Safety and activity of ibrutinib in combination with nivolumab in patients with relapsed non-Hodgkin lymphoma or chronic lymphocytic leukaemia: a phase 1/2a study

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Summary

Background Preclinical studies have shown synergistic antitumour effects between ibrutinib and immune-checkpoint blockade. The aim of this study was to assess the safety and activity of ibrutinib in combination with nivolumab in patients with relapsed or refractory B-cell malignant diseases.

Methods We did a two-part, open-label, phase 1/2a study at 21 hospitals in Australia, Israel, Poland, Spain, Turkey, and the USA. The primary objective of part A (dose escalation) was to assess the safety of daily oral ibrutinib (420 mg or 560 mg) in combination with intravenous nivolumab (3 mg/kg every 2 weeks) to ascertain a recommended phase 2 dose in patients with relapsed or refractory high-risk chronic lymphocytic leukaemia or small lymphocytic lymphoma (del17p or del11q), follicular lymphoma, or diffuse large B-cell lymphoma. Dose optimisation was investigated using a modified toxicity probability interval design. The primary objective of the part B expansion phase was to establish the preliminary activity (the proportion of patients who achieved an overall response) of the combination of ibrutinib and nivolumab in four cohorts: relapsed or refractory high-risk chronic lymphocytic leukaemia or small lymphocytic lymphoma (del17p or del11q), follicular lymphoma, diffuse large B-cell lymphoma, and Richter's transformation. All participants who received at least one dose of treatment were included in the primary analysis and analyses were done by disease cohort. This trial is registered with ClinicalTrials.gov, number NCT02329847. The trial is ongoing.

Findings Between March 12, 2015, and April 11, 2017, 144 patients were enrolled in the study. Three patients died before receiving study treatment; thus, 141 patients were included in the analysis, 14 in part A and 127 in part B. One dose-limiting toxicity (grade 3 hyperbilirubinaemia) was reported at the 420 mg dose in the diffuse large B-cell lymphoma cohort, which resolved after 5 days. The combination of ibrutinib and nivolumab led to overall responses in 22 (61%) of 36 patients with high-risk chronic lymphocytic leukaemia or small lymphocytic lymphoma, 13 (33%) of 40 patients with follicular lymphoma, 16 (36%) of 45 patients with diffuse large B-cell lymphoma, and 13 (65%) of 20 patients with Richter's transformation. The most common all-grade adverse events were diarrhoea (47 [33%] of 141 patients), neutropenia (44 [31%]), and fatigue (37 [26%]). 11 (8%) of 141 patients had adverse events leading to death; none were reported as drug-related. The most common grade 3–4 adverse events were neutropenia (40 [28%] of 141 patients) and anaemia (32 [23%]). The incidence of grade 3–4 neutropenia ranged from eight (18%) of 45 patients with diffuse large B-cell lymphoma to 19 (53%) of 36 patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma; incidence of grade 3–4 anaemia ranged from five (13%) of 40 patients with follicular lymphoma to seven (35%) of 20 patients with Richter's transformation. The most common serious adverse events included anaemia (six [4%] of 141 patients) and pneumonia (five [4%]). The most common grade 3–4 immune-related adverse events were rash (11 [8%] of 141 patients) and increased alanine aminotransferase (three [2%]).

Interpretation The combination of ibrutinib and nivolumab had an acceptable safety profile and preliminary activity was similar to that reported with single-agent ibrutinib in chronic lymphocytic leukaemia or small lymphocytic lymphoma, follicular lymphoma, and diffuse large B-cell lymphoma. The clinical response in patients with Richter's transformation was promising and supports further clinical assessment.

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Introduction

The emergence of targeted treatments and immune-checkpoint inhibitors has transformed the treatment of several haematological malignancies. Substantial clinical benefit has been shown by these drugs, even in difficult-to-treat populations including patients with high-risk chromosomal abnormalities or relapsed or refractory disease.[1–10] However, efficacy of these treatments might be

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Research in context

Evidence before this study

We searched PubMed from database inception up to March 20, 2018, using combinations of the terms "ibrutinib", "nivolumab", "pembrolizumab", "PD-1", "programmed cell death protein 1", "PD-L1", "programmed death ligand 1", "BTK", and "Bruton's tyrosine kinase". The combination search terms were also combined with "CLL", "chronic lymphocytic leukaemia", "SLL", "small lymphocytic lymphoma", "FL", "follicular lymphoma", "DLBCL", "diffuse large B-cell lymphoma", "Richter", or "Richter's transformation". The searches were not limited by language. We did not find publications on completed clinical trials evaluating the combination of ibrutinib and nivolumab in patients with B-cell non-Hodgkin lymphomas. We also searched abstracts from the American Society of Clinical Oncology and the American Society of Haematology (ASH) annual meetings from 2015 to 2017 and the European Society for Medical Oncology congress from 2016 to 2017. We identified one abstract from the ASH 2016 meeting presenting interim phase 2 results on the efficacy and safety of ibrutinib combined with nivolumab in patients with chronic lymphocytic leukaemia and Richter's transformation. Preliminary results from this study showed encouraging efficacy for the combination of ibrutinib and nivolumab in patients with Richter's transformation.

Added value of this study

In the present study, the combination of ibrutinib with nivolumab had a safety profile that was consistent with the known profile of each agent alone. The proportion of patients achieving an overall response with ibrutinib in combination with nivolumab was similar to that for single-agent ibrutinib in patients with relapsed or refractory chronic lymphocytic leukaemia or small lymphocytic lymphoma, follicular lymphoma, and diffuse large B-cell lymphoma. The clinical response in patients with Richter's transformation indicated promising activity.

Implications of all the available evidence

Ibrutinib combined with nivolumab showed preliminary activity and manageable safety for the treatment of haematological malignancies, with notable benefits in patients with Richter's transformation. The safety profile of the combination regimen was consistent with safety data from previous clinical studies of single-agent ibrutinib and nivolumab. The findings of this study warrant further clinical assessment of ibrutinib combined with nivolumab for the treatment of Richter's transformation.

limited by acquired resistance and variability in patient response, which can lead to disease relapse and progression. Overcoming these limitations is a goal in the development of new treatments or therapeutic combinations.

Ibrutinib is a Bruton's tyrosine kinase (BTK) inhibitor indicated for the treatment of chronic lymphocytic leukaemia or small lymphocytic lymphoma (including del17p subtype), mantle-cell lymphoma, Waldenström's macroglobulinaemia, marginal zone lymphoma, and chronic graft-versus-host disease.[11,12] The inhibition of BTK by ibrutinib disrupts B-cell signalling, leading to decreased survival, migration, and adhesion of malignant B cells.[13]

Nivolumab—a human monoclonal antibody against programmed cell death protein 1 (PD-1)—blocks the interaction of PD-1 with its ligands PD-L1 and PD-L2, thereby releasing the checkpoint inhibition and restoring T-cell-mediated antitumour responses.[14] Nivolumab is approved for the treatment of several cancer types, including Hodgkin lymphoma.[9,15]

See Online for appendix

Preclinical studies have shown synergistic antitumour effects between ibrutinib and inhibition of the PD-1 and PD-L1 pathway. In animal models of lymphoma, the combination of ibrutinib and an antibody against PD-L1 enhanced the modest effects seen with PD-L1 inhibition alone.[16] Decreased tumour growth and increased survival were recorded with the combination, even in models that were insensitive to ibrutinib treatment alone or did not express BTK.[16] These results suggest that ibrutinib might have a role in modulating the immune system, possibly through its effect as an inhibitor of interleukin 2-inducible T-cell kinase, which plays a part in T-cell proliferation and differentiation.[17,18] The enhanced effects seen with the addition of ibrutinib to PD-1 and PD-L1 blockade could point to a role for ibrutinib in potentiating the antitumour activity of immune-checkpoint inhibition.[16]

We did a phase 1/2a study to assess the safety and efficacy of ibrutinib in combination with nivolumab in patients with relapsed or refractory haematological malignancies including high-risk chronic lymphocytic leukaemia or small lymphocytic lymphoma, follicular lymphoma, diffuse large B-cell lymphoma, and Richter's transformation.

Methods

Study design and participants

We did an open-label, two-part, phase 1/2a study at 21 hospitals in Australia, Israel, Poland, Spain, Turkey, and the USA (for a full list of investigators and sites see appendix p 1). The study was approved by an independent ethics committee, and all patients provided written informed consent. The protocol is available in the appendix (pp 9–139).

Key eligibility requirements were age 18 years or older, Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less, and adequate bone marrow, liver, and renal function (for definitions of adequate bone marrow, liver, and renal function see appendix p 2). Additional inclusion criteria for part A of the study (dose escalation cohort) were histologically

confirmed and documented (by local laboratory) chronic lymphocytic leukaemia or small lymphocytic lymphoma (del17p or del11q confirmed by fluorescence in-situ hybridisation [FISH] analysis), follicular lymphoma, or diffuse large B-cell lymphoma; relapsed or refractory disease after at least one but not more than four previous lines of systemic treatment; and measurable disease, defined per Lugano classification[19] for follicular lymphoma and diffuse large B-cell lymphoma, and 5000 leukaemia cells per μL or more for chronic lymphocytic leukaemia or small lymphocytic lymphoma.

For part B of the study (dose expansion cohort), additional eligibility requirements for the chronic lymphocytic leukaemia or small lymphocytic lymphoma expansion cohort were diagnosis of chronic lymphocytic leukaemia (lymphocytosis with ≥5000 B lymphocytes per μL and prolymphocytes ≤55% of total blood lymphocytes) or small lymphocytic lymphoma (diagnosis required measurable disease per Lugano classification);[19] del17p or del11q confirmed by FISH analysis; relapsed or refractory disease after at least one previous line of systemic treatment, consisting of at least two cycles of a chemotherapy-containing regimen; and active disease, as defined by the International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) criteria.[20] For the follicular lymphoma expansion cohort, additional eligibility criteria were histologically confirmed grade 1, 2, or 3a follicular lymphoma, according to WHO criteria;[21] relapsed or refractory disease, defined as previous treatment with at least two previous lines of treatment using different regimens and separated by disease progression or relapse, or if the patient either received or was not eligible for previous treatment with anti-CD20 combination chemotherapy regimen; and at least one measurable site of disease per Lugano classification.[19] Additional inclusion criteria for the diffuse large B-cell lymphoma expansion cohort were histologically confirmed diffuse large B-cell lymphoma; previous treatment with a standard systemic chemotherapy regimen containing rituximab and anthracycline, or either received or were not eligible for high-dose chemotherapy and autologous stem-cell transplantation; and at least one measurable site of disease based on the Revised Response Criteria for Malignant Lymphoma.[19] For the Richter's transformation expansion cohort, eligible patients had histologically confirmed Richter's transformation, defined as transformation of chronic lymphocytic leukaemia or small lymphocytic lymphoma into an aggressive lymphoma; at least one previous line of systemic chemotherapy, or ineligible for treatment; and at least one measurable site of disease, based on the Revised Response Criteria for Malignant Lymphoma.[19]

Exclusion criteria were major surgery within 4 weeks of the first dose of ibrutinib; diagnosis or treatment of malignant disease other than the indication under study; required treatment with warfarin or equivalent vitamin K antagonists or strong CYP3A inhibitors; clinically significant cardiovascular disease; history of HIV, hepatitis B, or hepatitis C; CNS lymphoma; previous allogenic haemopoietic stem-cell transplant; active systemic infection, autoimmune disease, or any syndrome requiring corticosteroids; previous treatment with ibrutinib or other BTK inhibitors; and previous exposure to immune-checkpoint inhibitors. Additional antitumour treatments that were excluded are described in the appendix (p 2).

Procedures

In part A of the study (dose escalation), patients with relapsed or refractory chronic lymphocytic leukaemia or small lymphocytic lymphoma, follicular lymphoma, or diffuse large B-cell lymphoma were assigned by disease cohort to receive oral daily doses of 420 mg (chronic lymphocytic leukaemia or small lymphocytic lymphoma, follicular lymphoma, diffuse large B-cell lymphoma) or 560 mg (follicular lymphoma, diffuse large B-cell lymphoma) ibrutinib in combination with nivolumab at a dose of 3 mg/kg given as a 1 h intravenous infusion every 2 weeks. The duration of each treatment cycle was 14 days. Study drug was administered until disease progression or unacceptable toxicity, whichever occurred first. Dose reductions for ibrutinib to 280 mg were allowed; no dose reductions for nivolumab were allowed.

We used a modified toxicity probability interval (mTPI) design[22,23] for dose escalation in part A, using Toxicity Probability Intervals, version 2.1.[24] The mTPI method is a Bayesian-based approach that extends the traditional 3+3 design for maximum tolerated dose identification by providing guidance for dose assignments in a tabulated form, called the decision table. The dose assignment decision table we used for the study is based on the variation of mTPI table generated for the target toxicity probability of 0·30 using the equivalence interval (0·25–0·30).[24] We assessed operating characteristics of the mTPI decision table by simulations using internal software.

A study evaluation team reviewed all available data after completion of the first two cycles for all patients at each dose to establish dose-limiting toxicity. Patients remained on their assigned dose once the recommended phase 2 dose was identified in part A; those on the lower dose were not escalated.

In part B of the study (dose expansion), patients received the recommended phase 2 daily oral dose of ibrutinib in combination with 3 mg/kg intravenous nivolumab as a 1 h infusion every 2 weeks. In the chronic lymphocytic leukaemia or small lymphocytic lymphoma and follicular lymphoma cohorts, ibrutinib was given at the recommended phase 2 dose over an initial period of 7 days before the first dose of nivolumab, for assessment of the pharmacokinetics and pharmacodynamics of ibrutinib alone.

We assessed preliminary activity and clinical response by CT radiological assessments every five cycles for the first 15 months, then every 12 cycles until disease

progression, at the end of treatment, and every 6 months during the follow-up period. Lymphoma—including Richter's transformation—was assessed according to the Lugano classification;[19] chronic lymphocytic leukaemia was assessed according to IWCLL criteria.[20]

We obtained a few blood samples from all patients for determination of plasma concentrations of ibrutinib and serum concentrations of nivolumab. Plasma samples for assessment of ibrutinib were obtained before dosing and post dose at 1 h, 2 h, and 4 h on day –7 (for the chronic lymphocytic leukaemia or small lymphocytic lymphoma and follicular lymphoma expansion cohorts) or on day 1 (for the diffuse large B-cell lymphoma and Richter's transformation expansion cohorts) of cycle 1 and on day 1 of cycle 13, and before dosing on day 1 of cycle 3.

We obtained tumour tissue specimens, blood samples, fine-needle aspirates, and bone marrow aspirates or biopsy specimens for biomarker analyses. Diffuse large B-cell lymphoma subtyping was done by analysis of MAS5-normalised gene expression data generated using the GeneChip Human Genome U133 Plus 2.0 Array (Affymetrix, Santa Clara, CA, USA) on the basis of the classification algorithm of Wright and colleagues.[25] We assessed PD-L1 expression (percentage of tumour cells showing plasma membrane PD-L1 staining of any intensity in a minimum of 100 assessable tumour cells) using the Dako PD-L1 immunohistochemistry 28-8 pharmDx assay (Agilent Technologies, Glostrup, Denmark). The cutoff for elevated expression of PD-L1 was 5% or higher.[26]

Safety assessments were based on adverse events graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4. Adverse event monitoring was done on an ongoing basis throughout the study. Safety was also assessed through vital sign measurements, electrocardiograms, physical examination, clinical laboratory tests, and ECOG performance status. Details on laboratory monitoring are described in the appendix (p 2).

Outcomes

The primary objective of part A was to ascertain the recommended phase 2 dose for the combination of ibrutinib and nivolumab. The recommended phase 2 dose was established by dose modification of ibrutinib, while the dose of nivolumab was not changed. The objective of part B was to assess the preliminary clinical activity (efficacy) of ibrutinib in combination with nivolumab at the recommended phase 2 dose. These secondary efficacy endpoints were overall response (ie, the proportion of evaluable patients who achieved a complete response or partial response, as assessed by the investigators), duration of response, duration of stable disease, progression-free survival, and overall survival. Standard response criteria were applied.[19,20] Other secondary objectives were to assess the safety profile of the ibrutinib and nivolumab combination regimen and to characterise the pharmacokinetic profile of ibrutinib and nivolumab compared with existing single-agent profiles. Exploratory objectives included identification of biomarkers of response or resistance to the combination.

Statistical analysis

We aimed to assess whether ibrutinib combined with nivolumab could result in more than 20% of patients in each cohort of part B achieving an overall response (complete responses plus partial responses). A sample size of approximately 35 patients in each cohort was needed based on the following assumptions: the proportion of patients achieving an overall response under the null hypothesis is 20%; the proportion achieving an overall response under the alternative hypothesis is at least 38%; the probability of mistakenly rejecting the null hypothesis when it is actually true is 0·1 (one-sided); and the probability of correctly rejecting the null hypothesis when the alternative hypothesis is true is at least 0·8.

The treated population consisted of all patients who received at least one dose of either study drug and was used for all safety and activity analyses. The response-assessable population consisted of all patients who received at least one dose of both study drugs and had a pretreatment and at least one post-treatment disease assessment. The pharmacokinetics population consisted of all patients who received at least one dose of either study drug and had at least one post-treatment sample collected during treatment. All patients who received study drug were assessable.

We used SAS version 9.4 for statistical analyses. Summary statistics for continuous variables included mean (SD) and median (IQR). Categorical data were presented as frequencies and percentages. The proportion of patients achieving an overall response was assessed by investigators and calculated with 95% CIs for each disease-specific cohort. Progression-free survival and overall survival were assessed using the Kaplan-Meier method. We did a sensitivity analysis in the response-evaluable population. We summarised plasma concentrations of ibrutinib and serum concentrations of nivolumab at each timepoint using descriptive statistics. Population pharmacokinetic analysis of ibrutinib concentration–time data was done by estimating individual empirical Bayesian pharmacokinetic variables for ibrutinib using a Bayesian feedback method. We used Kaplan-Meier survival probability to analyse clinical response or time-to-event endpoints for the PD-L1-positive and PD-L1-negative subgroups, with a threshold of 5% or higher (elevated expression of PD-L1 *vs* not elevated) or positive versus negative. The association of biomarkers with clinical response was assessed using appropriate statistical methods (ANOVA, categorical, or survival model) based on the endpoint.

This study is registered with ClinicalTrials.gov, number NCT02329847.

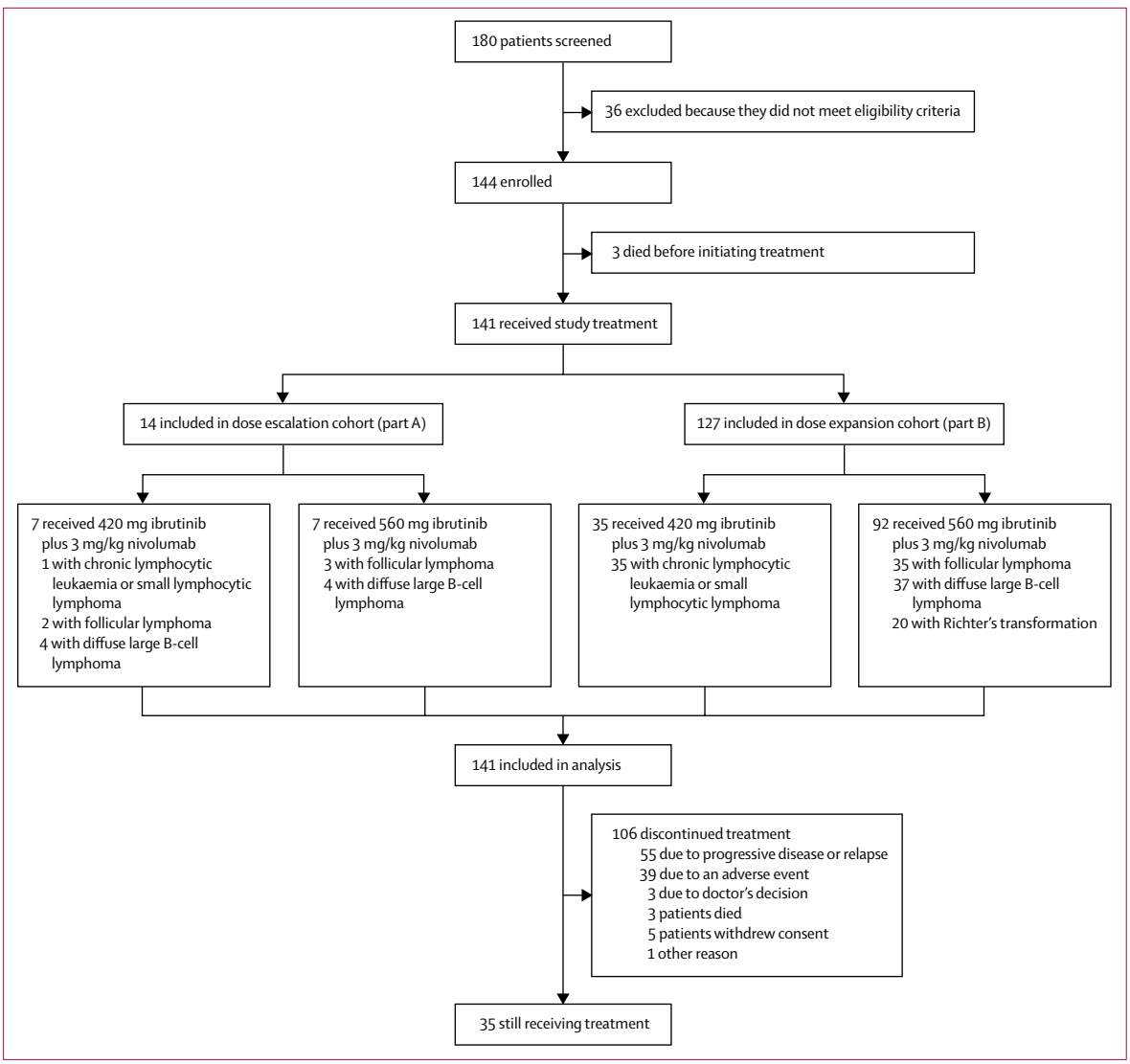

Figure 1: **Participant flow through the study**

Role of the funding source

The funder contributed to study design, data collection, data analysis, data interpretation, writing of the report (in addition to funding writing assistance), and the decision to submit for publication. All authors had access to raw data, and the corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 12, 2015, and April 11, 2017, 144 patients were enrolled in the study; three patients died before receiving study treatment and were not included in the analysis. 141 patients were analysed in this study, 14 patients in part A and 127 patients in part B (figure 1). Patients' demographics and baseline disease characteristics are presented in table 1. The all-treated patient population included 30 patients with relapsed or refractory chronic lymphocytic leukaemia (del17p [n=19] and del11q [n=17]), six patients with small lymphocytic lymphoma, 40 patients with follicular lymphoma, 45 patients with diffuse large B-cell lymphoma (including nine patients with transformed diffuse large B-cell lymphoma), and 20 patients with Richter's transformation. The median age of patients was 65·0 years (IQR 54·0–71·0) and the median number of previous lines of treatment was 3·0 (2·0–3·0). 35 (88%) of 40 patients with follicular lymphoma and 32 (71%) of 45 patients with diffuse large B-cell lymphoma received between two and four previous lines of treatment, compared with 19 (53%) of 36 patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma and 11 (55%) of 20 patients with Richter's transformation. The previous systemic treatments received by patients with chronic lymphocytic leukaemia or small lymphocytic

	Total (n=141)	Chronic lymphocytic leukaemia and small lymphocytic lymphoma (n=36)	Follicular lymphoma (n=40)	Diffuse large B-cell lymphoma (n=45)	Richter's transformation (n=20)
Age (years)	65·0 (54·0–71·0)	65·0 (57·0–71·0)	62·0 (52·5–70·0)	64·0 (46·0–74·0)	67·5 (56·0–70·5)
Sex					
Male	87 (62%)	27 (75%)	23 (58%)	29 (64%)	8 (40%)
Female	54 (38%)	9 (25%)	17 (43%)	16 (36%)	12 (60%)
Ethnic origin					
White	134 (95%)	36 (100%)	37 (93%)	41 (91%)	20 (100%)
Asian	5 (4%)	0	2 (5%)	3 (7%)	0
Other	1 (1%)	0	1 (3%)	0	0
Unknown or not reported	1 (1%)	0	0	1 (2%)	0
ECOG performance status					
0	70 (50%)	17 (47%)	30 (75%)	19 (42%)	4 (20%)
1	60 (43%)	18 (50%)	8 (20%)	21 (47%)	13 (65%)
2	11 (8%)	1 (3%)	2 (5%)	5 (11%)	3 (15%)
Previous lines of treatment	3·0 (2·0–3·0)	2·0 (1·0–2·5)	3·0 (2·5–4·0)	3·0 (2·0–3·0)	2·0 (1·0–3·0)
Previous alkylating agents	141 (100%)	36 (100%)	40 (100%)	45 (100%)	20 (100%)
Previous purine analogues	82 (58%)	28 (78%)	11 (28%)	32 (71%)	11 (55%)
Bulky disease (≥5 cm)	68 (48%)	26 (72%)	15 (38%)	17 (38%)	10 (50%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline demographic and disease characteristics**

lymphoma included fludarabine-based treatments (27 [75%] of 36 patients), bendamustine plus rituximab-based treatments (12 [33%]), and rituximab, cyclophosphamide, daunorubicin, vincristine, and prednisone (R-CHOP) or CHOP (four [11%]). The previous systemic treatments received by patients with follicular lymphoma included R-CHOP or CHOP (32 [80%] of 40 patients), bendamustine plus rituximab-based treatments (20 [50%]), rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) or CVP (nine [23%]), and fludarabine-based treatments (four [10%]). The previous systemic treatments received by patients with diffuse large B-cell lymphoma included R-CHOP or CHOP (42 [93%] of 45 patients), rituximab, ifosfamide, carboplatin, etoposide (R-ICE) or ICE (17 [38%]), rituximab, dexamethasone, cisplatin, and cytarabine (R-DHAP) or DHAP (ten [22%]), rituximab, etoposide, methylprednisonolone, cytarabine, and cisplatin (R-EHSAP) or EHSAP (seven [16%]), and bendamustine plus rituximab-based treatments (five [11%]). Among patients with Richter's transformation, seven (35%) had received cancer-related surgery and two (10%) had received radiotherapy. The previous systemic treatments received by patients with Richter's transformation included R-CHOP or CHOP (15 [75%] of 20 patients), fludarabine-based treatments (seven [35%]), and bendamustine plus rituximab-based treatments (five [25%]).

At the time of clinical cutoff (Oct 10, 2017), median treatment duration with ibrutinib was 14·4 months (IQR 4·5–21·7) for the chronic lymphocytic leukaemia or small lymphocytic lymphoma cohort, 5·0 months (2·3–14·8) for the follicular lymphoma cohort, 3·2 months (1·4–13·0) for the diffuse large B-cell lymphoma cohort, and 3·6 months (1·3–8·0) for the Richter's transformation cohort. At clinical cutoff, 106 (75%) of 141 patients had discontinued treatment, 23 (64%) of 36 patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma, 33 (83%) of 40 patients with follicular lymphoma, 36 (80%) of 45 patients with diffuse large B-cell lymphoma, and 14 (70%) of 20 patients with Richter's transformation. Reasons for treatment discontinuation in all patients were progressive disease or relapse (55 [39%] of 141), adverse events (39 [28%]; 28 [20%] were drug-related), doctor's decision (three [2%]), death (three [2%]), withdrawal of consent (five [4%]), and other (one [1%]; figure 1). Treatment discontinuation due to adverse events occurred in 11 (31%) of 36 patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma, 11 (28%) of 40 patients with follicular lymphoma, eight (18%) of 45 patients with diffuse large B-cell lymphoma, and nine (45%) of 20 patients with Richter's transformation. Of the three deaths, one patient with small lymphocytic lymphoma died of an unknown cause, and the causes of death for two patients with diffuse large B-cell lymphoma were respiratory arrest and gastric bleeding attributable to disease. At clinical cutoff, 35 (25%) of 141 patients remained on treatment.

In part A of the study, two doses of ibrutinib in combination with nivolumab were assessed, 420 mg and 560 mg. At the 420 mg ibrutinib dose with nivolumab, one dose-limiting toxicity was reported (grade 3 hyperbilirubinaemia) in the diffuse large B-cell lymphoma cohort, which resolved after 5 days. No dose-limiting toxicities were noted at the higher dose. Eight (6%) of 141 patients required dose reductions of ibrutinib: two patients in the chronic lymphocytic leukaemia or small lymphocytic lymphoma cohort had their doses reduced from 480 mg to 280 mg, five patients in the diffuse large B-cell lymphoma cohort had their doses reduced from 560 mg to 420 mg, and one patient in the Richter's transformation cohort had a dose reduction from 560 mg to 420 mg. The recommended phase 2 doses for part B were 420 mg ibrutinib plus 3 mg/kg nivolumab for patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma and 560 mg ibrutinib plus 3 mg/kg nivolumab for patients with follicular lymphoma, diffuse large B-cell lymphoma, and Richter's transformation.

In both parts of the study, the most common all-grade adverse events were diarrhoea (47 [33%] of 141 patients),

	Grade 1–2	Grade 3	Grade 4	Grade 5
Diarrhoea	44 (31%)	3 (2%)	0	0
Neutropenia	4 (3%)	19 (13%)	21 (15%)	0
Fatigue	34 (24%)	3 (2%)	0	0
Anaemia	3 (2%)	31 (22%)	1 (1%)	0
Upper respiratory tract infection	34 (24%)	1 (1%)	0	0
Pyrexia	32 (23%)	2 (1%)	0	0
Cough	29 (21%)	0	0	0
Hypokalaemia	19 (13%)	7 (5%)	1 (1%)	0
Rash	19 (13%)	8 (6%)	0	0
Thrombocytopenia	13 (9%)	7 (5%)	4 (3%)	0
Nausea	23 (16%)	0	0	0
Arthralgia	19 (13%)	2 (1%)	0	0
Increased lipase	10 (7%)	6 (4%)	3 (2%)	0
Back pain	18 (13%)	0	0	0
Peripheral oedema	16 (11%)	2 (1%)	0	0
Increased alanine aminotransferase	10 (7%)	4 (3%)	2 (1%)	0
Muscle spasms	16 (11%)	0	0	0
Headache	15 (11%)	0	0	0
Pain in extremities	10 (7%)	3 (2%)	0	0
Dyspnoea	7 (5%)	2 (1%)	0	2 (1%)
Increased amylase	4 (3%)	6 (4%)	0	0
Pneumonia	5 (4%)	4 (3%)	0	1 (1%)
Hypertension	5 (4%)	4 (3%)	0	0
Hyponatraemia	1 (1%)	7 (5%)	0	0
Hypotension	4 (3%)	4 (3%)	0	0
Bacterial pneumonia	1 (1%)	5 (4%)	0	0
Maculopapular rash	3 (2%)	3 (2%)	0	0
Acute kidney injury	2 (1%)	3 (2%)	0	0
Febrile neutropenia	0	5 (4%)	0	0

Data are n (%). Adverse events occurring in 10% or more of patients for grades 1–2 and 2% or more of patients for grades 3–5 are reported.

Table 2: **Adverse events by grade**

	Total (n=141)	Chronic lymphocytic leukaemia and small lymphocytic lymphoma (n=36)	Follicular lymphoma (n=40)	Diffuse large B-cell lymphoma (n=45)	Richter's transformation (n=20)
Haematological adverse events					
Neutropenia	40 (28%)	19 (53%)	8 (20%)	8 (18%)	5 (25%)
Anaemia	32 (23%)	9 (25%)	5 (13%)	11 (24%)	7 (35%)
Thrombocytopenia	11 (8%)	5 (14%)	1 (3%)	3 (7%)	2 (10%)
Febrile neutropenia	5 (4%)	4 (11%)	0	1 (2%)	0
Non-haematological adverse events					
Rash*	14 (10%)	2 (6%)	4 (10%)	6 (13%)	2 (10%)
Pneumonia†	12 (9%)	5 (14%)	4 (10%)	1 (2%)	2 (10%)
Increased lipase	9 (6%)	5 (14%)	1 (3%)	3 (7%)	0
Hypokalaemia	8 (6%)	3 (8%)	1 (3%)	4 (9%)	0
Hyponatraemia	7 (5%)	0	2 (5%)	5 (11%)	0
Increased amylase	6 (4%)	3 (8%)	0	2 (4%)	1 (5%)
Increased alanine aminotransferase	6 (4%)	1 (3%)	2 (5%)	3 (7%)	0
Dyspnoea	4 (3%)	0	0	2 (4%)	2 (10%)
Hypertension	4 (3%)	2 (6%)	2 (5%)	0	0
Hypotension	4 (3%)	0	0	1 (2%)	3 (15%)

Data are n (%). Adverse events occurring in 2% or more of patients are reported. *Includes rash, erythaematous rash, generalised rash, macular rash, and maculopapular rash. †Includes pneumonia, bacterial pneumonia, *Pneumocystis jirovecii* pneumonia, and *Klebsiella* spp pneumonia.

Table 3: **Grade 3–5 adverse events, by disease cohort**

neutropenia (44 [31%]), and fatigue (37 [26%]). Adverse events by grade are presented in table 2 and the appendix (pp 3–6).

Grade 3–5 adverse events were reported in 115 (82%) of 141 patients, irrespective of the relation to study drug (table 3). 82 (58%) patients had grade 3–4 adverse events considered to be related to study treatment by the investigators; no grade 5 adverse events were reported as drug-related. The most common haematological grade 3–4 adverse events were neutropenia (40 [28%] of 141 patients) and anaemia (32 [23%]); no grade 5 haematological adverse events were recorded. The incidence of grade 3–4 neutropenia ranged from eight (18%) of 45 patients with diffuse large B-cell lymphoma to 19 (53%) of 36 patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma; incidence of grade 3–4 anaemia ranged from five (13%) of 40 patients with follicular lymphoma to seven (35%) of 20 patients with Richter's transformation. The most common non-haematological grade 3–5 adverse events were rash (14 [10%] of 141 patients) and pneumonia (12 [9%]). All grade 5 adverse events are described in the appendix (pp 3–6).

77 patients had serious adverse events. Serious adverse events reported in at least two patients were anaemia (six [4%] of 141 patients), pneumonia (five [4%]), febrile neutropenia (three [2%]), bacterial pneumonia (three [2%]), and atrial fibrillation, cardiac failure, dyspnoea, gastroenteritis, haematuria, neutropenia, and *Pneumocystis jirovecii* pneumonia (two [1%] each). 30 (21%) of 141 patients had drug-related serious adverse events; the most common were febrile neutropenia (three [2%]) and anaemia (three [2%]), followed by bacterial pneumonia (two [1%]), neutropenia (two [1%]), cardiac failure (two [1%]), and pneumonitis (two [1%]). 25 drug-related serious adverse events were single events (encephalitis, otitis media, otitis media chronic, viral upper respiratory tract infection, cellulitis, *P jirovecii* pneumonia, pneumonia, respiratory syncytial virus infection, sepsis, lymphadenopathy, gastritis, colitis, diarrhoea, enterocolitis, gastrointestinal inflammation, stomatitis, hypersensitivity, increased aminotransferases, increased alanine aminotransferase, asthenia, mucosal inflammation, pyrexia, chronic obstructive pulmonary disease, organising pneumonia, and maculopapular rash).

Major haemorrhage was reported in five (4%) of 141 patients, including four (3%) grade 3 events, which were deemed unrelated to study treatment. Four of the

	Chronic lymphocytic leukaemia and small lymphocytic lymphoma (n=36)	Follicular lymphoma (n=40)	Diffuse large B-cell lymphoma (n=45)	Richter's transformation (n=20)
Overall response*	22 (61%)	13 (33%)	16 (36%)	13 (65%)
Overall response including partial response with lymphocytosis	27 (75%)	NA	NA	NA
Complete response	0	4 (10%)	7 (16%)	2 (10%)
Partial response	22 (61%)	9 (23%)	9 (20%)	11 (55%)
Partial response with lymphocytosis	5 (14%)	NA	NA	NA
Stable disease	5 (14%)	13 (33%)	6 (13%)	1 (5%)
Progressive disease	1 (3%)	11 (28%)	19 (42%)	5 (25%)
Treatment-related lymphocytosis	1 (3%)	0	0	0
Missing data	2 (6%)	3 (8%)	4 (9%)	1 (5%)

Data are n (%). NA=not applicable. *Patients achieving a complete response plus those achieving a partial response. Response assessed using International Workshop on Chronic Lymphocytic Leukaemia criteria for chronic lymphocytic leukaemia[20] and Lugano classification for small lymphocytic lymphoma, follicular lymphoma, diffuse large B-cell lymphoma, and Richter's transformation.[19]

Table 4: **Summary of responses achieved by patients**

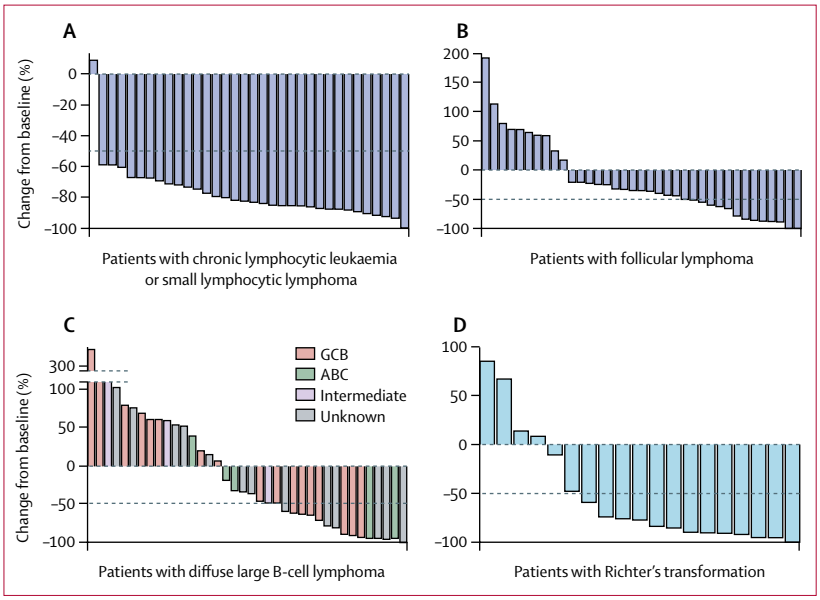

Figure 2: **Percentage change from baseline in the sum of perpendicular diameters of target lesions**
Changes in the sum of perpendicular diameters are shown for patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma (A; n=34 [two patients missing data]), follicular lymphoma (B; n=37 [three patients missing data]), diffuse large B-cell lymphoma (C; n=38 [seven patients missing data, two with GCB, one with intermediate subtype, and four with unknown subtype]; 25 patients had target lesion assessments), and Richter's transformation (D; n=19 [one patient missing data]). Horizontal line at –50% represents the reduction in the sum of perpendicular diameters needed to achieve a partial response.[19] ABC=activated B-cell subtype. GCB=germinal centre B-cell subtype.

five cases occurred in the diffuse large B-cell lymphoma cohort and were all grade 3–5. The fifth case occurred in the chronic lymphocytic leukaemia cohort. Atrial fibrillation was reported in nine (6%) of 141 patients, with eight grade 1–2 events and one grade 3 event. Immune-related adverse events are presented in the appendix (p 7) and were mostly grade 1–2. Grade 3–4 immune-related adverse events included rash (11 [8%] of 141 patients), increased alanine aminotransferase (three [2%]), diarrhoea (two [1%]), and increased aspartate aminotransferase, increased γ-glutamyltransferase, increased aminotransferases, hyperbilirubinaemia, enterocolitis, and colitis (one [1%] of each).

11 (8%) of 141 patients had grade 5 adverse events, none of which were reported as drug-related. Three patients died in the chronic lymphocytic leukaemia or small lymphocytic lymphoma cohort, one in the follicular lymphoma cohort, three in the diffuse large B-cell lymphoma cohort, and four in the Richter's transformation cohort.

Clinical responses were reported in all disease cohorts (table 4). An overall response was achieved by 22 (61%) of 36 patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma, with an overall response including partial response with lymphocytosis achieved by 27 (75%) patients. 13 (33%) of 40 patients with follicular lymphoma and 16 (36%) of 45 patients with diffuse B-cell lymphoma achieved an overall response. The best overall response was seen in the Richter's transformation cohort (13 [65%] of 20 patients), with two complete responses and 11 partial responses.

Reductions in the sum of perpendicular diameters of target lesions from baseline were reported for most patients in each disease cohort (figure 2). Among 28 patients with diffuse large B-cell lymphoma who had gene expression data for subtyping, 19 (68%) were germinal centre B-cell subtype, five (18%) were activated B-cell subtype, and four (14%) were considered intermediate. In 27 subtyped patients with diffuse large B-cell lymphoma who had reported responder or non-responder status, an overall response was achieved by eight (30%) patients; six (33%) of 18 patients with the germinal centre B-cell subtype achieved an overall response. Too few patients had the activated B-cell subtype to permit robust analysis.

The median duration of stable disease or better (≥12 months) was 19·7 months (IQR 17·0–20·5) for the chronic lymphocytic leukaemia or small lymphocytic lymphoma cohort, 15·9 months (14·1–20·0) for the follicular lymphoma cohort, 18·4 months (15·6–19·4) for the diffuse large B-cell lymphoma cohort, and 13·0 months (12·1–13·8) for the Richter's transformation cohort. The median duration of response was 19·2 months (IQR 9·4–19·4) for the chronic lymphocytic leukaemia or small lymphocytic lymphoma cohort, 10·2 months (6·7–14·2) for the follicular lymphoma cohort, not estimable (NE) for the diffuse large B-cell lymphoma cohort, and 6·9 months (1·4–NE) for the Richter's transformation cohort.

At a median follow-up of 19·7 months (IQR 16·0–20·9), 17 patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma had disease progression or died; median progression-free survival for the cohort was not

estimable because of the small number of patients, which made it difficult to draw definitive conclusions (figure 3A). Median progression-free survival for the follicular lymphoma cohort was 9·1 months (95% CI 3·1–14·0) at a median follow-up of 19·6 months (IQR 14·1–20·7); 28 patients had disease progression or died. In the diffuse large B-cell lymphoma cohort, median progression-free survival was 2·6 months (95% CI 1·9–7·6) at a median follow-up of 18·4 months (IQR 14·8–19·4); 30 patients had disease progression or died. In the Richter's transformation cohort, median progression-free survival was 5·0 months (95% CI 2·4–NE) at a median follow-up of 8·7 months (IQR 6·5–12·1); 11 patients had disease progression or died.

At the time of clinical cutoff (Oct 10, 2017), 51 deaths had been reported during the study, three of which led to treatment discontinuation. The causes of death were disease progression in 29 patients, adverse events in 16 patients (none were related to study drug), unknown cause in one patient, and other causes in five patients (unknown cause and disease progression [n=1], multi-organ failure [n=1], pleural empyema [n=1], septic shock [n=1], and grade 4 exacerbation of chronic obstructive pulmonary disease, grade 4 sepsis infection, and grade 4 congestive heart failure [n=1]). 12 patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma died; median overall survival was not reached at a median follow-up of 21·5 months (IQR 19·6–22·6; figure 3B). Ten patients with follicular lymphoma died; median overall survival was also not reached at a median follow-up of 19·2 months (IQR 18·6–21·0). 21 patients with diffuse large B-cell lymphoma died; median overall survival was 13·5 months (95% CI 6·5–NE) at a median follow-up of 19·6 months (IQR 14·3–20·9). Eight patients with Richter's transformation died; median overall survival was 10·3 months (95% CI 4·8–NE) at a median follow-up of 8·9 months (IQR 6·5–11·9).

Pharmacokinetic data for ibrutinib are reported in the appendix (p 8); data for nivolumab are not shown. The frequency of nivolumab antibody formation was low (data not shown).

PD-L1 expression was assessed by immunohistochemistry in 84 patients' samples. 18 (100%) of 18 samples from the chronic lymphocytic leukaemia or small lymphocytic lymphoma cohort and 22 (88%) of 25 samples from the follicular lymphoma cohort had low to no measurable PD-L1 expression. Measurable PD-L1 expression was seen in 13 (50%) of 26 samples from the diffuse large B-cell lymphoma cohort, eight of which had elevated (≥5%) PD-L1 expression. In post-hoc analyses, five (63%) of eight patients with elevated (≥5%) PD-L1 expression achieved an overall response compared with three (19%) of 16 without elevated expression of PD-L1, although this finding was not significant (p=0·065). A significant (p=0·028) association with complete response was noted in patients with elevated expression of PD-L1: reportable PD-L1 values were seen in three of five patients who achieved a complete response, and all three had elevated expression of PD-L1. In the Richter's transformation cohort (n=15), three of five patients with measurable PD-L1 expression had elevated expression (≥5%) of PD-L1, and all three had a partial response with durable overall survival (data not shown).

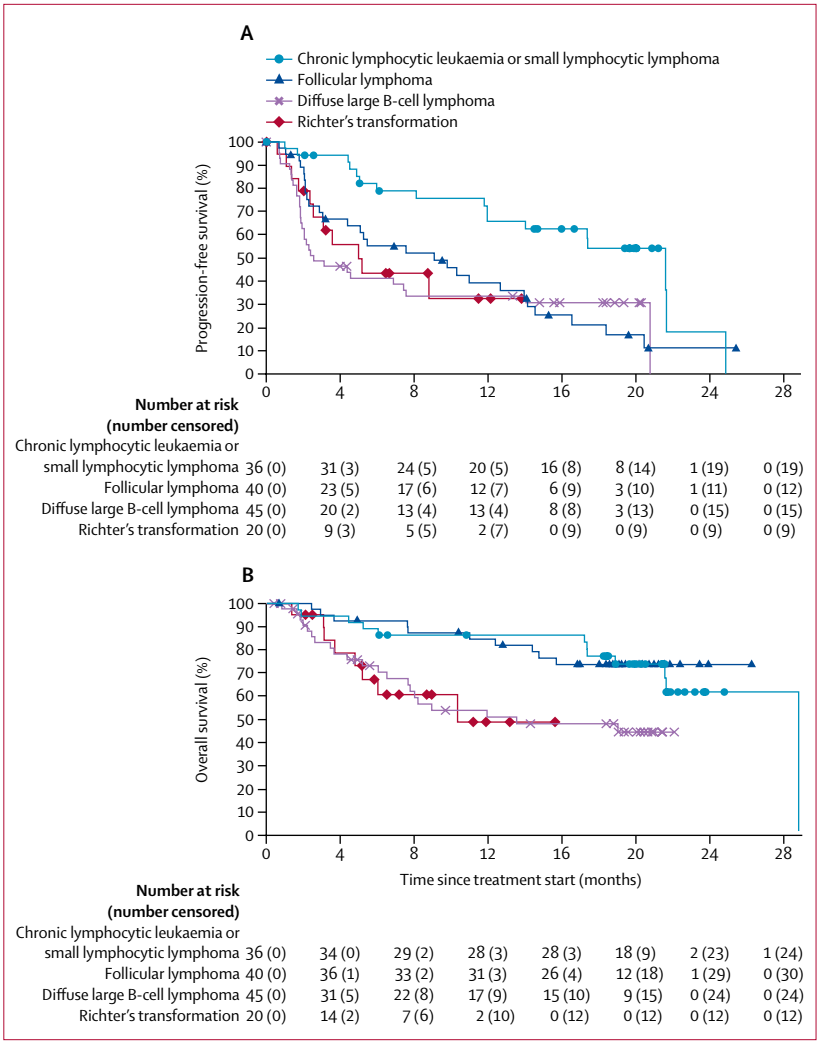

***Figure 3*: Progression-free survival and overall survival**
Kaplan-Meier curves are shown for progression-free survival (A) and overall survival (B), by disease cohort.

Discussion

The combination of ibrutinib with nivolumab showed a manageable safety profile in patients with relapsed or refractory chronic lymphocytic leukaemia or small lymphocytic lymphoma, follicular lymphoma, diffuse large B-cell lymphoma, and Richter's transformation. The safety of the combination regimen was generally similar to previously reported safety profiles of the single agents alone.[2,4–7,9] Clinical response with the combination

regimen was observed in all disease cohorts, with a notable overall response in 13 (65%) of 20 patients in the Richter's transformation cohort.

Pharmacokinetic data for ibrutinib were consistent with those reported in previous clinical studies in various B-cell malignant diseases,[27–29] indicating that the combination of ibrutinib with nivolumab did not affect ibrutinib pharmacokinetics. Nivolumab pharmacokinetic data were also consistent with those in previous reports.[30–33] The low frequency of nivolumab antibody formation was in line with observations in monotherapy studies.[15,34]

The proportion of grade 3–5 adverse events in our study (82%) was higher than equivalent data reported in studies of single-agent ibrutinib in similar patient populations of advanced and heavily pretreated haematological malignant diseases. In the phase 3 RESONATE study,[4] 57% of patients with pretreated chronic lymphocytic leukaemia had grade 3–5 adverse events. In two phase 2 studies in patients with follicular lymphoma, 42·5%[2] had grade 3–4 adverse events and 61·8%[10] had grade 3–5 adverse events. In a phase 1b study of nivolumab in patients with relapsed or refractory haematological malignancies,[35] 22% of patients had grade 3–5 adverse events.

The proportions of patients with grade 3–4 neutropenia (28%) and anaemia (23%) were slightly higher in our study than in studies of single-agent ibrutinib or nivolumab in similar patient populations. In patients with B-cell malignancies, 23% of patients reported grade 3–4 neutropenia and 3% of patients reported grade 3–4 anaemia.[11] In a phase 1b study of single-agent nivolumab in patients with relapsed or refractory haematological malignancies,[35] only 1% of patients had grade 3 or worse neutropenia and 4% had grade 3 or worse anaemia. The increased proportion of patients with grade 3–4 anaemia in the current study might be attributable to the requirement for blood transfusion and not to low haemoglobin levels. NCI CTCAE grade 3 criteria were applied; therefore, for every transfusion that was reported, corresponding grade 3 anaemia was also reported. The frequency of potentially severe adverse events (grade ≥3) reported for single-agent ibrutinib in patients with haematological malignancies (eg, haemorrhage and infections)[11] was similar to that reported with the combination regimen. Also, the proportion of immune-related adverse events with the combination regimen was similar to that noted in patients treated with single-agent nivolumab.[35]

The proportion of treatment discontinuations attributable to adverse events in the chronic lymphocytic leukaemia or small lymphocytic lymphoma cohort (31%), and in the follicular lymphoma cohort (28%), was higher with the combination regimen than with single-agent treatments. In studies undertaken in similar patient populations, discontinuation of single-agent ibrutinib because of adverse events occurred in only 4% of patients with chronic lymphocytic leukaemia[4] and 7·5% of patients with relapsed or refractory follicular lymphoma.[2] For single-agent nivolumab, 15% of patients with relapsed or refractory haematological malignancies discontinued treatment because of adverse events.[35] Based on these data, the addition of nivolumab to ibrutinib might have contributed to the higher proportion of treatment discontinuations because of adverse events.

The proportion of patients achieving an overall response with chronic lymphocytic leukaemia or small lymphocytic lymphoma, follicular lymphoma, and diffuse large B-cell lymphoma was similar to that for single-agent ibrutinib or nivolumab in previous studies.[1,2,4,8,27,35] However, the proportion achieving an overall response with Richter's transformation (65%) exceeded expectations. It should be noted that the 20 patients with Richter's transformation were not exposed to previous ibrutinib treatment for their underlying chronic lymphocytic leukaemia. Previously, ibrutinib showed activity in Richter's transformation in exploratory single-institution studies. In a study of four patients with Richter's transformation, Tsang and colleagues[36] described responses in three patients—one complete response and two partial responses. In two separate case studies, Giri and colleagues[37] described two patients with Richter's transformation, of whom one had a partial response whereas the second patient had progressive disease within 3 months of ibrutinib treatment. Master and colleagues[38] reported a patient with chronic lymphocytic leukaemia who developed Richter's transformation and achieved a response with single-agent ibrutinib that lasted for up to 16 months. Interim results of a phase 2 trial assessing the combination of ibrutinib and nivolumab in chronic lymphocytic leukaemia also showed promising responses in patients with Richter's transformation (n=5; 60% achieved an overall response),[39] consistent with the findings of our study. In a study with the PD-1 inhibitor pembrolizumab, Ding and colleagues[40] reported a 44% overall response in patients with heavily pretreated Richter's transformation. The median overall survival for patients with Richter's transformation was similar between the pembrolizumab study and our study (10·7 months *vs* 10·3 months).

All patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma in our study were high-risk patients with either del17p or del11q, or both. The proportion of patients in this high-risk cohort who achieved an overall response is in line with data reported previously[41] in a population of relapsed or refractory patients with del17p chronic lymphocytic leukaemia or small lymphocytic lymphoma treated with single-agent ibrutinib. O'Brien and colleagues[41] reported that 64% of patients in their study had an overall response, according to independent review committee assessment, and 83% had an overall response, according to investigator assessment. 33% of patients with relapsed or refractory follicular lymphoma achieved an overall response in our study, which falls in between the 20·9% and 37·5% reported

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in two phase 2 studies in similar populations.[2,10] In the diffuse large B-cell lymphoma cohort, an overall response was achieved by 36% of patients in our study, which is better than the 25% overall response previously reported for ibrutinib alone.[8] Six (33%) of 18 patients with the germinal centre B-cell subtype achieved an overall response, which is better than the 5% overall response reported for ibrutinib alone in germinal centre B-cell subtype;[8] this finding could be attributed to the combination with nivolumab.

In the diffuse large B-cell lymphoma cohort, elevated PD-L1 expression (≥5%) was significantly associated with complete response (p=0·028), although the number of patients was small. In the Richter's transformation cohort, three patients had elevated PD-L1 expression and all three had a partial response with durable overall survival. The biomarker results in the Richter's transformation cohort are consistent with those reported in a study with pembrolizumab, in which increased PD-L1 expression was associated with confirmed responses in patients with Richter's transformation.[40] Because the number of patients assessed was small, these results will need to be confirmed in a larger cohort of patients.

Our study has several limitations. It was an exploratory study, and because of the relatively small number of patients in each disease cohort, definitive conclusions cannot be reached. Genetic aberrations were not confirmed centrally, and only local laboratory data were available. Because the clinical cutoff was 6 months after the last patient received the first dose, many patients had relatively short follow-up. This factor is important for the chronic lymphocytic leukaemia or small lymphocytic lymphoma cohort, in which responses have been shown to improve with time.[42] The Richter's transformation cohort was opened later than the other cohorts in the study and was challenging to enrol. Therefore, enrolment was stopped after 20 patients were enrolled, a population large enough to describe preliminary activity.

In conclusion, oral ibrutinib (420 mg or 560 mg daily) in combination with nivolumab (3 mg/kg every 2 weeks) showed an acceptable safety profile in high-risk patients with previously treated, relapsed or refractory B-cell malignant disease. The clinical activity of the combination regimen was generally similar to the activity reported for single-agent ibrutinib in patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma, follicular lymphoma, and diffuse large B-cell lymphoma; however, because of the added toxic effects, the risk:benefit ratio does not favour the combination regimen for these patients. The overall response with the ibrutinib and nivolumab combination regimen in patients with Richter's transformation was promising and warrants confirmation in patients with Richter's transformation who did not respond to previous ibrutinib single-agent therapy.

Contributors

SB, JB, JdJ, NF, MSt, S-SW, and AY contributed to study design. JA, IA, MDCB, DB-Y, FB, JB, CC, RCo, RCe, JdJ, FD, BF, NF, AH, NAH, WJ, BK, AL-G, DDFM, PM, AN, MO, MSt, S-SW, TW, MY, and AY contributed to data collection. JA, IA, SB, JB, DB, JdJ, NF, BPH, WJ, MSt, MSc, S-SW, and AY contributed to data analysis. JA, IA, SB, FB, JB, DB, CC, JdJ, FD, BF, NF, BPH, NAH, WJ, BK, DDFM, PM, MO, MSt, MSc, S-SW, MY, and AY contributed to data interpretation. IA, WJ, BK, PM, and AN contributed to patients' accrual and management. All authors contributed to writing of the report.

Declaration of interests

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Data sharing statement

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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References

1 Advani RH, Buggy JJ, Sharman JP, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. *J Clin Oncol* 2013; **31:** 88–94.

2 Bartlett NL, Costello BA, LaPlant BR, et al. Single-agent ibrutinib in relapsed or refractory follicular lymphoma: a phase 2 consortium trial. *Blood* 2018; **131:** 182–90.

3 Burger JA, Keating MJ, Wierda WG, et al. Safety and activity of ibrutinib plus rituximab for patients with high-risk chronic lymphocytic leukaemia: a single-arm, phase 2 study. *Lancet Oncol* 2014; **15:** 1090–99.

4 Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med* 2014; **371:** 213–23.

5 Noy A, de Vos S, Thieblemont C, et al. Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma. *Blood* 2017; **129:** 2224–32.

6 Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenstrom's macroglobulinemia. *N Engl J Med* 2015; **372:** 1430–40.

7 Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med* 2013; **369:** 507–16.

8 Wilson WH, Young RM, Schmitz R, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. *Nat Med* 2015; **21:** 922–26.

9 Younes A, Santoro A, Shipp M, et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. *Lancet Oncol* 2016; **17:** 1283–94.

10 Gopal AK, Schuster SJ, Fowler NH, et al. Ibrutinib as treatment for patients with relapsed/refractory follicular lymphoma: results from the open-label, multicenter, phase II DAWN study. *J Clin Oncol* 2018; **36:** 2405–12.

11 Pharmacyclics and Janssen Biotech. Imbruvica (ibrutinib) prescribing information. August, 2018. https://www.imbruvica.com/docs/librariesprovider7/default-document-library/prescribing-information.pdf (accessed Dec 11, 2018).

12 European Medicines Agency. Imbruvica (ibrutinib) summary of product characteristics. August, 2018. https://www.medicines.org.uk/emc/product/3414/smpc (accessed Dec 11, 2018).

13 Buggy JJ, Elias L. Bruton tyrosine kinase (BTK) and its role in B-cell malignancy. *Int Rev Immunol* 2012; **31:** 119–32.

14 Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. *Proc Natl Acad Sci USA* 2002; **99:** 12293–97.

15 Bristol-Myers Squibb. Opdivo (nivolumab) prescribing information. November, 2018. https://packageinserts.bms.com/pi/pi_opdivo.pdf (accessed Dec 11, 2018).

16 Sagiv-Barfi I, Kohrt HE, Czerwinski DK, Ng PP, Chang BY, Levy R. Therapeutic antitumor immunity by checkpoint blockade is enhanced by ibrutinib, an inhibitor of both BTK and ITK. *Proc Natl Acad Sci USA* 2015; **112:** E966–72.

17 Andreotti AH, Schwartzberg PL, Joseph RE, Berg LJ. T-cell signaling regulated by the Tec family kinase, Itk. *Cold Spring Harb Perspect Biol* 2010; **2:** a002287.

18 Dubovsky JA, Beckwith KA, Natarajan G, et al. Ibrutinib is an irreversible molecular inhibitor of ITK driving a Th1-selective pressure in T lymphocytes. *Blood* 2013; **122:** 2539–49.

19 Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol* 2014; **32:** 3059–68.

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

21 Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood* 2011; **117:** 5019–32.

22 Li J, Zhi J, Wenger M, et al. Population pharmacokinetics of rituximab in patients with chronic lymphocytic leukemia. *J Clin Pharmacol* 2012; **52:** 1918–26.

23 Li Z, Li F, Yi S, et al. Superior efficacy of rituximab-based chemoimmunotherapy as an initial therapy in newly diagnosed patients with B cell indolent lymphomas: long-term results from a single center in China. *BMC Cancer* 2015; **15:** 555.

24 Ji Y, Herrick R. Toxicity Probability Intervals version 2.1. Oct 5, 2012. https://biostatistics.mdanderson.org/SoftwareDownload/SingleSoftware.aspx?Software_Id=72 (accessed Jan 3, 2019).

25 Wright G, Tan B, Rosenwald A, Hurt EH, Wiestner A, Staudt LM. A gene expression-based method to diagnose clinically distinct subgroups of diffuse large B cell lymphoma. *Proc Natl Acad Sci USA* 2003; **100:** 9991–96.

26 Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med* 2015; **373:** 23–34.

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

28 Marostica E, Sukbuntherng J, Loury D, et al. Population pharmacokinetic model of ibrutinib, a Bruton tyrosine kinase inhibitor, in patients with B cell malignancies. *Cancer Chemother Pharmacol* 2015; **75:** 111–21.

29 Scheers E, Leclercq L, de Jong J, et al. Absorption, metabolism, and excretion of oral 14C radiolabeled ibrutinib: an open-label, phase I, single-dose study in healthy men. *Drug Metab Dispos* 2015; **43:** 289–97.

30 Center for Drug Evaluation and Research. Clinical pharmacology and biopharmaceutics review of Opdivo (nivolumab): application number: 1255540orig1s000. July 30, 2014. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125554Orig1s000ClinPharmR.pdf (accessed Dec 11, 2018).

31 Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015; **373:** 123–35.

32 Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. *J Clin Oncol* 2010; **28:** 3167–75.

33 Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 2015; **372:** 320–30.

34 Agrawal S, Statkevich P, Bajaj G, et al. Evaluation of immunogenicity of nivolumab monotherapy and its clinical relevance in patients with metastatic solid tumors. *J Clin Pharmacol* 2017; **57:** 394–400.

35 Lesokhin AM, Ansell SM, Armand P, et al. Nivolumab in patients with relapsed or refractory hematologic malignancy: preliminary results of a phase Ib study. *J Clin Oncol* 2016; **34:** 2698–704.

36 Tsang M, Shanafelt TD, Call TG, et al. The efficacy of ibrutinib in the treatment of Richter syndrome. *Blood* 2015; **125:** 1676–78.

37 Giri S, Hahn A, Yaghmour G, Martin MG. Ibrutinib has some activity in Richter's syndrome. *Blood Cancer J* 2015; **5:** e277.

38 Master S, Leary C, Takalkar A, et al. Successful treatment of Richter transformation with ibrutinib in a patient with chronic lymphocytic leukemia following allogeneic hematopoietic stem cell transplant. *Case Rep Oncol* 2017; **10:** 534–41.

39 Jain N, Basu S, Thompson PA, et al. Nivolumab combined with ibrutinib for CLL and Richter transformation: a phase II trial. *Blood* 2016; **128:** 59.

40 Ding W, LaPlant BR, Call TG, et al. Pembrolizumab in patients with CLL and Richter transformation or with relapsed CLL. *Blood* 2017; **129:** 3419–27.

41 O'Brien S, Jones JA, Coutre SE, et al. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study. *Lancet Oncol* 2016; **17:** 1409–18.

42 O'Brien S, Furman RR, Coutre S, et al. Single-agent ibrutinib in treatment-naive and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience. *Blood* 2018; **131:** 1910–19.