LEUKEMIA & LYMPHOMA
2019, VOL. 60, NO. 14, 3375–3385
https://doi.org/10.1080/10428194.2019.1633632

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ORIGINAL ARTICLE

Rituximab biosimilar RTXM83 versus reference rituximab in combination with CHOP as first-line treatment for diffuse large B-cell lymphoma: a randomized, double-blind study

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ABSTRACT

This multicenter, double-blind, randomized study compared the efficacy, pharmacokinetics (PKs)/pharmacodynamics (PDs), safety and immunogenicity profile of RTXM83 vs. reference rituximab (R-rituximab), both with CHOP, as first-line treatment of diffuse large B-cell lymphoma (DLBCL). A total of 272 patients <65 years of age, with good prognosis (136 per arm) were randomized (1:1) to receive six cycles of either RTXM83 or R-rituximab. The primary efficacy endpoint was achieved (overall response rate of 83.6% for RTXM83 and 82.9% for R-rituximab) with a difference 0.7% between arms (95%CI: [–8.77% to 10.17%]) fulfilling the predefined non-inferiority margin (–13%). Similar number of patients reported at least one adverse event (AE) (131 per arm) or one serious AE (47 with RTXM83 and 45 with R-rituximab). Anti-drug antibody development was comparable between the arms. PK/PD secondary endpoint results support similarity between the compounds. RTXM83 exhibits non-inferior efficacy and similar safety/immunogenicity to R-rituximab, being an accessible alternative for the treatment of patients with previously untreated DLBCL.

ARTICLE HISTORY
Received 26 March 2019
Revised 31 May 2019
Accepted 7 June 2019

KEYWORDS
Rituximab; RTXM83; biosimilar drug; diffuse large B-cell lymphoma; clinical trial

Introduction

Rituximab is a chimeric anti-CD20 monoclonal antibody approved for the treatment of several types of non-Hodgkin lymphoma (NHL) including diffuse large B-cell lymphoma (DLBCL), where it is considered a standard of care for first-line treatment [1,2]. Rituximab exhibits a clear rate of response in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) in DLBCL [3,4] that is sustained over time with 74.3% survival at 6 years and with well-known adverse events (AEs) [5]. Due to the large benefits that have been demonstrated, rituximab was identified as an essential drug and was included in the 2015 WHO Model List of essential medicines for cancer [6].

CHOP regimen chemotherapy is comprised of old, off-patent drugs, but rituximab is a costly treatment especially in under-resourced parts of the world [6]. The arrival of the rituximab biosimilars is offering more affordable alternatives and, in some countries, increased access for patients to product classes that were previously unavailable [7]. Biosimilars are biological drugs similar to the reference product in terms of analytical and functional structure, pharmacokinetic (PK) and clinical behavior. Approval of biosimilars by the relevant regulatory agencies worldwide, requires a

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Supplemental data for this article can be accessed https://doi.org/10.1080/10428194.2019.1633632.

stepwise comparison, which begins with an exhaustive characterization and a comprehensive comparability study of the critical quality attributes, strongly related to the functionality and safety of the biosimilar. This is followed by a confirmatory clinical trial as the last step of the comparability exercise, which includes the comparative assessment in an adequately sensitive population of the PK, pharmacodynamic (PD) and efficacy similarity in the absence of meaningful differences in safety and immunogenicity [8,9].

RTXM83 is a proposed biosimilar developed by mAbxience Research S.L. (Madrid, Spain) to the reference product rituximab (MabThera®/Rituxan®), that showed similarity in psychochemical, structural properties, and biological functions in *in vitro* studies [10,11], further complemented by an *in vivo* PK and PD study in cynomolgus monkeys, where RTXM83 was found to be comparable to reference rituximab (R-rituximab) in terms of PK and PD response (CD20+ cell depletion) and toxicological profile (data on file).

According to guidelines [8,9,12], similarity should be confirmed at the clinical level by a head-to-head comparison in a representative subject population, sensitive enough to detect any product-related differences, if present. A study of PK similarity between RTXM83 and R-rituximab in healthy volunteers was discarded for being unethical for safety reasons [12] and, a unique study in patients was designed instead, to assess PK and PD equivalence and confirm efficacy, immunogenicity, and safety similarity. To this end, a homogeneous population of DLBCL patients was chosen, among the approved indications for rituximab, as a sensitive indication that exhibits good clinical responses to rituximab [2,13]. Consequently, a prospective, multicenter, double-blind, randomized clinical study was conducted to confirm comparable clinical performance (efficacy, PK, PD, safety, and immunogenicity) of RTXM83 vs. R-rituximab, both in combination with CHOP chemotherapy as first-line treatment in DLBCL patients. The RTXM83-AC-01-11 study has been completed and the main results are described here, while a detailed description of the PK/PD and immunogenicity results have been reported elsewhere [14].

Materials and methods

Eligibility criteria

Newly diagnosed patients, aged ≥18 and ≤65 years, with a confirmed pathologic diagnosis of DLBCL with untreated CD20+, at stage I (only with bulky disease) or stages II to IV disease according to the Cotswolds modification of the Ann Arbor classification [15], and with ≤1 risk factor according to the age-adjusted International Prognostic Index (IPI) were enrolled. Patients had at least one objectively measurable disease parameter and an ECOG performance status ≤2. Exclusion criteria were the same as those described in the MInT study [5].

The study was conducted at 58 sites in 12 countries (Supplementary Table S1) after approval by the Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) of each participating site and the relevant regulatory authorities, and according to the provisions of the Declaration of Helsinki and the ICH Good Clinical Practice guidelines. All patients signed an IRB/IEC approved informed consent form before any study-specific procedures were performed. Study oversight was provided by an independent data monitoring committee.

Randomization and masking

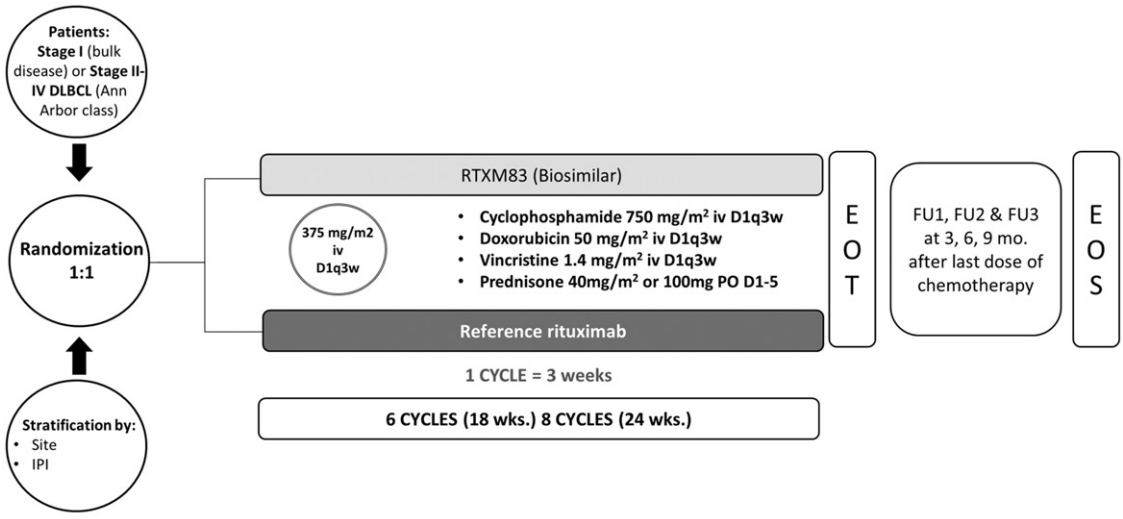
Patients were randomized (1:1) to receive either RTXM83 or R-rituximab, both combined with CHOP, through an interactive web-response system. Randomization was done using a stochastic minimization algorithm and was stratified by study center and age-adjusted IPI scores (0 versus 1) to ensure equal distribution of potentially influential factors in the two study arms. Neither patients nor investigators and study teams from the sponsor and clinical research organization were informed of the treatment allocation to ensure blinding. The blind was broken after all randomized patients in the evaluable population had completed six cycles of treatment or discontinued treatment before cycle 6. Patients were followed up for 9 months after last study dose (Figure 1).

Treatment

Rituximab biosimilar (RTXM83; mAbxience research S.L., Madrid, Spain) and R-rituximab (MabThera®; Roche, Basel, Switzerland) were both administered intravenously at a dose of 375 mg/m^2 on day 1 of each 3-week cycle with CHOP chemotherapy for six cycles. Two additional cycles of treatment were permitted at the Investigator's discretion. Pre-medication with an anti-pyretic or an antihistamine drug was administered before each study drug infusion.

Study assessments

Physical examination, hematology, and serum chemistry analysis were done at baseline and on day 1 of



D1q3w: on Day 1 every 3 weeks; D1-5: From Day 1 to Day 5; PO: per oral; iv: intravenous; FU: Follow-up; mo: months; wks: weeks; EOT: end of treatment; EOS: end of study

Figure 1. Study design.

each cycle until end of treatment. Bone marrow biopsy/aspirate was performed at baseline, and if positive, it was repeated after cycle 6 if clinically indicated.

Radiological tumor assessments were done at baseline (within 30 days before day 1 cycle 1), after cycle 6, and during follow-up period whenever disease progression was suspected by positron-emission tomography (PET) scan, or by computed tomography (CT) scan and/or magnetic resonance imaging if PET scan was not feasible. Regardless of the method selected, the same method of assessment and the same technique were used during the study in each patient.

Tumor response was classified according to the International Working Group criteria [16].

Safety assessments (12-lead ECGs, physical examinations, laboratory tests, and vital signs) were obtained at baseline and at designated intervals throughout the study. AEs were collected during the study and up to one month after the end of study treatment. AEs were graded using the National Cancer Institute common toxicity criteria v4.0 and summarized using the Medical Dictionary for Regulatory Activities v16.0 terminology.

Details on sampling and bioanalytical methods for PK measurement, PD analysis (serum levels of CD20+/CD19+ lymphocyte B-cells) and immunogenicity assessment (level of anti-drug antibodies (ADAs)) were reported elsewhere [14].

Study endpoints

The primary efficacy endpoint was to compare the overall response rate (ORR, proportion of patients with complete remission (CR) or partial response (PR)) in each treatment arm after study treatment (cycle 6 or within 30 days after last administration of study treatment).

PK, PD, event-free survival (EFS), safety, and immunogenicity profiles were assessed as secondary study endpoints during treatment and during follow-up period for late safety, PD, immunogenicity, and EFS. EFS was defined as the time (months) from randomization to any of the following events: progressive disease, no achievement of CR, PR associated with treatment more than that per protocol, stable disease, relapse after achievement of CR, or death from any cause, whichever comes first. The safety of RTXM83 was compared with R-rituximab by the incidence of treatment-emergent AEs (TEAEs), serious AEs (SAEs), and AEs of interest (i.e. the infusion-related reactions (IRRs)) in each treatment arm.

Statistical considerations

After adjusting for a dropout rate of $\leq$10%, 250 patients were planned to be enrolled to obtain 224 evaluable patients (112 per treatment arm). Based on the historical studies for rituximab (MInt trial [4,5]), an ORR of 86% after up to six cycles of treatment with a non-inferiority margin of 13% was assumed, and with $\geq$80% power to detect treatment differences.

The ORR, with the corresponding 95%CI, was calculated for each treatment arm and was compared using Fisher's exact test at a one-sided 0.025 type I error rate. A Cochran–Mantel–Haenszel test stratified by the

randomization strata was used as a sensitivity analysis (at a two-sided 0.05 Type I error rate). Non-inferiority was concluded if the lower bound of the 95%CI was above the −13% margin. Descriptive statistics were used for the other study variables, and 95%CIs were calculated when appropriate.

The efficacy was assessed in the intention-to-treat (ITT) and per-protocol populations. Herein, the ITT results are presented as it represents a more conservative approach and comprised all treated patients that were evaluable for response, i.e. with an available evaluation of ORR at cycle 6 or within 30 days after last dose of study treatment; or study drug discontinuation due to progressive disease or death before cycle 6. Safety was assessed in all patients receiving at least one dose of the study treatment.

Results

Patients

Between July 2013 and December 2016, 400 patients were screened and 272 patients (a core of 256 patients plus a cohort extension of 16 patients from the Islamic Republic of Iran that were included as per local regulatory requirements) were randomized in the study (136 patients to each treatment arm) and received at least one dose of the study treatment (Figure 2). The extension cohort of Iran was only considered for safety analysis. Baseline demographic and clinical characteristics were comparable between treatment arms (Table 1).

Treatment exposure

Most of the patients (85%) completed six cycles of treatment, whereas study treatment was discontinued before cycle 6 in 16 (12%) and 20 (15%) patients in the RTXM83 arm and R-rituximab arm, respectively. See Figure 2 for reasons for treatment discontinuation. The proportion of patients receiving a maximum of six cycles (57% patients in each arm) or eight cycles (29% patients in each arm) was similar in both treatment arms (Supplementary Table S2).

The exposure to study treatment in both arms was comparable. Study dose interruption was necessary in 11 (8%) and 20 (15%) patients in the RTXM83 and R-rituximab arms, respectively. Principal causes of dose interruption were skin rash or other symptoms of IRR.

Median follow-up in the study was 12.5 months for patients in each treatment arm.

Efficacy

Tumor assessments were done by CT in 159 patients and by PET in 97 patients. From the core of 256 patients, 239 patients were included in the ITT population (122 patients in the RTXM83 arm and 117 patients in the R-rituximab arm). After six cycles of treatment, the ORR showed a difference of 0.7% in favor of RTXM83 (83.6% vs. 82.9% with R-rituximab) that was not statistically significant (Fisher's exact test $p = .5109$). The lower bound of the 95%CI of this difference (–8.77%) was above the non-inferiority margin of −13% set for the study (Figure 3). Best overall response achieved in both treatment groups had a similar distribution for CR, PR, stable disease, and progressive disease.

Median EFS reached in the RTXM83 and R-rituximab arms was similar (median EFS: 12.5 vs. 8.6 months, respectively; $p=.4613$). The estimated hazard ratio (HR) was 0.87 with 95%CI [0.60; 1.26] (Figure 4).

PK

The ratios (90%CI) of geometric least-square means (RXTM83 to R-rituximab) for AUC and C_{max} at cycle 1 (0.992 [0.936–1.05] and 0.996 [0.939–1.05], respectively) and at steady state (1.03 [0.985–1.07] and 1.04 [0.995–1.09], respectively) were within the predefined bioequivalence interval of 0.80–1.25 [14].

PD

During the study, B-cell (CD20+ and CD19+) count fell to barely detectable levels shortly after administration of rituximab and in the same magnitude in both treatment arms, and then gradually recovered to baseline after 6–9 months of the last dose. Therefore, the depletion, length of suppression, or time to recovery of B cells was similar in both treatment arms [14].

Safety

The proportion of patients with at least one TEAE or one SAE was comparable, and a similar proportion of patients discontinued treatment due to an AE in each treatment arm (Table 2).

The nature and frequency of the events reported were in line with the safety profile described for rituximab in combination with CHOP chemotherapy, with hematological toxicities, infections, and IRRs among the most common AEs (Supplementary Table S3).

Almost all AEs were considered by the investigator to be associated to the study treatment and occurred

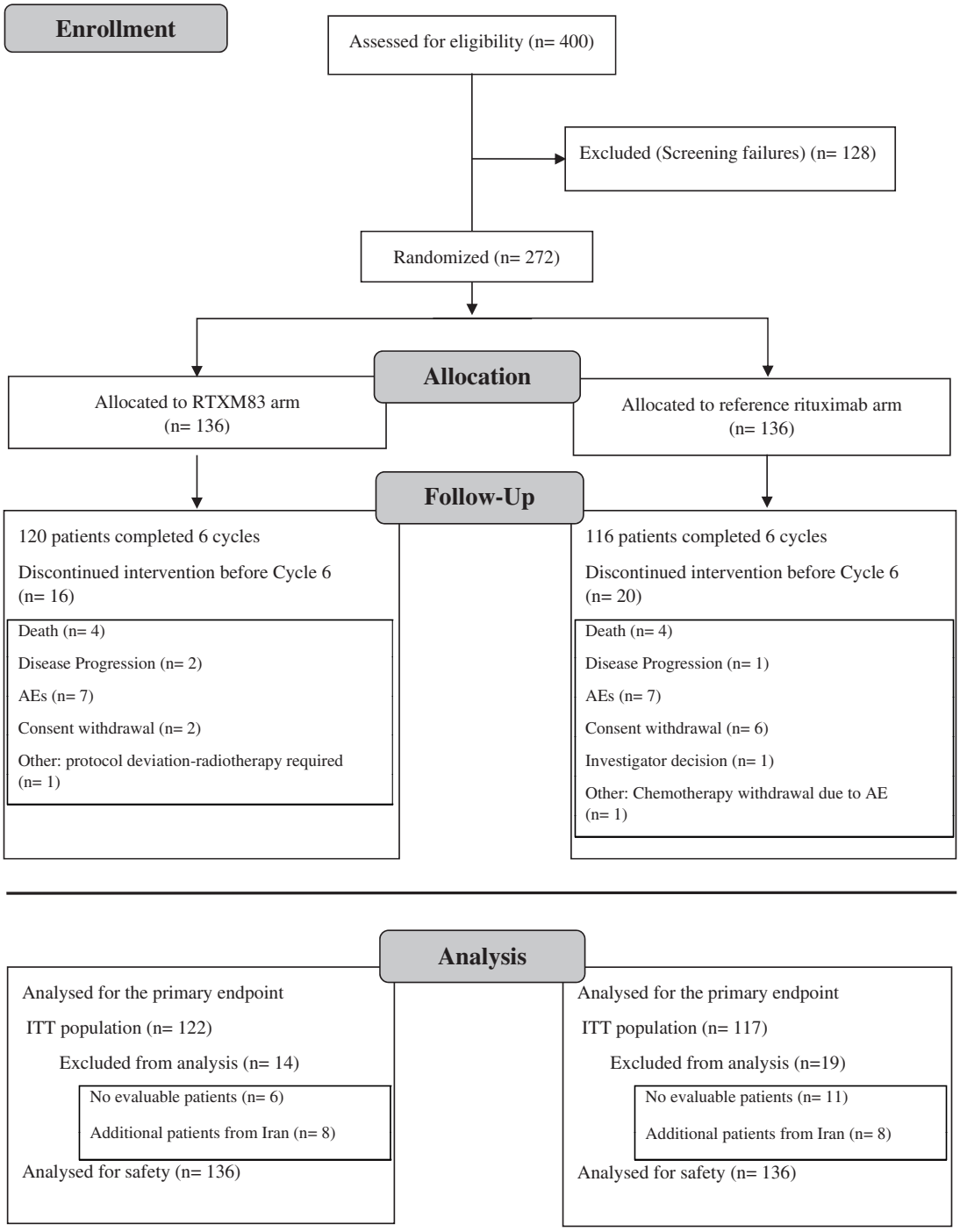


Figure 2. Patient disposition.

in similar proportion and comparable severity in both treatment arms. Most were mild or moderate in severity in both treatment arms and, were rated as grades 3 and 4 in 130 (48%) patients with hematological disorders (40%) and infections (10%) as the most commonly reported (Table 2).

IRRs associated with rituximab occurred in 25 (18%) and 30 (22%) patients in RTXM83 and R-rituximab, respectively, which were generally of mild intensity with grades 3 and 4 reactions occurring only in four (3%) patients in each treatment arm. Most of them occurred at cycle 1 and led to infusion interruption. Discontinuation due to IRR happened in one patient (R-rituximab arm).

Incidence and pattern of SAEs reported in each arm were comparable. Most common treatment-related

Table 1. Patient baseline characteristics (safety population).

	RTXM83-CHOP $N = 136$	R-CHOP $N = 136$	All $N = 272$
Age (years), median (Q1; Q3)	49.0 (40.0;57.0)	51.0 (41.0;59.0)	51.0 (40.0;58.0)
Gender, *n* (%)			
Female	58 (43%)	59 (43%)	117 (43%)
Male	78 (57%)	77 (57%)	155 (57%)
Race, *n* (%)			
White	75 (55%)	78 (57%)	153 (56%)
Asian	50 (37%)	53 (39%)	103 (38%)
Black	6 (4%)	3 (2%)	9 (3%)
Other	5 (4%)	2 (2%)	7 (3%)
Initial disease stage, *n* (%)			
I (with bulky)	19 (14%)	19 (14%)	38 (14%)
II	64 (47%)	53 (39%)	117 (43%)
III	30 (22%)	32 (24%)	62 (23%)
IV	23 (17%)	32 (24%)	55 (20%)
Presence of extra nodal lesions, *n* (%)			
No	88 (65%)	81 (60%)	169 (62%)
Yes	48 (35%)	55 (40%)	103 (38%)
ECOG PS, *n* (%)			
0	84 (62%)	84 (62%)	168 (62%)
1	52 (38%)	50 (37%)	102 (38%)
Missing data	0	2 (1%)	2 (<1%)
High lactate dehydrogenase, *n* (%)			
No	103 (76%)	109 (80%)	212 (78%)
Yes	32 (24%)	27 (20%)	59 (22%)
Missing data	1 (<1%)	0	1 (<1%)
Age-adjusted IPI, *n* (%)			
0	48 (35%)	50 (37%)	98 (36%)
1	85 (63%)	79 (58%)	164 (60%)
2[a]	3 (2%)	7 (5%)	10 (4%)

[a]Patients with IPI 2 were not considered in the efficacy analysis.
Q1: first quartile; Q3: third quartile; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; ECOG: Eastern Cooperative Oncology Group; PS: performance status; IPI: International Prognostic Index.

SAEs included febrile neutropenia, neutropenia, anemia, and leukopenia. There were 20 deaths reported during the study, eight (6%) in the RTXM83 arm and 12 (9%) in the R-rituximab arm. Six of eight deaths in the RTXM83 arm (one respiratory failure; three septic-related episodes; one pulmonary embolism; and one of unknown origin) and all 12 deaths in the R-rituximab arm (six septic-related episodes; one bacterial meningitis; one pulmonary embolism; one pneumonia; one acute respiratory failure; and two of unknown origin) were reported to be caused by AEs suspected by the investigator to be related to study drug. All these events were considered expected for rituximab and important underlying risk factors were present in most cases.

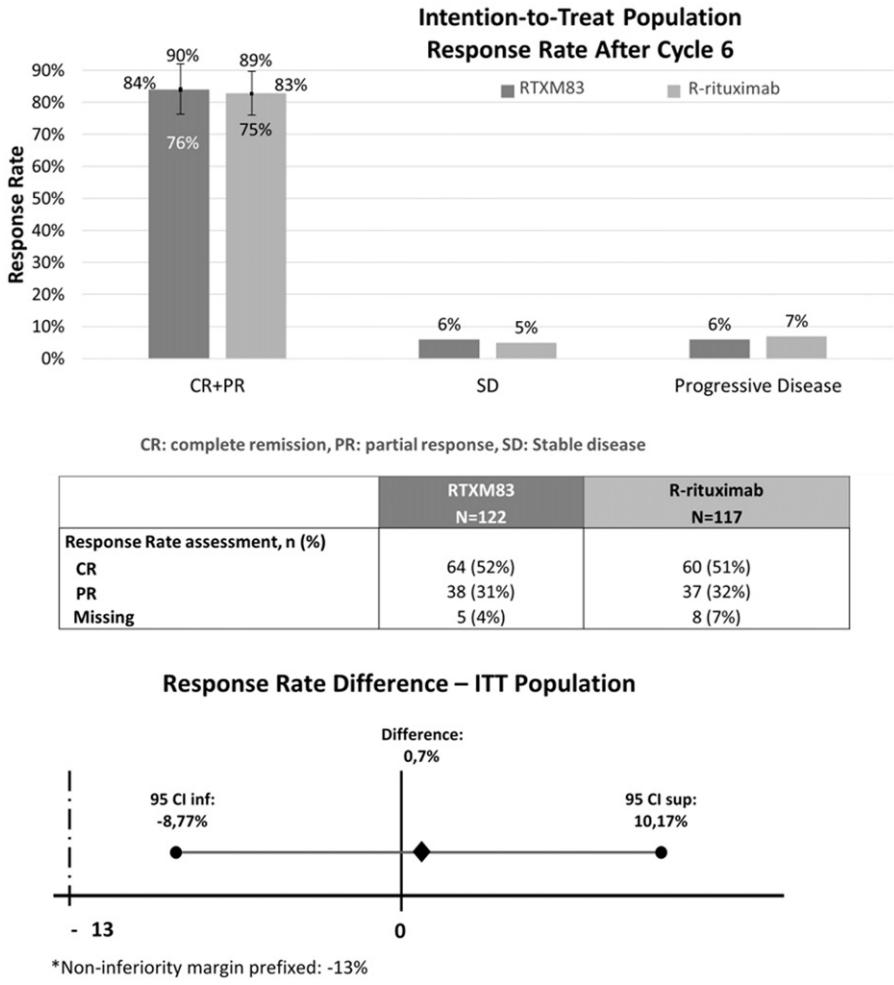
Immunogenicity

Immunogenicity results show a low prevalence in the ADA incidence for both treatment arms. The proportion of patients who developed ADA *de novo* (seroconversion) following rituximab administration was similar (2.3% patients in RTXM83 arm and 3.2% patients in the R-rituximab arm). In these ADA-positive subjects, the efficacy and safety behavior were within those expected for the reference product, and the serum concentrations levels were in line with median levels observed in the rest of the patients [14].

Discussion

This comparative unique study met its primary endpoint by confirming the non-inferior efficacy (in terms of ORR) of RTXM83, proposed rituximab biosimilar, to R-rituximab in the first-line treatment of DLBCL with the lower bound of the CI of the treatment effect difference (–8.77%) not exceeding –13%. Additionally, the secondary objectives of PK/PD equivalence, efficacy (in terms of EFS), safety, and immunogenicity support the similarity between RTXM83 and the R-rituximab.

Besides some unsuccessful attempts from other biosimilar drugs as part of their clinical development [17], to our knowledge, this is the first randomized, double-blind study with a biosimilar monoclonal antibody in DLBCL. To date in Europe, two biosimilar rituximab products have been approved, CT-P10 (Truxima) [17] (also approved by FDA) and GP2013 (Rixathon, Riximyo) [18], both compounds demonstrated their comparable efficacy in patients with newly diagnosed



	RTXM83 N=122	R-rituximab N=117
Response Rate assessment, n (%)		
CR	64 (52%)	60 (51%)
PR	38 (31%)	37 (32%)
Missing	5 (4%)	8 (7%)

Figure 3. Response rate (ITT population).

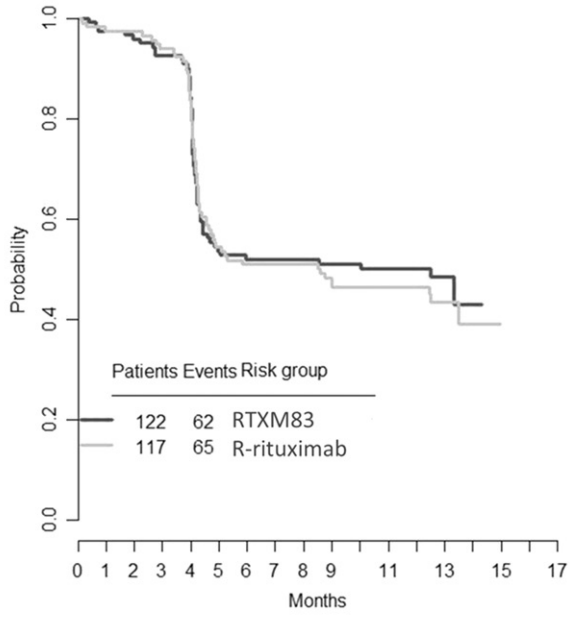
advanced-stage follicular lymphoma. Unlike previous studies, we aimed to select a homogenous population of well-fitted, quite young (<65 years) DLBCL patients with IPI 0–1 and ECOG performance ≤2, and it was a huge recruitment challenge. These selected DLBCL patients represent a feasible population to assess comparability in terms of efficacy because the addition of rituximab to CHOP in this setting shows a large treatment effect [3–5], making it a sensitive condition to detect potential differences.

The primary efficacy endpoint, as per EMA and FDA guidance [9,12], is the proportion of patients who achieved an ORR. These regulatory recommendations consider ORR, a sensitive indicator of activity, sufficiently sensitive and, an appropriate primary endpoint for a biosimilar antibody such as rituximab due to its treatment effect. Although care should be taken when data from different trials are compared, the overall response reported in our study after six cycles of treatment (83.6% with RTXM83 and 82.9% with R-rituximab) is within the data reported in the literature for the R-rituximab (76–88%) [3–5,19,20].

EFS results, included as a secondary endpoint, showed no statistically significant difference in the median EFS achieved in both treatment groups (p=.4613). However, these results should be placed in context and viewed with caution provided that the study was not designed to use it as a primary efficacy endpoint. In addition, some distinctive factors should be considered: first, EFS definition used was that of the MInT study which included the 'no achievement of CR' as 'event', thus, increasing the total number of events and; second, and as expected in a biosimilar development, a short follow-up period (9 months) was considered in the present study. Nevertheless, EFS achieved in both treatment arms was comparable and HR was nearly 1 which indicates that the rate of events occurring in the biosimilar arm and the R-rituximab were nearly the same.

The results of the PK assessment demonstrated a similar PK profile of RTXM83 and R-rituximab. The ratio of geometric means of AUC and C_{max} at cycle 1 and at steady state were within the predefined bioequivalence interval (0.80–1.25) demonstrating bioequivalence of

RTXM83 to R-rituximab. Moreover, consistent with the PK/PD relationship for rituximab described by Golay et al. [21], the pattern of CD20+ and CD19+ B-cell depletion and recovery was comparable between arms, confirming the PD similarity between RTXM83 and R-rituximab [14].



Stratified Logrank[a]: Two-sided p-value=0.4570
Unstratified Logrank: Two-sided p-value=0.6805

Stratified Cox model[a]: Two-sided p-value=0.4613
HR (RTXM83 vs R-rituximab): 0.87; 95% CI [0.60; 1.26]

Unstratified Cox model: Two-sided p-value=0.6830
HR (RTXM83 vs R-rituximab): 0.93; 95% CI [0.66; 1.32]

Figure 4. Event-free survival (EFS) – (ITT population).

The overall safety profile of RTXM83 observed in the study was consistent with the known safety profile of rituximab plus CHOP in DLBCL [22], with hematological disorders, infections, and IRRs as the most common reactions. Both treatments showed a comparable safety profile, with no differences in terms of the nature, frequency and severity of AEs and no new safety signals were identified in the study. Special consideration merits the incidence of febrile neutropenia, which is among the 'very common' adverse reactions reported with rituximab and is also frequently seen in patients receiving CHOP chemotherapy, with a reported incidence between 18 and 19% in patients receiving R-CHOP regimens [23,24]. Generally, the most serious outcomes related to febrile neutropenia are infections and mortality [25] but, even though in the study there was a higher number of grades 3 and 4 related febrile neutropenia episodes and grades 3 and 4 related infections in the biosimilar arm, it was not correlated with any difference in the occurrence of sepsis (septic shock/neutropenic sepsis) nor in the mortality rate attributable to infections in each treatment arm. The mortality rate should be considered in the context of low-income countries where the study was performed.

The IRRs are the most frequently observed TEAEs in patients receiving rituximab. The overall incidence of IRRs in clinical trials was 23% [22], and includes a variety of reactions such as pulmonary events, fever, chills, rigors, hypotension, urticaria, angioedema, and other symptoms [3]. In our study, we included these

Table 2. Summary of TEAEs in the study (safety population).

	RTXM83 arm ($n = 136$)		Rituximab reference arm ($n = 136$)	
Total number of TEAEs	996		1008	
Patients with at least one TEAE (any causality)	131 (96%)		131 (96%)	
TEAEs grade ≥3	75 (55%)		80 (59%)	
TEAEs related to treatment	125 (92%)		119 (88%)	
Serious TEAEs	47 (35%)		45 (33%)	
TEAE leading to treatment discontinuation	6 (4%)		7 (5%)	
Common treatment-related[a] TEAEs	Grades 1 and 2	Grades 3 and 4	Grades 1 and 2	Grades 3 and 4
Neutropenia	12 (9%)	37 (27%)	14 (10%)	40 (29%)
Anemia	23 (17%)	15 (11%)	18 (13%)	14 (10%)
Leukopenia	9 (7%)	22 (16%)	13 (10%)	21 (15%)
Febrile neutropenia	0	20 (15%)	1 (<1%)	9 (7%)
Thrombocytopenia	1 (<1%)	6 (4%)	2 (1%)	7 (5%)
Nausea	28 (21%)	0	30 (22%)	4 (3%)
Alopecia	34 (25%)	0	25 (18%)	1 (<1%)
Any infection	25 (18%)	15 (11%)	31 (23%)	12 (9%)
Any respiratory disorder	20 (15%)	7 (5%)	13 (10%)	4 (3%)
Any nervous system disorder	46 (34%)	4 (3%)	39 (29%)	3 (2%)
Any general and admin. site disorder	45 (33%)	6 (4%)	43 (32%)	7 (5%)
Any metabolism and nutrition disorder	30 (22%)	6 (4%)	22 (16%)	8 (6%)
Any infusion-related TEAEs	23 (17%)	4 (3%)	27 (20%)	4 (3%)

TEAE: treatment emergent adverse events.
Data are *n* (%) patients. Adverse events are shown for grades 1 and 2 in 20% or more of patients or grades 3 and 4 in 5% or more.
[a]Related to any study treatments: rituximab (RTXM83 or reference rituximab) or CHOP or both.

symptoms in the definition of IRRs, observing a similar incidence, generally reported at first infusion, in both study treatment arms. Severe IRRs were rare (3%) and no fatalities due to this event were noted. Considering that all patients had received pre-medication treatment, these results are low and comparable to those declared in the SmPC (7% of grade 3 or 4 reactions) [22] or reported in the literature with R-rituximab [26].

Rituximab is considered as a low risk, but potentially immunogenic, antibody since it does not exhibit cross-reactions with endogenous antibodies or autoimmunity induction [27]. The rates of immunogenicity observed in our study [14], using more sensitive techniques, were also low (<4%) and similar in both treatment arms and, raised no concern around the efficacy or safety as compared to the R-rituximab safety profile [22].

This study was designed as the last step of the comparability exercise in the biosimilar development program of RTXM83 under presumption that a molecule shown to be structurally and functionally highly similar to the reference product is anticipated to behave like the reference product in the clinical setting. One novel approach is the confirmation of PK/PD equivalence together with the clinical similarity in the same population of patients. One of the reasons behind this approach is that no PK interference from the chemotherapy regimen used for DLBCL (CHOP) was expected [28]. But, more importantly, a single study allows one to obtain the PK, PD, efficacy, safety, and immunogenicity values of rituximab from each study patient to analyze possible relationships between all variables in every patient, and to detect any minimal clinically significant difference in the same population, instead of performing two studies with different and non-comparable populations. Actually, our results demonstrate that the similar PK (AUC and C_{max} after one single dose or at steady state) and PD (B-cell kinetics) behavior [14] of RTXM83 and R-rituximab is translated into a similar efficacy (in terms of ORR), safety and immunogenicity behavior in DLBCL patients.

The main limitation of this study is the use of short-term efficacy endpoints as the final step in assessing biosimilarity which is consistent with the planned development of all biosimilars.

Currently, several hemato-oncological societies [29–31] recognize that biosimilars can positively impact on the financial sustainability of healthcare systems. Specifically, for a rituximab biosimilar, the most evident benefit will be placed in the potential savings in the treatment of rheumatoid arthritis and cancer [32]. RTXM83, which has demonstrated to have biologic activity comparable to R-rituximab, is expected to enhance treatment options, improve patient access, and potentially stimulate price competition with the reference medicine, particularly in low-income countries.

Acknowledgements

The authors thank all study staff and patients, and the following study investigators for their participation in this study: Syafrizal Syafei; N. Bhatt; S. Bhattacharyya; A. Mukhopadhyay; A. Salvatierra; V. Radhakrishnan; D. Bhurani; S. Jasuja; R. D. Kowalyszyn; S. Shusterschitz da Silva Araújo; S. Syafei; J. Caffaro/G. De Stefano; JJ García; E. Cilião Munhoz; C. Bermudez; G. Gin Gin; R. Raman; E. M. Villegas; F. G. P. Martinez-Lapus; G. R. Molina Barrios; B. J. Tiangco; P. A. Viktorovich; M. G. Moiseevich; G. I. Avila; M. Muñoz; M. M. Saslavsky; G. Z. Beguelin; L. Fogliatto; M. A. Salvino de Araujo; J. Pereira; J. S. Rodrigues de Oliveira; R. Luiz da Silva; E.R de Mattos; P. Xavier Santi; M. Debiasi; N. Lazaretti; K. Galvez; J. D. Rosales; C. Teng Keat; N. A. Uy; Melnichenko V. Y.; Burdaeva O. N.; Osmanov D. S.; F. Bassa; L. Jones; M. L. Furque; E. Bullorsky; V. B. Heller; G. Jarchum; A. C. Basso; E. L. Cigno; R. Schaffel; C. Boquimpani; F. Meton; C. E. Miguel; B Pinto Simões; R. Sampaio Tavares; F. A. Franke; J. Schmidt Filho; A. Dantas da Cunha Júnior; AVS Suresh Attili; K. S. Kirushnakumar; P. Chakrabarti; V. Arumugan; H. Fadjari; Alekseev S. M.; Ilyin N. V.; Udovitsa D. P.; Vladimirov V. I.; Kaplanov K. D.; Lysenko I. B.; Ponomarev R S.; Lifirenko I. D.; W. Szpak. The authors also want to thank the members of the independent data monitoring committee (S. R. Loggetto; D. Leão; M. A. Ozcan and S. Michiels) and A. Flórez (mAbxience); the local supporting companies (Laboratorio Elea S.A.C.I.F. y A. [Argentina], LIBBS Pharmaceuticals Ltda. [Brazil], Laboratorios ETICOS SA [Paraguay], Tecnoquímicas S.A. [Colombia], PiSA Farmacéutica S.A. de C.V. [Mexico], Innogene Kalbiotech Pte. Ltd. [Indonesia, Malaysia and Phillippines], Key Oncologics (Pty) Ltd [South Africa], Actoverco [Iran] and LLC Nanolek [Russian federation] for their support; and A. Del Campo García (mAbxience) and Dr D. Stamatiadis (MAIA consulting) for writing assistance.

Disclosure statement

L. Perez Díaz, A. Paravisini are employees of mAbxience Research SL. The rest of authors do not have any relationships to disclose.

Funding

This work was supported by mAbxience Research S.L.

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