0	0	0	0	4 (1%)	1 (<1%)	0	0
White blood cell decreased	41 (11%)	107 (28%)	96 (25%)	0	25 (7%)	24 (6%)	31 (8%)	0

Grade 1–2 in ≥10% of participants and any grade 3–5 occurring in the safety population.

Table 2: **Adverse events reported within 1-year post-randomisation**

two adverse events occurred in two patients (1%). All the febrile neutropenia adverse events reported were grade 3 or higher. Granulocyte colony stimulating factor was used in 236 patients (62%) treated in the fludarabine, cyclophosphamide, and rituximab group and 66 patients (17%) treated in the ibrutinib and rituximab group.

Adverse events in the ibrutinib and rituximab group after year 1 are given in the appendix (pp 25–30). The longitudinal occurrence of white blood cell decrease in the ibrutinib and rituximab group was lower than those apparent in the treatment phase in the fludarabine, cyclophosphamide, and rituximab group (appendix p 30). Serious adverse events were reported in 203 (54%) of 378 patients receiving fludarabine, cyclophosphamide, and rituximab compared with 205 (53%) of 384 patients receiving ibrutinib and rituximab (appendix p 31). The most common serious adverse event was infections in both groups.

Discussion

The NCRI FLAIR trial is, to the best of our knowledge, the largest study comparing ibrutinib-based therapy with fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy and shows that the primary endpoint of progression-free survival is superior for ibrutinib plus rituximab with an HR of 0·44 (95% CI 0·32–0·60; p<0·0001). This is consistent with the ECOG1912 trial, which showed an HR in favour of ibrutinib and rituximab over fludarabine, cyclophosphamide, and rituximab of 0·35 (95% CI 0·22–0·56; p<0·001)[24] and other phase 3 studies. The total fludarabine, cyclophosphamide, and rituximab dosing was bioequivalent between FLAIR and ECOG1912, but in FLAIR both fludarabine and cyclophosphamide were given orally and over 5 days per cycle whereas in ECOG1912 they were given intravenously over 3 days per cycle. Other key differences were that FLAIR participants were older; the median age in FLAIR was 62 years with 34% over 65 years, whereas in ECOG1912 the median age was 56·7 years with 40·1% 60 years or older. The objective response rate for the fludarabine, cyclophosphamide, and rituximab group in ECOG1912 was 81·1% at 12 months compared with oral fludarabine, cyclophosphamide, and rituximab in FLAIR which had an objective response rate of 88% at 9 months post-treatment. Sub-group analysis in FLAIR suggests a progression-free survival advantage for the ibrutinib and rituximab treated group in the *IGHV* unmutated-CLL subgroup but not in the *IGHV* mutated-CLL group. The 5 years estimated progression-free survival for I*GHV* mutated-CLL sub-group in the fludarabine, cyclophosphamide, and rituximab group of FLAIR is 81·3% as compared with 68% and 66·6% in the ECOG1912 and CLL8 studies. This might or might not become significant with prolonged follow-up as the progression-free survival advantage in the *IGHV* mutated-CLL group has been shown to be significant in the ECOG1912 study update, which was not the case in the first report.[2]

The clinical course of CLL is highly variable with a median survival from diagnosis of approximately 7 years. The overall survival in FLAIR reflects the improved outcome for patients treated with fludarabine, cyclophosphamide, and rituximab compared with historical series and ECOG1912. In FLAIR there was little difference in overall survival between fludarabine, cyclophosphamide, and rituximab and ibrutinib and rituximab with 4-year survival of 93·5% in the fludarabine, cyclophosphamide, and rituximab group compared with 92·1% in the ibrutinib and rituximab group. However, the overall survival with fludarabine, cyclophosphamide, and rituximab in FLAIR is improved compared with fludarabine, cyclophosphamide, and rituximab in previous NCRI trials recruited between 2009 and 2012 (ADMIRE[25] and ARCTIC[26]), which had the same inclusion criteria, the same centres and an identical fludarabine, cyclophosphamide, and rituximab schedule. However, these trials were done before widespread availability of targeted therapies in the relapse setting (4-year overall survival for fludarabine, cyclophosphamide, and rituximab in FLAIR was 93·5% compared with 84·2% for fludarabine, cyclophosphamide, and rituximab in ADMIRE–ARCTIC).[27] In addition when compared with ECOG1912, the 3-year overall survival for the fludarabine, cyclophosphamide, and rituximab group in ECOG1912 was 91·5% compared with 96·4% in the fludarabine, cyclophosphamide, and rituximab group in FLAIR. Mature follow-up at final analysis will aid in establishing whether there was no difference in overall survival owing to treatment switching.

As expected, relatively few patients in the ibrutinib and rituximab group in FLAIR attained undetectable measurable residual disease, which was only observed in 3·9% of patients 9 months post-randomisation. This suggests that the addition of rituximab to ibrutinib might have little benefit which is consistent with results from the Alliance Trial[24] and the MDACC trial.[28]

A notable feature of the FLAIR trial was the observation of a small but substantial number of sudden unexplained or cardiac deaths, which were more frequent in the ibrutinib and rituximab group. Given that six patients with hypertension or cardiovascular history who had events on ibrutinib and rituximab were on an ACE inhibitor at study entry, the coincidence of these factors probably confounds the interpretation of the ACE inhibitor analysis. When comparing with previous randomised phase 3 trials in which ibrutinib was studied, it is clear that sudden deaths have been reported in most of them. ECOG1912 reported only one cardiac death in the ibrutinib and rituximab group but the median age was sustantially lower than any of the other studies. It is possible that the longer-term follow-up of the FLAIR study done in UK NHS hospitals, which are

often close to the residence and where treatment was free might have favoured a better capture of sudden and cardiac deaths than other studies. The FLAIR data suggests that the increased risk is predominantly in hypertensive patients before the initiation of ibrutinib. There was no class of anti-hypertensive drug that was clearly associated with these events. There was an apparently slightly higher risk in patients receiving ACE inhibitors, but the relative risk was not significantly higher than for patients on other therapies and any difference might be caused by differences in the severity of cardiovascular disease rather than therapies given. Indeed, among those treated in the ibrutinib and rituximab group, 117 patients (31%) reported cardiac disease or hypertension requiring treatment at baseline and 157 patients (41%) reported this at the date of trial analysis or last follow-up before death. Thus, we would suggest that in patients already receiving treatment for hypertension or other cardiac conditions, that a formal cardiac assessment is done before initiating ibrutinib and in patients with substantial cardiac comorbidity, alternative class therapies are considered. Stricter monitoring and control of hypertension along with cardiac assessments are incorporated into the trial protocol to ascertain whether managing these issues will reduce any sudden cardiac events and the effect of these changes will be updated in future follow-up.

All-cause infections were one of the main causes of death in both treatment arms of the study. This is in line with other phase 3 studies.[8,24] Of interest, three patients died in each group at the time of reporting due to COVID-19. COVID-19 vaccines were not available until the final months before reporting for this study hence it is difficult to draw any conclusions. Further details of the effect of COVID-19 will be reported in a later manuscript.

Randomised controlled trials that report early for efficacy have been suggested to overestimate the effect size.[29] However, when a stringent and predefined stopping rule is in place[30] and 50% of the required events have been reported, reporting early has been suggested to have a negligible effect on estimated effect sizes.[31] This study had a planned interim analysis included in the protocol for this comparison with an appropriate stopping rule. The primary endpoint analysis was done when 177 (47%) of the required events had been reported, suggesting that the estimated effect could be at most minimally inflated. Therefore, these findings need to be interpreted with caution while awaiting the final analysis planned when 379 events have been observed. Another limitation includes the unblinded nature of the treatment; both the patient and local investigator were aware of the treatment being delivered, and the outcome assessor was aware of the treatment being delivered.

In conclusion, the NCRI FLAIR trial shows that ibrutinib plus rituximab is superior compared with fludarabine, cyclophosphamide, and rituximab. There was no difference in overall survival, possibly because of effective second-line targeted therapy in patients progressing after fludarabine, cyclophosphamide, and rituximab. However, overall survival data is immature and requires further follow-up.

Contributors

PH was chief investigator. PH, DRH, AH, JMB, and TM designed the trial and developed the protocol. AP, DRH, and DAC developed and carried out the statistical analysis plan. PH, ABl, ABr, MY, BK, RW, MF, GP, JRN, NP, GS, NM, KC, AS, FF, NE, SP, CPF, PEMP, DA, and TM participated in recruitment of patients. NM, JS, SD, AR, and NW coordinated the central laboratory investigations. NG, SJ, and AH coordinated the data collection and regulatory and governance requirements. PH, AP, ABl, DAC, AR, DA, and TM interpreted the data. AP, DAC, TM, and PH developed the first drafts of the manuscript. AP and DAC have accessed and verified all the data in the study. All authors had access to all the data reported in the study. All authors contributed to the review and amendments of the manuscript for important intellectual content and approved this final version for submission. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

PH reports funding for the study and provision of investigational medicinal products from Janssen and AbbVie; personal consulting fees from Janssen, AbbVie, and AstraZeneca; personal speaker fees from Janssen, AbbVie, AstraZeneca, and BeiGene; institutional support of clinical trials from Janssen, AbbVie, Gilead Sciences, and F Hoffman-La Roche. AP reports unrestricted educational grants to her institution from Janssen, Pharmacyclics, and AbbVie. ABl reports speaker fees from Janssen and AbbVie and support for conference attendance from AbbVie. ABr reports personal payment for presentations from Janssen-Cilag and AstraZeneca and personal payment for attending meetings from AbbVie. BK reports personal payment or honoraria for lectures from AbbVie and AstraZeneca and a voluntary unpaid role as CLL Support Associate Trustee. RW reports payment for lectures from AbbVie, AstraZeneca, Janssen, and BeiGene; support for attending meetings from AbbVie and Janssen; and participation on a data safety monitoring board or advisory board for AstraZeneca, Janssen, SecuraBio, and AbbVie. MF reports travel support for conference attendance from AbbVie and remunerated participation on an advisory board for AstraZeneca. GP reports honoraria for delivering educational sessions from Janssen-Cilag and Roche. NM reports payment or honoraria for presentations from Amgen and Kite Gilead; support for attending meetings or travel from Takeda; and participation on a data safety monitoring board or advisory board for Kite Gilead, Amgen, and AbbVie. KC reports personal speakers fees from Roche, Takeda, Kite, Gilead, and Incyte; support for travel and registration for meetings from Roche, Takeda, Kite, and BMS; and participation on a data safety monitoring board or advisory board for Roche, Takeda, Celgene, Atara, Gilead, Kite, Janssen, and Incyte. AS reports receipt of part of her salary from the Oxford Biomedical Research Centre; grants from Janssen and AstraZeneca; honoraria for presentations from Roche, AbbVie, Janssen, BeiGene, and AstraZeneca; and receipt of equipment, materials, drugs, medical writing, gifts, or other services from Illumina, Oxford Nanopore Technology, and Adaptive Biotechnology. FF reports grants from Cancer Research UK and AbbVie; consulting fees from BC Platform; payment or honoraria for presentations from AbbVie, Janssen-Cilag, Acerta, and BeiGene; support for attending meetings or travel from AbbVie; and participation on a data safety monitoring board or advisory board for BeiGene. NE reports personal speaker payments from AstraZeneca and Roche and support for attending meetings and travel from AbbVie. SP reports personal honoraria for presentations from Gilead, AstraZeneca, AbbVie, BeiGene, and Takeda. CPF reports personal consultancy fees from AbbVie, AstraZeneca, Atarabio, BMS, GenMab, Gilead–Kite, Incyte, Lilly, Morphosys, Ono, Roche, and Takeda; payment for educational events from Janssen, Incyte, and Roche; institution research funding from BeiGene; support for attending meetings or travel from Roche; and participation on trial steering committees for GenMab, Morphosys, and Roche. DRH is employed by Roche and holds

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Data sharing

De-identified participant data will be made available when all trial primary and secondary endpoints have been met. Any requests for trial data and supporting material (data dictionary, protocol, and statistical analysis plan) will be reviewed by the trial management group in the first instance. Only requests that have a methodologically sound proposal and whose proposed use of the data has been approved by the independent trial steering committee will be considered. Proposals should be directed to the corresponding author in the first instance; to gain access, data requestors will need to sign a data access agreement.

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