Combination of ibrutinib with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for treatment-naive patients with CD20-positive B-cell non-Hodgkin lymphoma: a non-randomised, phase 1b study

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Summary

Background Present first-line therapy for diffuse large B-cell lymphoma, a subtype of non-Hodgkin lymphoma, is rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Ibrutinib, a novel oral Bruton's tyrosine kinase inhibitor, has shown single-drug activity in relapsed or refractory B-cell malignancies. We investigated the safety and efficacy of ibrutinib in combination with R-CHOP for patients with previously untreated CD20-positive B-cell non-Hodgkin lymphoma.

Methods In this phase 1b, open-label, non-randomised study, patients were recruited across six centres in the USA and France. Eligibility was age 18 years or older and treatment-naive histopathologically confirmed CD20-positive B-cell non-Hodgkin lymphoma. In the dose-escalation phase (part 1), patients with diffuse large B-cell lymphoma, mantle-cell lymphoma, or follicular lymphoma were enrolled. The primary objective was to determine a recommended phase 2 dose of ibrutinib with a standard R-CHOP regimen, by assessing safety in all patients who received treatment. Patients received ibrutinib 280 mg, 420 mg, or 560 mg per day in combination with a standard R-CHOP regimen every 21 days. Safety of the recommended phase 2 dose was then assessed in a dose-expansion population, which consisted of patients with newly diagnosed diffuse large B-cell lymphoma (part 2). Secondary objectives included assessments of the proportion of patients who had an overall response, pharmacokinetics, and pharmacodynamics. This trial is registered with ClinicalTrials.gov, number NCT01569750.

Findings From June 22, 2012, to March 25, 2013, 33 patients were enrolled (part 1: 17; part 2: 16) and 32 received ibrutinib plus R-CHOP treatment (one patient in the part 2 cohort withdrew). The maximum tolerated dose was not reached and the recommended phase 2 dose for ibrutinib was 560 mg per day. The most common grade 3 or greater adverse events included neutropenia (73% [24 of 33 patients]), thrombocytopenia (21% [seven patients]), and febrile neutropenia and anaemia (18% each [six patients]). The most frequently reported serious adverse events were febrile neutropenia (18% [six patients]) and hypotension (6% [two patients]). 30 (94%) of 32 patients who received one or more doses of combination treatment achieved an overall response. All 18 patients with diffuse large B-cell lymphoma who received the recommended phase 2 dose had an overall response. For those subtyped and treated at the recommended phase 2 dose, five (71%) of seven patients with the germinal centre B-cell-like subtype and two (100%) patients with the non-germinal centre B-cell-like subtype had a complete response. R-CHOP did not affect pharmacokinetics of ibrutinib, and ibrutinib did not alter the pharmacokinetics of vincristine. Pharmacodynamic data showed Bruton's tyrosine kinase was fully occupied (>90% occupancy) at the recommended phase 2 dose.

Interpretation Ibrutinib is well tolerated when added to R-CHOP, and could improve responses in patients with B-cell non-Hodgkin lymphoma, but our findings need confirmation in a phase 3 trial.

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Introduction

Recent estimates show roughly 70 800 new cases of non-Hodgkin lymphoma are expected to occur in the USA in 2014, whereas throughout Europe the expected incidence should reach 96 788 new cases by 2015.[1,2] Diffuse large B-cell lymphoma, a subtype of non-Hodgkin lymphoma, accounts for 30–40% of all adult cases in high-income countries.[3,4] Gene expression profiling shows two major subtypes of diffuse large B-cell lymphoma: activated B-cell-like and germinal centre B-cell-like, which arise by different genetic mechanisms.[5] The activated B cell-like (non-germinal centre B-cell-like) subtype generally has a poorer outcome.[6]

At present, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is frequently used as treatment for diffuse large B-cell lymphoma because of proven efficacy.[7–10] Both mantle-cell lymphoma and follicular lymphoma are also treated with R-CHOP.[11–13]

However, many patients are not cured by standard therapy and their prognosis is generally poor.[14] As such, improved outcomes from present first-line regimens are needed.

See Online for appendix

Ibrutinib, an oral Bruton's tyrosine kinase inhibitor, forms a covalent bond at the cysteine 481 site on the Bruton's tyrosine kinase enzyme. It has single-drug activity in relapsed and refractory B-cell malignancies with few toxic side-effects.[15–18] In a phase 1 study, patients with relapsed or refractory B-cell malignancies had an overall response of 60%, with 16% of patients in complete remission when given ibrutinib.[16] In phase 2 studies of patients with relapsed B-cell malignancies, ibrutinib produced an overall response in 71% of patients with chronic lymphocytic leukemia and in 68% of patients with mantle-cell lymphoma,[15,17] and showed an improvement in progression-free survival and overall survival in patients with relapsed or refractory chronic lymphocytic leukemia.[19] In patients with relapsed diffuse large B-cell lymphoma, ibrutinib showed preferential activity against tumours with the activated B-cell-like subtype with a response of 40%.[20] Because improvements are needed for outcomes in patients with diffuse large B-cell lymphoma, especially those with activated B cell-like or non-germinal centre B-cell-like subtype, we did a phase 1b study to assess the safety and efficacy of ibrutinib in combination with R-CHOP in patients with untreated B-cell non-Hodgkin lymphoma.

Methods

Study design and participants

We did an open-label, non-randomised, dose-escalation, phase 1b study across six centres in the USA and France (appendix). The study consisted of two parts: dose escalation (part 1) and dose expansion (part 2). Patients received up to six cycles of R-CHOP with concurrent daily oral administration of ibrutinib. Cycles were repeated every 21 days.

Eligible patients were aged 18 years or older and had histopathologically confirmed CD20-positive B-cell non-Hodgkin lymphoma. In the dose-escalation phase (part 1), patients with diffuse large B-cell lymphoma, mantle-cell lymphoma, or follicular lymphoma were enrolled. In the expansion cohort (part 2), only patients with newly diagnosed diffuse large B-cell lymphoma were included. Other eligibility criteria included stage IAX (bulk defined as a single lymph node mass ≥10 cm in diameter) to stage IV disease; Eastern Cooperative Oncology Group (ECOG) performance status score 2 or less; one or more measurable disease sites based on the Revised Response Criteria for Malignant Lymphoma;[21] and adequate bone marrow, liver, and renal function.

Patients were excluded if they had any previous lymphoma treatment; history of stroke or intracranial haemorrhage within the 6 months before the first dose of study drug; major surgery within 3 weeks before enrollment; known bleeding diatheses or platelet dysfunction disorders or need for therapeutic anti-

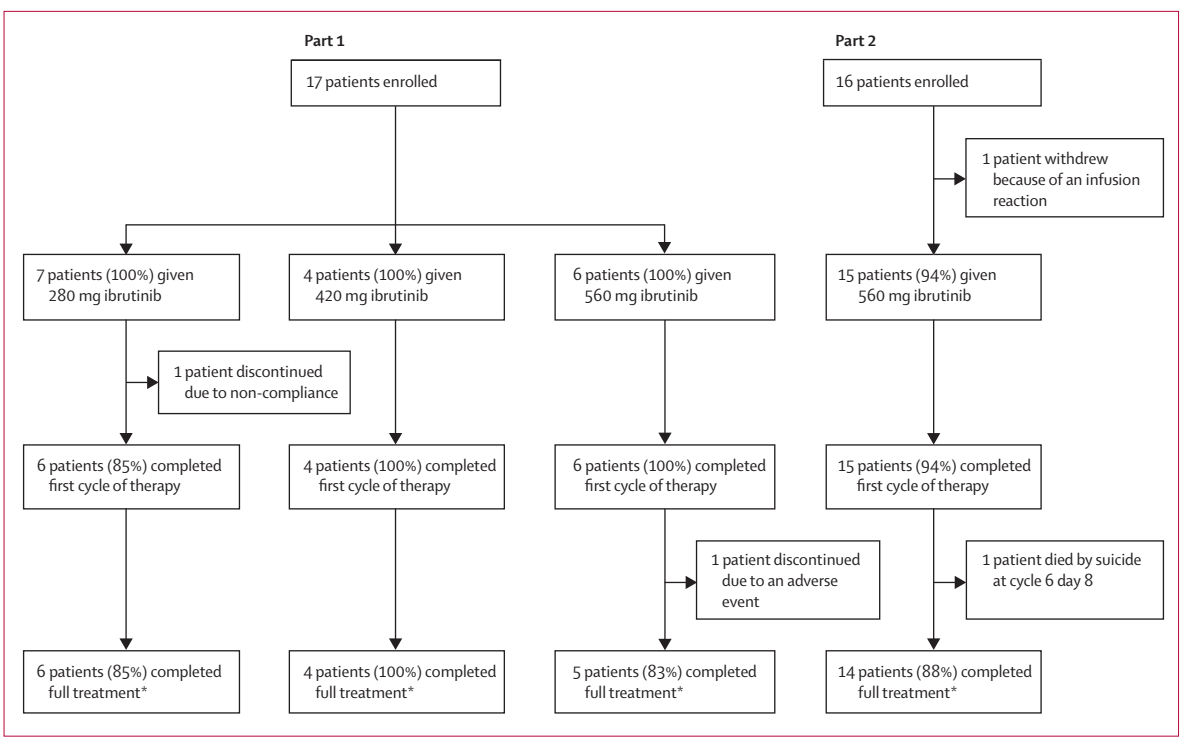

Figure 1: **Trial profile**
*Completed six cycles of treatment (ie, six cycles of ibrutinib plus six cycles of R-CHOP).

coagulation; use of aspirin, low-molecular-weight heparin, or other anticoagulants; known CNS involvement of lymphoma; uncontrolled heart disease; or any disorder that would compromise the patient or the study, in the opinion of the investigator.

An institutional review board approved the protocol at every study site. The study was conducted according to the principles of the Declaration of Helsinki and the International Conference of Harmonisation Guideline for Good Clinical Practice. Before any study-related activity, all patients provided written informed consent.

Procedures

During the dose-escalation period, the standard 3 + 3 design was applied. However, if four patients were eligible, the site investigator allowed them to start a new dose level, and patients were assigned to increasing doses of ibrutinib (Pharmacyclics Inc, Sunnyvale, CA, USA; 280, 420, and 560 mg) taken at roughly the same time every day in combination with R-CHOP (intravenous rituximab 375 mg/m², intravenous cyclophosphamide 750 mg/m², intravenous doxorubicin 50 mg/m², intravenous vincristine 1·4 mg/m² [maximum total of 2 mg] on day 1, and oral prednisone 100 mg on days 1–5 of every 21 day cycle). During the first cycle, the ibrutinib dosing started on day 3 to allow pharmacokinetic assessments for vincristine.

A study evaluation team, consisting of the principal investigators, and the sponsor's medical monitors and clinical pharmacologist or their designees, reviewed all data after cycle 1 to determine dose-limiting toxicities; they recommended if dose escalation was acceptable. Dose escalation continued until a maximum tolerated dose was achieved. A dose-limiting toxicity was defined as the occurrence of any of the following: any grade 3 or greater non-haematological toxicity at least possibly related to study drug, any grade 2 or greater haemorrhagic event requiring medical intervention or any intracranial haemorrhage, grade 4 thrombocytopenia or neutropenia for more than 7 days, or any complete, continuous dose interruption more than 7 days for ibrutinib-related toxicities of grade 2 or greater within cycle 1. If a dose-limiting toxicity definitely attributed to ibrutinib per the investigator's assessment occurred, dosing with ibrutinib was withheld. Ibrutinib treatment resumed at a lower dose only after toxicity was resolved. Dose re-escalations for ibrutinib were not allowed for patients after recovery from toxicity. No intrapatient dose escalation was allowed. For dose adjustments with R-CHOP components, the investigator referred to the prescribing information for the respective chemotherapeutic drug.

Upon completion of part 1, the study evaluation team determined a recommended phase 2 dose for ibrutinib in combination with R-CHOP based on an observed maximum tolerated dose, defined as the highest dose at which 33% or less of patients had a dose-limiting toxicitiy.

Pharmacokinetic assessments were completed to determine the systemic exposure of ibrutinib when combined with standard R-CHOP. The systemic exposure of vincristine was also assessed in the presence of ibrutinib as both drugs are CYP3A4 substrates and a potential drug–drug interaction might have resulted. The pharmacokinetics parameters were derived from the nominal plasma concentration–time curves. Pharmacodynamic assessments were done in peripheral blood mononuclear cells collected before and 4 h after the first dose of ibrutinib (on cycle 1, day 3) to measure the level of drug binding to Bruton's tyrosine kinase using a labeled probe (Bruton's tyrosine kinase occupancy). Cell-of-origin subtypes of diffuse large B-cell lymphoma were determined by central immunohistochemistry (IHC) analysis according to the Hans algorithm.[22]

Outcomes

The primary outcome, safety, was assessed by physical examination, clinical laboratory tests, and ECOG performance status at screening, day 1 of every cycle, and

	Ibrutinib plus R-CHOP				All* (n=33)
	280 mg (n=7)	420 mg (n=4)	560 mg (n=21)	Combined (n=32)	
Age (years)	68·0 (60–81)	58·0 (46–74)	54·0 (22–77)	60·5 (22–81)	61·0 (22–81)
Sex					
Male	4 (57%)	3 (75%)	10 (48%)	17 (53%)	17 (52%)
Female	3 (43%)	1 (25%)	11 (52%)	15 (47%)	16 (48%)
Ethnic origin					
White	5 (71%)	3 (75%)	16 (76%)	24 (75%)	25 (76%)
Black or African–American	2 (29%)	0	1 (5%)	3 (9%)	3 (9%)
Other	0	1 (25%)	1 (5%)	2 (6%)	2 (6%)
Not reported	0	0	3 (14%)	3 (9%)	3 (9%)
Height (cm)	170·00 (155·0–186·0)	169·50 (159·5–175·0)	165·00 (151·0–190·5)	165·50 (151·0–190·5)	165·00 (151·0–190·5)
Weight (kg)	86·10 (58·2–111·9)	87·90 (73·9–135·5)	81·00 (47·0–145·7)	81·30 (47·0–145·7)	81·00 (47·0–145·7)
Body surface area (m²)	2·00 (1·6–2·4)	2·05 (1·9–2·5)	1·90 (1·4–2·7)	1·90 (1·4–2·7)	1·90 (1·4–2·7)
ECOG performance status					
0	1 (14%)	1 (25%)	10 (48%)	12 (38%)	12 (36%)
1	5 (71%)	3 (75%)	9 (43%)	17 (53%)	17 (52%)
2	1 (14%)	0	2 (10%)	3 (9%)	4 (12%)
Type					
Diffuse large B-cell lymphoma	3 (43%)	2 (50%)	18 (86%)	23 (72%)	24 (73%)
Mantle-cell lymphoma	3 (43%)	0	2 (10%)	5 (16%)	5 (15%)
Follicular lymphoma	1 (14%)	2 (50%)	1 (5%)	4 (13%)	4 (12%)
Previous radiotherapy					
No	7 (100%)	4 (100%)	21 (100%)	32 (100%)	33 (100%)

Data are n (%) or median (range). ECOG=Eastern Cooperative Oncology Group. *One patient received only rituximab.

Table 1: **Baseline characteristics**

at the end of treatment. Patients were monitored weekly for adverse events, which were graded for severity with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). Thereafter, long term safety assessments were done every 3 months.

Secondary assessments included response, pharmacokinetics of ibrutinib with R-CHOP, potential drug–drug interactions between ibrutinib and vincristine, and pharmacodynamic markers of ibrutinib in peripheral blood mononuclear cells. Response assessments were done with computed tomography and whole body PET scans, after three and six cycles and every 3 months thereafter, according to the Revised Response Criteria for Malignant Lymphoma.[21] Bone marrow aspiration, biopsy sampling, or both were done to confirm a complete response in patients who initially had bone marrow involvement.

Statistical analysis

No hypothesis testing, or formal sample size calculations were made in this study because we used a 3+3 design. All patients who received any component of the study therapy were included, per protocol, in the treatment evaluation, safety, and efficacy analyses. Summary statistics were provided for continuous, categorical, and time-to-event data. All statistical analyses were done with SAS version 9.2.

This study is registered with ClinicalTrials.gov, number NCT01569750.

Role of the funding source

The authors and funders were responsible for designing the study protocol and statistical analysis. The investigators and their respective research teams collected the data, and the sponsor confirmed the accuracy of the data and compiled them for summation and analysis. Statistical analyses were done by Janssen. All authors had full access to the data and analyses. Report drafts were prepared by authors with editorial support from a professional medical writer paid by Janssen. All authors attest to the accuracy and integrity of the data report. The corresponding author had full access to all of the data and had final responsibility to submit for publication.

	Ibrutinib plus R-CHOP (n=33*)			
	Grade 1–2	Grade 3	Grade 4	Grade 5
Nausea	22 (67%)	1 (3%)	0	0
Vomiting	19 (58%)	1 (3%)	0	0
Fatigue	15 (45%)	0	0	0
Constipation	14 (42%)	0	0	0
Thrombocytopenia	14 (42%)	7 (21%)	0	0
Diarrhoea	12 (36%)	1 (3%)	0	0
Headache	11 (33%)	0	0	0
Peripheral sensory neuropathy	10 (30%)	0	0	0
Alopecia	9 (27%)	0	0	0
Dyspnoea	9 (27%)	0	0	0
Anaemia	8 (24%)	6 (18%)	0	0
Hypomagnesaemia	7 (21%)	0	0	0
Insomnia	7 (21%)	0	0	0
Muscle spasms	7 (21%)	0	0	0
Peripheral neuropathy	7 (21%)	1 (3%)	0	0
Asthenia	6 (18%)	0	0	0
Gastro-oesophageal reflux disease	6 (18%)	0	0	0
Paraesthesia	6 (18%)	0	0	0
Dysgeusia	5 (15%)	0	0	0
Hypersensitivity	5 (15%)	0	0	0
Hypokalemia	5 (15%)	0	0	0
Peripheral oedema	5 (15%)	0	0	0
Pruritus	5 (15%)	0	0	0
Upper respiratory tract infection	5 (15%)	0	0	0
Bone pain	4 (12%)	1 (3%)	0	0
Chills	4 (12%)	0	0	0
Cough	4 (12%)	0	0	0
Decreased appetite	4 (12%)	0	0	0

(Table 2 continues on next page)

Results

From June 22, 2012, to March 25, 2013, 33 patients were enrolled (figure 1). 32 patients received one or more doses of ibrutinib plus R-CHOP; one patient assigned to the ibrutinib 560 mg expansion cohort received rituximab only and had a grade 3 rituximab infusion reaction. Of those who received therapy, the median age was 60·5 years (range 22–81; table 1). Most (66%) patients had stage IV disease and no patients had received previous lymphoma or radiotherapy. The median follow-up time for the population who received one or more doses of ibrutinib plus R-CHOP was 7·1 months (IQR 5·26–10·38).

29 patients completed treatment (six cycles), and four (12%) patients prematurely discontinued (three patients because of an adverse event [one grade 3 rituximab infusion reaction, one patient with grade 2 gastritis, and one death] and one patient because of non-compliance with the study drug) and were withdrawn from the study. Of 24 patients with diffuse large B-cell lymphoma, 23 (96%) received one or more doses of ibrutinib plus R-CHOP, and 21 patients (88%) completed six cycles of study treatment. Most (61%) patients with diffuse large B-cell lymphoma who received one or more doses of combination therapy had stage IV disease. 21 (91%) of 23 patients had low-intermediate to high-intermediate risk of disease (ie, International Prognostic Index score[23] ranging from 0 to 3) and two patients (9%) had high-risk disease (ie, score of 4 or 5). The median time in the study for the patients with diffuse large B-cell lymphoma who received one or more doses of ibrutinib plus R-CHOP was 5·6 months (range 0·7–13·3). Of the population with diffuse large B-cell lymphoma who received one or more doses of ibrutinib plus R-CHOP,

13 patients were available for cell-of-origin subtyping data: nine (69%) patients had germinal centre B-cell-like diffuse large B-cell lymphoma and four (31%) patients had non-germinal centre B-cell-like diffuse large B-cell lymphoma.[22]

Three dose-limiting toxicities were noted in the study; two were reported with ibrutinib 280 mg (one transient syncope event and one periorbital cellulitis requiring intravenous administration of antibiotics). Because intervention was required, National Cancer Institute Common Terminology Criteria for Adverse Events defines this as a grade 3 event, but the study evaluation team determined that enrolling one additional patient would allow for six patients evaluable for dose-limiting toxicities at this dose, and further dose escalation was allowed. The third dose-limiting toxicity was reported at ibrutinib 560 mg in one patient with a previous history of grade 2 gastro-oesophageal reflux disease who had grade 2 gastritis that resulted in a dose interruption of more than 7 days during the first treatment cycle, and qualified as a dose-limiting toxicity per protocol definition. After the six patients at the highest dose in part 1 were assessed through cycle 1, the study evaluation team concluded that the maximum tolerated dose had not been reached and that the recommended phase 2 daily dose should be ibrutinib 560 mg.

All 33 treated patients were evaluable for adverse events (table 2) and of 32 patients that received one or more doses of ibrutinib and R-CHOP, 15 (47%) patients received full doses of R-CHOP. All patients had one or more adverse events, and 27 (82%) had a grade 3 event or worse. The most common grade 3 or greater adverse events included neutropenia (73% [24 of 33 patients]), thrombocytopenia (21% [seven patients]), and febrile neutropenia and anaemia (18% each [six patients]). The most frequently reported serious adverse events were febrile neutropenia (18% [six patients]) and hypotension (6% [two patients]). 13 (39%) of 33 patients had an adverse event leading to dose modification of any of the study drugs; three (9%) patients had serious adverse events leading to dose reduction (grade 3 febrile neutropenia and pyrexia, grade 3 febrile neutropenia, and grade 3 diarrhoea, in one patient, each). 11 (34%) of 32 patients had single-dose reductions of vincristine and one patient (3%) each had one or two dose reductions of cyclophosphamide, doxorubicin, or prednisone; no rituximab dose reductions were noted. Five (16%) patients had an ibrutinib dose reduction. Nine (27%) patients had an adverse event leading to treatment discontinuation of one or more study drug. One patient died during the study, but cause of death (suicide) was considered unrelated to treatment.

30 (94%) of 32 patients who received one or more doses of combination treatment achieved an overall response. Table 3 shows the best response to treatment for each treatment group. 23 (72%) of 32 patients who received one or more doses of ibrutinib plus R-CHOP had a complete response.

	Ibrutinib plus R-CHOP (n=33*)			
	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)				
Dizziness	4 (12%)	1 (3%)	0	0
Dry skin	4 (12%)	0	0	0
Oropharyngeal pain	4 (12%)	0	0	0
Pneumonia	4 (12%)	0	0	0
Rash	4 (12%)	0	0	0
Febrile neutropenia	0	6 (18%)	0	0
Hypotension	1 (3%)	2 (6%)	0	0
Syncope	0	2 (6%)	0	0
Acute coronary syndrome	0	1 (3%)	0	0
Back pain	2 (6%)	1 (3%)	0	0
Cellulitis	1 (3%)	1 (3%)	0	0
Escherichia coli urinary tract infection	1 (3%)	1 (3%)	0	0
Herpes zoster	0	1 (3%)	0	0
Hyperglycaemia	1 (3%)	1 (3%)	0	0
Hypertensive crisis	0	1 (3%)	0	0
Hypophosphataemia	0	1 (3%)	0	0
Infusion-related reaction	1 (3%)	1 (3%)	0	0
Leukocytosis	0	1 (3%)	0	0
Neutropenia	1 (3%)	1 (3%)	23 (70%)	0
Parainfluenzae virus infection	0	1 (3%)	0	0
Periorbital cellulitis	0	1 (3%)	0	0
Pyrexia	3 (9%)	1 (3%)	0	0
Testicular oedema	0	1 (3%)	0	0
Urinary tract infection	2 (6%)	1 (3%)	0	0
Completed suicide	0	0	0	1 (3%)

Data are n (%). *One patient received only rituximab.

***Table 2*: Adverse events that occurred in 10% or more of patients and all grade 3–5 events**

	280 mg (n=7)	420 mg (n=4)	560 mg (n=21)	Combined (n=32)	All (n=33)*
Overall response	6 (86%)	4 (100%)	20 (95%)	30 (94%)	30 (91%)
Complete response	5 (71%)	3 (75%)	15 (71%)	23 (72%)	23 (70%)
Partial response	1 (14%)	1 (25%)	5 (24%)	7 (22%)	7 (21%)
Stable disease	0	0	0	0	0
Progressive disease	0	0	0	0	0
Not evaluable	1 (14%)	0	1 (5%)	2 (6%)	3 (9%)

Data are n (%). *One patient received only rituximab.

***Table 3*: Best response to treatment, assessed by Revised Response Criteria for Malignant Lymphoma[21]**

22 (95%) of 23 patients with diffuse large B-cell lymphoma who received one or more doses of ibrutinib plus R-CHOP had an overall response. Of 13 patients who were subtyped for cell-of-origin of tumour, 11 were assessable. Seven tumours were confirmed to be germinal centre B-cell-like subtype and four were non-germinal centre B-cell-like; the overall response was 100% regardless of subtype. Five patients with germinal centre B-cell-like subtype achieved a complete response and two had a partial response, leading to a complete

response rate of 71% (five of seven patients). All four patients with confirmed non-germinal centre B-cell-like subtype achieved a complete response.

Of the 18 patients with diffuse large B-cell lymphoma who received the recommended phase 2 dose, 15 complete responses and three partial responses were achieved (one patient who was initially reported as having a partial response was confirmed as having a complete response based on bone marrow aspirate data that were available after database lock). Of these, nine patients had confirmed subtyping data, with a complete response of 71% (five of seven patients) for the germinal centre B-cell-like subtype and 100% (two of two patients) for the non-germinal centre B-cell-like subtype.

Figure 2 shows the average concentration–time profiles of ibrutinib after a single dose or at steady state after intake of ibrutinib 280 mg, 420 mg, and 560 mg per day. Steady-state conditions were considered achieved at cycle 2, day 1. In the first period (cycle 1, day 3) of observation, the area under the curve in the first 24 h (AUC_{0-24}) was not evaluable for ibrutinib 280 mg and 420 mg, but was 502 ng·h/mL for a single dose of ibrutinib 560 mg. Ibrutinib C_{max} and AUC increased across the dose range tested and were higher during cycle 2 compared with cycle 1 (table 4). After one cycle of ibrutinib administration, mean vincristine (CYP3A4 substrate) concentrations were similar to those observed after vincristine administration alone (appendix). The systemic exposure of ibrutinib seemed not to have been affected by the presence of the other components of R-CHOP. Pharmacodynamic measurements in peripheral blood mononuclear cells 4 h after receiving the first dose of ibrutinib showed that Bruton's tyrosine kinase was fully occupied (>90% occupancy) at the recommended ibrutinib dose of 560 mg (data not shown).

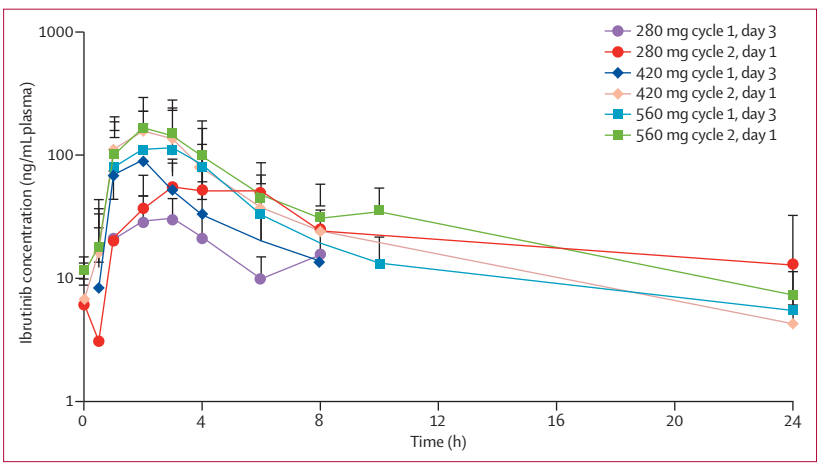

Figure 2: **Mean plasma concentration-time profiles of ibrutinib**

	t_{max} (h)	C_{max} (ng/mL)	AUC_{24} (ng·h/mL)	AUC_{last} (ng·h/mL)
280 mg				
Cycle 1 day 3 (n=6)	3·0 (0·5–8·0)	44·4 (16·4)	NA	150 (48·1)
Cycle 2 day 1 (n=5)	4·0 (1·0–6·3)	80·3 (28·9)	619 (278)	619 (278)
420 mg				
Cycle 1 day 3 (n=4)	2·0 (1·0–2·0)	92·0 (86·8)	NA	322 (280)
Cycle 2 day 1 (n=7)	2·0 (1·0–3·0)	190 (135)	762 (465)*	785 (429)
560 mg				
Cycle 1 day 3 (n=19)	2·0 (1·0–24·0)	147 (125)	502 (332)	554 (406)
Cycle 2 day 1 (n=18)	2·0 (0·0–3·0)	187 (198)	1014 (785)†	882 (741)

Data are mean (SD) or median (range). t_{max}=time to reach C_{max}. C_{max}=maximum plasma concentration. AUC_{24}=area under the plasma concentration–time curve from time 0 h to 24 h. AUC_{last}=area under the plasma concentration-time curve from time 0 h to the time of last quantifiable concentration. NA=not assessable, no 24 h samples. *n=6. †n=14.

Table 4: **Ibrutinib pharmacokinetic parameters by dose**

Discussion

Our study has shown that ibrutinib 560 mg is well tolerated when added to R-CHOP in treatment-naive patients with CD20-positive B-cell non-Hodgkin lymphoma. Three dose-limiting toxicities were reported during the study (escalation part only) but a maximum tolerated dose was not reached, establishing ibrutinib 560 mg once daily as the recommended phase 2 dose in combination with R-CHOP. In patients treated with the ibrutinib 560 mg plus R-CHOP, most (95%) patients (100% of patients with diffuse large B-cell lymphoma) completed six cycles of R-CHOP and most adverse events were manageable with concomitant drugs or dose modifications.

The safety profile of ibrutinib plus R-CHOP was assessed in all patients who received one or more doses of any of the study drugs. All patients had one or more adverse events and 82% of patients had a grade 3 or more adverse event. Primarily, these adverse events affected the haematological system. Neutropenia was managed with colony-stimulating factors, and no clinically relevant differences in the incidence of neutropenia and febrile neutropenia were noted, although the number of patients in each dose cohort was small. In a study of more than 1000 patients with diffuse large B-cell lymphoma, standard R-CHOP 21-day therapy resulted in 71% of patients having an serious adverse event, with neutropenia (60%), febrile neutropenia (11%), and infection (23%) the most commonly (≥10% of patients) reported events.[24] An observational study assessing the effect of febrile neutropenia on chemotherapy in patients with diffuse large B-cell lymphoma showed that febrile neutropenia occurs in the first cycle of R-CHOP in both 14-day (24/81 [30%]) and 21-day cycles (63/133 [47%]).[25] Because febrile neutropenia resulted in suboptimum chemotherapy delivery and increased incidence of admissions to hospital, international guidelines recommend use of granulocyte colony-stimulating factors for primary prophylaxis of febrile neutropenia,[26,27] which were used in the present study. The combination regimen was generally well tolerated and in line with known toxicities associated with R-CHOP treatment (panel). Notably, the addition of ibrutinib to R-CHOP did not lead to any new toxicities, including no increased incidence of substantial bleeding adverse events.

Treatment with ibrutinib plus R-CHOP showed clinical activity across all dose cohorts, including in patients with treatment-naive diffuse large B-cell lymphoma, follicular lymphoma, and mantle-cell lymphoma, with most patients achieving complete or partial response. 94% of patients in the combined population had an overall response. Excluding patients who did not undergo response evaluation because of premature termination of the study treatment because of toxicity, an overall response was noted in all patients, with more than three-quarters of patients having a complete response. For patients with treatment-naive diffuse large B-cell lymphoma who received the recommended phase 2 dose of ibrutinib 560 mg plus R-CHOP, the overall response was 100%. Although single-drug ibrutinib showed a preferential activity against the non-germinal centre B-cell-like subtype,[20] we did not note any difference in the overall response rate in the 13 patients whose tumours were subtyped.

The pharmacokinetic evaluation of ibrutinib in combination with R-CHOP showed consistent exposure of ibrutinib when compared with pharmacokinetics data from previous trials.[15] The C_{max} and AUC increased with increasing doses after both a single dose and at steady state. Our exposure analysis also showed that neither ibrutinib nor vincristine affects the pharmacokinetic behaviour of the other drug.

The pharmacodynamic potency of ibrutinib was assessed in the presence of R-CHOP. The results of this study at the clinically recommended dose were similar to previous single-drug data for ibrutinib in which full receptor occupancy occurred in 4 h.[15,16] This finding is promising, because preclinical models show the importance of probe binding and its tight correlation to blocking BCR signalling and in-vivo efficacy.[28]

In conclusion, the maximum tolerated dose was not reached in the phase 1 dose-escalation part of this study; the recommended phase 2 dose of ibrutinib was established at 560 mg once daily in combination with R-CHOP in treatment-naive patients with non-Hodgkin lymphoma. The combination of ibrutinib plus R-CHOP had an acceptable safety profile, because no new clinically meaningful toxicities were noted with the addition of ibrutinib to this standard regimen. The recommended phase 2 daily dose regimen showed an overall response of 100% in the 18 patients with diffuse large B-cell lymphoma. Although the data for median duration of response, progression-free survival, and overall survival were not mature at the time of this report, further clinical development is warranted. One patient with follicular lymphoma developed progressive disease and one patient with diffuse large B-cell lymphoma died before disease progression. Final survival data will become available 1 year after the last patient's completion of study treatment; efficacy data will be updated accordingly. Because ibrutinib has shown preferential single-agent activity in relapsed or refractory non-germinal centre B-cell-like diffuse large B-cell lymphoma,[20] a phase 3 clinical trial (NCT01855750) to assess the clinical outcome of ibrutinib 560 mg per day in combination with R-CHOP in patients with newly diagnosed non-germinal centre B-cell-like subtype diffuse large B-cell lymphoma is ongoing.

***Panel:* Research in context**

Systematic review

We searched PubMed with the terms "diffuse large B-cell lymphoma", "CHOP chemotherapy", and "rituximab" or "ibrutinib" for reported randomised clinical trials published in English between Jan 1, 2005, and April 30, 2014, and American Society of Hematology and American Society of Clinical Oncology conference abstracts published between Jan 1, 2010, and April 30, 2014. We identified primary publications for these therapies, which show that for R-CHOP chemotherapy, efficacy is favourable but varies and safety concerns include neutropenia and neutropenic fever, [7–10,24,25] and previous ibrutinib studies[15–20,28] show efficacy in B-cell malignancies and acceptable tolerability. Ibrutinib added to R-CHOP, if well tolerated, could improve first-line therapies.

Interpretation

When added to R-CHOP, ibrutinib does not add any new toxicities. Ibrutinib 560 mg per day plus R-CHOP could improve responses in patients with treatment-naive B-cell non-Hodgkin lymphoma. A randomised phase 3 trial of R-CHOP with and without ibrutinib is ongoing (NCT01855750) in newly diagnosed non-germinal centre B-cell-like diffuse large B-cell lymphoma.

Contributors

AY contributed to the protocol development, study design, patient accrual, data collection and interpretation, and writing of the report. CT contributed to patient recruitment, data collection, and interpretation, and writing of the report. FM and IF were involved in patient recruitment, data collection, analysis, and interpretation, and writing of the report. JWF contributed to the study design, provision of patients, data collection, analysis, and interpretation. SA was involved in data collection. BH contributed to patient accrual and data collection. JW helped with data collection and interpretation and patient accrual. JV contributed to data analysis and interpretation and manuscript writing. NB contributed to data analysis and interpretation, figures, and manuscript writing. RdV contributed to bioanalysis of samples and description of bioanalytical procedures. SB contributed to data analysis and interpretation and manuscript writing. PH contributed to the protocol development, study design, and data analysis and interpretation. JWS contributed to protocol development, data analysis and interpretation, figures, and writing of the report. NF contributed to the protocol development, study design, data analysis and interpretation, and manuscript writing. YO enrolled patients, contributed to data collection, analysis, and interpretation. All authors have reviewed drafts of the manuscript and have approved the final version.

Declaration of interests

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References

1 Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin* 2014; **64:** 9–29.

2 Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer; 2013. http://globocan.iarc.fr (accessed May 17, 2014).

3 No authors listed. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. *Blood* 1997; **89:** 3909–18.

4 Coiffier B. Diffuse large cell lymphoma. *Curr Opin Oncol* 2001; **13:** 325–34.

5 Shaffer AL 3rd, Young RM, Staudt LM. Pathogenesis of human B cell lymphomas. *Ann Rev Immunol* 2012; **30:** 565-610.

6 Lenz G, Davis RE, Ngo VN, et al. Oncogenic CARD11 mutations in human diffuse large B cell lymphoma. *Science* 2008; **319:** 1676–79.

7 Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol* 2005; **23:** 4117–26.

8 Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. *J Clin Oncol* 2006; **24:** 3121–27.

9 Pfreundschuh M, Trumper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol* 2006; **7:** 379–91.

10 Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). *Lancet Oncol* 2008; **9:** 105–16.

11 Kluin-Nelemans HC, Hoster E, Hermine O, et al. Treatment of older patients with mantle-cell lymphoma. *N Engl J Med* 2012; **367:** 520–31.

12 Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood* 2005; **106:** 3725–32.

13 Dreyling M, Ghielmini M, Marcus R, Salles G, Vitolo U. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2011; **22:** 59–63.

14 Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol* 2010; **28:** 4184–90.

15 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.

16 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.

17 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.

18 O'Brien S, Furman RR, Coutre SE, et al. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label, multicentre, phase 1b/2 trial. *Lancet Oncol* 2014; **15:** 48–58.

19 Byrd JC, Barrientos JC, Devereux S, et al. A randomized, multicenter, open-label, phase III study of the Bruton tyrosine kinase (BTK) inhibitor ibrutinib (PCI-32765) versus ofatumumab in patients (pts) with relapsed or refractory (RR) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): RESONATE. *Proc Am Soc Clin Oncol* 2013; **31:** abstrTPS8619.

20 Wilson WH, Gerecitano JF, Goy A, et al. The Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib (PCI-32765), has preferential activity in the ABC subtype of relapsed/refractory de novo diffuse large B-cell lymphoma (DLBCL): interim results of a multicenter, open-label, phase 2 study. *Blood* 2012; **120:** 686.

21 Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007; **25:** 579–86.

22 Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood* 2004; **103:** 275–82.

23 Project TIN-HsLPF. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med* 1993; **329:** 987–94.

24 Cunningham D, Hawkes EA, Jack A, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. *Lancet* 2013; **381:** 1817–26.

25 Pettengell R, Johnsen HE, Lugtenburg PJ, et al. Impact of febrile neutropenia on R-CHOP chemotherapy delivery and hospitalizations among patients with diffuse large B-cell lymphoma. *Support Care Cancer* 2012; **20:** 647–52.

26 Aapro MS, Bohlius J, Cameron DA, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. *Eur J Cancer* 2011; **47:** 8–32.

27 Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006; **24:** 3187–205.

28 Honigberg LA, Smith AM, Sirisawad M, et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. *Proc Natl Acad Sci USA* 2010; **107:** 13075–80.