Efficacy, pharmacokinetics, and safety of the biosimilar CT-P10 in comparison with rituximab in patients with previously untreated low-tumour-burden follicular lymphoma: a randomised, double-blind, parallel-group, phase 3 trial

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Summary

Background Studies in patients with rheumatoid arthritis and advanced follicular lymphoma have shown that CT-P10, a rituximab biosimilar, has equivalent or non-inferior efficacy and pharmacokinetics to rituximab. We aimed to assess the therapeutic equivalence of single-agent CT-P10 and rituximab in patients with newly diagnosed low-tumour burden follicular lymphoma.

Methods In this ongoing, randomised, double-blind, parallel-group, active-controlled, phase 3 trial, adult patients (≥18 years) with stage II–IV low-tumour-burden follicular lymphoma were randomly assigned (1:1) using an interactive web or voice response system stratified by region, stage, and age to CT-P10 or US-sourced rituximab. Patients received CT-P10 or rituximab (375 mg/m² intravenous) on day 1 of four 7-day cycles (induction period). Patients who had disease control after the induction period continued to a maintenance period of CT-P10 or rituximab administered every 8 weeks for six cycles and, if completed, a second year of maintenance therapy of additional CT-P10 (every 8 weeks for six cycles) was offered. The study was partially unmasked after database lock (Feb 23, 2018) for all data up to 7 months (before cycle 3 of the maintenance period). The primary endpoint was the proportion of patients who achieved an overall response by 7 months in the intention-to-treat population. Efficacy equivalence was shown if the two-sided 90% CIs for the treatment difference in the proportion of responders between CT-P10 and rituximab was within the equivalence margin of 17%. This trial is registered with ClinicalTrials.gov, number NCT02260804.

Findings Between Nov 9, 2015, and Jan 4, 2018, 402 patients were assessed for eligibility, of whom 258 were randomly assigned: 130 to CT-P10 and 128 to rituximab. 108 (83%) of 130 patients assigned to CT-P10 and 104 (81%) of 128 assigned to rituximab achieved an overall response by month 7 (treatment difference estimate 1·8%; 90% CI –6·43 to 10·20). Therapeutic equivalence was shown (90% CIs were within the prespecified margin of 17%). The most common grade 3 or 4 treatment-emergent adverse events were decreased neutrophil count (two grade 3 in the CT-P10 group) and neutropenia (one in each group); all other grade 3 or 4 treatment-emergent adverse events occurred in one patient each. Six (5%) of 130 patients who received CT-P10 and three (2%) of 128 who received rituximab experienced at least one treatment-emergent serious adverse event.

Interpretation CT-P10 was equivalent to rituximab in terms of efficacy and was well tolerated. CT-P10 monotherapy is suggested as a new therapeutic option for patients with low-tumour-burden follicular lymphoma.

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Introduction

Rituximab is a chimeric monoclonal antibody that binds to the CD20 protein found on the surface of normal and malignant B cells. Rituximab plays a key role in the treatment of inflammatory conditions such as rheumatoid arthritis, and is used to treat patients with B-cell non-Hodgkin lymphomas, including follicular lymphoma.[1] Originator biologics such as rituximab, which have revolutionised cancer therapy, are associated with high treatment prices owing to the complex development and manufacturing processes involved in their production. The European Medicines Agency defines a biosimilar as "a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product".[2] To gain regulatory approval, similarity between the biosimilar and originator product (also known as the reference product), must be shown in terms of quality,

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed using the terms "rituximab" and "follicular lymphoma" or "rituximab" and "non-Hodgkin's lymphoma" for articles published up to July 14, 2015, with no language restrictions when planning this study. We found 96 articles, of which seven were clinical studies. The search showed that several rituximab biosimilars were in development, including some that had reached late-stage clinical trials in patients with previously untreated advanced-stage follicular lymphoma. Although these trials included patients with a low tumour burden, no reports had been published of a clinical trial designed to evaluate a rituximab biosimilar given as monotherapy in this patient population.

Added value of this study

To our knowledge, this is the first full report of a phase 3 clinical trial of a rituximab biosimilar given as monotherapy in patients with follicular lymphoma. This study showed that CT-P10 has equivalent efficacy, as assessed by the proportion of patients achieving an overall response, and similar pharmacokinetics, pharmacodynamics, and safety including immunogenicity to rituximab in patients with grade 1–3a CD20-positive follicular lymphoma and a low tumour burden. Overall, the similar profiles observed in the present study add to the accumulating evidence showing that CT-P10 and rituximab are bioequivalent and that there are no clinically meaningful differences between the two drugs.

Implications of all the available evidence

Rituximab monotherapy is a cost-effective strategy for induction treatment of asymptomatic follicular lymphoma as compared with a watchful waiting strategy, and is recommended treatment for this patient population according to guidance from the National Institute for Health and Care Excellence (UK) and National Comprehensive Cancer Network (USA). Results from our multinational, phase 3, randomised controlled trial suggest a role for CT-P10 as a potential alternative to rituximab for patients with low-tumour-burden follicular lymphoma.

biological activity, efficacy, and safety. Proof of similarity is achieved by a comprehensive series of stepwise comparability studies incorporating analytical, in-vitro, and clinical analyses.[3,4] Biosimilars are generally associated with a 20–35% reduction in price versus their reference products.[5] Thus, owing to their increased affordability, the introduction of biosimilar versions of effective anticancer biologics is expected to result in cost savings for health-care systems and is likely to enable more patients to be treated.[6,7]

CT-P10 (Truxima; Celltrion, Incheon, South Korea) was the first rituximab biosimilar approved in several regions and countries, including Europe, Australia, and South Korea, for the same indications as originator rituximab.[8] CT-P10 has an identical primary structure to both US-sourced rituximab (Rituxan; Genentech, South San Francisco, CA, USA) and European Union (EU)-sourced rituximab (MabThera; Roche, Basel, Switzerland), and is similar in all other physicochemical and structural attributes and in terms of biological activity.[9] A phase 1 clinical trial[10] showed equivalent pharmacokinetics and comparable efficacy, pharmacodynamic, and safety profiles in patients with rheumatoid arthritis who were treated with CT-P10 or EU-sourced rituximab. These findings were substantiated in a phase 3 study[11,12] in patients with rheumatoid arthritis in which equivalent efficacy and pharmacokinetics were shown between CT-P10 and both US-sourced and EU-sourced rituximab. CT-P10 and rituximab have shown non-inferiority of efficacy, equivalent pharmacokinetics, and comparable safety in treatment-naive patients with advanced-stage follicular lymphoma in combination with cyclophosphamide, vincristine, and prednisone chemotherapy.[13]

In this multinational, phase 3, randomised, controlled trial, we aimed to assess the therapeutic equivalence of single-agent CT-P10 and rituximab in patients with newly diagnosed low-tumour-burden follicular lymphoma.

Methods

Study design and participants

This ongoing, randomised, double-blind, parallel-group, active-controlled, phase 3 study was done in 112 centres, of which 96 centres randomly assigned patients, in Europe, Asia–Pacific, North America, and other (defined as all countries outside of the previous categories; appendix pp 2–3). The study protocol can be found in the appendix (pp 18–118).

To be eligible for inclusion, patients had to be at least 18 years of age and have CD20-positive follicular lymphoma of grade 1–3a, histologically confirmed by central pathological review; at least one measurable tumour mass in two dimensions; Ann Arbor stage II–IV disease; Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; adequate bone marrow, hepatic, and renal function; and low tumour burden according to Groupe D'Etude des Lymphomes Folliculaires (GELF) criteria.[14] Low tumour burden was defined as having absence of B symptoms; normal serum lactate dehydro-genase (LDH); no tumour mass greater than 7 cm; fewer than three nodal sites with a diameter of at least 3 cm; no serous effusions; no splenomegaly larger than 16 cm; no risk of organ compression; and no cytopenia (defined as platelets <100 000 per µL, haemoglobin <10 g/dL, or absolute neutrophil count <1500 per µL). Patients were excluded if they had previously received treatment for non-Hodgkin lymphoma; received treatment with rituximab or a rituximab biosimilar; or had evidence of histological transformation to high-grade or diffuse large B-cell lymphoma. A full list of inclusion and exclusion criteria is provided in the appendix (pp 4–5).

The study was done according to the principles of the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines. The study protocol was approved by the ethics committee at each centre and relevant regulatory authorities. All patients provided written informed consent before being admitted to the clinical study.

Randomisation and masking

Patients were randomly assigned (1:1) to receive CT-P10 or US-sourced rituximab using a computer-generated randomisation schedule prepared before the study by a contract research organisation. An interactive web or voice response system was used by the investigators for permuted block randomisation (block size is unavailable as this study is ongoing and this detail has not yet been unblinded to the sponsor), stratified by region (Asia–Pacific *vs* Europe *vs* North America and other), stage (II *vs* III *vs* IV), and age (≥60 *vs* <60 years). To mask the treatment assignment to investigators, patients, study teams from the sponsor, and designee from the contract research organisation responsible for the study, CT-P10 and rituximab were provided in indistinguishable kits identified with a unique material number. These identifying numbers were assigned by an interactive web or voice response system based on the randomly assigned treatment group. At a protocol-defined timepoint (Feb 24, 2018), the study was partially unmasked to the predefined study personnel of the sponsor (Celltrion) and the individual (contract research organisation) responsible for the study, after database lock (Feb 23, 2018) for all data up to 7 months for all patients, so that the available data could be reported. However, the study will remain masked to Celltrion individuals who are involved in the analysis and reporting of the results, investigators, and patients, until all patients have completed the study and the database has been finalised for study completion.

Procedures

Patients received intravenous infusions of 375 mg/m² CT-P10 or US-sourced rituximab weekly for 4 weeks (induction period). Patients who had a complete response, unconfirmed complete response, partial response, or stable disease at month 3 were eligible to begin maintenance treatment with 375 mg/m² CT-P10 or rituximab (the same treatment that they had received during the induction period), every 8 weeks for six cycles (1 year). Patients who completed the first year of the maintenance period were offered additional CT-P10, which was administered every 8 weeks for six cycles (1 year). The total maintenance treatment did not exceed 12 cycles over 2 years. Follow-up was planned until death or 27 months from the date of first study drug administration for the last patient enrolled. No dose modifications or dose omissions were permitted for CT-P10 or rituximab. Patients were withdrawn from the study treatment at investigators' discretion in the interest of patient safety or if they developed progressive disease.

Efficacy assessments were done at baseline, month 3, and month 7 using contrast-enhanced CT with or without MRI. After month 7, efficacy assessments were planned every 6 months until the end of the study. Clinical parameters, including B symptoms (defined as clinically significant unexpected fever [>38°C]; unexplained, recurrent, drenching night sweats; and unexplained loss of >10% bodyweight within the previous 6 months), LDH abnormality, bone marrow involvement, and organ enlargement, were assessed at the same time as evaluation of tumour response. A bone marrow trephine biopsy was required to confirm complete response or unconfirmed complete response at the investigator's discretion at post-treatment visits; if the bone marrow did not meet the criterion for complete response or unconfirmed complete response, a suboptimal response was recorded.

Tumour responses were evaluated according to the modified response criteria for malignant lymphoma on the basis of the International Working Group (IWG) response criteria.[15] Radiographic images obtained during the induction and maintenance periods were evaluated locally by investigators for confirmation of eligibility and treatment practice, and centrally by an independent tumour review committee for reporting purposes. Two independent central radiologists evaluated the radiological response using CT images; a third radiologist adjudicated only if there was a disagreement between the two central radiologists. Final disease response was evaluated by an independent oncologist on the basis of confirmed radiological responses and clinical parameters.

For pharmacokinetic analyses, samples were collected before the dose and 1 h after completing the study drug infusion at each cycle up to 7 months. To measure B-cell kinetics, blood samples were collected at each cycle up to 7 months. Adverse events were monitored throughout, according to the Medical Dictionary for Regulatory Activities, and were graded with the Common Terminology Criteria for Adverse Events (version 4.03). Adverse events of special interest were infusion-related reactions, infection, and progressive multifocal leuko-encephalopathy. Blood samples were assessed for routine laboratory parameters, β-2 microglobulin, and immuno-globulins (IgM, IgG, and IgA). Serum anti-drug antibodies (ADAs) and neutralising antibodies were monitored throughout the study, using an enhanced chemiluminescence assay and a complement-dependent cytotoxicity assay (developed by Celltrion, Incheon, South Korea), respectively.

Outcomes

The primary objective was to measure therapeutic equivalence in the intention-to-treat (ITT) population in terms of overall response. The primary endpoint was the proportion of patients who had an overall response

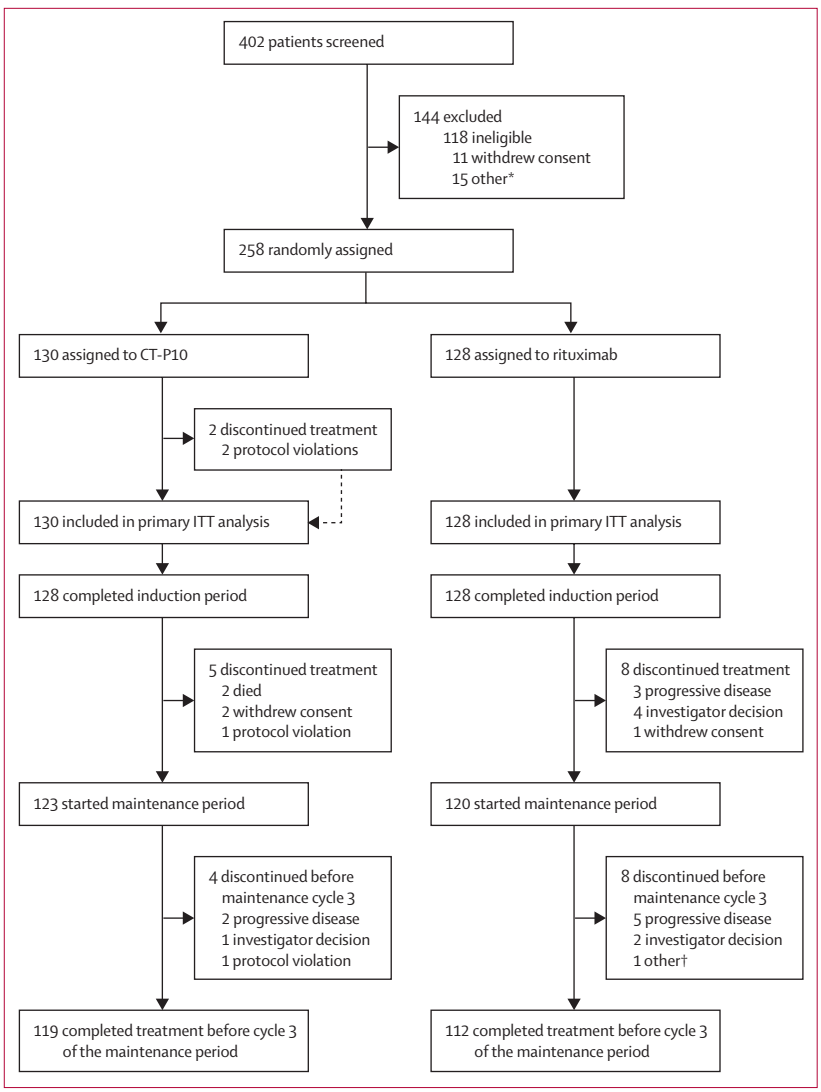

Figure 1: **Patient disposition**
ITT=intention-to-treat. *Two patients had insurance problems, 12 patients were out of the screening window, and for one patient adequate equipment was not prepared for the study (no CT). †Discontinued treatment to receive prohibited treatment.

(defined as a complete response, unconfirmed complete response, or partial response) by 7 months (before cycle 3 of the maintenance period). Assessments of total tumour lesion size, bone marrow involvement, and B symptoms, done as part of the tumour response evaluation, are also reported here. Secondary efficacy endpoints (overall response during the whole study period, progression-free survival, time to progression, and overall survival) will be reported in a subsequent paper after study completion (up to 27 months from the first infusion for the last patient). Other secondary endpoints of pharmacokinetics (maximum [C_{max}] and trough [C_{trough}] serum concentrations), pharmacodynamics (B-cell counts), and overall safety including immunogenicity up to 7 months are presented here.

Statistical analysis

A sample size of 174 patients (87 per treatment group) was calculated to give 91% statistical power in the ITT population and 86% statistical power in the per-protocol population, assuming a dropout rate of 13%, for showing equivalence of the primary endpoint. This calculation was done on the basis of an estimated proportion of patients with an overall response of 88% and an equivalence margin of 17% using two one-sided 5% significance levels. Since the assumed 88% overall response was based solely on the result from a previous low-tumour-burden follicular lymphoma study,[16] it is probably an overestimate of the effect of rituximab. Therefore, as planned in the protocol, when the primary endpoint evaluation was available for 50–60% of patients, a masked reassessment of sample size, accounting for the actual dropout rate and the observed proportion of patients with an overall response, was done for the constancy assumption and to ensure adequate statistical power for the primary endpoint. After reassessment with 102 (54%) evaluable patients from a recruited total of 190 patients on April 27, 2017, we realised that an increase in the total same size for this study to at least 228 patients was required to achieve adequate statistical power (at least 80% power in the per-protocol population).

The ITT population was the primary efficacy analysis population and was defined as all patients enrolled and randomly assigned to receive a dose of study drug, regardless of whether or not any study drug dosing was received. A preplanned supportive analysis was done in the per-protocol population, which was defined as all randomly assigned patients who had at least one response evaluation after receiving at least one full dose of study drug without any major protocol violation that might affect the interpretation of study results for efficacy.

A point estimate and 90% CIs of the difference in the proportion of responders between the two treatment groups were calculated using an exact binomial method; 95% CIs, which are traditionally accepted, were also calculated. A sensitivity analysis was done on the primary efficacy endpoint using a logistic regression model, with treatment as a fixed effect and region (Asia–Pacific *vs* Europe *vs* North America and other), Ann Arbor stage (≤II *vs* III *vs* IV) and age (≥60 *vs* <60 years) as covariates. To assess the effect of patients with no tumour response evaluation for the primary endpoint, tipping point analyses were done with varying assumptions about the proportion of patients who would achieve an overall response using the imputed response in patients for whom any response evaluation results did not exist up to 7 months for any reason and the observed response in each group. Post-hoc subgroup analyses of the primary endpoint according to age, sex, ECOG performance score, disease grade and stage, bone marrow status, Follicular Lymphoma Prognostic

	CT-P10 (n=130)	Rituximab (n=128)
Age (years)	57·7 (12·7)	57·7 (11·5)
Sex		
Male	66 (51%)	57 (45%)
Female	64 (49%)	71 (55%)
Race		
White	77 (59%)	75 (59%)
Asian	47 (36%)	49 (38%)
Other	6 (5%)	4 (3%)
Follicular CD20-positive lymphoma diagnosis*		
Yes	130 (100%)	128 (100%)
No	0	0
Disease duration (months)†	2·7 (1·8–4·4)	2·5 (1·7–4·8)
Follicular lymphoma grade*		
1	26 (20%)	32 (25%)
2	92 (71%)	84 (66%)
3a	12 (9%)	12 (9%)
Ann Arbor principal stage		
I	1 (1%)‡	0
II	31 (24%)	30 (23%)
III	47 (36%)	53 (41%)
IV	51 (39%)	45 (35%)
FLIPI score		
Low (0–1)	58 (45%)	52 (41%)
Intermediate (2)	46 (35%)	49 (38%)
High (3–5)	26 (20%)	27 (21%)
GELF criteria		
No B symptoms	130 (100%)	128 (100%)
Normal serum LDH	128 (98%)	126 (98%)
No target nodal or extranodal mass >7 cm	130 (100%)	128 (100%)
<3 nodal sites, each with a diameter ≥3 cm	127 (98%)	127 (99%)
No serous effusions	130 (100%)	128 (100%)
No splenomegaly (defined as ≤16 cm)§	128 (98%)	128 (100%)
Platelet count ≥100 000/mm³	130 (100%)	128 (100%)
Baseline lesions SPD (mm²)	2164 (2075)	1881 (1453)

(Table 1 continues in next column)

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	CT-P10 (n=130)	Rituximab (n=128)
ECOG performance status		
0	109 (84%)	108 (84%)
1	21 (16%)	20 (16%)
Bone marrow involvement	46 (35%)	41 (32%)
β-2 microglobulin (mg/L)		
<3·0	105 (81%)	104 (81%)
≥3·0	18 (14%)	21 (16%)
Unknown	7 (5%)	3 (2%)
B-cell count (cells/μL)¶	95 (56·0–171·5)	120 (64·0–182·0)

Data are mean (SD), number (%), or median (IQR). Some percentages do not add up to 100 because of rounding. ECOG=Eastern Cooperative Oncology Group. GELF=Groupe d'Etude des Lymphomes Folliculaires. FLIPI=Follicular Lymphoma International Prognostic Index. LDH=lactate dehydrogenase. SPD=sum of the products of the greatest perpendicular diameters. *From central pathological review. †Calculated as duration=(date of first infusion–date of initial diagnosis+1)/30·4. ‡A patient in the CT-P10 group was enrolled with stage II disease. This was corrected to stage I after the investigator's reconfirmation. §Includes patients for whom data were missing (14 in the CT-P10 group and 18 in the rituximab group), but whose spleen was confirmed to be smaller than the cutoff for inclusion according to study criteria by the investigator. Patients who had undergone previous splenectomy (one patient in the CT-P10 group) or had spleen >16 cm (one patient in the CT-P10 group) were excluded. ¶120 in the CT-P10 group and 123 in the rituximab group.

***Table 1*: Demographics, baseline characteristics, GELF components, and disease status**

Index score, and β-2 microglobulin concentrations were also done.

Pharmacokinetic and pharmacodynamic data were summarised by treatment group for the pharmacokinetic and pharmacodynamic populations, respectively (ie, all patients who received at least one full dose of study drug and provided pharmacokinetic or pharmacodynamic data for at least one post-treatment assessment). Safety was assessed in the safety population, which included all randomly assigned patients who received at least one full or partial dose of study drug.

Statistical analyses were done using SAS (version 9.1.3 or later). The exact binomial method was applied using StatXact (version 11).

The study is registered with ClinicalTrials.gov, number NCT02260804.

Role of the funding source

The funder was involved in conception and design of the study and in data collection, analysis, and interpretation. All authors, including employees of the sponsor, participated in writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication. SJL, SYL, and YJB had access to the raw data that was available to the sponsor.

Results

Between Nov 9, 2015, and Jan 4, 2018, 402 patients were assessed for eligibility, of whom 258 were randomly assigned: 130 to the CT-P10 group and 128 to the rituximab group (figure 1). 231 patients (119 [92%] of 130 in the CT-P10 group and 112 [88%] of 128 in the rituximab group) completed up to month 7 (figure 1). Median follow-up was 6·25 months (IQR 6·25–6·48). The appendix (p 7) provides details of the analysis populations.

Patient demographics and baseline disease characteristics were well balanced between treatment groups (table 1, appendix p 8). All patients were enrolled with

	CT-P10	Rituximab	Treatment difference estimate*	90% CI*	95% CI*
Intention-to-treat population					
Overall response	108/130 (83%)	104/128 (81%)	1·8%	−6·43 to 10·20	−8·22 to 11·53
Complete response	36/130 (28%)	43/128 (34%)	..	..	..
Unconfirmed complete response	6/130 (5%)	2/128 (2%)	..	..	..
Partial response	66/130 (51%)	59/128 (46%)	..	..	..
Stable disease	17/130 (13%)	18/128 (14%)	..	..	..
Relapsed or progressive disease	0/130	4/128 (3%)	..	..	..
Unable to assess	0/130	1/128 (1%)†	..	..	..
Data missing‡	5/130 (4%)	1/128 (1%)	..	..	..
Per-protocol population					
Overall response	99/114 (87%)	100/120 (83%)	3·5%	−4·56 to 11·56	−6·28 to 13·01
Complete response	35/114 (31%)	41/120 (34%)	..	..	..
Unconfirmed complete response	6/114 (5%)	2/120 (2%)	..	..	..
Partial response	58/114 (51%)	57/120 (48%)	..	..	..
Stable disease	15/114 (13%)	15/120 (13%)	..	..	..
Relapsed or progressive disease	0	4/120 (3%)	..	..	..
Unable to assess	0	1/120 (1%)†	..	..	..
Data missing‡	0	0	..	..	..

Data are n/N (%) *Calculated using the exact binomial method. †Patient had incomplete target lesion assessment. ‡Patients who discontinued treatment early without tumour response evaluation at post-treatment visits.

***Table 2*: Response evaluation to month 7, by central review**

CD20-positive follicular lymphoma and were Ann Arbor stage II, III, or IV, apart from one patient with stage I disease who was incorrectly classified initially as stage II. All patients except for ten had low tumour burden, defined by GELF criteria: two in each group had abnormal LDH concentrations; three in the CT-P10 group and one in the rituximab group had at least three nodal sites with a diameter of at least 3 cm; and two in the CT-P10 group did not meet the criterion of a spleen that was 16 cm or smaller by CT measurement (table 1). The mean (SD) relative dose intensity during cycles up to 7 months was similar in the two treatment groups: 99·0% (4·23) for CT-P10 and 99·6% (2·44) for rituximab.

As evaluated by an independent tumour review committee, in the ITT population, 108 (83%) of 130 patients in the CT-P10 group and 104 (81%) of 128 in the rituximab group had an overall response by month 7 (treatment difference estimate 1·8%, 90% CI −6·43 to 10·20; table 2). A similar result was observed in the per-protocol population (table 2). For both populations, the two-sided 90% CIs for the primary endpoint were within the predefined equivalence margin of 17%, which suggested therapeutic equivalence between the two treatment groups. In the sensitivity analysis of overall response based on central review using logistic regression, the 90% CIs of the treatment difference estimate were −6·20 to 9·36 for the ITT analysis and −4·11 to 10·80 for the per-protocol analysis, both within the equivalence margin. The overall response results based on local review were consistent with the primary analyses (appendix p 9). In tipping point analyses, under all scenarios using the assumed number of responders in each group, the 90% CIs were contained within the equivalence margin (appendix p 10). In post-hoc analyses of overall response to assess the effect of potential prognostic factors on efficacy, no differences in treatment effect were observed between groups for any of the subgroups analysed (figure 2).

The change in the sum of the target lesions from baseline to the smallest size at post-baseline evaluations, and to the last assessed size, were similar between the two treatment groups (appendix pp 11–12). 87 (34%) of 258 patients had bone marrow involvement at screening (46 in the CT-P10 group and 41 in the rituximab group), and 48 (19%; 29 in the CT-P10 group and 19 in the rituximab group) underwent bone marrow examination at post-treatment visits, at the investigator's discretion. Of these 48 patients, 43 (90%) had a negative result: 27 (93%) of 29 in the CT-P10 group and 16 (84%) of 19 in the rituximab group. We did not observe any instances of new or relapsed bone marrow involvement after treatment. No patients in either group had B symptoms at baseline; three patients had at least one B symptom reported at post-treatment visits (two [2%] of 130 in the CT-P10 group and one [1%] of 128 in the rituximab group). The proportion of patients with β-2 microglobulin of at least 3·0 mg/L decreased to a similar extent from baseline to month 7 in both groups (from 18 [14%] to nine [7%] of 130 patients in the CT-P10 group, and from 21 [16%] to nine [7%] of 128 in the rituximab group). The ECOG performance status of patients up to month 7 are shown in the appendix (p 13).

Similar pharmacokinetic profiles were shown in the CT-P10 and rituximab groups. Mean serum

con-centrations of study drug versus time (figure 3), C_{max}, and C_{trough} (appendix p 14) were similar between the two treatment groups over 7 months.

B-cell depletion over the 7 months of treatment was similar in both treatment groups. The median number of B cells decreased to the lower limit of quantification (LLOQ; 20 cells/μL) 1 h after the end of the first study drug infusion and remained at the LLOQ at each subsequent cycle to month 7 (appendix p 15).

A similar frequency of treatment-emergent adverse events were reported in the CT-P10 and rituximab groups (table 3). The most frequently reported treatment-emergent adverse events were infusion-related reactions, followed by upper respiratory tract infections and fatigue (table 3). All infusion-related reactions were grade 1–2 in severity, with the exception of one grade 3 infusion-related reaction reported in the CT-P10 group (table 4). Infections occurred in 35 (27%) patients in the CT-P10 group and 27 (21%) patients in the rituximab group (table 3). One treatment-emergent serious adverse event classified as malignancy (squamous cell carcinoma of lung) was reported for a patient in the CT-P10 group (appendix p 16). Because the lesion was visible in the CT scan at screening but was only detected later in the study, the patient discontinued study treatment owing to the protocol violation (exclusion criteria included the presence of any cancer other than lymphoma). No patients in either group had a treatment-emergent adverse event due to progressive multifocal leukoencephalopathy during the 7 months of the study. Treatment-emergent serious adverse events were reported in six (5%) of 130 patients in the CT-P10 group and three (2%) of 128 in the rituximab group (appendix p 16). Two patients in the CT-P10 group reported treatment-emergent serious adverse events related to study drug (one myocardial infarction and one constipation) and none were reported in the rituximab group.

By the cutoff date (Jan 4, 2018), two deaths had been reported in the CT-P10 group (one due to myocardial infarction and one with respiratory failure). Both deaths occurred after the completion of four cycles of induction therapy, and predisposing factors were present in both patients. The patient who died of myocardial infarction had a history of lipidosis and hypertension, with abnormal echocardiogram results with mild left axis deviation and suspected anteroseptal infarction (V1, V2) observed at the screening visit. The event was conservatively considered by the investigator to be possibly related to the study drug, although there was no convincing clinical or laboratory evidence to support this. The patient who experienced fatal respiratory failure, secondary to bronchiolitis obliterans organising pneumonia, had underlying risk factors of pulmonary fibrosis and lymphoma. This event was not considered related to the study drug.

Two patients in the CT-P10 group discontinued the study drug owing to study drug-related treatment-emergent adverse events: one owing to a serious myocardial infarction and one owing to non-serious

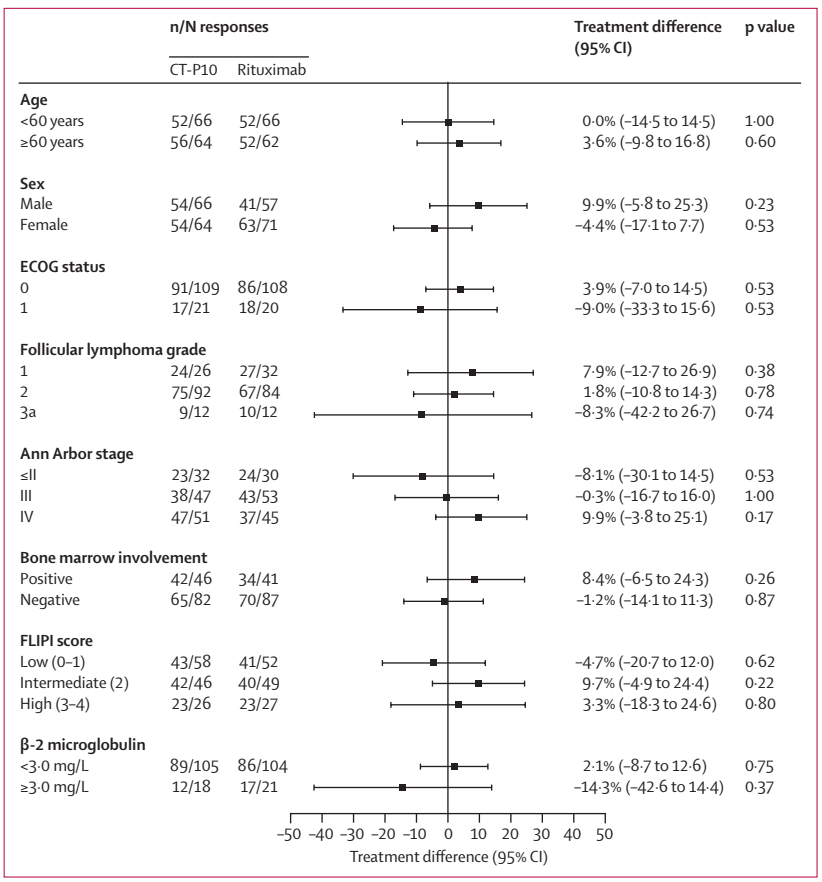

Figure 2: **Post-hoc subgroup analyses of the proportion of patients achieving an overall response**
Differences were calculated using percentages, not the rounded off values. 95% CIs and p values were estimated using the exact binomial method. ECOG=Eastern Cooperative Oncology Group. FLIPI=Follicular Lymphoma Prognostic Index.

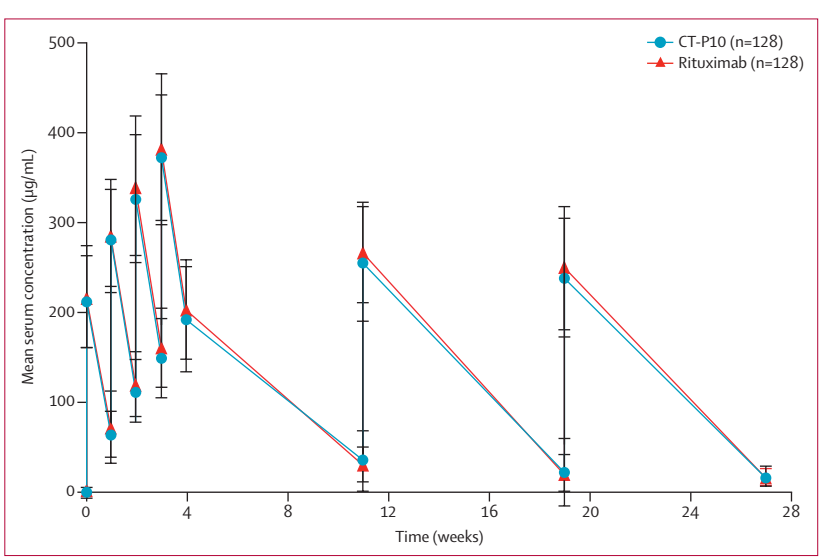

Figure 3: **Serum concentrations of CT-P10 and rituximab over time in the pharmacokinetic population**
Bars are SDs. Values below the LLOQ before dose for induction period cycle 1 (time 0) were set to zero. Concentrations below the LLOQ after study drug exposure were set to the LLOQ. Blood samples for pharmacokinetic assessment were collected a maximum of 14 times for each patient up to 7 months. LLOQ=lower limit of quantification.

	CT-P10 (n=130)	Rituximab (n=128)
Patients with ≥1 TEAE	92 (71%)	86 (67%)
Patients with ≥1 TEAE due to IRRs	40 (31%)	37 (29%)
Patients with ≥1 TEAE due to infection	35 (27%)	27 (21%)
TEAEs in ≥5% of patients in either group		
Diarrhoea	7 (5%)	6 (5%)
Fatigue	9 (7%)	12 (9%)
Headache	4 (3%)	6 (5%)
IRR	40 (31%)	37 (29%)
Nausea	6 (5%)	7 (5%)
Upper respiratory tract infection	16 (12%)	14 (11%)
Urinary tract infection	5 (4%)	6 (5%)
Worsening haematological events* by laboratory assessment		
Anaemia	13 (10%)	18 (14%)
Neutropenia	28 (22%)	28 (22%)
Thrombocytopenia	10 (8%)	9 (7%)

Data are number of patients (%). IRR=infusion-related reaction. TEAE=treatment-emergent adverse event. *Worsened Common Terminology Criteria for Adverse Events grade compared with baseline.

***Table 3*: Summary of TEAEs in the safety population**

	CT-P10 (n=130)			Rituximab (n=128)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Spontaneous abortion	0	1 (1%)	0	0	0	0
Increased alanine aminotransferase	2 (2%)	1 (1%)	0	2 (2%)	0	0
Acute kidney injury	0	0	0	0	0	1 (1%)
Ureteric calculus	0	1 (1%)	0	0	0	0
Constipation	2 (2%)	1 (1%)	0	4 (3%)	0	0
Fatigue	9 (7%)	0	0	11 (9%)	1 (1%)	0
Gastrointestinal surgery	0	1 (1%)	0	0	0	0
Genital prolapse	0	0	0	0	1 (1%)	0
Hypertriglyceridaemia	0	0	0	0	1 (1%)	0
Hyperuricaemia	2 (2%)	0	0	4 (3%)	0	1 (1%)
Hypotension	2 (2%)	1 (1%)	0	0	0	0
Infusion-related reaction	39 (30%)	1 (1%)	0	37 (29%)	0	0
Lens discolouration	0	0	0	0	1 (1%)	0
Myocardial infarction	0	0	0	0	0	0
Neutropenia	0	1 (1%)	0	2 (2%)	1 (1%)	0
Decreased neutrophil count	2 (2%)	2 (2%)	0	3 (2%)	0	0
Respiratory failure	0	0	0	0	0	0
Squamous cell carcinoma of the lung	0	1 (1%)	0	0	0	0
Syncope	0	0	0	0	1 (1%)	0
Upper respiratory tract infection	16 (12%)	0	0	14 (11%)	0	0
Decreased white blood cell count	1 (1%)	1 (1%)	0	3 (2%)	0	0

Data are number of patients (%). All grade 1–2 adverse events occurring in ≥10% of patients in either treatment group and all grade 3 and 4 events are reported.

***Table 4*: Summary of treatment-emergent adverse events by intensity in the safety population**

dermatitis. No patients in the rituximab group discontinued the study drug owing to treatment-emergent adverse events.

Most patients tested negative for ADAs up to month 7. Four patients (one in the CT-P10 group and three in the rituximab group) had at least one positive ADA result at their post-treatment visits before maintenance cycle 3. These patients displayed one or more of the following: low serum drug concentration, B-cell reappearance at post-treatment visits, inefficacy, or onset of infusion-related reaction. Among them, one patient (in the CT-P10 group) tested positive for neutralising antibodies. Median changes from baseline in IgM, IgG, and IgA concentrations were similar in both treatment groups (appendix p 17).

Discussion

In this study we show therapeutic equivalence, as assessed by the proportion of patients achieving an overall response, between CT-P10 and rituximab in patients with low-tumour-burden follicular lymphoma treated with monotherapy in both the ITT and per-protocol populations by central review. Pharmacokinetic profiles were similar in the CT-P10 and rituximab groups. Mean trough serum concentrations increased with weekly dosing and were maintained during the 8-weekly cycles in the maintenance period.

The adverse event profile of CT-P10 in this study was comparable to rituximab, with no new, unexpected safety findings. Adverse events of special interest, including infections and infusion-related reactions, were less common than in the registrational rituximab clinical studies, in which infections were reported in 30–55% of patients with non-Hodgkin lymphoma and infusion-related reactions in more than 50% of patients with non-Hodgkin lymphoma or chronic lymphocytic leukaemia.[17] The low incidence of ADAs reported in our study after rituximab treatment is similar to the incidence found in historical reports.[18–20] Among the four patients who were ADA positive, we noted low serum drug concentrations, B-cell reappearance at post-treatment visits, inefficacy, or onset of infusion-related reaction, or a combination thereof. However, given the low incidence of ADA positivity in our study, we could not draw any firm conclusions about the effect of ADAs on rituximab treatment for patients with low-tumour-burden follicular lymphoma.

Since low-tumour-burden follicular lymphoma has more uniform disease characteristics and less heterogeneity than other subtypes of non-Hodgkin lymphoma, and we used rituximab monotherapy in this trial, our study and study population can be regarded as a more sensitive model for assessing the biosimilarity of CT-P10 and rituximab than trials done in clinically heterogeneous subtypes of non-Hodgkin lymphoma that used rituximab in combination with chemotherapy.[13]

Standard treatment for low-tumour-burden follicular lymphoma varies from a watchful waiting approach to rituximab monotherapy with maintenance.[21,22] In view of the benefits of improved long-term survival and quality of life associated with maintenance therapy,[23] we designed

this study to provide maintenance therapy for a maximum of 12 cycles over 2 years. European and US guidelines recommend that single-agent rituximab can be used to treat patients with low-tumour-burden follicular lymphoma,[21,22] on the basis of clinical trial data that showed that single-agent rituximab is associated with high response rates and low toxicity in this population.[16,24,25] In a long-term survival analysis, rituximab induction therapy (four weekly doses [375 mg/m²]) was associated with a median progression-free survival of 23·5 months (95% CI 13·6–36·7) and a 7-year overall survival of 92%.[24] In a phase 3 randomised controlled trial,[16] treatment with rituximab monotherapy substantially delayed the need for chemotherapy or radiotherapy as compared with a watchful waiting approach, the current standard of care, in patients with asymptomatic advanced low-tumour-burden follicular lymphoma. Overall, 46% of patients in the watchful waiting group in that study did not need treatment at 3 years versus 78% who received single-agent rituximab induction therapy and 88% who received rituximab induction treatment followed by rituximab maintenance therapy. At 7 months, 88% of patients receiving rituximab maintenance therapy, with the same treatment regimen and schedule as the one in our study, achieved an overall response.[16] The proportion of patients who achieved an overall response in our study was comparable with that reported in other trials of rituximab[16,25,26] in low-tumour-burden follicular lymphoma, which showed a response in 71–77% of patients after rituximab induction treatment.

We based the modified response criteria for malignant lymphoma used in this study on the 1999 IWG response criteria,[15] with CT as the primary imaging technique. CT was chosen because PET imaging equipment was not readily available, or was not used as a routine diagnostic method, in many of the participating countries. The 1999 IWG criteria were the first universally accepted response criteria for non-Hodgkin lymphoma. They were updated in 2007 to provide clearer guidance for assessment of lymph node response and progression.[27] The updated criteria also incorporated extranodal lesions into the assessment and removed the unconfirmed complete response category.[27] Despite the clarity of the revisions, the 2007 IWG guidelines have been subject to variations in user interpretation.[28] More recently, the Lugano classification[28] was developed for categorisation of treatment response in patients with non-Hodgkin lymphoma. We developed the modified criteria for use in our study after thorough review of several classifications, including the 1999 IWG,[15] 2007 IWG,[27] and Lugano classifications,[28] to overcome the limitations of each individual set of criteria. Depending on the magnitude of lymph node regression, patients with unconfirmed complete response according to the 1999 IWG criteria[15] would be classed as either complete or partial responders by the 2007 IWG criteria.[27] Thus, changing the definitions for response categories could affect the proportion of patients with a complete response (complete response plus unconfirmed complete response), but would not affect the overall response (complete response plus unconfirmed complete response plus partial response), which was the primary endpoint in our study. We also considered other newly clarified efficacy parameters from the Lugano classification.[28] Additionally, to reduce variability in overall response assessment, our study used a masked, central independent review committee that followed the predefined criteria. Although PET imaging was not used in this study, it was used to assess response in another recent study comparing CT-P10 with rituximab (NCT02162771).[13]

One limitation of our study is that it was not powered to formally assess progression-free survival, overall survival, or safety, which restricts the extent to which these data can be interpreted. Although survival outcomes are the preferred endpoints in trials of novel anticancer biologics,[29] the proportion of patients who achieve an overall response is considered a more realistic endpoint in biosimilar cancer trials, because assessment of survival outcomes such as progression-free survival or overall survival requires thousands of patients to be treated over several years.[30] Since the goal of biosimilar trials is to show comparability between the biosimilar drug and its reference product, we selected the proportion of patients achieving an overall response as the primary efficacy endpoint of this trial, which is consistent with regulatory guidance for biosimilars.[31] A limitation of our analysis is the median follow-up period of 6·25 months, meaning that long-term efficacy and safety could not be assessed. In view of the importance of long-term parameters, we will evaluate overall response over the whole study period (27 months), progression-free survival, time to progression, overall survival, and long-term safety after study completion to further understand the effect of CT-P10 on survival and safety outcomes, which will be reported separately.

CT-P10 was the first rituximab biosimilar to receive marketing authorisation by the European Medicines Agency. Rituximab biosimilar availability is expected to reduce treatment costs and improve patient access in those countries where a rituximab biosimilar is made available. In one budget impact analysis,[7] the introduction of CT-P10 in the EU was predicted to save between €90 and €150 million over 1 year, depending on market uptake, which could allow up to 12 551 new patients to be treated with CT-P10.[7] Widespread adoption of a rituximab biosimilar could have a substantial effect on health-care budgets and might also have effects at a societal level.[7]

In conclusion, this multinational, randomised, phase 3 study provides further evidence to the published data for the clinical comparability of CT-P10 and rituximab. In patients with low-tumour-burden follicular lymphoma, CT-P10 monotherapy was equivalent to rituximab in terms of overall response, and similar to rituximab with respect to pharmacokinetics, pharmacodynamics, safety, and immunogenicity over 7 months of treatment. Thus, CT-P10

monotherapy is suggested as a new therapeutic option for patients with low-tumour-burden follicular lymphoma. Further data from this trial will be reported once available.

Contributors

MO, BC, CB, W-SK, SJL, SYL, YJB, and LWK conceived and designed the study and analysed and interpreted data. JMS, S-GC, HN, JS, GT, JSK, AL, JM, NI, WJ, ALM, OS, EZ, EYR, MT, and LP collected data. EZ analysed and interpreted data. All authors reviewed drafts of the manuscript and approved the final version.

Declaration of interests

MO has received research funding from Symbio, and personal fees from Celltrion, Celgene, AstraZeneca, Takeda, Mundipharma, and Meiji Seika Pharma. JS has received grants from Celltrion, Chugai-Roche, Eisai, Takeda, Celgene, Sumitomo Dainippon, Taiho Pharmaceutical, Pfizer, Symbio Pharmaceutical, Astellas, and Toyama Chemical; personal fees from Chugai-Roche, Eisai, Takeda, Celgene, Bristol-Myers Squibb, AbbVie, and Sumitomo Dainippon; and consultancy or advisory fees from Celgene, AbbVie, and Zenyaku Kogyo. WJ has received research funding from Celltrion and research and personal fees from Sandoz Novartis and Roche. MT has received grants from Roche and AbbVie; and personal fees from Roche, Celgene, Takeda, Gilead, Janssen, Bristol-Myers Squibb, MorphoSys, Incyte, and AbbVie. LP has received travel expenses from Celltrion. BC has received personal fees from Celltrion, Mundipharma, Celgene, and Novartis. SJL, SYL, and YJB are employees of Celltrion. LWK is a consultant for Celltrion Inc. and has received travel expenses and personal fees from Celltrion and Celltrion Healthcare. JMS, S-GC, HN, GT, JSK, AL, JM, NI, ALM, OS, EZ, EYR, CB, and W-SK declare no competing interests.

Data sharing

De-identified participant data from the study will be freely available to the public through ClinicalTrials.gov (NCT02162771) and the EU Clinical Trials Register (EudraCT number: 2014-005324-10) after the end of the study. The study protocol is available in the appendix (pp 18–118). Other additional documents related to the study (eg, statistical analysis plan, informed consent form) will not be available.

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