Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study

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Summary

Background The *TP53* gene, encoding tumour suppressor protein p53, is located on the short arm of chromosome 17 (17p). Patients with 17p deletion (del17p) chronic lymphocytic leukaemia have poor responses and survival after chemoimmunotherapy. We assessed the activity and safety of ibrutinib, an oral covalent inhibitor of Bruton's tyrosine kinase, in relapsed or refractory patients with del17p chronic lymphocytic leukaemia or small lymphocytic lymphoma.

Methods We did a multicentre, international, open-label, single-arm study at 40 sites in the USA, Canada, Europe, Australia, and New Zealand. Patients (age ≥18 years) with previously treated del17p chronic lymphocytic leukaemia or small lymphocytic lymphoma received oral ibrutinib 420 mg once daily until progressive disease or unacceptable toxicity. The primary endpoint was overall response in the all-treated population per International Workshop on Chronic Lymphocytic Leukaemia 2008 response criteria modified for treatment-related lymphocytosis. Preplanned exploratory analyses were progression-free survival, overall survival, sustained haematological improvement, and immunological improvement. Patient enrolment is complete, but follow-up is ongoing. Treatment discontinuation owing to adverse events, unacceptable toxicity, or death were collected as a single combined category. This study is registered with ClinicalTrials.gov, number NCT01744691.

Findings Between Jan 29, 2013, and June 19, 2013, 145 patients were enrolled. The all-treated population consisted of 144 patients with del17p chronic lymphocytic leukaemia or small lymphocytic lymphoma who received at least one dose of study drug, with a median age of 64 years (IQR 57–72) and a median of two previous treatments (IQR 1–3). At the prespecified primary analysis after a median follow-up of 11·5 months (IQR 11·1–13·8), 92 (64%, 95% CI 56–71) of 144 patients had an overall response according to independent review committee assessment; 119 patients (83%, 95% CI 76–88) had an overall response according to investigator assessment. In an extended analysis with median follow-up of 27·6 months (IQR 14·6–27·7), the investigator-assessed overall response was reported in 120 patients (83%, 95% CI 76–89). 24-month progression-free survival was 63% (95% CI 54–70) and 24-month overall survival was 75% (67–81). Sustained haematological improvement was noted in 72 (79%) of 91 patients with any baseline cytopenia. No clinically relevant changes were noted from baseline to 6 months or 24 months in IgA (median 0·4 g/L at baseline, 0·6 g/L at 6 months, and 0·7 g/L at 24 months), IgG (5·0 g/L, 5·3 g/L, and 4·9 g/L), or IgM (0·3 g/L at each timepoint) concentrations. Common reasons for treatment discontinuation were progressive disease in 34 (24%) patients and adverse events, unacceptable toxicity, or death in 24 (17%) patients. Major bleeding occurred in 13 (9%) patients (11 [8%] grade 3–4). Grade 3 or worse infections occurred in 43 (30%) patients, including pneumonia in 19 (13%) patients. In the extended analysis, 38 patients died, 18 as a result of adverse events (four pneumonia, three chronic lymphocytic leukaemia, two Richter's syndrome, two sepsis, and one each of acute myocardial infarction, septic shock, encephalopathy, general deterioration in physical health, abnormal hepatic function, myocardial infarction, and renal infarction).

Interpretation A high proportion of patients had an overall response to ibrutinib and the risk:benefit profile was favourable, providing further evidence for use of ibrutinib in the most difficult subset of patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma. Ibrutinib represents a clinical advance in the treatment of patients with del17p chronic lymphocytic leukaemia and has been incorporated into treatment algorithms as a primary treatment for these patients.

Funding Pharmacyclics LLC, an AbbVie Company.

Introduction

The p53 tumour suppressor protein plays a crucial role in oncogenesis and response to chemotherapy in human cancers. The *TP53* gene is found on the short arm of chromosome 17 (17p) and is deleted or mutated in over 50% of malignancies.[1] Historically, patients with chronic lymphocytic leukaemia with 17p deletion (del17p) have a poor prognosis with diminished overall survival and inferior clinical outcomes compared with those without del17p when treated with chemotherapy and

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Research in context

Evidence before this study

Based on a review of US and European chronic lymphocytic leukaemia clinical practice guidelines available at the time of study concept development, no standard treatment existed for patients with 17p deletion (del17p) chronic lymphocytic leukaemia and inclusion in clinical trials was recommended for these patients. Ibrutinib showed single-drug activity in patients with del17p chronic lymphocytic leukaemia or small lymphocytic lymphoma in a subgroup analysis of a phase 1b/2 study, with a median progression-free survival that more than doubled that reported for patients with treatment-naive del17p chronic lymphocytic leukaemia treated with fludarabine, cyclophosphamide, and rituximab. This study was undertaken at a time when there was no universally accepted standard of care for patients with del17p chronic lymphocytic leukaemia.

Added value of this study

This prospective study of patients with relapsed or refractory del17p chronic lymphocytic leukaemia or small lymphocytic lymphoma with median extended follow-up of over 27 months reported outcomes of overall response, progression-free survival, duration of response, overall survival, and safety that compare favourably with those of historical chemoimmunotherapy regimens for this difficult-to-treat subset of patients with chronic lymphocytic leukaemia.

Implications of all the available evidence

This study provides evidence for the practice change in which ibrutinib is now approved for the treatment of all patients with del17p chronic lymphocytic leukaemia and has been incorporated into treatment algorithms as a primary treatment for patients with del17p chronic lymphocytic leukaemia. Ibrutinib marks an era of targeted therapeutics that is improving outcomes for a high-risk patient population that has historically had few treatment options.

chemoimmunotherapy-based regimens.[2] As such, the International Workshop on Chronic Lymphocytic Leukaemia[3] recommends testing for del17p before each line of treatment, and the European Research Initiative on CLL[4] recommends *TP53* mutational analysis in patients with chronic lymphocytic leukaemia before a treatment decision.

Even in the front-line setting, patients with del17p chronic lymphocytic leukaemia had poor outcomes with standard chemoimmunotherapy, with a median progression-free survival of 11·3 months with fludarabine, cyclophosphamide, and rituximab (FCR).[5] The presence of a *TP53* mutation or del17p in chronic lymphocytic leukaemia adversely affected survival outcomes after FCR treatment.[6] Alternative therapeutic approaches with monoclonal antibodies in combination with corticosteroids, which do not rely on functional p53, have low efficacy in relapsed or refractory del17p chronic lymphocytic leukaemia, with median progression-free survival ranging from 6·5 months to 12 months.[7–9] Before the approval of ibrutinib, no universal standard of care existed for patients with del17p chronic lymphocytic leukaemia. Historically, consensus guidelines recommended enrolment in clinical trials as the primary mode of treatment.[10] Additionally, early consideration for allogeneic stem cell transplantation was recommended in appropriate patients with del17p chronic lymphocytic leukaemia.[10,11]

See Online for appendix

Ibrutinib is a first-in-class, once-daily, oral, covalent inhibitor of Bruton's tyrosine kinase, an essential enzyme in the B-cell receptor signalling pathway. In a phase 1b/2 study,[12] treatment with ibrutinib 420 mg or 840 mg once daily in patients with relapsed or refractory chronic lymphocytic leukaemia resulted in a high proportion of patients with a response with durable remissions. In a 3-year follow-up,[13] median progression-free survival was 28 months in patients with del17p chronic lymphocytic leukaemia (n=23), which was shorter than that in patients without del17p or del11q chronic lymphocytic leukaemia, 87% of whom remained progression free at 30 months. In the randomised, phase 3 RESONATE study[14] of ibrutinib 420 mg once daily versus ofatumumab, progression-free survival and overall survival were significantly higher and responses were durable in the ibrutinib group in patients with relapsed or refractory del17p chronic lymphocytic leukaemia, with a median progression-free survival of not reached for ibrutinib versus 5·8 months for ofatumumab (hazard ratio 0·25, 95% CI 0·14–0·45).[14]

The absence of an historical standard of care for patients with del17p chronic lymphocytic leukaemia, the unmet medical need in this high-risk population, and the promising activity and safety profile of ibrutinib served as the basis for the RESONATE-17 study. In this study, we assessed the safety and activity of once-daily oral ibrutinib in patients with del17p chronic lymphocytic leukaemia or small lymphocytic lymphoma.

Methods

Study design and participants

In this phase 2, open-label, multicentre study, participants at least 18 years old were enrolled from 40 sites in the USA, Canada, Europe, Australia, and New Zealand (appendix pp 9–10) from Jan 29, 2013, to June 19, 2013. Eligible patients had a diagnosis of chronic lymphocytic leukaemia or small lymphocytic lymphoma as defined by the International Workshop on Chronic Lymphocytic Leukaemia, del17p centrally confirmed prospectively by fluorescence in-situ hybridisation in peripheral blood, one to four previous lines of systemic treatment (including at least two cycles of chemotherapy or immunotherapy for chronic lymphocytic leukaemia or

small lymphocytic lymphoma), adequate haematological function (absolute neutrophil count ≥0·75 cells×10⁹/L and platelet count ≥30 cells×10⁹/L), and met International Workshop on Chronic Lymphocytic Leukaemia criteria for needing treatment.[3] Additionally, patients had an Eastern Cooperative Oncology Group performance status of 0 or 1 and adequate organ function (aminotransferases ≤2·5×upper limit of normal, total bilirubin ≤1·5×upper limit of normal, and estimated creatinine clearance ≥0·5 mL/s). Exclusion criteria included history of Richter's transformation, prolymphocytic leukaemia, uncontrolled autoimmune haemolytic anaemia, or idiopathic thrombocytopenic purpura; previous stem cell transplantation within 6 months of study enrolment; previous chemotherapy or immunotherapy, radiation therapy, or investigational drug within 4 weeks of treatment start; previous ibrutinib treatment; and corticosteroid use within 1 week of first dose except for inhaled steroids for asthma or topical steroids. A full list of exclusion criteria is provided in the appendix (p 3). There were no requirements for estimated life expectancy for entry into the study.

The protocol was approved by institutional review boards at the respective sites, and the study was done according to the principles of the Declaration of Helsinki, the International Conference on Harmonisation, and Good Clinical Practice guidelines. All patients provided written informed consent before enrolment.

The protocol was amended three times: on Feb 22, 2013, to change the eligibility criteria for the number of previous lines of systemic treatment for chronic lymphocytic leukaemia allowed from one to three to one to four; on Dec 16, 2015, to include all patients who received at least one dose of study drug in the efficacy and safety analyses; and on Jan 5, 2015, to provide the timing for the end of the study and confirm availability of an extension study for patients at the time of study closure.

Procedures

Eligible participants received oral ibrutinib 420 mg (three 140 mg capsules) once daily continuously until progressive disease or unacceptable toxicity. Patients were monitored by history, physical examination, and peripheral blood analysis. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Haematological toxicities were graded according to International Workshop on Chronic Lymphocytic Leukaemia 2008 criteria.[3] Major haemorrhage was defined as any grade 3 or worse bleeding or haemorrhage of any grade resulting in intraocular bleeding causing loss of vision, the need for at least 2 units of red blood cell transfusion, hospital admission, extension of hospital stay, or intracranial haemorrhage. Sustained haematological improvement was also assessed (≥50% increase over baseline or improvement to absolute neutrophil count >1·5 cells×10⁹/L, haemoglobin >110 g/L, or platelets >100 cells×10⁹/L that was sustained continuously for ≥56 days without a need for blood transfusion or growth factors).

Ibrutinib treatment was temporarily stopped in the event of absolute neutrophil count less than 0·5×10⁹/L occurring for more than 7 days; platelets less than 50×10⁹/L in patients with normal baseline platelet count or any patients with platelets less than 25×10⁹/L; a decrease from baseline platelet count of at least 50% in the presence of substantial bleeding or at least 75% without bleeding; grade 3 or worse nausea, vomiting, or diarrhoea if persistent despite optimum supportive care; any other grade 4 toxicity; or any unmanageable grade 3 toxicity. Ibrutinib could be resumed at the original 420 mg dose when these toxicities resolved after the first occurrence, at 280 mg once daily after the second occurrence, and at 140 mg once daily after the third occurrence; ibrutinib was discontinued after a fourth occurrence.

Response was assessed using CT radiological examination at the end of weeks 9, 17, 25, 37, 49, 61, 73, and 85, and every 24 weeks thereafter until progressive disease. CT-based responses served as the basis for independent review committee assessments and required confirmation of a response by at least two CT scans done 12 weeks apart. Bone marrow biopsy samples were needed to confirm a complete response. Ibrutinib could be discontinued because of confirmed progressive disease, unacceptable toxicity, withdrawal of consent, investigator decision, requirement for treatment prohibited by protocol, study termination by the sponsor, or patient pregnancy. Treatment discontinuation owing to adverse events, unacceptable toxicity, or death was collected as a single combined category. 30 days after discontinuation, patients underwent an end-of-treatment visit and continued to be followed up for initiation of subsequent anticancer treatment and assessment of disease progression and survival.

Outcomes

The primary endpoint was overall response, defined as the proportion of patients who received at least one dose of ibrutinib (ie, the all-treated population) and achieved a complete response, complete response with incomplete bone marrow recovery, partial response, partial response with lymphocytosis, or nodular partial response, per the International Workshop on Chronic Lymphocytic Leukaemia 2008 criteria modified for treatment-related lymphocytosis.[3,15] An independent review committee did the overall response assessment up to the primary analysis timepoint (ie, throughout the study), which was planned to be about 12 months after the last patient's first dose of ibrutinib. Investigator assessments were collected for overall response and all other endpoints for the entirety of the study, and were used for analysis of these endpoints in the extended analysis. Secondary endpoints were duration of response, defined for responders as the interval between

date of initial documentation of response and date of first documented evidence of progressive disease, death, or date of censoring if applicable, and safety and tolerability of ibrutinib in the all-treated population. Preplanned exploratory analyses were progression-free survival; overall survival; sustained haematological improvement in the subset of patients with cytopenia at baseline (haemoglobin concentration ≤110 g/L, platelet count ≤100 000 cells per μL, or absolute neutrophil count ≤1500 cells per μL), assesed by time to and percentage of patients with improvement in blood counts, defined as improvement in cytopenia by 50%, or haemoglobin concentration greater than 110 g/L, platelet count greater than 100 000 cells per μL, or absolute neutrophil count greater than 1500 cells per μL, with the duration of improvement lasting for 56 days without use of blood transfusion or growth factors; and immunological improvement, measured by a descriptive summary of IgG, IgM, and IgA concentrations over time and by the change in concentrations from baseline. Since immunological improvement was an exploratory endpoint, thresholds for improvement were not predefined.

Statistical analysis

A sample size of about 111 eligible patients receiving at least one dose of ibrutinib in the all-treated population (patients who had received at least one dose of study drug) was needed to exclude an overall response of 25% (ie, the lower bound of the 95% CI exceeds 25%) at the two-sided 0·05 significance level with 90% power, assuming an overall response of 39% (based on historical responses to chemoimmunotherapy or alemtuzumab treatment of patients with del17p chronic lymphocytic leukaemia) by Wilson's score method.

We calculated the proportion of patients achieving an overall response using an exact binomial 95% CI. We used the Kaplan-Meier method for time-to-event analysis (ie, curves and corresponding overall survival at the last known date alive). No imputation was done for missing data. Assessment of overall response and duration of response by investigator was used as a preplanned sensitivity analysis. Exploratory analyses to identify characteristics associated with response according to subgroup were compared for patients achieving a response with an exact binomial 95% CI, which is only used as indicative for identification of potential prognostic factors for future trials. Although the clinical and prognostic variables for subgroup analyses were not specified in the protocol because of the non-randomised trial design, these variables were specified in the statistical analysis plan before any data analyses. The variables age, sex, race, Eastern Cooperative Oncology Group performance status, Rai stage, number of previous systemic treatments, del11q, bulky disease, and geographical region were prespecified in the statistical analysis plan. Previous fludarabine, lactate dehydrogenase concentration, beta-2-microglobulin concentration, median percentage of cells with del17p, and percentage of cells with del17p by quartiles were added in a post-hoc analysis. Assessment of progression-free survival by investigator was used as a sensitivity analysis. No adjustment for multiplicity was done.[16] Patients who withdrew from the study or were lost to follow-up without previous documentation of disease progression were censored on the date of the last disease assessment. Patients who started new anticancer treatment before documentation of disease progression were censored on the date of last disease assessment before the start of the new anticancer treatment. All analyses were done using SAS version 9.3. Patient enrolment is complete, but follow-up is ongoing.

This study is registered with ClinicalTrials.gov, number NCT01744691.

Role of the funding source

The funder of the study was responsible for study design, data analysis, data interpretation, compiling data for summation and analysis, confirmation of accuracy of data, and writing of the report. SO'B, YL, FC, DFJ, and ADC had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 29, 2013, and June 19, 2013, 145 patients were enrolled and 144 patients with symptomatic relapsed or refractory del17p chronic lymphocytic leukaemia (n=137) or small lymphocytic lymphoma (n=7) received at least one dose of study drug. One patient found to be hepatitis B positive after enrolment was deemed ineligible and withdrawn before receiving study drug. Eight (6%) of 144 patients were not assessable because they discontinued study drug within 2 months of study start and did not have an efficacy assessment. Baseline characteristics are shown in table 1. At the prespecified primary analysis after a median follow-up for all treated patients of 11·5 months (IQR 11·1–13·8), 92 (64%, 95% CI 56–71) of 144 patients had an overall response (92 [64%] of patients had a partial response) according to independent review committee assessment. Additionally, at the same timepoint, according to investigator assessment, 119 patients (83%, 95% CI 76–88) had an overall response (91 [63%] had a partial response, 25 [17%] had a partial response with lymphocytosis, two [1%] had a complete response, and one [1%] had a complete response with incomplete bone marrow recovery). Median progression-free survival (95% CI 14 to not estimated) and overall survival (95% CI not estimated) per investigator assessment were not reached.

The median follow-up of the subsequent post-hoc investigator-assessed extended analysis was 27·6 months (IQR 14·6–27·7). Overall response was reported in 120 (83%) of patients (95% CI 76–89; 92 [64%] had a partial response, ten [7%] had a partial response with

	Patients (n=144)
Diagnosis	
Chronic lymphocytic leukaemia	137 (95%)
Small lymphocytic lymphoma	7 (5%)
Age (years)	64 (57–72)
Age ≥65 years	69 (48%)
Rai stage III–IV	91 (63%)
Bulky disease	
≥5 cm	71 (49%)
≥10 cm	15 (10%)
Proportion of cells with 17p deletion (%)	66% (32–86)
13q deletion	106 (74%)
Trisomy 12	25 (17%)
11q deletion	23 (16%)
IGHV gene	
Not mutated	97 (67%)
Mutated	19 (13%)
Missing, not reported, or polyclonal*	28 (19%)
TP53 gene†	
Mutated	107/116 (92%)
Not mutated	9/116 (8%)
Beta-2 microglobulin (mg/L)	5 (4–7)
≥3·5 mg/L	113 (78%)
<3·5 mg/L	27 (19%)
Missing	4 (3%)
Lactate dehydrogenase (μkat/L)	4 (4–6)
≥4·17 μkat/L	77 (53%)
Absolute lymphocyte count (×10⁹/L)	33 (9–96)
≥25·0 × 10⁹/L	82 (57%)
Haemoglobin (g/L)	110 (100–130)
Platelet count (×10⁹/L)	112 (75–162)
Number of previous treatments	2 (1–3)
≥3	56 (39%)
Types of previous treatments	
Alkylating drug	117 (81%)
Anti-CD20 antibody	120 (83%)
Purine analogue	87 (60%)
Alemtuzumab	32 (22%)
Lenalidomide or thalidomide	7 (5%)
Phosphoinositide 3-kinase inhibitor	3 (2%)

Data are number (%), median (IQR), or n/N (%). *Two patient samples were categorised as polyclonal, in which no single subfamily of the VH3 immunoglobulin gene family was in ≥50% abundance by PCR. †Sample not available or of insufficient quality in 28 patients.

Table 1: **Baseline disease characteristics**

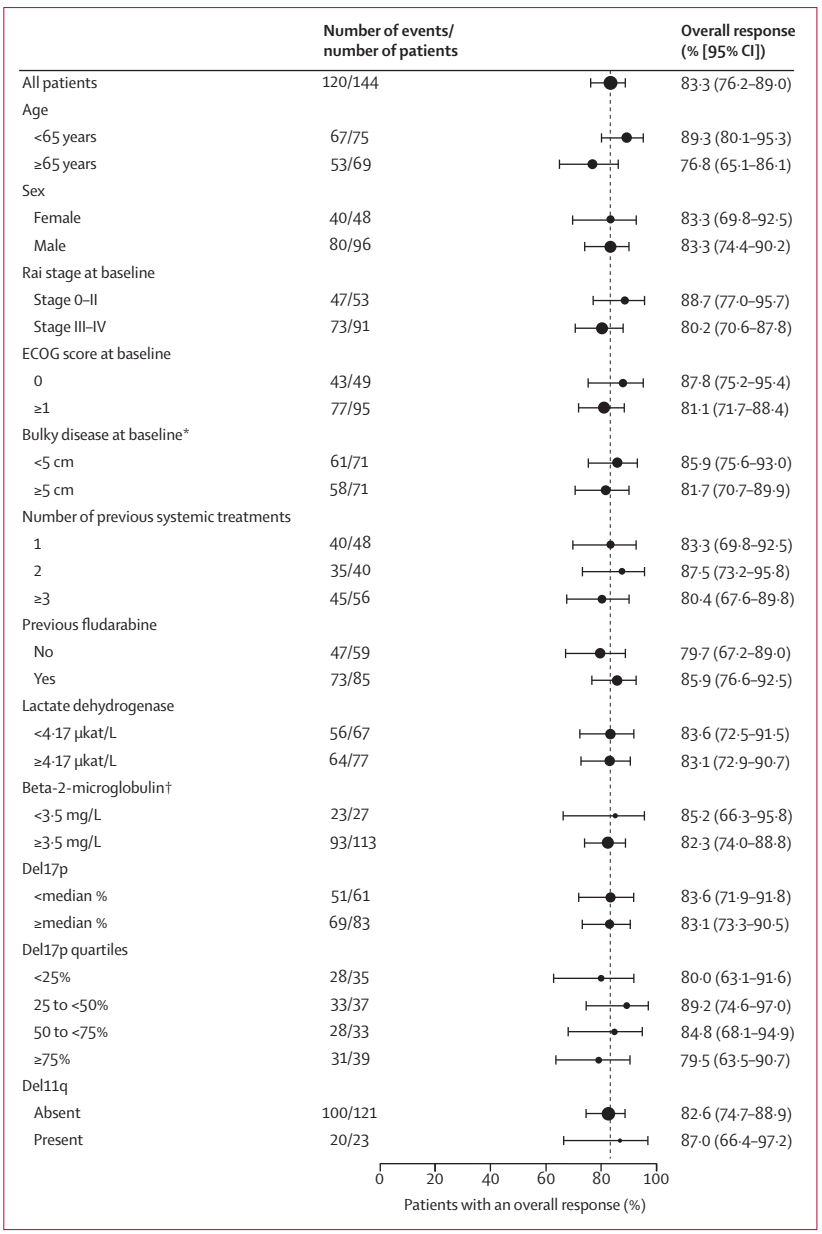

Figure 1: **Subgroup analysis of investigator-assessed overall response**
The sizes of the circles are proportional to the size of the subgroups. ECOG=Eastern Cooperative Oncology Group. Del=deletion. *Two patients did not have a vaild test sample. †Four patients did not have a vaild test sample.

lymphocytosis, three [2%] had a nodular partial response, 12 [8%] had complete response, and three [2%] had complete response with incomplete bone marrow recovery), with 72 (50%) of 144 patients continuing on ibrutinib treatment. 15 patients (10%) had a best response of stable disease, and one (1%) had a best response of progressive disease. Median duration of response was not reached (95% CI not estimated), with estimated rates of continuous remission of 88% (95% CI 80–93) at 12 months and 70% (60–78) at 24 months, among 110 patients with a best response of partial response or better.

As part of the extended analysis, in a subgroup analysis of patients achieving an overall response for prognostic variables prespecified in the statistical analysis plan, overall response was similar for all patients irrespective of subgroup (figure 1).

Sustained haematological improvement occurred in 72 (79%) of 91 patients with any baseline cytopenias, including 23 (88%) of 26 patients with a baseline absolute neutrophil count of 1·5×10⁹/L or lower, 37 (59%) of

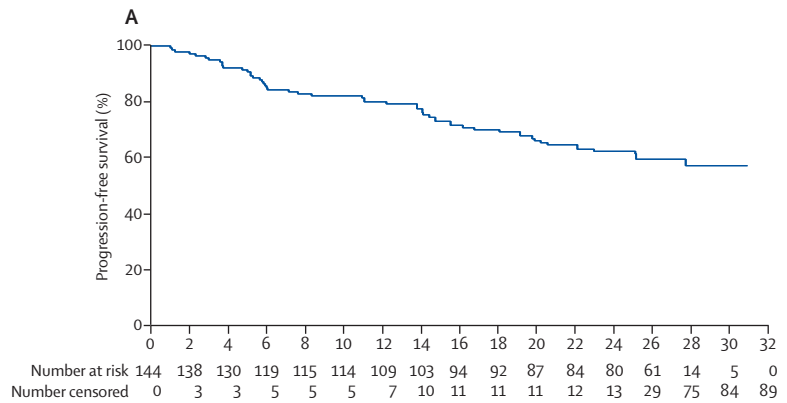

Figure 2: **Survival outcomes at in the extended analysis**
Progression-free survival (A) and overall survival (B) in patients with 17p deletion chronic lymphocytic leukaemia.

	Richter transformation (n=17)	Non-Richter-transformation progressive disease (n=22)	Non-progressive disease (n=105)
Proportion of cells with 17p deletion (%)	74% (38–87)	71% (30–86)	65% (28–84)
11q deletion present	3 (18%)	2 (9%)	18 (17%)
Beta-2 microglobulin (mg/L)	7 (5–9)	5 (3–7)	5 (4–7)
Lactate dehydrogenase* (μkat/L)	8 (6–10)	4 (3–6)	4 (4–5)
Number of previous treatments	2 (1–3)	2 (1–3)	2 (1–3)
Bulky disease	..	..	..
≥5 cm	10 (59%)	14 (64%)	47 (45%)
≥10 cm	2 (12%)	4 (18%)	9 (9%)
Time to progressive disease (days)	180 (95% CI 113–550)	440 (95% CI 253–583)	NA

Data are median (IQR) or number (%), unless otherwise specified. NA=not available. *Upper limit of normal at central laboratory 4·17 μkat/L.

Table 2: **Baseline characteristics and time to progression of patients according to progressive disease status at extended follow-up**

63 patients with a baseline haemoglobin concentration of 110 g/L or lower, and 44 (76%) of 58 patients with a baseline platelet count of 100×10^9/L or lower. No clinically relevant changes were noted from baseline to 6 months or 24 months in IgA (median 0·4 g/L at baseline, 0·6 g/L at 6 months, and 0·7 g/L at 24 months), IgG (5·0 g/L, 5·3 g/L, and 4·9 g/L), or IgM (0·3 g/L at each timepoint).

In the extended analysis, median progression-free survival was not reached (95% CI 27·7 to not estimated), with an estimated progression-free survival at 24 months of 63% (95% CI 54–70; figure 2A). During extended follow-up, 39 patients died and 55 patients had a progression-free survival event. 39 (27%) of 144 patients had progressive disease, including 17 with Richter's transformation (table 2). In these 17 patients with Richter's transformation, progressive disease occurred within the first 6 months in 11 patients and within 25 months in the remainder. Baseline characteristics for patients developing progressive disease (with or without Richter's transformation), and for those remaining progression free are summarised in table 2. The *TP53* mutation status of patients at time of progressive disease was not assessed. Median overall survival was not reached (95% CI 29·5 to not estimated), and the estimated 24-month overall survival was 75% (95% CI 67–81; figure 2B).

72 (50%) of 144 patients discontinued treatment: 34 because of progressive disease, 24 because of unacceptable toxicity, adverse events, or death; nine because of withdrawal of consent; and five because of an investigator decision (three because they proceeded to stem cell transplantation and two for unknown reasons). Because of adverse events, ten (7%) of 144 patients received dose reductions of ibrutinib from 420 mg to 280 mg and four (3%) received dose reductions to 140 mg. Adverse events leading to dose reductions were pneumonia in two patients, spontaneous haematoma in two patients, and fungal pneumonia, nasopharyngitis, hypertension, haematuria, thrombocytopenia, purpura, iritis, uveitis, gastrointestinal pain, and skin lesion in one patient each. Among the patients who had dose reductions, eight remained on treatment and six discontinued (three because of progressive disease and three because of adverse events [immune thrombocytopenic purpura, iritis, and sepsis]). Among the all-treated population, 22 patients discontinued treatment owing to adverse events (excluding clinical progression): four because of pneumonia, two because of myocardial infarction, and one each because of *Pneumocystis jirovecii* pneumonia, sepsis, septic shock, immune thrombocytopenic purpura, subdural haematoma, intracranial haemorrhage, renal infarction, iritis, erythema nodosum, gastric ulcer bleeding, vessel puncture site haematoma, abnormal hepatic function, pulmonary oedema, mouth ulceration, gastritis, and general physical health deterioration. Table 3 lists treatment-emergent adverse events for the duration of the study through the extended analysis. Common grade 3–5 treatment-emergent adverse events occurring in at least 5% of patients were neutropenia in 24 (18%),

pneumonia in 19 (13%), hypertension in 18 (13%), thrombocytopenia in 12 (8%), anaemia in 14 (10%), and atrial fibrillation in eight (6%) of 144 patients. In the extended analysis, 38 patients died, 18 as a result of adverse events (four pneumonia, three chronic lymphocytic leukaemia, two Richter's syndrome, two sepsis, and one each of acute myocardial infarction, septic shock, encephalopathy, general deterioration in physical health, abnormal hepatic function, myocardial infarction, and renal infarction). The complete list of all grade 3–5 treatment-emergent adverse events that occurred is provided in the appendix (pp 4–6).

There were no deaths from atrial fibrillation and no treatment discontinuations owing to atrial fibrillation. Major bleeding events occurred in 13 (9%) of 144 patients (11 [8%] grade 3–4), with no deaths. Nine (69%) of the 13 patients had at least one potential confounding factor, including grade 3 thrombocytopenia, factor XI deficiency, syncope or fall, trauma, or use of an anticoagulant or antiplatelet drug, or both, during the event (appendix p 7). Among patients who had major bleeding events, indications for use of anticoagulants and antiplatelet drugs included prophylaxis, deep-vein thrombosis, thrombophlebitis, non-functional central venous access device, cardiovascular protection, and pain. Of 131 patients without a major bleeding event, 27 (21%) had received an anticoagulant and 48 (37%) had received an antiplatelet drug (appendix p 8).

	Grade 1–2	Grade 3*	Grade 4*	Grade 5*
Diarrhoea	59 (41%)	..	..	..
Fatigue	46 (32%)	..	..	..
Cough	44 (31%)	..	..	..
Arthralgia	38 (26%)	..	..	..
Nausea	33 (23%)	..	..	..
Pyrexia	30 (21%)	..	..	..
Decreased appetite	28 (19%)	..	..	..
Muscle spasms	27 (19%)	..	..	..
Peripheral oedema	26 (18%)	..	..	..
Upper respiratory tract infection	25 (17%)	..	..	..
Anaemia	24 (17%)	12 (8%)	2 (1%)	..
Hypertension	24 (17%)	18 (13%)	..	..
Increased tendency to bruise	23 (16%)	..	..	..
Urinary tract infection	23 (16%)	7 (5%)	..	..
Back pain	22 (15%)	..	..	..
Night sweats	21 (15%)	..	..	..
Constipation	19 (13%)	..	..	..
Dyspnoea	18 (13%)	..	..	..
Dyspepsia	17 (12%)	..	..	..
Headache	17 (12%)	..	..	..
Weight increased	17 (12%)	..	..	..
Myalgia	16 (11%)	..	..	..
Nasopharyngitis	16 (11%)	..	..	..
Vomiting	16 (11%)	..	..	..
Pneumonia	15 (10%)	16 (11%)	1 (<1%)	4 (3%)
Sinusitis	15 (10%)	..	..	..
Neutropenia	..	13 (9%)	19 (13%)	..
Thrombocytopenia	..	11 (8%)	4 (3%)	..
Atrial fibrillation	..	7 (5%)	3 (2%)	..
Hyponatraemia	..	7 (5%)	..	..

Data are number of patients (%). Adverse events in ≥10% of patients for grades 1–2 and ≥5% of patients for grades 3–5 are reported. *Patients with several events in different grades for a given preferred term are counted in each grade category.

Table 3: **Treatment-emergent adverse events for the duration of the study through the extended analysis by preferred term**

Discussion

RESONATE-17 is, to our knowledge, the largest prospective, multicentre study so far specifically designed for relapsed or refractory del17p chronic lymphocytic leukaemia or small lymphocytic lymphoma, and the only ibrutinib study to report outcomes from patients with del17p confirmed by central diagnostics, with a median extended follow-up of over 2 years. At the prespecified primary analysis, the investigator-assessed overall response was 83% (95% CI 76–88). This overall response was maintained in the subsequent extended analysis. The number of patients who achieved a complete response and complete response with incomplete bone marrow recovery increased from three (2%) at the primary analysis to 15 (10%) at the extended analysis; these results are consistent with an increase in complete responses over time with ibrutinib reported in other studies.[13,17] Median progression-free survival and duration of response were not reached. These results substantiate findings from a cohort of patients with relapsed or refractory del17p chronic lymphocytic leukaemia (n=34) from a post-hoc subgroup analysis of the phase 1b/2 ibrutinib study[13] that reported an overall response of 79% (6% complete response, 65% partial response, and 9% partial response with lymphocytosis) and a median progression-free survival of 28 months. The long-term effect of the number of previous treatment regimens on the activity of ibrutinib remains to be elucidated, and may be clarified with longer follow-up of patients in RESONATE-17. Overall survival in RESONATE-17 was similar to that in a small single-centre study[17] that assessed ibrutinib in high-risk populations with del17p chronic lymphocytic leukaemia or *TP53* mutations and reported an estimated overall survival at 24 months of 74% in a subgroup of relapsed or refractory patients (n=15).

The median follow-up of over 27 months in RESONATE-17 is substantially longer than the median follow-up of 9·4 months in the phase 3 RESONATE study[14] of single-drug ibrutinib versus ofatumumab, which showed a median progression-free survival of not reached for ibrutinib versus 5·8 months for ofatumumab in patients with relapsed or refractory del17p chronic

lymphocytic leukaemia. The progression-free survival outcomes in RESONATE-17 compare favourably with those with monoclonal-antibody-containing regimens.[7–9] In patients with high-risk chronic lymphocytic leukaemia with del17p or *TP53* mutation (n=13) who were receiving high-dose methylprednisolone plus rituximab, overall response was 69% and median progression-free survival was 12 months.[8] In the phase 2 CLL206 trial[7] of high-dose methylprednisolone plus alemtuzumab in patients with del17p and *TP53* mutation, high overall responses (overall response in 77% and complete response in 14%) in patients with previously treated chronic lymphocytic leukaemia (n=22) did not translate to improved outcomes (median progression-free survival 6·5 months *vs* 18·3 months in treatment-naive patients). In the phase 2 German CLL2O trial[9] of alemtuzumab plus dexamethasone followed by alemtuzumab maintenance or allogeneic transplantation in patients with ultra-high-risk chronic lymphocytic leukaemia, patients with relapsed del17p chronic lymphocytic leukaemia (n=28) had an overall response of 79% and a median progression-free survival of 10·3 months.[9] The progression-free survival outcomes in the current study also compare favourably with the median progression-free survival of 11 months with FCR or alemtuzumab in treatment-naive patients with del17p chronic lymphocytic leukaemia.[5,18,19] How RESONATE-17 progression-free survival outcomes will compare with those of other B-cell-signalling inhibitors in del17p chronic lymphocytic leukaemia is yet to be determined. In a study with idelalisib plus rituximab,[20] median progression-free survival was not reached in the relapsed chronic lymphocytic leukaemia population, with a short median idelalisib treatment of 3·8 months. Treatment of relapsed or refractory chronic lymphocytic leukaemia with idelalisib in combination with chemoimmunotherapy resulted in a median overall progression-free survival of 20·3 months for patients with del17p or *TP53* mutations.[21] In a phase 2 study of venetoclax in patients with relapsed or refractory del17p chronic lymphocytic leukaemia, the overall response was 79%, with a 12-month progression-free survival of 72% after a median time on study of 12 months;[22] follow-up is ongoing.

In the current study, few patients developed disease progression (n=39). The rate of development of Richter's transformation decreased over time, with 11 of 17 Richter's transformation events occurring within the first 6 months and the remainder within 25 months. Inactivation of the *TP53* gene represented by del17p is a genetic aberration commonly found in Richter's transformation.[23] As such, the cases of Richter's transformation that occurred in this study might have been due in part to pre-ibrutinib presence of a transformed clone, perhaps induced by ineffective chemotherapy or chemoimmunotherapy in combination with del17p, which might have led to a shorter median time to progression compared with the median time to progression in patients without Richter's transformation. Richter's transformation appeared early in the course of treatment but was uncommon (4·5% at 12 months) in a large series of ibrutinib-treated patients with chronic lymphocytic leukaemia.[24] The randomised RESONATE study[14] had an equal proportion of patients with Richter's transformation in the ibrutinib and ofatumumab groups (n=2 each). In the randomised HELIOS study[25] of bendamustine and rituximab plus ibrutinib or placebo in patients without del17p chronic lymphocytic leukaemia, three patients had Richter's transformation in the placebo group versus none in the ibrutinib group. In RESONATE-2,[26] in patients with treatment-naive chronic lymphocytic leukaemia, one patient in the non-ibrutinib group had Richter's transformation. Therefore, the data from these three randomised controlled studies across different chronic lymphocytic leukaemia populations do not suggest an association of ibrutinib treatment with development of Richter's transformation; additional follow-up to investigate this is underway.

The safety profile of ibrutinib-treated patients in this study was consistent with previous reports, with most adverse events being mild to moderate in severity.[12–14,17] Adverse events leading to death occurred in 18 patients with extended follow-up. The most commonly reported grade 3–4 events were neutropenia, hypertension, pneumonia, and anaemia. Grade 3–4 atrial fibrillation occurred in a similar proportion of patients that had been previously reported in studies of ibrutinib in chronic lymphocytic leukaemia (3–6%).[13,14] Hypertension of any grade was reported in 39 (27%) of patients; none were serious events. There were no discontinuations of ibrutinib owing to atrial fibrillation or hypertension. Major bleeding events were reported in 13 (9%) patients, with nine (69%) having potential confounding factors for bleeding risk. Infections of grade 3 or worse occurred in 43 (30%) of patients over the total duration reported. In the phase 2 studies of alemtuzumab plus corticosteroids in high-risk chronic lymphocytic leukaemia (including relapsed or refractory del17p chronic lymphocytic leukaemia), grade 3–4 infections were reported in 36–51% of patients.[7,9] Grade 3–4 haematological adverse events, including neutropenia (36–64%), anaemia (31–36%), and thrombocytopenia (31–39%)[7,9] also occurred at a higher frequency with these regimens than with ibrutinib in our study. Overall, these results suggest that treatment with ibrutinib in patients with ultra-high-risk chronic lymphocytic leukaemia is associated with a favourable risk:benefit profile.

Since RESONATE-17 is a single-arm, non-randomised study that used an independent review committee only through primary analysis of activity, we also reported investigator-assessed responses. We used a central laboratory to identify and enrol patients with del17p, excluding those with *TP53* mutation alone without del17p. Longer follow-up will be needed to reach median progression-free survival and overall survival. Despite these limitations, these results support use of ibrutinib

in patients with del17p chronic lymphocytic leukaemia or small lymphocytic lymphoma. Although we did not do a formal, randomised comparison of ibrutinib and chemoimmunotherapy in this population, a randomised trial does not seem justified because of the favourable indirect evidence in historical comparisons.

Ibrutinib is indicated by the US Food and Drug Administration for treatment of patients with chronic lymphocytic leukaemia and for chronic lymphocytic leukaemia with del17p, and in the European Union for first-line treatment in patients with del17p or *TP53* mutation who are unsuitable for chemoimmunotherapy.[14,27,28] Ibrutinib is also incorporated into the European Society for Medical Oncology[29] and National Comprehensive Cancer Network (NCCN)[30] treatment guidelines as a standard of care for first-line and relapsed or refractory del17p chronic lymphocytic leukaemia. This study provides further evidence for the use of ibrutinib to treat del17p chronic lymphocytic leukaemia, as put forward in these clinical guidelines. Alongside data from other emerging treatments, ibrutinib might contribute to a reassessment of the role and timing of stem cell transplantation by changing the choice and sequence of treatments used for management of high-risk chronic lymphocytic leukaemia.[11] These data mark an era of targeted therapeutics that is changing historical treatment algorithms for patients with del17p chronic lymphocytic leukaemia or small lymphocytic lymphoma, the most difficult subset of patients to treat.

Contributors

SO'B, YL, FC, DFJ, and ADC had access to and interpreted the raw data. SO'B wrote the first draft of the manuscript. As members of the steering committee, SO'B, PH, CT, MJK, and SS provided scientific and clinical advice on the study protocol or its amendments, or both; provided input on key issues encountered during the study; and participated in study communication and education at sites as needed. All authors reviewed drafts of the manuscript and approved the final version.

Declaration of interests

SO'B has consulted for and received honoraria from Janssen and Pharmacyclics, and received research funding from Pharmacyclics. JAJ has consulted for and received research support from Pharmacyclics, AbbVie, and Janssen. SEC has served in an advisory role for Janssen and Pharmacyclics, and has received research funding from AbbVie and Pharmacyclics. ARM has consulted for Celgene, Gilead, AbbVie, Janssen, and Pharmacyclics, and has received travel expenses from TG Therapeutics. PH has consulted for, received honoraria from, and received research funding from Roche, GSK, Janssen, Gilead, and AbbVie; has received honoraria and research funding from Novartis and Pharmacyclics; and has received research funding from Celgene. CT has received honoraria from Janssen, has received research funding from Janssen, and has served in an advisory role for Janssen. AÖ has received honoraria from Gilead and Janssen, and research funding from GlaxoSmithKline, Gilead, Janssen, and Pharmacyclics. TS has served on a speakers' bureau for Pharmacyclics and Janssen and has received research funding from Pharmacyclics. MJT has received research funding from AbbVie, Gilead, Merck, and Pharmacyclics. RRF has served on speakers' bureau and received honoraria from Pharmacyclics, and has served in an advisory role for Pharmacyclics. JRB has received honoraria from and served in an advisory role for Pharmacyclics, Janssen, Celgene, Gilead, Infinity, and Pfizer; has received honoraria from Roche/Genentech and Sun BioPharma; has consulted for Genentech; and has received travel expenses from Janssen, Gilead, Sun BioPharma, and Pfizer. MS-B was previously employed by Pharmacyclics LLC, an AbbVie Company, and YL, FC, DFJ, and ADC are employed by Pharmacyclics LLC, an AbbVie Company, and declare stock ownership in AbbVie. MH has consulted for Pharmacyclics and has served on a speakers' bureau for Pharmacyclics and Janssen. SS has consulted for, received honoraria from, and received research funding from AbbVie, Amgen, Boehringer Ingelheim, Celgene, Genentech, Genzyme, Gilead, GlaxoSmithKline, Janssen, Mundipharma, Novartis, Pharmacyclics, and Hoffman-La Roche; and has served on a speakers' bureau for and received travel expenses from AbbVie, Janssen, and Pharmacyclics. OI, MJK, and TGC declare no competing interests.

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