30 January 2020
EMA/CHMP/133144/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

MabThera

International non-proprietary name: rituximab

Procedure No. EMEA/H/C/000165/II/0168

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	adverse drug reaction
AE	adverse event
ALT	alanine transferase
AST	aspartate transferase
AUC	area under the concentration-time curve
B-AL	Burkitt Leukemia
BL	Burkitt Lymphoma
BLL	Burkitt-like Lymphoma
B-NHL	B-cell Non-Hodgkin's Lymphoma
BSA	body surface area
Cmax	maximum concentration
Ctrough	trough concentration (pre-dose concentration)
CD20	cluster of differentiation 20
CI	confidence interval
CNS	central nervous system
COG	Children's Oncology Group
COP	cyclophosphamide, Oncovin (vincristine), prednisone
COPADM	cyclophosphamide, Oncovin (vincristine), prednisolone, Adriamycin (doxorubicin), methotrexate
CR	complete response
CSF	cerebrospinal fluid
CSR	Clinical Study Report
CYM	cytarabine (Aracytine, Ara-C), methotrexate
CYVE	cytarabine (Aracytine, Ara-C), VePesid (VP-16)
DLBCL	diffuse large B-cell lymphoma
ECHO	echocardiogram
EFS	event-free survival
GR	Gustave Roussy
HDMTX	high-dose methotrexate
IA	interim analysis
ICU	intensive care unit
IDMC	independent data monitoring committee
Ig	immunoglobulin
IRR	infusion-related reaction
IT	intrathecal
ITT	intention to treat
KBE	Key Binding Element
LDH	lactate dehydrogenase
LMB	Lymphome Malin B
LVEF	left ventricular ejection fraction
LVSF	left ventricular shortening fraction
MAH	Marketing Authorization Holder
NHL	Non-Hodgkin Lymphoma
OS	overall survival
PIP	Paediatric Investigation Plan
PK	pharmacokinetics
PMLBL	primary mediastinal large B-cell lymphoma
RBC	red blood cell
SAE	serious adverse event
SC	subcutaneous
SmPC	Summary of Product Characteristics
SOC	system organ class
ULN	upper limit of normal

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 5 June 2019 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	IIIB

Extension of indication to include treatment of paediatric patients (aged ≥6 months to <18 years old) with previously untreated advanced stage diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukaemia (mature B-cell acute leukaemia) (BAL) or Burkitt-like lymphoma (BLL) in combination with chemotherapy for MabThera; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 21 of the RMP has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0064/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0064/2019 was completed.

The PDCO issued an opinion on compliance for the PIP P/0064/2019.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH submitted a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Sinan B. Sarac Co-Rapporteur: Paula Boudewina van Hennik

Timetable	Actual dates
Submission date	5 June 2019
Start of procedure	22 June 2019
CHMP Rapporteur's preliminary assessment report circulated on	16 August 2019
PRAC Rapporteur's preliminary assessment report circulated on	22 August 2019
PRAC RMP advice and assessment overview adopted by PRAC on	5 September 2019
CHMP Rapporteur's updated assessment report circulated on	12 September 2019
Request for supplementary information and extension of timetable adopted by the CHMP on	19 September 2019
MAH's responses submitted to the CHMP on	18 December 2019
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	9 January 2020
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	15 January 2020
PRAC RMP advice and assessment overview adopted by PRAC on	16 January 2020
CHMP opinion adopted on	30 January 2020
The CHMP adopted a report on similarity of MabThera with Kymriah, Yescarta, and Polivy on (Appendix 1)	30 January 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Non-Hodgkin's lymphoma (NHL) is a collective term for a heterogeneous group of lymphoproliferative malignancies, ranging from indolent and incurable diseases, such as follicular lymphoma to more aggressive intermediate- to high-grade NHL, such as diffuse large B-cell lymphoma (DLBCL) and Burkitt leukaemia/lymphoma, with differing patterns of behaviour and responses to treatment (Armitage, 1993). This is an extension of indication in previously untreated, advanced stage paediatric B-cell Non-Hodgkin's Lymphoma (B-NHL).

Epidemiology

Non-Hodgkin lymphoma (NHL) comprises a heterogeneous group of lymphoid malignancies. The World Health Organization's classification of hematopoietic and lymphoid neoplasms is accepted as the common classification system with the latest update in 2016 (Swerdlow et al. 2016). Non-Hodgkin lymphoma is the

fourth most common malignancy in childhood and adolescence. Mature B-cell lymphoma (B-NHL) accounts for approximately 60% of all cases of childhood NHL, of which the majority are high-grade. Within this group of pediatric BNHL, the main histological subtypes are BL, B-AL – analogous to acute mature B-cell French-American-British (FAB) L3 leukemia, DLBCL, primary mediastinal large B-cell.

lymphoma (PMLBL) and aggressive mature B-NHL, not further classifiable (Worch et al. 2013). Burkitt lymphoma and B-AL account for 80% of pediatric mature B-NHL. The disease is diagnosed at a median age of 9 years with a predominance in boys (>4:1). Frequent manifestations of the disease occur in the abdomen as well as the head and neck region.

Approximately 25% of patients present with bone marrow involvement and approximately 5-10% present with central nervous system (CNS) involvement. Diffuse large B-cell lymphoma accounts for 10-20% of pediatric B-NHL and occurs more frequently in adolescents, with a median age of 11-12 years and a moderate sex ratio towards males (1.7:1). Children most often present with nodal disease with involvement of the peripheral lymph nodes, the abdomen, and the mediastinum. Bone marrow and

CNS involvement are rarely observed in these patients. Primary mediastinal large B-cell lymphoma accounts for 2% of B-NHL, typically occurs in older teenagers and affects more females than males. The disease typically presents with a large mediastinal mass in the thymic region, including pericardial and pleural effusions and metastatic lung disease (Worch et al. 2013, Minard-Colin et al. 2015, Giulino-Roth 2018). Risk group allocation for determining the therapy strategy incorporates data on disease stage, site and surgical resection, as well as lactate dehydrogenase (LDH) level (see Section 1.4).

Biologic features

NHL usually originates in the lymphoid tissues and can spread to other organs. Most NHLs (80-85%) are of B-cell origin (Chisti et al, 2017). Many B-cell non-Hodgkin lymphoma (B-NHL) subtypes frequently observed in adults are rarely diagnosed in children and adolescents.

The CD20 surface antigen is expressed on 100% of childhood BL/B-AL and 98% of DLBCL (Perkins et al. 2003). CD20 is expressed to the same extent in adult and pediatric patients (Plosker and Figgit 2003, Perkins et al. 2003).

Clinical presentation, diagnosis and stage/prognosis

Mature B-NHL represents the fourth most common pediatric cancer diagnosis in Europe and accounts for around 60% of all NHL in children and adolescents. They encompass Burkitt lymphoma (BL)/ Burkitt leukemia (B-AL), DLBCL, primary mediastinal B-cell lymphoma and other less common histologies (Lones et al, 2000). BL accounts for more than 80% of childhood B-NHL. It generally arises in the abdomen and/or head and neck region and presents as advanced-stage disease involving the bone marrow (BM) and/or central nervous system (CNS) in approximately 20% to 25% of patients. DLBCL accounts for 10% to 20% of B-NHL in children (Minard-Colin et al, 2015). B-cell non-Hodgkin's lymphoma can occur at any age, but it is rare in children younger than 3 years of age (Minard-Colin et al, 2015). The median age at diagnosis is approximately 10 years (Hochberg et al, 2016).

The prognosis is good in stage I/II B-NHL; however, there is a treatment gap for an improvement in outcome in pediatric patients with advanced stage B-NHL. Though effective, the treatment required for pediatric mature B-NHL is associated with major short- and long-term toxicities. Patients with advanced-stage disease are still at high risk of death (approximately 3%) from treatment complications during the first phase of therapy (Reiter 2007). More than 80% of the patients still experience febrile neutropenia requiring IV antibiotics, and more than 50% require transfusions. Acute therapeutic morbidity for patients with high-risk disease is substantial: 95% of patients experience Grade ≥ 3 infection, 81% experience

Grade ≥ 3 stomatitis due to the combination of high-dose methotrexate (HDMTX) and doxorubicin; and greater than 25% of patients experience Grade ≥ 3 hemorrhage, transaminase elevation, and diarrhea. Acute tumor lysis syndrome is another serious risk in the first days of treatment. Short-term toxicity is much less substantial for patients with intermediate risk disease, but approximately 75% of patients experience at least one Grade ≥ 3 toxicity (Patte et al. 2007). Long-term toxicities include infertility and hormonal failure, impaired growth, cardiac dysfunction, and secondary malignancies. With current treatments, EFS rates in children and adolescents with NHL of up to 90% can be reached (Link et al. 2006, Reiter 2007).

Management

Treatment of childhood B-NHL consists of systemic chemotherapy and includes the use of short intensive courses of non–cross-resistant chemotherapy agents. The current most used treatment regimens for pediatric B-NHL were developed by the Berlin-Frankfurt-Münster (BFM) group and Lymphome Malin B (LMB) group, which use drugs with different mechanisms of action and non-overlapping toxicities. Based on the extremely high proliferative activity of BL, a basic principle is to maintain cytotoxically active drug concentrations over a period that is sufficient to affect as many lymphoma cells as possible during the vulnerable active cell cycle, using either fractionated administration or continuous infusion. In addition, efficient CNS-directed therapy by intrathecal drug application addresses the strong tendency for invasion of the CNS, especially that of BL. The 2 treatment strategies used in the BFM and LMB group studies became the most frequently applied for these patients. Per the combined analysis of results from these studies, patients with CNS involvement (blasts in cerebrospinal fluid [CSF]), cranial nerve palsies, intra-cerebral mass) had the worst outcome and hence were considered to be very high-risk patients.

The combined review of the BFM and LMB data showed that among the patients with CNS involvement, there was a clear difference between those with presence of blasts in CSF vs. those without. In the BFM series, the event-free survival (EFS) was 70.2% (n = 54) vs. 84.3% (n = 26), respectively. In the FAB LMB96 series of patients treated with arm C1, EFS was 75% (n = 24) vs. 94.7% (n = 19), respectively. In the LMB 2001 g therapeutic Group C3 (patients until 2006), EFS was 84.6% (n = 13) vs. 97.1% (n = 39), respectively. A trend was observed implying improved outcome with the C3 regimen; however, the numbers were very small. The proportion of patients with blasts in CSF was very low in this last series (Cairo et al, 2007).

Cure rates of children with mature B-cell lymphoma (BCL), mainly Burkitt but also DLBCL, have significantly improved over the past 25 years (Patte et al, 2007). The 5-year survival rate of children diagnosed with B-NHL in Europe, excluding BL, was 84% in the EUROCARE-5 project (Gatta et al, 2014).

The international, open-label, randomized cooperative FAB LMB 96 study of children and adolescents could demonstrate that the reduction of dose intensity of chemotherapy in the intermediate risk group, did not jeopardize survival and demonstrated a 4-year EFS over 90% for children and adolescents with intermediate risk B-NHL who showed an early disease response and complete remission (CR) after the first consolidation course (Patte et al, 2007). Chemotherapy reduction was not possible for patients with high-risk disease such as combined bone marrow and CNS involvement and poor response to induction chemotherapy (Cairo et al, 2007). Based on the results of this trial, the FAB/LMB 96 risk adapted treatment strategy was adopted as the standard chemotherapy regimen for children with newly diagnosed B-NHL within the FAB/LMB96 cooperative international study group.

Current Treatment Overview and Outcomes of Pediatric Mature B-NHL

Over recent decades, results from several prospective clinical trials have shown a significant improvement of outcomes in pediatric patients with mature B-NHL. Two highly effective chemotherapy treatment strategies have been established: The French LMB protocol and the German, Austrian, Switzerland NHL-

Berlin-Frankfurt-Münster (BFM) protocol. Effective therapy for children and adolescents with B-NHL includes the use of intense short courses of non-cross resistant chemotherapy agents, with the specific regimen defined by the patient risk group allocation (limited, intermediate and advanced stages of disease) and including essential CNS prophylaxis. Risk group definitions have been similar, but not identical, between cooperative groups. Treatment intensity and outcome depend on established stratification criteria. Patients with low risk disease (resected stage I, or completely resected stage II abdominal disease, about 10-20% of the B-NHL patients) have excellent outcomes with two courses of multi-agent chemotherapy (3-year EFS of 94% in BFM-protocol, 4-year EFS of 98% in the FAB/LMB96 protocol). The intermediate risk group disease is the largest and most heterogeneous. Event-free survival rates with four courses of chemotherapy were about 92% at 4 years within the LMB group and 94% at 3 years within the BFM group. The highest risk patients in BFM studies are those with LDH ≥1000 u/l with bone marrow, CNS disease, or multifocal bone involvement. In the FAB/LMB studies, the highest risk group included those with leukemic disease and those with CNS disease.

Three-year EFS rate was 81% after six courses of chemotherapy within the BFM group; 4-year EFS rate was 79% after four to six courses chemotherapy within the FAB/LMB studies. Of the high-risk patients, those with measurable disease in their cerebrospinal fluid (CSF) at diagnosis, had the worst outcomes. Both BL/B-AL and DLBCL are included in the same therapy regimen and no differences have been identified in outcomes based on histology, except for PMLBL (Worch et al. 2013, Minard-Colin et al. 2015, Egan et al. 2019).

Table 1 overview of outcomes in pediatric B-NHL patients of the BFM and FAB/LMB group by risk group prior to the testing of rituximab in these protocols.

Table 2 Berlin-Frankfurt Münster Risk Groups and Outcomes prior to the Use of Rituximab

Risk Group	Definition	3-year EFS
R1	Stages I or II, resected	94%
R2	Stages I or II, not resected; Stage III, LDH <500 u/l	94%
R3	Stage III, LDH 500 – 999 u/l; Stage IV and LDH <1000 u/l and CNS negative	85%
R4	Stage III or IV and LDH >1000 u/l and/or CNS involvement	81%

CNS = central nervous system; EFS = event-free survival; LDH = lactate dehydrogenase.
Source: adapted from Woessmann et al. 2005.

Table 3 French-American-British/Lymphome Malin B 96 Risk Groups and Outcomes prior to the Use of Rituximab

Group	Definition	4-year EFS
A	Completed resected Stage I/II	98%
B	All others[1]	90%
C	Leukemic (>25% blasts) and/or CNS positive disease[2]	79%

[1] Non-resected stage I/II and advanced stage III/IV without CNS involvement or leukemia.
[2] CNS disease defined as cerebrospinal fluid blasts, cranial nerve palsies, spinal cord compression, intra-cerebral mass or para-meningeal extension.
CNS = central nervous system; EFS = event-free survival.
Source: adapted from Cairo et al. 2007, Patte et al. 2007, Gerrard et al. 2008.

2.1.2. About the product

Rituximab is a chimeric murine/human monoclonal antibody that binds to CD20 protein, a hydrophobic transmembrane protein present on the cell surface of pre-B- and mature B-lymphocytes. In particular, CD20 is present on malignant B cells in most patients with mature B-NHL and leukemia. As CD20 expression begins at early pre-B-cell stage and is lost during plasma cell differentiation, it is expressed during all stages of B-cell differentiation; however, CD20 is not expressed on stem cells and plasmocytes. CD20 is essential for the regulation of cell cycles and cell differentiation. It has stable expression, with no modulation or internalization, which makes it an ideal pharmaceutical target (Cartron et al, 2004). Rituximab binds to CD20 on B-lymphocytes and eliminates these cells via several possible mechanisms (antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, apoptosis, and synergism with a variety of chemotherapeutic agents). The relative contribution of these individual mechanisms to overall killing of target cells in vivo is not known.

The benefit of the addition of rituximab to the standard CHOP chemotherapy for adults with B-NHL, including DLBCL, BL and PMLBL, has been established in clinical trials and is now considered as standard treatment.

To evaluate the effect of rituximab in the treatment of pediatric patients with B-NHL, Study BO25380 investigated the impact of adding 6 infusions of rituximab on the improvement of EFS of newly diagnosed children and adolescents with advanced-stage B-NHL/B-AL treated with a LMB-based chemotherapy regimen in a controlled, prospective clinical trial.

In this application Mabthera was proposed to be used, in combination with chemotherapy, for the treatment of paediatric patients (aged ≥6 months to <18 years old) with previously untreated advanced stage CD20 positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukaemia (mature B-cell acute leukaemia) (BAL) or Burkitt-like lymphoma (BLL).

The recommended initial rate for infusion is 0.5 mg/kg/h (maximum 50 mg/h); it can be escalated by 0.5 mg/kg/h every 30 minutes if there is no hypersensitivity or infusion-related reactions, to a maximum of 400 mg/h. Subsequent doses of MabThera can be infused at an initial rate of 1 mg/kg/h (maximum 50 mg/h); it can be increased by 1 mg/kg/h every 30 minutes to a maximum of 400 mg/h.

Table 1 Posology of MabThera administration for Non-Hodgkin's lymphoma paediatric patients

Cycle	Day of treatment	Administration details
Prephase (COP)	No MabThera given	-
Induction course 1 (COPDAM1)	Day -2 (corresponding to day 6 of the prephase) 1st MabThera infusion	During the 1st induction course, prednisone is given as part of the chemotherapy course, and should be administered prior to MabThera.
	Day 1 2nd MabThera infusion	MabThera will be given 48 hours after the first infusion of MabThera.
Induction course 2 (COPDAM2)	Day -2 3rd MabThera infusion	In the 2nd induction course, prednisone is not given at the time of MabThera administration.
	Day 1 4th MabThera infusion	MabThera will be given 48 hours after the third infusion of MabThera.
Consolidation course 1 (CYM/CYVE)	Day 1 5th MabThera infusion	Prednisone is not given at the time of MabThera administration.
Consolidation course 2 (CYM/CYVE)	Day 1 6th MabThera infusion	Prednisone is not given at the time of MabThera administration.

Maintenance course 1 (M1)	Day 25 to 28 of consolidation course 2 (CYVE) No MabThera given	Starts when peripheral counts have recovered from consolidation course 2 (CYVE) with ANC> 1.0 x $10^9$9/l and platelets > 100 x $10^9$9/l
Maintenance course 2 (M2)	Day 28 of maintenance course 1 (M1) No MabThera given	-
ANC = Absolute Neutrophil Count; COP = Cyclophosphamide, Vincristine, Prednisone; COPDAM = Cyclophosphamide, Vincristine, Prednisolone, Doxorubicin, Methotrexate; CYM = CYtarabine (Aracytine, Ara-C), Methotrexate; CYVE = CYtarabine (Aracytine, Ara-C), VEposide (VP16)		

Table 2 Treatment Plan for Non-Hodgkin's lymphoma paediatric patients: Concomitant Chemotherapy with MabThera

Treatment Plan	Patient Staging	Administration details
Group B	Stage III with high LDH level (> N x 2), Stage IV CNS negative	Prephase followed by 4 courses: 2 induction courses (COPADM) with HDMTX 3g/m^2 and 2 consolidation courses (CYM)
Group C	Group C1: B- AL CNS negative, Stage IV & BAL CNS positive and CSF negative	Prephase followed by 6 courses: 2 induction courses (COPADM) with HDMTX 8g/m^2, 2 consolidation courses (CYVE) and 2 maintenance courses (M1 and M2)
	Group C3: BAL CSF positive, Stage IV CSF positive	
Consecutive courses should be given as soon as blood count recovery and patient's condition allows except for the maintenance courses which are given at 28 day intervals		
B-AL = Burkitt leukaemia (mature B-cell acute leukaemia); CSF = Cerebrospinal Fluid; CNS = Central Nervous System; HDMTX = High-dose Methotrexate; LDH = Lactic Acid Dehydrogenase		

This application for a new indication is based on the efficacy and safety data from an investigator-sponsored study conducted by Institut Gustave Roussy (IGR) from France and the Children's Oncology Group (COG) from the United States - Inter-B-NHL Ritux 2010 [IGR2009/1593 (IGR)/ANHL1131 (COG)]. This study is the sole clinical measure (Study 1) in the MabThera Paediatric Investigation Plan (PIP) EMEA-00030-PIP01-08-M04, and is a phase III, open-label, randomized, controlled, parallel-group, multicentre trial to evaluate the pharmacokinetics, pharmacodynamics, safety and efficacy of rituximab add-on to standard chemotherapy in children from 6 months to less than 18 years of age with advanced stage B-cell lymphoma (excluding primary mediastinal B-cell lymphoma), Burkitt and Burkitt-like lymphoma/leukaemia.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 2

Table 1 Summary of Studies Contributing to Efficacy[a] Evaluation

Study No. (Phase)	Study Design, Control Type	Population	No. of Patients	Dose, Route, and Regimen
BO25380; Inter-B-NHL Ritux 2010 (Phase III)	Multicenter, open-label, randomized trial comparing the efficacy of LMB chemotherapy versus LMB chemotherapy plus rituximab	Pediatric patients aged ≥6 months to <18 years with untreated advanced stage B-cell NHL (except PMLBL) or stage III plus LDH > ULN × 2, stage IV, or mature B-AL	Total number of enrolled patients: 484 ITT sets: Chemo: n=164 R-Chemo: n=164 Safety sets: Chemo: n=153 R-Chemo: n=162 Rituximab safety set: n=309	Rituximab was administered by IV infusion at a dose of 375 mg/m^2. Patients received a total of 6 infusions of rituximab: 1 infusion each on Day −2 and Day 1 of each of the 2 COPADM courses, and 1 infusion on Day 1 of each of the 2 consolidation courses (either CYM or CYVE, depending on therapeutic group assignment).

B-AL=B-cell acute leukemia; COPADM=cyclophosphamide, Oncovin (vincristine), prednisolone, Adriamycin (doxorubicin), methotrexate; CYM=cytarabine (Aracytine, Ara-C), methotrexate; CYVE=cytarabine (Aracytine, Ara-C), VePesid (VP-16); ITT=intent-to-treat; LDH=lactate dehydrogenase; LMB=Lymphome Malin B; NHL=non-Hodgkin lymphoma; PMLBL=primary mediastinal large B-cell lymphoma; ULN=upper limit of normal.

[a] Efficacy analyses included patients in the randomized portion only. All efficacy analyses were produced in the ITT set (all patients enrolled in the randomized portion), unless otherwise specified.

2.3.2. Pharmacokinetics

Study BO25380 evaluated the efficacy, safety and pharmacokinetics (PK) in pediatric patients ≥6 months to <18 years of age with newly diagnosed, advanced stage mature B-cell non-Hodgkin lymphoma (B-NHL). PK of rituximab in combination with LMB chemotherapy has been investigated in a subset of patients as an exploratory secondary objective.

A dose-dense rituximab dosing regimen was applied to account for the high tumor burden expected in this patient population. This dosing regimen included two doses of rituximab within 48 hours in the first two chemotherapy cycles (induction cycles), followed by one rituximab dose per chemotherapy cycle for Cycle 3 and Cycle 4 (consolidation cycles). In total, six doses of rituximab were administered. Similar to adults, the standard rituximab dose of 375 mg/m^2 body surface area (BSA) was administered as an IV infusion. Rituximab serum concentrations and cluster of differentiation (CD)19/CD20 B-cells were measured.

The clinical pharmacology data in the pediatric population were compared with those obtained in adult patients with non-Hodgkin lymphoma (NHL) to confirm the suitability of the dose-dense dosing regimen of rituximab in pediatric patients.

The current application is in support of a label update to include rituximab IV for the treatment of pediatric patients (≥6 months to <18 years of age) with advanced stage mature B-NHL.

Methods

A PK study was performed in selected European centres, and planned in at least 34 patients (≥ 15 patients each in the 2 age groups: 3 to 11 years, and 12 to 18 years; and ≥ 4 patients in the age group 6 months to < 3 years). PK sampling was performed during the 4 treatment cycles which included rituximab, with the frequency of sampling dependent on patient age. PK samples were analysed in 3 age subsets of patients (6 months to < 3 years, 3 to 11 years, and 12 to 18 years). For Cycle 1 and 2 pre- and post-dose serum concentrations of rituximab were collected, for Cycle 3 pre-dose concentrations of rituximab were collected and for Cycle 4 a full PK profile of rituximab was collected for patients ≥ 3 years. The schedule of PK sampling by age group is presented in Table 2.

Table 2 Schedule of Pharmacokinetic Sampling by Age Group

Age Group	Cycle	Day of Cycle	Time Point (*)
3-11 years old; 12-18 years old	1	-2	Pre-dose
		-2	Post-dose
		1	Pre-dose
		1	Post-dose
	2	-2	Pre-dose
		-2	Post-dose
		1	Pre-dose
		1	Post-dose
	3	1	Pre-dose
	4	1	Pre-dose
		1	Post-dose
		6	Post-dose
		29 (1 months)	Post-dose
		57 (2 months)	Post-dose
		85 (3 months)	Post-dose
6 months – < 3 years old	3	1	Pre-dose
		1	Post-dose
	4	1	Pre-dose
		1	Post-dose

(*) For Days -2 and 1, pre-dose samples were collected 1±1 hour before start of infusion and post-dose samples were collected 30±15 minutes after infusion end. For other days, PK samples were collected at any time during the site visit.

Pharmacokinetic Data Analysis

At Cycle 4, the following PK parameters were calculated for each patient by standard non-compartmental analysis methods using Phoenix WinNonlin version 8.0 (Pharsight, Mountain View, California, United States), as appropriate and as data permitted:

- Minimum drug serum concentration (Cmin), defined as the minimum observed concentration after the 6th infusion of rituximab during Cycle 4 sampling schedule.
- Maximum drug serum concentration (Cmax), defined as the maximum observed concentration after the 6th infusion of rituximab during Cycle 4 sampling schedule.
- Area under the drug serum concentration-time curve (AUC0-∞): AUC measurement up to the last quantifiable concentration, plus an additional area extrapolated to infinity, calculated as: AUC0-t+Ct/lambda_z where Ct = the last observed nonzero serum concentration.
- Area under the drug serum concentration-time curve, corrected (AUC0-∞,corr): This parameter was adjusted to subtract the area contribution from previous doses to obtain the results for the 6th dose only. AUC0-∞,corr was calculated as AUC0-∞ on Cycle 4 – (Ctrough [pre-dose concentration on Cycle 4, Day 1]/lambda_z).

- Clearance (CL), calculated as dose/AUC0-∞,corr.
- Volume of distribution (V), estimated from CL/lambda_z.
- Elimination half-life (t1/2), calculated as ln 2/lambda_z.

The PK parameters of Cycle 4 were summarized by age group and overall using descriptive statistics including arithmetic mean, standard deviation, geometric mean, coefficient of variation, median, and range. All pre-dose (trough) and post-dose serum concentrations of rituximab for each age group and overall were presented for each cycle descriptively including arithmetic mean, standard deviation, geometric mean, coefficient of variation, median, and range.

Comparison of Rituximab Pharmacokinetics Between Pediatric and Adult Patients

To compare the PK of rituximab between pediatric and adult patients, a population PK model (Study BO22334/SABRINA Report No. 1071510) previously developed with software NONMEM® in 399 adult patients with NHL from SABRINA phase III trial was used to predict the expected PK profiles in pediatric patients and overlay the observed PK data from this study.

Following IV administration in adults, rituximab PK was described by a 2-compartment model comprising a time-varying clearance component corresponding to the decrease in capacity of a target-mediated clearance pathway and a constant clearance component related to the endogenous catabolic processes of IgG. The covariates influencing the rituximab PK parameters were tumor size at baseline, B-cells count at baseline, and BSA. As common for monoclonal antibodies, BSA has an impact on clearance and volume parameters, with the dependence of clearances and volumes on BSA consistent with the allometric scaling.

The expected PK profiles in the pediatric patients were simulated using the following covariates:

- BSA values from 233 pediatric patients with juvenile immune arthritis from NP25737, WA19977 and WA28117 trials (1077893, 1074871), were used as they were representative of the BSA distribution in Study BO25830.
- Tumor size at baseline was expected to be similar between pediatric and adult patients with the same lymphoid malignancy, and therefore, the tumor size at baseline distribution from the SABRINA trial (1071510) was used to simulate a tumor size at baseline for each of the 233 BSA values (assuming that there is no correlation between BSA and tumor size at baseline). This was done because tumor size was not measured in Study BO25830.
- Mean and standard deviation of B-cell counts at baseline from Study BO25830 were used to simulate the B-cell counts at baseline for each of the 233 BSA values, assuming there is no correlation between BSA and B-cell counts at baseline.

Summary statistics of those covariates are shown in Table 3.

Table 3 Covariates Used to Predict Rituximab Exposure in Pediatric Patients

Label	Mean	Standard deviation	Min-max	Sources
Body surface area (m^2)	1.18	0.40	0.35-2.06	[1] and [2]
Age (years)	10.38	4.54	0.87-17.67	[1] and [2]
B-cell count at baseline (10^9/L)	842.2	826.4	127-3482	Source: Table 14.2.6.1.1
Tumor size at baseline (mm^2)	7104	8151	165-29552	[3]

Min = Minimum; max = Maximum.

[1] Hsu et al, 2017a.

[2] Hsu et al, 2017b.

[3] Study BO22334/SABRINA Report No. 1071510.

The dosing regimen of the present study consisted of 6 IV doses of 375 mg/m2 of rituximab, with an infusion rate of 2 hours. For the simulations, the mean actual dosing times per age group were used.

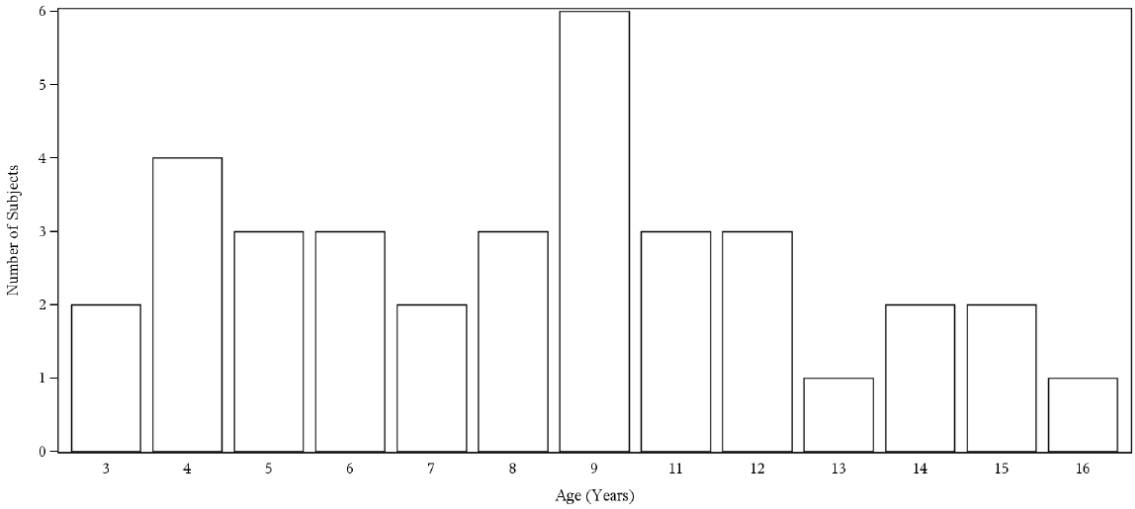
The 250 simulated pediatric rituximab serum concentration-time courses were summarized using median concentration – time profiles and 5th and 95th percentiles (90% prediction interval). The adequacy between

observed rituximab concentrations of the present study and predicted PK profiles was assessed graphically by overlaying the observed PK data with the predictions.

Pharmacokinetic results

The PK set included 35 patients, 22 patients randomized to R-Chemo in the randomized portion, 3 patients randomized to R-Chemo from the crossover portion, plus 10 patients from the single-arm portion. Of the 35 patients in the PK set, 26 patients were in the ≥ 3 to < 12 year age group and 9 patients were in the ≥ 12 to < 18 year age group; there were no patients ≥ 6 months to < 3 years in the PK set.

Figure 1 Number of Patients of the PK Population in Study BO25380



Pharmacokinetics of Rituximab overall

The key PK parameters of rituximab following a dose-dense rituximab dosing regimen with two rituximab doses of 375 mg/m2 BSA (48 hours apart) per cycle for the first 2 cycles followed by one rituximab dose of 375 mg/m2 BSA per cycle in Cycle 3 and Cycle 4 are listed in Table 3, Table 4, and Table 5. The interpatient variability for these parameters was 16% to 52%.

Table 3 Key Trough Concentrations (Pre-dose Concentrations; µg/mL)

	Pre-dose Conc. of Cycle 2 before 3rd infusion after 1 cycle	Pre-dose Conc. of Cycle 3 before 5th infusion after 2 cycles	Pre-dose Conc. of Cycle 4 before 6th infusion after 3 cycles
N	27	30	32
Median(range)	46.6 (8.50, 63.2)	76.3 (24.9, 153)	58.2 (19.2, 126)
GM (CV%)	41.8 (47.4)	67.7 (44.7)	58.5 (51.8)

Pre-dose samples were collected 1±1 hours before start of infusion.
CV=coefficient of variation; GM=geometric mean.

Table 4 Key Post-dose Concentrations (µg/mL)

	Post-dose Conc. after 2nd infusion Cycle 1	Post-dose Conc. after 4th infusion Cycle 2	Post-dose Conc. after 6th infusion Cycle 4
N	31	30	31
Median(range)	290 (116, 431)	365 (242, 446)	257 (181, 389)
GM (CV%)	287 (24.1)	347 (16.4)	259 (18.2)

Post-dose samples were collected 30±15 minutes after end of infusion.
CV=coefficient of variation; GM=geometric mean.

Table 5 Key Pharmacokinetic Parameters of Cycle 4

	$AUC_{6th\ dose}$ [d*µg/mL]	C_{max} [µg/mL]	$T_{1/2}$ [d]
N	23	29	23
Median (range)	3040 (1770, 5540)	248 (129, 389)	25.7 (16.9,31.9)
GM (CV%)	3160 (31.7)	247 (24.6)	24.8 (19.3)

$AUC_{6th\ dose}$=area under the concentration-time curve of the 6th dose; C_{max}=maximum concentration of concentration-time profile; CV=coefficient of variation; GM=geometric mean; $T_{1/2}$=elimination half-life

Pharmacokinetics of Rituximab by age group

The pre-dose (trough) and post-dose serum concentrations of rituximab for each of the six infusions over time by age group and overall are shown in Table 1. Boxplots of pre-dose concentrations by cycle and age group and post-dose concentrations by cycle and age group are shown in Figure 1 and 2 respectively.

Rituximab PK parameters at Cycle 4 in patients ≥3 years by age group and overall are summarized in Table 2.

On average, the highest serum rituximab concentrations were reached following the fourth infusion (second infusion of Cycle 2) with a geometric mean of 367 µg/mL (age group ≥3 to <12 years) and 297 µg/mL (age group ≥12 to <18 years) (Table 1). Three months after the last rituximab dose, the median serum concentration of rituximab was 13.0 µg/mL in both age groups (Table 2).

The systemic exposure (Cycle 4: area under the concentration-time curve [AUC], maximum concentration [C_{max}]; Cycle 1 to 4: pre- and post-dose concentrations) in pediatric patients with advanced stage mature B-NHL was comparable overall between the ≥3 to <12 year age group and the ≥12 to <18 year age group (Table 1, Table 2, Figure 1 to 4). However, the sample size in the older age group was small (N ≤ 9) and, therefore, no formal comparison was performed.

The elimination half-life of rituximab in pediatric patients with advanced stage mature B-NHL was similar between the two age groups (median: 25.7 days [≥3 to <12 years] vs. 26.3 days [≥12 to <18 years]) (Table 2) and similar to the median value of 22 days (range: 6.1 to 52 days [Li et al. 2007]) observed in adult patients with NHL.

Table 1 Pre-dose and Post-dose Serum Concentrations (µg/mL) over Time by Age Group and Overall

Scheduled Time		≥3 to <12 Years (N=26*)		≥12 to <18 Years (N=9*)		Overall (N=35*)	
		Pre-dose	Post-dose	Pre-dose	Post-dose	Pre-dose	Post-dose
Cycle 1 Day -2 Infusion 1	N	24	24	9	7	33	31
	Median	n.a.	204	n.a.	137	n.a.	195
	Range	n.a.	103, 260	n.a.	14.3, 165	n.a.	14.3, 260
	GM	n.a.	199	n.a.	93.9	n.a.	168
	GM CV%	n.a.	20.9	n.a.	104.4	n.a.	57.2
Cycle 1 Day 1 Infusion 2	N	24	22	8	9	32	31
	Median	112	314	89.3	243	111	290
	Range	80.6, 395	237, 431	49.3, 116	116, 277	49.3, 395	116, 431
	GM	118	314	87.7	228	110	287
	GM CV%	34.5	15.7	29.3	26.3	35.6	24.1
Cycle 2 Day -2 Infusion 3	N	22	21	5	5	27	26
	Median	48.7	252	38.9	204	46.6	250
	Range	8.50, 63.2	197,351	18.4, 56.3	141, 250	8.50, 63.2	141, 351
	GM	43.6	257	34.5	200	41.8	245
	GM CV%	47.2	15.0	47.6	21.7	47.4	19.0
Cycle 2 Day 1 Infusion 4	N	23	22	9	8	32	30
	Median	178	374	132	297	164	365
	Range	121, 222	292, 446	73.6, 157	242, 394	73.6, 222	242, 446

	GM	168	367	123	297	154	347
	GM CV%	16.7	12.3	23.4	16.8	23.5	16.4
Cycle 3	N	22	-	8	-	30	-
Day 1	Median	70.3	-	81.5	-	76.3	-
Infusion 5	Range	24.9, 153	-	34.4, 109	-	24.9, 153	-
	GM	66.0	-	72.8	-	67.7	-
	GM CV%	47.8	-	37.4	-	44.7	-
Cycle 4	N	24	22	8	9	32	31
Day 1	Median	61.4	272	39.5	223	58.2	257
Infusion 6	Range	34.9, 126	214, 389	19.2, 93.2	181, 291	19.2, 126	181, 389
	GM	66.3	276	40.1	224	58.5	259
	GM CV%	40.0	16.0	64.6	14.6	51.8	18.2

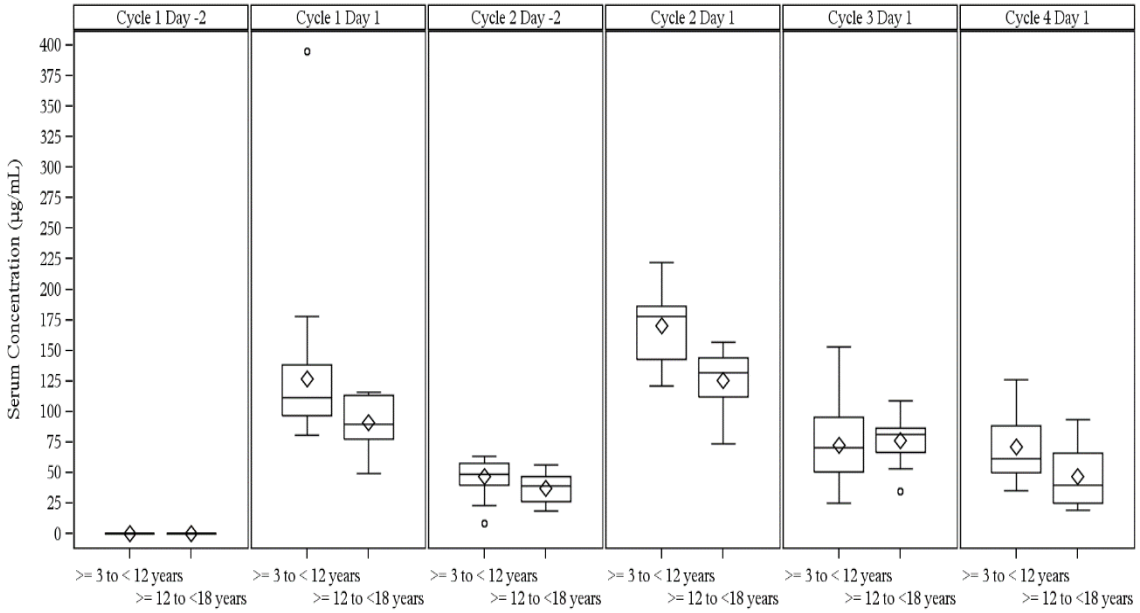
*Total number of patients with PK samples (please note that not all patients had samples taken at each visit).
Post-dose samples were collected 30±15 minutes after end of infusion; Pre-dose samples were collected 1±1 hours before start of infusion.
CV=coefficient of variation; GM=geometric mean; n.a.=not available (all pre-dose concentrations at Cycle 1 before 1st rituximab dose were below limit of quantification).
Source: End-of-text Table 14.2.6.2.1 Study BO25380 Primary CSR.

Table 2 Pharmacokinetic Parameters at Cycle 4 in Patients ≥3 Years Old by Age Group and Overall

	≥3 to <12 Years (N=26)	**≥12 to <18 Years (N=9)**	**Overall (N=35)**
$AUC_{0-\infty}$ (d*µg/mL)			
N	17	6	23
Median (range)	5040 (3380, 10400)	5040 (2740, 6970)	5040 (2740, 10400)
GM (CV%)	5390 (40.9)	4900 (32.5)	5260 (38.3)
$AUC_{6th\ dose}$ (d*µg/mL)			
N	17	6	23
Median (range)	2940 (1770, 5350)	3300 (2180, 5540)	3040 (1770, 5540)
GM (CV%)	3100 (32.4)	3340 (31.8)	3160 (31.7)
C_{min} (µg/mL)			
N	24	7	31
Median (range)	13.0 (2.00, 124)	13.0 (3.00, 39.0)	13.0 (2.00, 124)
GM (CV%)	14.8 (110.9)	11.2 (96.2)	13.9 (106.7)
C_{max} (µg/mL)			
N	22	7	29
Median (range)	265 (129, 389)	219 (181, 258)	248 (129, 389)
GM (CV%)	259 (25.9)	214 (11.7)	247 (24.6)
Clearance (L/d)			
N	17	6	23
Median (range)	0.104 (0.0467, 0.333)	0.179 (0.0813, 0.202)	0.132 (0.0467, 0.333)
GM (CV%)	0.113 (49.2)	0.153 (35.2)	0.122 (47.4)
V (L)			
N	17	6	23
Median (range)	4.13 (2.09, 11.4)	5.20 (2.99, 8.40)	4.34 (2.09, 11.4)
GM (CV%)	4.08 (46.5)	5.35 (36.4)	4.37 (45.1)
$T_{1/2}$ (d)			
N	17	6	23
Median (range)	25.7 (18.0, 31.0)	26.3 (16.9, 31.9)	25.7 (16.9, 31.9)
GM (CV%)	25.0 (18.2)	24.2 (24.1)	24.8 (19.3)

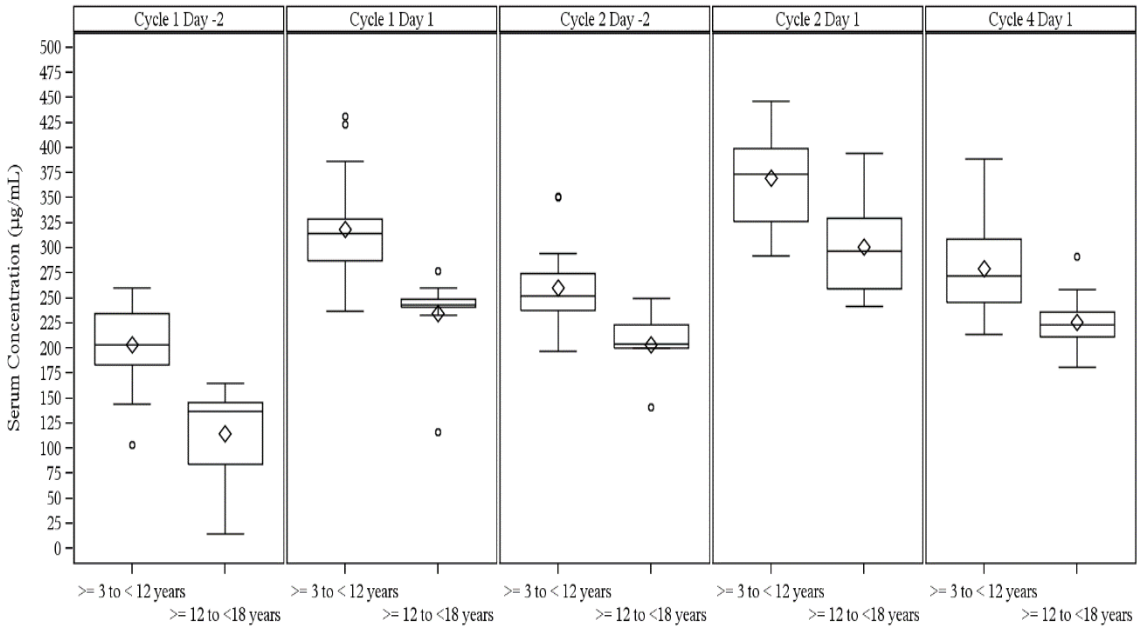
PK parameters estimated by standard noncompartmental analysis.
$AUC_{0-\infty}$=Area under the concentration-time curve from time zero to infinity after the 6th infusion; $AUC_{6th\ dose}$=Area under the concentration-time curve of the 6th dose; C_{max}=maximum concentration of concentration-time profile; C_{min}=lowest concentration of concentration-time profile, which with the sampling schedule of Study BO25380 corresponds mostly to the concentration 3 months post-dose (not to be confounded with a trough concentration or pre-dose concentration); CV=coefficient of variation; GM=geometric mean; V=volume of distribution during the terminal phase estimated from clearance/lambda_z.

Figure 1 Boxplot of Pre-dose Concentrations of Rituximab by Cycle and Age Group



Pre-dose samples were collected 1±1 hours before start of infusion. line=median; diamond=arithmetic mean.
Source: Boxplot produced from data of Study BO25380.

Figure 2 Boxplot of Post-dose Concentrations of Rituximab by Cycle and Age Group

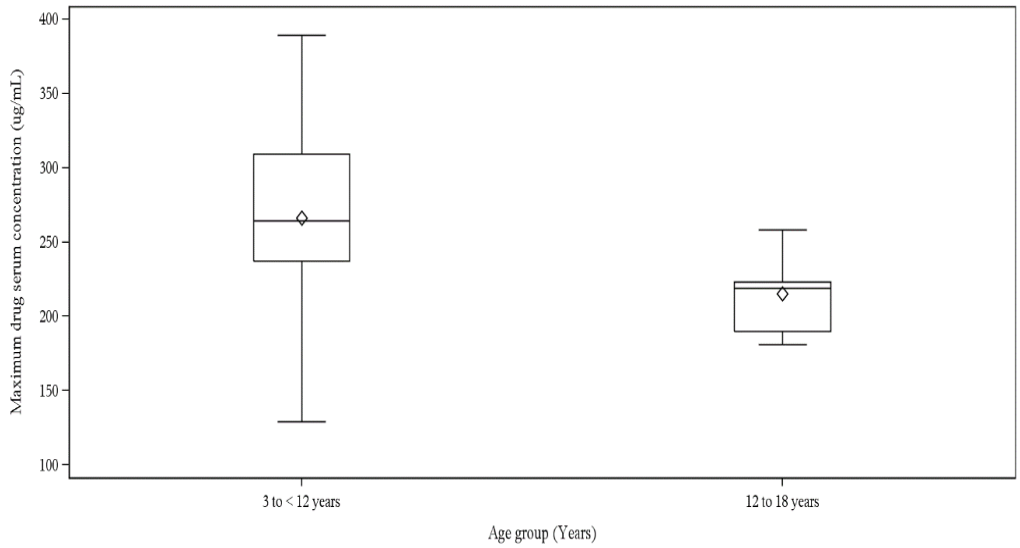


Post-dose samples were collected 30±15 minutes after end of infusion. line=median; diamond=arithmetic mean.
Source: Boxplot produced from data of Study BO25380.

Figure 3 Boxplot of $AUC_{6th\ dose}$ of Cycle 4 in Pediatric Patients of 3 Years and Older by Age Group

AUC6th dose (=AUC0-∞,corr): Area under the concentration-time curve of the 6th dose (). line=median; diamond=arithmetic mean.
Source: Boxplot produced from data of Study BO25380.

Figure 4 Boxplot of C_{max} of Cycle 4 in Pediatric Patients of 3 Years and Older by Age Group



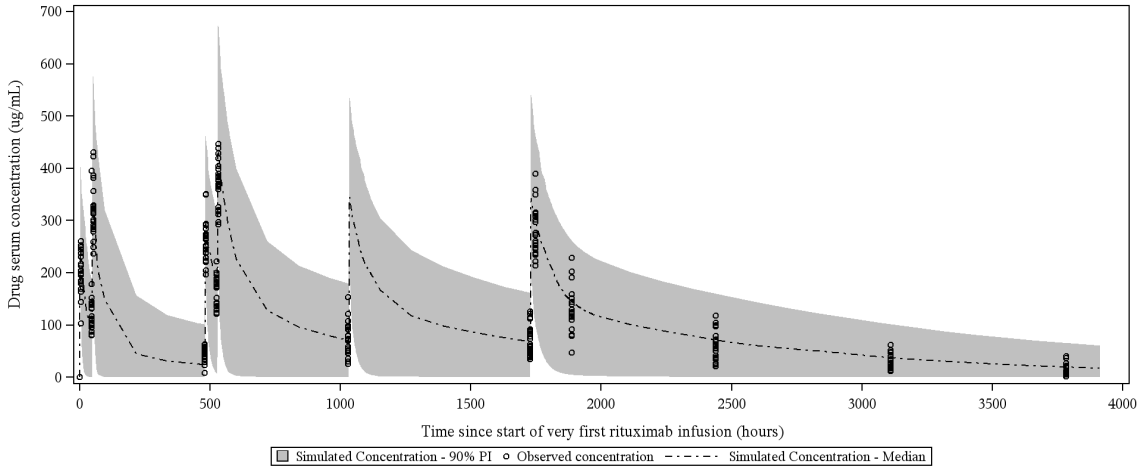
Cmax=maximum concentration of concentration-time profile. line=median; diamond=arithmetic mean.
Source: Boxplot produced from data of Study BO25380.

Comparison of Rituximab Pharmacokinetics Between Pediatric and Adult Patients with Mature B-cell Malignancies

Simulated rituximab serum concentrations in 233 pediatric patients with advanced stage mature B-NHL are summarized in

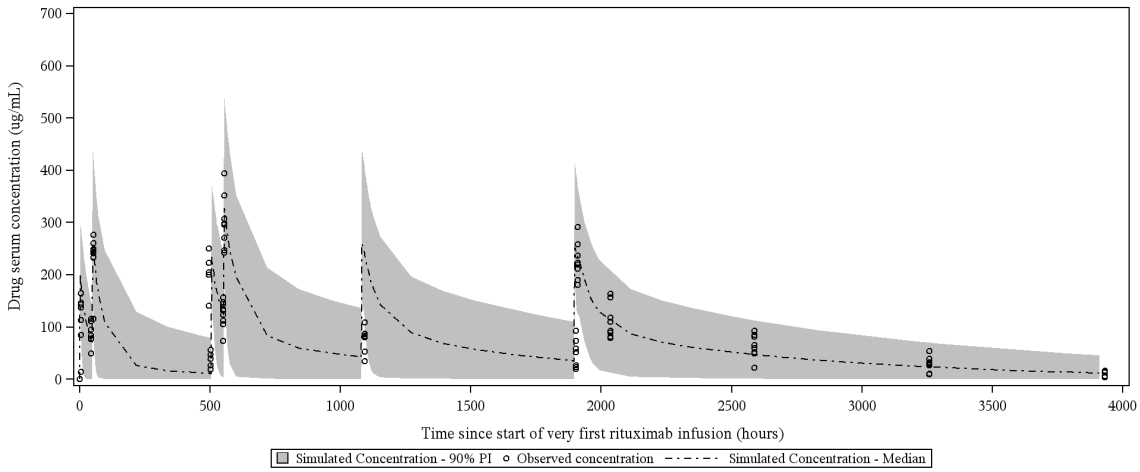
Figure 5 for the ≥3 to <12 year age group (N=125) and in Figure 6 for the ≥12 to <18 year age group (N=108) and superimposed with data from the BO25380 trial. Observed rituximab serum concentration time courses from Study BO25380 were within the 90% prediction interval (PI), indicating that the PK data in pediatric patients were in alignment with the PK characteristics of rituximab in adult patients with hematological malignancies, established previously using population PK methods.

Figure 5 Observed and Simulated Concentrations of Rituximab Against Time for the Age Group ≥3 to <12 years



PI=Prediction Interval (range 5th to 95th percentile).
Source: End-of-text Figure 14.2.6.2.4 Study BO25380 Primary CSR

Figure 6 Observed and Simulated Concentrations of Rituximab Against Time for the Age Group ≥12 to <18 years



PI=Prediction Interval (range 5th to 95th percentile).
Source: End-of-text Figure 14.2.6.2.4 Study BO25380 Primary CSR.

Effect of BSA

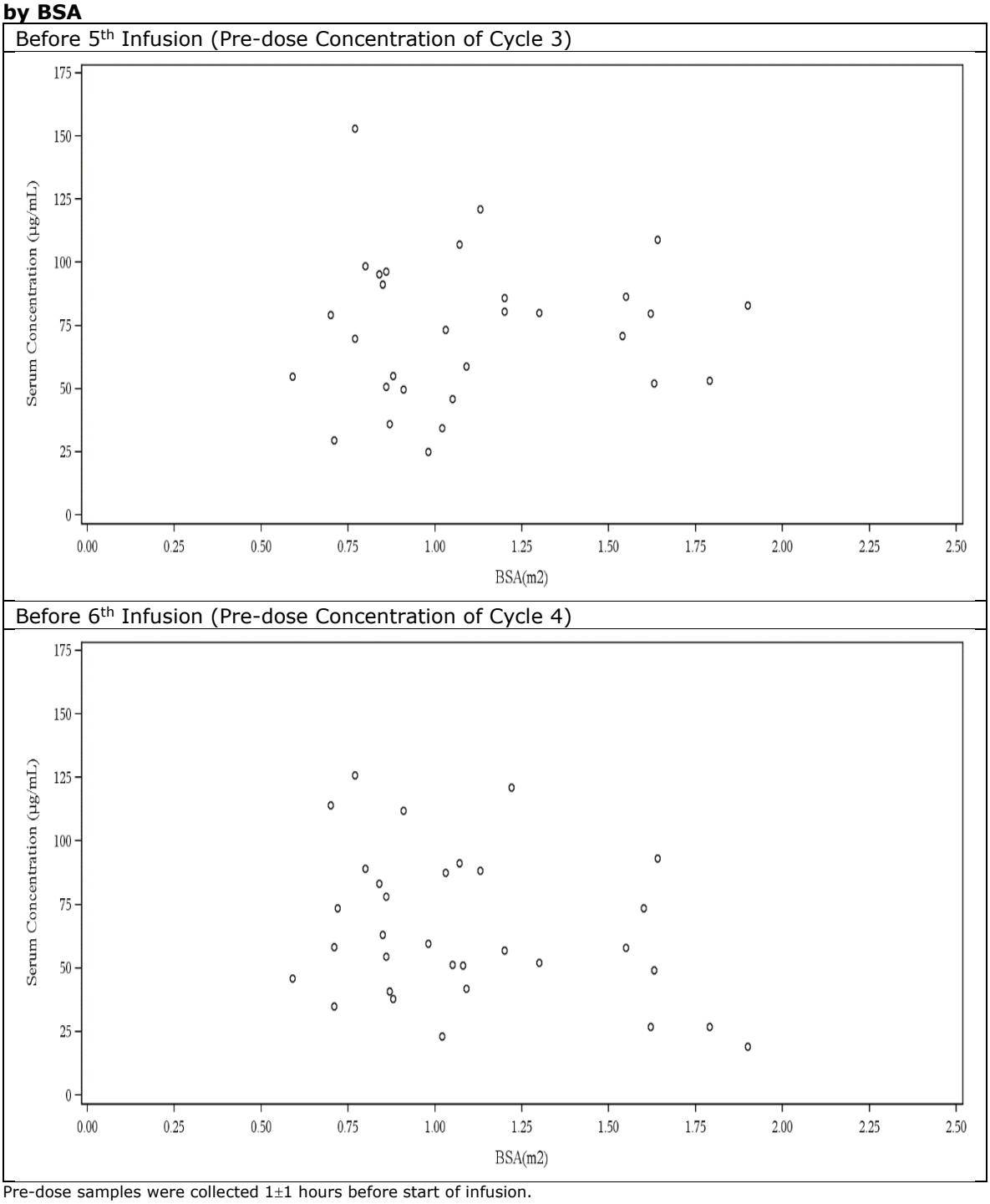
As is typical for monoclonal antibodies, rituximab PK parameters depend on body size measurements. Clearance and volume parameters increased with BSA. BSA was the most important covariate for clearance and volume parameters in the population PK model in adults (1071510).

Across the BSA range of 0.5 to 2 m^2, there was no trend for a BSA effect on the trough concentrations of rituximab and the AUC of rituximab in the scatter plots (Figure 7, Figure 8), whereas the maximum concentrations of rituximab tended to be higher in patients with a lower BSA (Figure 9).

The adjustment of rituximab dose by BSA was effective for the trough concentrations and the AUC values, which are both important drivers for efficacy. For C_{max}, which is mainly dependent on volume of distribution, the BSA adjustment of dose lead to slightly higher C_{max} values for patients with a lower BSA, but they remained mostly within the range observed in adults after 3 weekly dosing (mean C_{max} [Cycle 7]: 255 µg/mL, range: 153 to 381 µg/mL and were well within the range after 1 weekly dosing (mean C_{max}

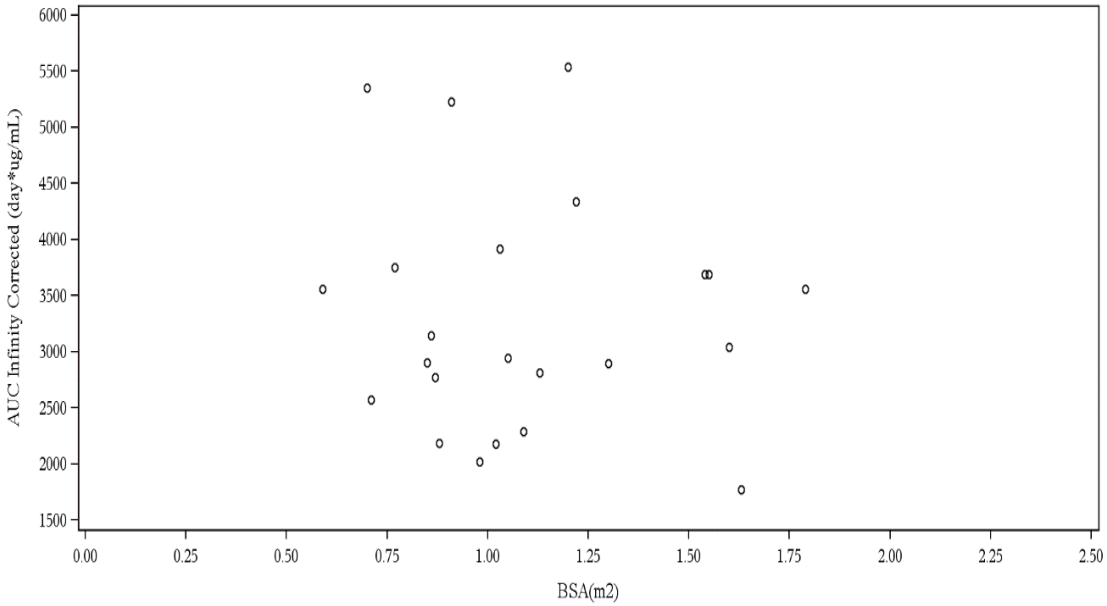
after fourth infusion: 486 µg/mL, range: 77.5 to 996.6 µg/mL [MabThera SmPC]). Thus, dosing rituximab by BSA was considered appropriate for pediatric patients with advanced stage mature B-NHL.

Figure 7 Scatterplot of Observed Trough Concentrations of Rituximab of Study BO25380 by BSA



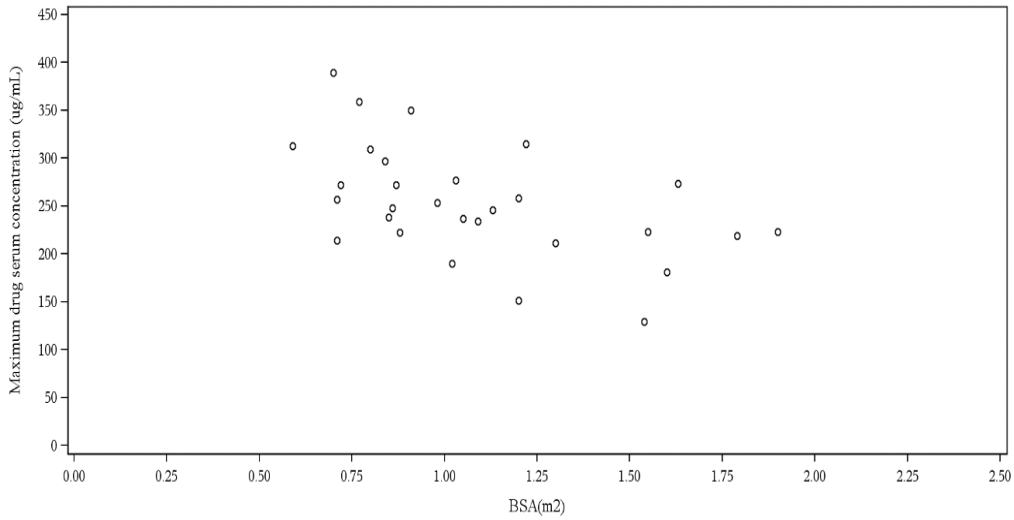
Pre-dose samples were collected 1±1 hours before start of infusion.
Source: Scatterplots produced from data of Study BO25380.

Figure 8 Scatterplot of Observed $AUC_{6th\ dose}$ of Cycle 4 of Study BO25380 by BSA



$AUC_{6th\ dose}$ (=$AUC_{0-\infty,corr}$): Area under the concentration-time curve of the 6th dose (**Error! Reference source not found.**).
Source: Scatterplot produced from data of Study BO25380.

Figure 9 Scatterplot of Observed C_{max} of Cycle 4 of Study BO25380 by BSA

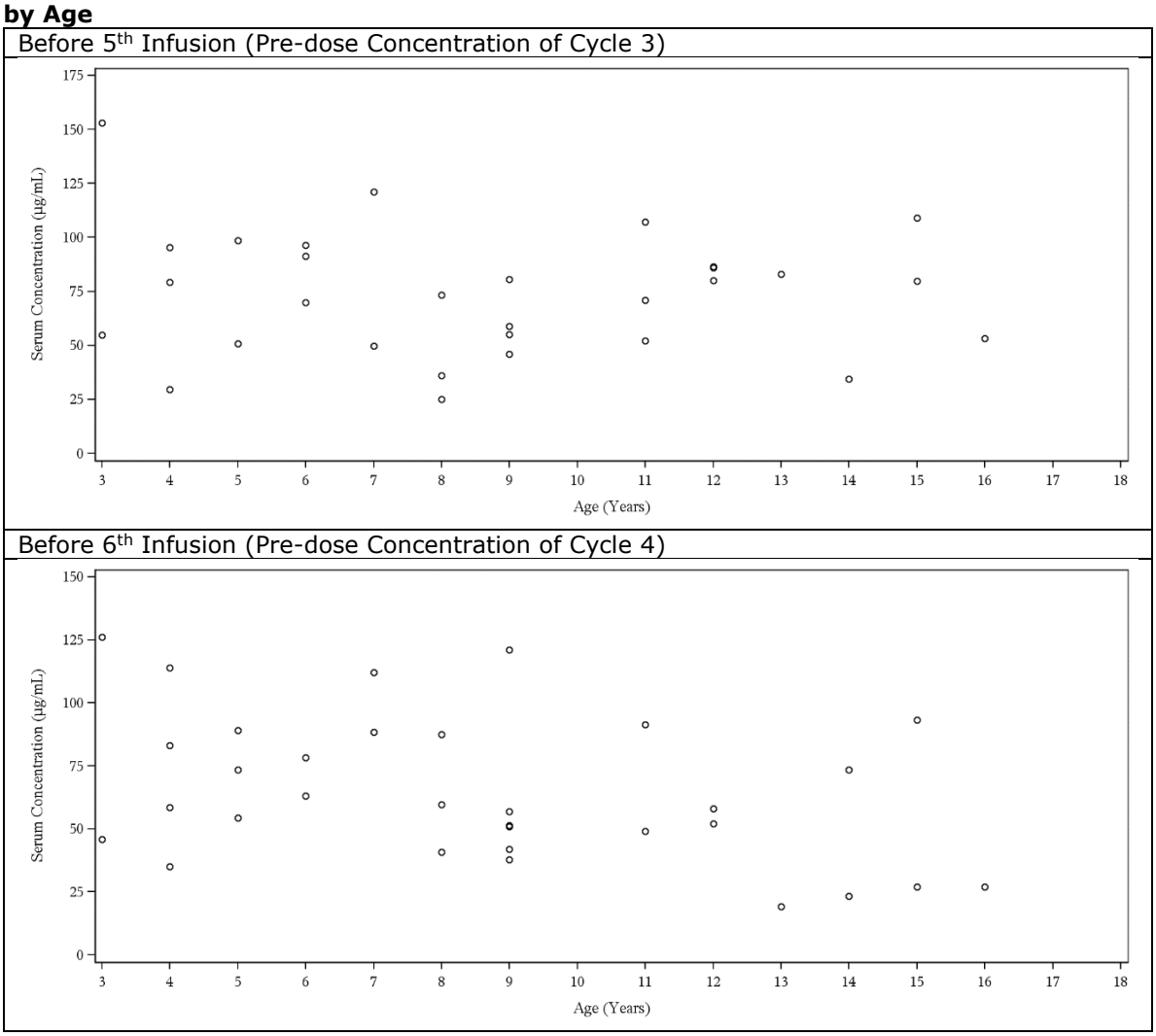


C_{max}=maximum concentration of concentration-time profile. Source: Scatterplot produced from data of Study BO25380.

Effect of Age

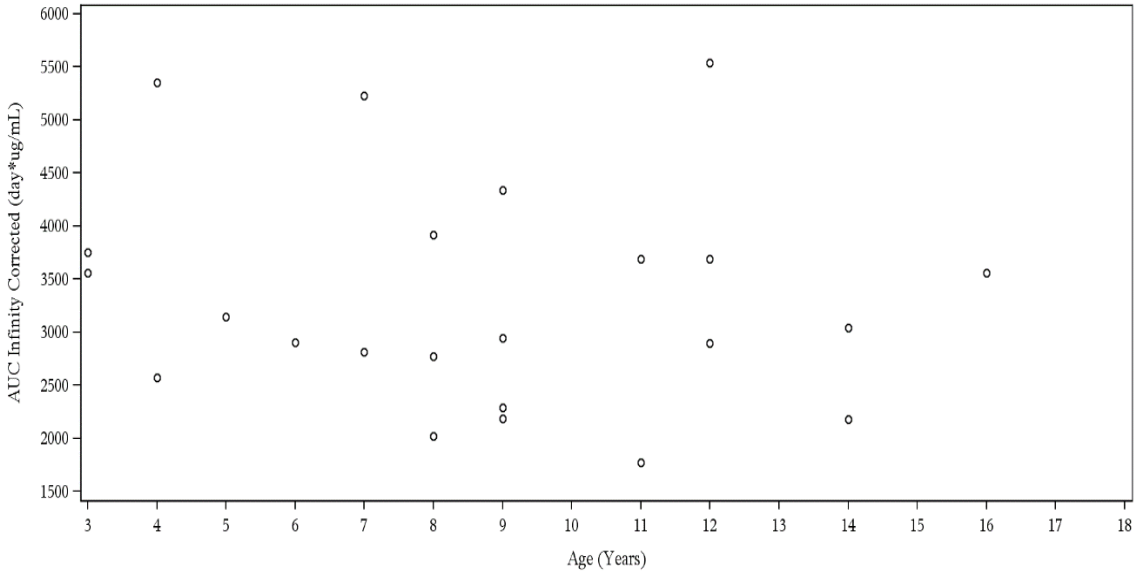
Since age is correlated with BSA, a similar pattern was observed for the effect of age on systemic exposure (C_{max}, AUC, C_{trough}) of rituximab as was seen for BSA. Across the age range of ≥3 to <18 years, there was no trend for an age effect on the trough concentrations (Figure 10) and the AUC (Figure 12) in the scatterplots, whereas, the maximum concentrations of rituximab tended to be higher in younger patients (Figure 12). However, they mostly remained within the range observed in adult patients after 3 weekly dosing (mean C_{max} [Cycle 7]: 255 µg/mL, range: 153 to 381 µg/mL and were well within the range after 1 weekly dosing (mean C_{max} after fourth infusion: 486 µg/mL, range: 77.5 to 996.6 µg/mL [MabThera SmPC]).

Figure 10 Scatterplot of Observed Trough Concentrations of Rituximab of Study BO25380 by Age



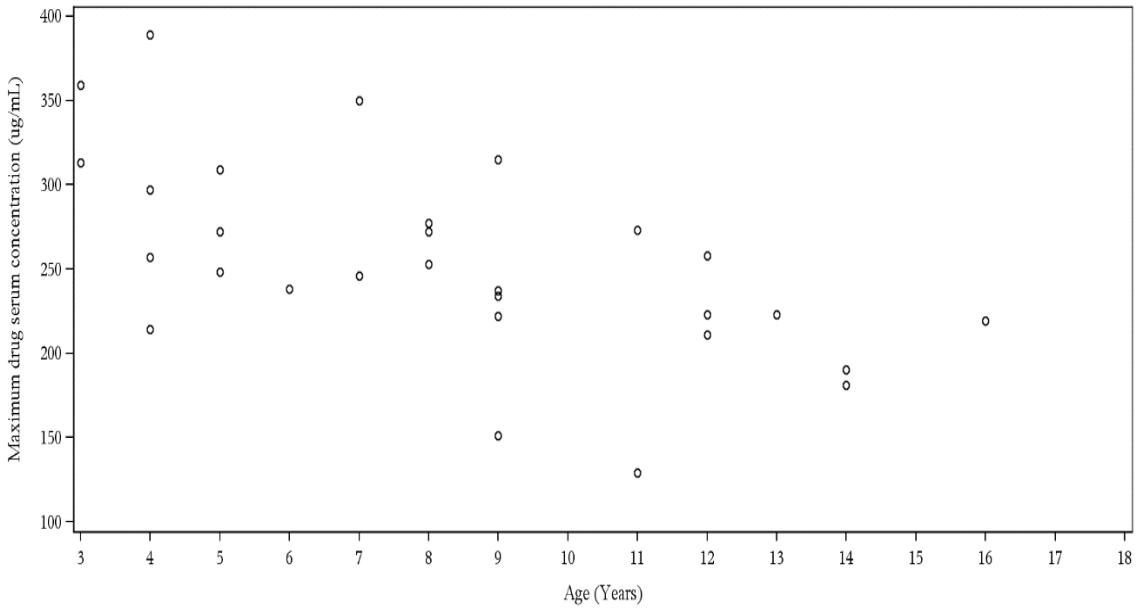
Pre-dose samples were collected 1±1 hours before start of infusion. Source: Scatterplots produced from data of Study BO25380.

Figure 11 Scatterplot of Observed $AUC_{6th\ dose}$ of Cycle 4 of Study BO25380 by Age



$AUC_{6th\ dose}$ (=$AUC_{0-\infty,corr}$): Area under the concentration-time curve of the 6th dose (**Error! Reference source not found.**).
Source: Scatterplot produced from data of Study BO25380.

Figure 12 Scatterplot of Observed C_{max} of Cycle 4 of Study BO25380 by Age



C_{max}=maximum concentration of concentration-time profile. Source: Scatterplot produced from data of Study BO25380.

The Applicant presented an updated pop PK model and included a maturation factor to the constant clearance component to take into account the effect of the FcRn variation with age. The time independent clearance component was mostly dependent on B-cell count and tumour size and these are not expected to be linked to maturation. Values for covariates had been taken from the literature. The Applicant adequately justified why a PBPK model not would be expected to provide additional information compared to the updated population PK model.

Simulations had been conducted with the updated model to predict exposure in children < 3 years. Ctrough and cumulative $AUC_{1\text{-}4\ cycles}$ are comparable, but Cmax higher in the youngest population.

Table 3 Predicted PK Parameters following two Rituximab Doses of 375 mg/m² (48 hours apart) per Cycle for the first 2 Cycles followed by one Rituximab Dose of 375 mg/m² per Cycle in Cycle 3 and Cycle 4

Age group	≥ 6 mo - < 3 years	≥ 3 mo - < 12 years	≥ 12 mo - < 18 years
C_{trough} (µg/mL)	47.5 (0.01 - 179)	51.4 (0.00 - 182)	44.1 (0.00 - 149)
C_{max} (µg/mL)	605 (243 - 950)	395 (140 - 851)	357 (114 - 666)
$AUC_{1\text{-}4\ cycles}$ (µg*day/mL)	13501 (278 - 31070)	11609 (135 - 31157)	11467 (110 - 27066)

Results are presented as median (min – max)

Pharmacokinetic data from literature search

A systematic literature search was conducted to identify external rituximab PK/PD data in pediatric patients with mature B-cell malignancies in the following databases: BIOSIS Previews®, Derwent Drug File, Embase®and Medline®. The search terms included PK/PD-related concepts such as absorption, distribution, elimination, and bioavailability. These terms were combined with the drug term "rituximab" (including synonyms) and "B-cell malignancies". The results were restricted to studies in children and no date or language restriction was applied. Based on these criteria, publications providing supportive evidence for the PK/PD of rituximab in children with B-cell malignancies qualified for inclusion.

A total of 17 articles were retrieved from the literature search, 7 of which contained PK data in pediatric patients with mature B-cell malignancies exposed to rituximab. All 7 articles described the same data i.e. the PK of rituximab which was studied in children and adolescents with de novo intermediate and advanced mature B-cell lymphoma/leukemia by the Children's Oncology Group (COG), which was the pilot study of Study BO25380 (ClinicalTrials.gov identifier: NCT0057811; other identifiers: CDR0000271941, COG-ANHL01P1, U2334S).

The pilot study was designed for children and young adults up to the age of 29 years. The rituximab dose and dosing regimen was the same as in Study BO25830. The authors noted that children of Group B (<13 years) tended to exhibit higher post-dose concentrations, similar trough levels and shorter elimination half-life than adolescents (≥13 years) of Group B while acknowledging that the patient numbers were too small to demonstrate an age-dependent difference.

The dose-dense rituximab dosing in the two induction cycles followed by 2 consolidation cycles with 1 dose of rituximab per treatment cycle, resulted in average post-dose rituximab concentrations of 245-384 µg/mL with sustained trough concentrations of 55 and 107 µg/mL. The elimination half-life was 26-29 days. The authors concluded that rituximab can be safely added to FAB chemotherapy with high early rituximab post-dose/trough levels and long elimination half-life.

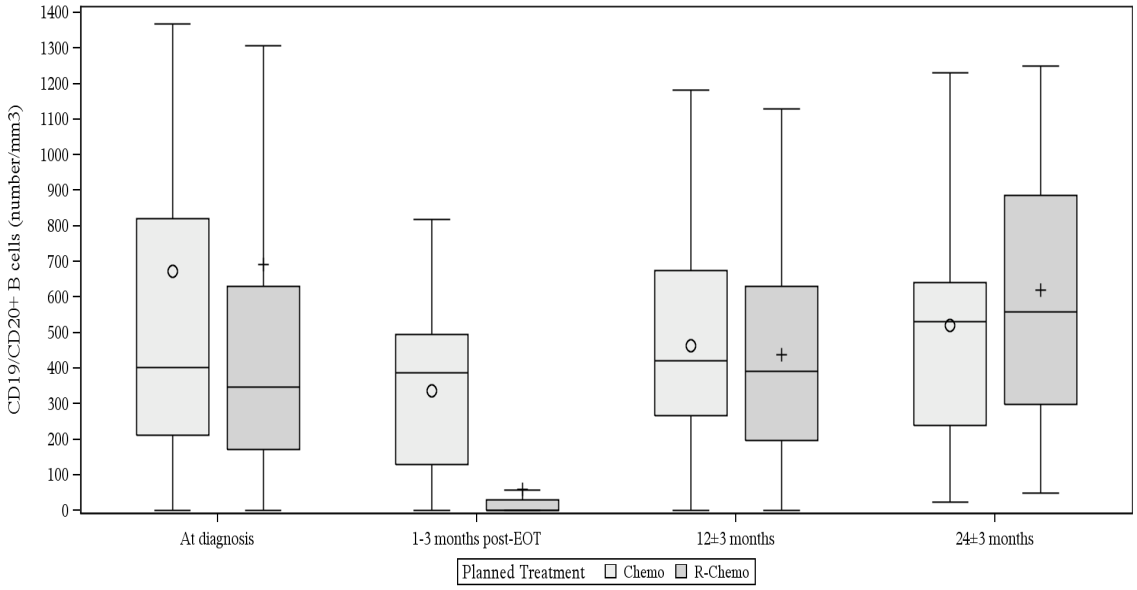
2.3.3. Pharmacodynamics

Primary and secondary pharmacology

In Study BO25380, CD19/CD20 B-cells were not measured during rituximab treatment. The first post-rituximab treatment sample was taken 1 to 3 months post-treatment. Overall, consistent with the mode of action of rituximab, B-cell counts were lower in the rituximab plus chemotherapy (R-Chemo) group

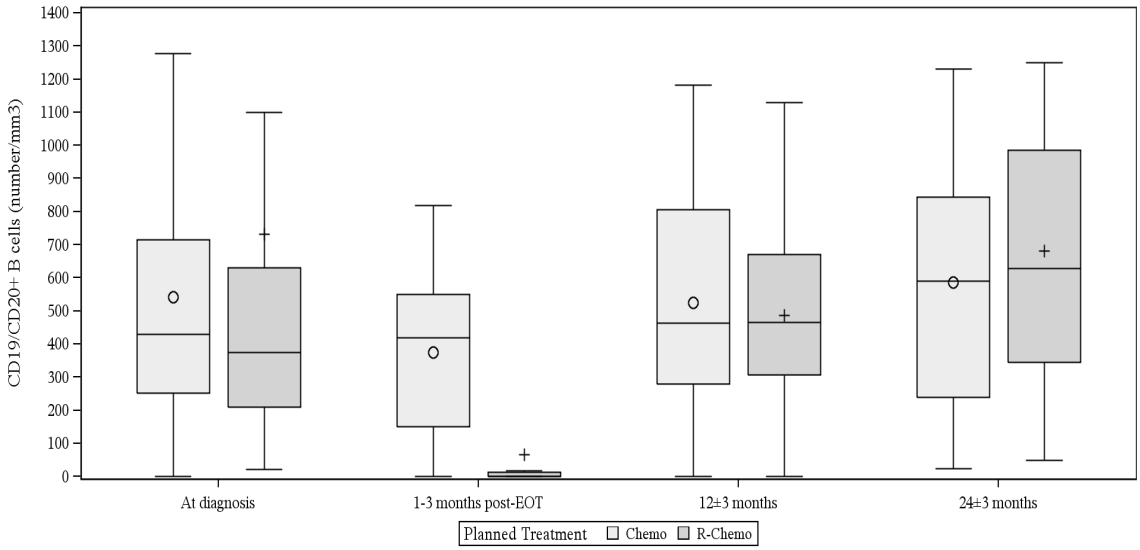
compared to the chemotherapy alone (Chemo) group 1 to 3 months post-treatment; but, B-cell counts became comparable between the two groups at the subsequent time points 12±3 months and 24±3 months post-treatment.

Figure 13 Overall Time-course of B-cell Count



[a]Chemo: N=63 (at diagnosis); 22 (1-3 months post-treatment); 45 (12±3 months post-treatment); 9 (24±3 months post-treatment)
R-Chemo: N=99 (at diagnosis); 58 (1-3 months post-treatment); 85 (12±3 months post-treatment); 18 (24±3 months post-treatment)

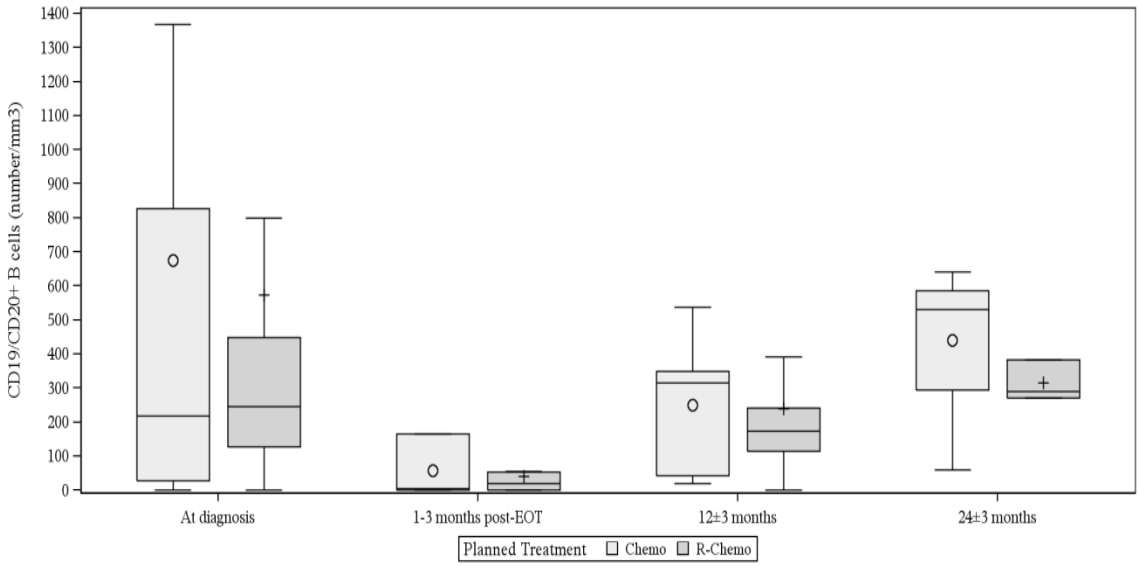
Figure 14 Time-course of B-cell Count in the Age Group ≥3 to <12 Years[b] in the two Treatment Groups



[b]Chemo: N=45 (at diagnosis); 18 (1-3 months post-treatment); 35 (12±3 months post-treatment); 5 (24±3 months post-treatment)
R-Chemo: N=73 (at diagnosis); 47 (1-3 months post-treatment); 61 (12±3 months post treatment); 15 (24±3 months post treatment)

Figure 15 Time-course of B-cell Count in the Age Group ≥12 to <18 Years

Age Group [c]



[c]Chemo: N=17 (at diagnosis); 3 (1-3 months post-treatment); 10 (12±3 months post-treatment); 4 (24±3 months post-treatment)
R-Chemo: N=25 (at diagnosis); 8 (1-3 months post-treatment); 21 (12±3 months post-treatment); 3 (24±3 months post-treatment)
[a,b,c]line=median; circle/cross=arithmetic mean.
[a,b,c]At diagnosis=at screening diagnosis prior to treatment (baseline).
[a,b,c]Source: Boxplots produced from data of Study BO25380; no boxplot produced for age group 6 months to <3 years as there were many missing values and only 3 patients with CD19/CD20 B-cell data.

Based on the mode of action of rituximab in which the antibody binds to CD20 on B-lymphocytes and eliminates these cells via a number of different mechanisms, including antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), no significant differences in PK properties were anticipated between pediatric patients and adult patients. This is supported by the fact that CD20 is expressed to the same extent in adult and pediatric patients with the same lymphoid malignancy (Perkins et al. 2003; Plosker and Figgitt 2003) and B-cell counts and distribution are expected to be similar in adult and pediatric patients (Duchamp et al. 2014).

Immunogenicity

Antidrug-antibodies were not measured in Study BO25820.

2.3.4. Discussion on clinical pharmacology

A medical need of rituximab in the condition Treatment of diffuse large B-cell lymphoma has been identified in children from 6 months to less than 18 years. The proposed dose of Rituximab is 375mg/m² intravenous use for the entire paediatric age range. In clinical practice, rituximab is used in the EU paediatric community in paediatric B-NHL and the proposed dose of 375 mg/m2 is the dose referred to in the various published papers.

The PK of rituximab was investigated in a subset of subjects in Study BO25380, treated with a dose dense rituximab dosing regimen of six 375 mg/m2 doses (2+2+1+1). In total, 35 paediatric subjects were included in the PK sub study: 26 in the ≥ 3 to < 12-year age group and 9 in the ≥ 12 to < 18-year age group. Despite of a protocol amendment to included subjects below 3 years of age in the PK study, no

subjects in the youngest age group ≥ 6 months to < 3 years were included. Subjects were evenly distributed within the 3-16-year age range.

Fifteen PK samples were planned during treatment, including trough values before each dose. Inter-patient variability was moderate (16 – 52 %). The highest serum rituximab concentrations were reached following the fourth infusion (second infusion of Cycle 2) with a geometric mean of 367 µg/mL (age group ≥3 to <12 years) and 297 µg/mL (age group ≥12 to <18 years). The elimination half-life was 25,7 days, similar between the two age groups and comparable to the median adult value of 22 days.. Besides a trend towards higher Cmax in younger patients, rituximab exposure were comparable both between and within age groups. A previously developed PK model was initially used to compare PK of rituximab in paediatric and adult subjects. The model indicates comparable PK in adult and paediatric subjects with hematological malignancies in both age groups ≥3 to <12 year and ≥12 to <18 year, but differences in body composition, extravasation, and capillary permeability may have an impact on distribution, especially in infants and toddlers. The Applicant had not addressed how the model is relevant for the youngest children. The Applicant presented an updated adult NHL pop PK model and included a maturation factor to the constant clearance component to consider the effect of the FcRn variation with age. The time independent clearance component is mostly dependent on B-cell count and tumour size and these are not expected to be linked to maturation. Values for covariates had been taken from the literature. It was adequately justified why a PBPK model not would be expected to provide additional information compared to the updated population PK model.

Simulations had been conducted with the updated model to predict exposure in children < 3 years. Ctrough and cumulative AUC1-4 cycles were comparable across age groups, but Cmax higher in the youngest population. It is agreed that the higher Cmax (over)predicted with the model not is expected to have clinical relevance. This is supported by paediatric rituximab data from other indications. The covariates influencing the rituximab PK parameters were tumor size at baseline, B-cells count at baseline, and BSA. BSA values from a study with tocilizumab in children with juvenile immune arthritis was used as representative of BSA distribution and tumor size at baseline was simulated from the SABRINA trial in adults with follicular lymphoma. Patients down to the age of 3 are included in the PK data set. The Applicant presented sensitivity analyses to show how differences in tumor size could have a impact on rituximab PK in children**.** Tumor size only has an impact on time dependent clearance, and smaller tumor size equals higher exposure. In the sensitivity analysis, predicted values of Ctrough, AUC1-4 cycles and Cmax are presented. Notably, Cmax- which would be expected to be the most relevant parameter for safety concerns – is mostly slightly affected. Ctrough and AUC1-4 cycles are considerably higher for lower tumor sizes.

BSA is the most important covariate for rituximab clearance and volume parameters in adults. Across the BSA range of 0.5 to 2 m^2, there was no trend for a BSA effect on the trough concentrations of rituximab and the AUC of rituximab in the scatter plots but Cmax tended to be higher in patients with a lower BSA. The Applicant was asked to discuss if even lower BSA e.g. in children from 6 months to 3 years of age would be expected to have even higher exposure and if a BSA based dose also is appropriate in this age group**.** The updated pop PK model includes a maturation factor, and in the simulations, BSA ranging from 0.35m2 to 2.06 m2 were included. This range is relevant for children < 3 years. The predicted exposure values support a BSA based dose.

Across the age range of ≥3 to <18 years, there was no trend for an age effect on rituximab exposure. The proposed indication is intended to be in children from 6 months of age. As previously mentioned, no PK data are available in children in the age group 6 month to 3 years of age, but published data and safety data from safety databases support that rituximab 375 mg/m2 is safe and efficacious in B-NHL also in the smallest children. In clinical practice, rituximab is used in the EU paediatric community in paediatric B-NHL and the proposed dose of 375 mg/m2 is the dose referred to in the various published papers. The PK of monoclonal antibodies in smaller children has not been fully elucidated, e.g. differences in ECF could influence Vd and expectedly smaller tumor sizes in the youngest children and differences in B-cell counts

could have impact on clearance (Mailk and Edginton 2018, Edlund et al 2014), but simulations and sensitivity analysis with an updated pop PK model taking maturation into account support the proposed dose in the youngest age group 6 months to 3 years.

2.3.5. Conclusions on clinical pharmacology

A BSA-based dose-dense rituximab regimen of 375 mg/m2 is acceptable in paediatric subjects from the age of 3 years, even though no PK data are available in subjects below the age of 3.

Rituximab exposure in both age groups ≥ 3 to < 12 year age group and ≥ 12 to < 18 year is comparable and simulations using an updated pop PK model including a maturation factor to the constant clearance component to take into account the effect of the FcRn variation with age support an extension of the indication B-NHL indication to the age group 6 months to 3 years can be accepted despite lack of clinical PK data in the age group.

The following measures are considered necessary to address issues related to pharmacology:>

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

In this study, rituximab was administered at a dose of 375 mg/m2 in a dose-dense way whereby in each of the 2 induction cycles 2 infusions of rituximab were administered within 48 hours followed by the consolidation cycles with one rituximab infusion per Clinical Study Report Final IGR2009/1593 (IGR), ANHL1131 (COG) 43 treatment cycle. The basis for this dose-dense rituximab regimen were the results of the pilot study ANHL01P1 conducted by the COG where it was demonstrated that the dose-dense rituximab therapy can be safely added to chemotherapy and can result in a 95% 3-year EFS (Goldman et al, 2013; Barth et al, 2013).

The PK of rituximab has been well studied in adults with NHL and is best described by a 2-compartment model with time-varying clearance (Li et al, 2007). As common for monoclonal antibodies, body surface area (BSA) had an impact on clearance and volume parameters. Therefore a BSA-based dosing is expected to provide similar exposure in adult and pediatric patients. Based on the mechanism of action of rituximab, in which the antibody binds to CD20 on B-lymphocytes and eliminates these cells via a number of different mechanisms including antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity, no significant differences in PK were anticipated between pediatric patients and adult patients since CD20 is thought to be expressed to the same extent in adult and pediatric patients with the same lymphoid malignancy. Therefore, and in line with the pilot study ANHL01P1, the same dose as for adults, i.e., 375 mg/m2, was administered in the study.

2.4.2. Main study

Title of Study:

Phase 3 Study IGR2009/1593 (IGR)/ANHL1131 (COG), Intergroup Trial for Children or Adolescents With B-Cell NHL or B-AL: Evaluation of Rituximab Efficacy and Safety in High Risk Patients. (Inter B NHL Ritux 2010 study).

Methods

Study participants

Inclusion Criteria

- Histologically or cytologically proven*B-cell malignancies, either BL or B-AL (=Burkitt leukemia, = L3-AL) or diffuse large B-cell NHL or aggressive mature B-cell NHL not otherwise specified or specifiable.
- Stage III with elevated LDH level ("B high," LDH > ULN × 2), or any stage IV or B-AL.
- *Slides were reviewed by the national pathology panel, but review was not mandatory before registration.
- 6 months to less than 18 years of age at the time of consent.
- Males and females of reproductive potential agreed to use an effective contraceptive method during the treatment, and after the end of treatment for 12 months for women, taking into account the characteristics of rituximab, and for 5 months for men, taking into account the characteristics of methotrexate.
- Completed initial work-up within 8 days prior to treatment that allowed definite staging.
- Patients were able to comply with scheduled follow-up and with management of toxicity.
- Patients and/or their parents or legal guardians provided signed informed consent.

Exclusion Criteria

• Patients with follicular lymphoma, mucosa-associated lymphoid tissue, or nodular marginal zone.

• Patients with congenital immunodeficiency, chromosomal breakage syndrome, prior organ transplantation, previous malignancy of any type, or known positive human immunodeficiency virus serology.

• Evidence of pregnancy or lactation period.

• There was no exclusion criterion based on organ function. Dosing guidelines for organ dysfunction are provided in Annexure D1 of the protocol (Appendix 12.1.1).

• Past or current anti-cancer treatment except corticosteroids of less than 7 days duration in total.

• Tumor cell negative for CD20 (absence of result due to technical problems in the presence of other characteristics suggestive of BL/DLBCL, including genetic and phenotypic features, was not an exclusion criterion).

• Prior exposure to rituximab.

• Severe active viral infection, especially hepatitis B. Severe infection (such as sepsis, pneumonia, etc.) was to be clinically controlled at the time of randomization.

• Hepatitis B carrier status history of hepatitis B virus (HBV) or positive serology. A patient was considered an HBV carrier or to have had HBV infection in case of:

o Unimmunized and hepatitis B surface antigen and/or anti-hepatitis B surface antibody and/or anti-hepatitis B core antibody positive

o Immunized and hepatitis B surface antigen and/or anti-hepatitis B core antibody positive

• Participation in another investigational drug clinical trial.

• Patients who, for any reason, were not able to comply with the national legislation. To note, PMLBL patients were not enrolled under the phase III portion of the Inter-B-NHL Ritux 2010 protocol. Those

patients were enrolled under a separate phase II single-arm study, as they usually require a different chemotherapy regimen. Data for phase II study will be reported in a separate CSR.

Withdrawal Criteria

The only criteria for patient withdrawal from the trial were:

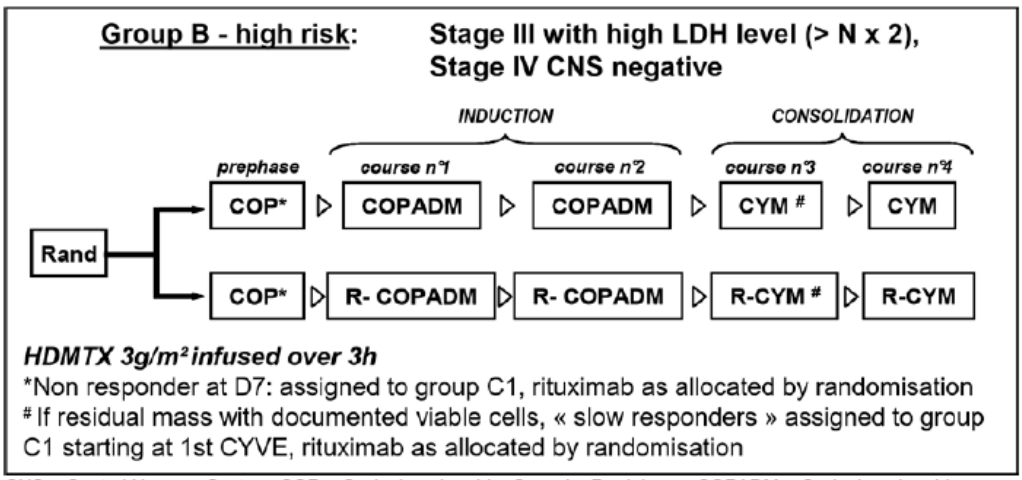
- Hepatitis B virus-positive serology known after randomization.
- Parent or patient consent withdrawal.

Treatments

Therapeutic Group B

In therapeutic Group B, the pre-phase was followed by 4 courses of chemotherapy: 2 induction courses (COPADM) and 2 consolidation courses (CYM). Study treatment administration details for therapeutic Group B are schematically presented :

Figure 2 Study Treatment Schema - Group B



CNS = Central Nervous System; COP = Cyclophosphamide, Oncovin, Prednisone; COPADM = Cyclophosphamide, Oncovin, Prednisolone, Adriamycin, Methotrexate; CYM = Cytarabine, Methotrexate; HDMTX = High-dose Methotrexate; LDH = Lactate Dehydrogenase; R = Rituximab; RAND = Randomization

Source: Protocol (Appendix 12.1.1), Section 10.3, Group B High-risk schema

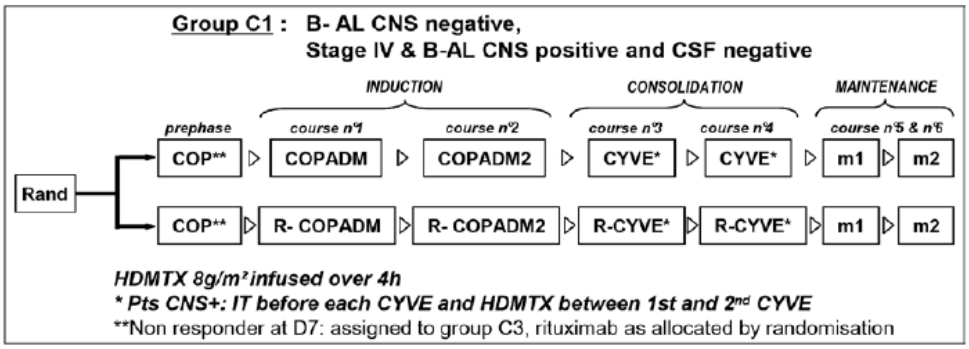
November 2015: The randomization was halted and all patients received the arm of treatment with rituximab.

Consolidation: 2 courses of CYM or R-CYM (November 2015 all patients received R-CYM). Following recovery from first (R-)CYM, if CR was not obtained the patient ("slow responder") was to be switched to C1 regimen, – starting at (R-CYVE). If they were randomized to receive rituximab, they were to receive rituximab only with the first (R-)CYVE in order to receive a total of 6 courses.

Therapeutic Group C1

In Groups C1 and C3, the pre-phase was followed by 4 courses: 2 induction courses (COPADM) with HDMTX, and 2 consolidation courses (CYVE). In those patients who were responders at completion of the consolidation phase, 2 maintenance courses (M1 and M2) were planned. Study treatment administration details for therapeutic Group C1 are schematically presented in Figure 3.

Figure 3 Study Treatment Schema - Group C1



B-AL = Burkitt Leukemia; CNS = Central Nervous System; COP = Cyclophosphamide, Oncovin, Prednisone; COPADM = Cyclophosphamide, Oncovin, Prednisolone, Adriamycin, Methotrexate; CSF = Cerebrospinal Fluid; CYVE = Cytarabine, Vepeside; HDMTX = High-dose Methotrexate; Pts = Patients; R = Rituximab; RAND = Randomization

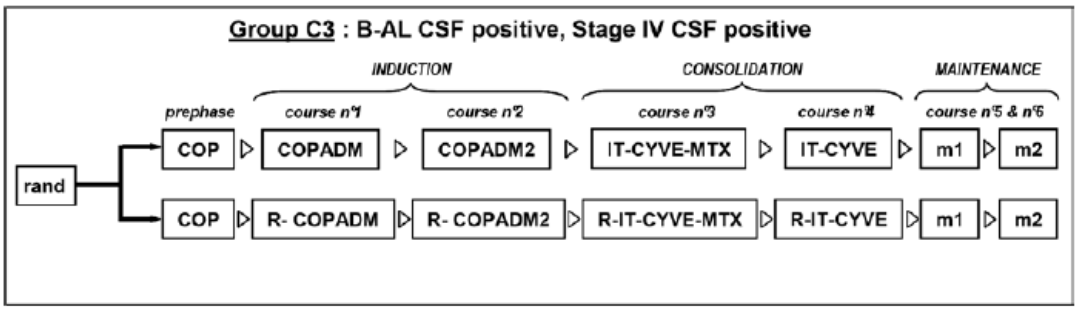
Source: Protocol (Appendix 12.1.1), Section 10.4, Group C1 (CSF Negative) schema

November 2015: The randomization was halted and all patients received the arm of treatment with rituximab.

Therapeutic Group C3

Study treatment administration details for Group are schematically presented in Figure 4.

Figure 4 Study Treatment Schema - Group C3



B-AL = Burkitt Leukemia; COP = Cyclophosphamide, Oncovin, Prednisone; COPADM = Cyclophosphamide, Oncovin, Prednisolone, Adriamycin, Methotrexate; CSF = Cerebrospinal Fluid; CYVE = Cytarabine, Vepeside; HDMTX = High-dose Methotrexate; IT = Intrathecal; MTX = Methotrexate; R = Rituximab; RAND = Randomization

Source: Protocol (Appendix 12.1.1), Section 10.5, Group C3 (CSF Positive) schema

HDMTX 8 g/m2 infused over 24 hours except in 1st COPADM.

November 2015: The randomization was halted and all patients received the arm of treatment with rituximab.

Please refer to Section 10 of the protocol (Appendix 12.1.1) for details related study drug administration for each group.

In all those 3 groups and between 2 courses of the induction or the consolidation phases, if the next course was postponed due to safety reasons, the patients had to receive waiting COP courses.

Objectives

The primary objective of the study was to test whether adding 6 rituximab to the standard LMB chemotherapy regimen improved the EFS compared with LMB chemotherapy alone in the untreated children and adolescent patients with advanced-stage B-cell NHL/B-AL (stage III and lactate dehydrogenase [LDH] > upper limit of normal [ULN] × 2, any stage IV, or B-AL). EFS was defined as the time between randomization and occurrence of progressive disease, relapse, second malignancy, death from any cause

or nonresponse as evidenced by detection of viable cells in residue after the second CYVE course (for therapeutic Group C patients and therapeutic Group B patients who switched to therapeutic Group C), whichever event occurred first.

The secondary objectives were as follows:

• To study the CR rate and OS.

• To evaluate safety in all study arms, including toxic deaths, adverse events (AEs) recorded using the National Cancer Institute–Common Terminology Criteria (NCI-CTC) Version 4 (non-hematological toxicity Grade ≥ 3, infections Grade 3 to 5), cardiac toxicity (CTC Grade 2 to 5 and evolution of left ventricular ejection fraction [LVEF] and left ventricular shortening fraction [LVSF]), number of days with platelet transfusions, intensive care unit admission, number of days with red blood cell (RBC) transfusions, and rituximab IRRs.

• To study the rate of patients with immunoglobulin (IgG, IgA, and IgM) level abnormally low and lymphocyte count abnormally low at 1 year and until 5-year follow-up, and to study the need for immunoglobulin infusions and levels of post (previous and re-) vaccination antibodies at 1 year.

• To study long-term (at least 5 years) risks of the use of rituximab plus chemotherapy compared with LMB chemotherapy alone in children and adolescents with advanced-stage B-NHL/B-AL (all events related [certain and probable] to therapy).

Exploratory objectives were:

• To evaluate the potential prognostic value of Minimal Disseminated Disease (MDD) and Minimal Residual Disease (MRD) in correlation with outcome*.

• To perform an economic study comparing the cost-effectiveness ratio between 2 therapeutic strategies: LMB chemotherapy with vs LMB chemotherapy without rituximab*.

• To obtain data on positron-emission tomography (PET) (-computed tomography [CT]) scan in childhood pediatric B-cell NHL*.

• To characterize the PK of rituximab in combination with LMB chemotherapy in a subset of patients.

*The MabThera PIP did not require these evaluations and therefore they are not presented in this CSR (see Section 3.10.9).

Tumour Assessment

All abnormal tumor sites at diagnosis were evaluated using the most appropriate modality and taking into account the possible context of emergency treatment to do the minimal necessary work-up. This included chest x-ray, ultrasound, CT, or magnetic resonance imaging scans for solid tumors. The response following pre-phase COP was reported into the electronic case report form (eCRF) and classified as:

• CR: Complete disappearance of all measurable or evaluable lesions (except bone), no blasts in the bone marrow or in the CSF.

• Incomplete response: 20% to 99% reduction in the product of the 2 largest diameters of measurable lesions (as long as no regrowth occurred by Day 7 after earlier shrinkage).

• Nonresponse: < 20% tumor reduction of the product of the 2 largest diameters of measurable lesions, or tumor progression, or tumor regrowth after initial shrinkage. The response status was to be evaluated after 1st (R-) CYM (therapeutic Group B) or 2nd (R-) CYVE (therapeutic Group C1 or C3) and was classified as follows:

• CR: Complete disappearance of all measurable or evaluable lesions (except bone), no blasts in the bone marrow or in the CSF.

• Considered as CR: Patients could still be considered to be in CR, even if bone lesions were not completely normalized on x-ray, if all other evidence of disease had disappeared. Similarly, a patient could still be in CR in the presence of a residual mass, provided large biopsies showed no viable cells. A small residual mass (< 2 cm) not accessible to surgery could also be considered to be in CR

(provided all other disease sites were in CR).

• Persistent disease: Existence of histologically proven residual disease.

• Disease progression or relapse: Any progression of more than 25% in the product of the 2 largest diameters of any measurable lesion, appearance of new lesions, or appearance or reappearance of Burkitt cells or tumoral large cells in BM or CSF.

Evaluation During Treatment

Response after COP at Day 7 was evaluated by clinical, radiological, and/or ultrasound examination to determine if there was any tumor reduction. Details related to investigations at diagnosis and during treatment is provided in Section 10.7 of the protocol (Appendix 12.1.1).

In case of B-AL, with only BM involvement, a BM aspirate was required to assess the response. In case of no response at Day 7 of the first pre-phase COP, the treatment was switched to a more intensive treatment (see sections 10.3.1 and 10.4.1 of the protocol (Appendix 12.1.1).

• The patient's general condition (Lansky or Karnofsky index)*.

• Full blood count, differential, and serum biochemistry (urea, creatinine, calcium, phosphorous, serum glutamic oxaloacetic transaminase, and serum glutamic pyruvic transaminase, gamma-glutamyl transferase, and electrolytes)*.

• In case of tumor lysis or evidence of renal dysfunction during initial chemotherapy glomerular filtration rate was determined by diethylenetriaminepentaacetic acid or ethylenediaminetetraacetic acid excretion before proceeding with HDMTX of the first course*.

• All known tumor sites easily evaluable clinically by standard x-rays and by abdominal ultrasonography were evaluated before each course of chemotherapy until complete regression.

• CSF was examined at time of lumbar puncture for IT therapy.

• Echocardiogram: After COP if not done prior to start of treatment and every 2 administrations of doxorubicin in therapeutic Group C.

Evaluation planned during each chemotherapy course:

Blood counts were measured at least twice weekly after every cycle, generally 3 times weekly at the time of nadir. The patient's general condition (Lansky or Karnofsky index) was documented regularly during therapy in the patient's medical records*.

Evaluation of remission:

Remission had to be evaluated at a specified time point. For evaluation of CR, all sites with initial tumor involvement were fully evaluated. PET (-CT) scan was recommended, and the result was reported in the eCRF.

Patients treated in therapeutic Group B had to be in CR after course n°3 [1st (R-)CYM. In case of a residual mass with documented viable cells (histologically proven persistent disease), patients were to be switched to therapeutic Group C1 to be treated more intensively starting at consolidation CYVE 1 (course n 3), rituximab as allocated by randomization.

*These data are not reported in the CSR because the laboratory data were not collected in the clinical database.

Tumor Investigations at Completion of Treatment

At completion of treatment, all initially positive sites were evaluated to confirm remission. This included radiological examinations, BM aspirate, and lumbar puncture examination, as appropriate.

Follow-up of Immune Status

Immune functions will be assessed:

• At diagnosis prior to treatment,

• 1 month after the end of treatment, i.e., 2 months after the start of the last course of chemotherapy, and

• Prior to immunoglobulin substitution if decided, - 1 year following study entry in all patients - and yearly, if not normalized at 1 year. This immune functions evaluation is only for patients without event or before event (event as defined in EFS). The immune functions evaluation includes:

• The total peripheral blood lymphocyte count and CD19+CD20+ B cells evaluated using flow cytometry,

• The serum levels of IgG, IgA, and IgM

• Serum antibodies to polioviruses and tetanus and diphtheria toxoids will be measured using enzyme-linked immunosorbent assays, as well as serum antibodies to *pneumococcus* and *Haemophilus influenzae*, andx

• Optional evaluation: peripheral blood counts of various lymphocytes subsets [CD3+, CD3+CD4+, CD3+CD8+, as well as CD3−CD16+ (or CD3−CD56+, or CD3−CD56+ CD16+) natural killer cells] using flow cytometry.

Outcomes/endpoints

Primary endpoint: EFS

The primary endpoint of the study is EFS, defined as time between randomization and progressive disease, relapse, second malignancy, death from any cause, or non-response, as evidenced by detection of viable cells in residue after the second CYVE course (for therapeutic Group C patients and therapeutic Group B patients who switched to therapeutic Group C), whichever event occurred first.

Secondary endpoints: Overall survival (OS, time from randomization to death from any cause) and CR.

Exploratory endpoints: CR rate in therapeutic group B, response to COP

Sample size

The 3-year EFS for these patients was estimated to be about 84% with the standard chemotherapy FABLMB-96. As this study compared standard treatment with rituximab added to the standard treatment, 1-sided test was employed to prove that the addition of rituximab improves outcomes. At a 1-sided 5% level of statistical significance and using 1:1 randomization, observing 72 events would provide 90% power for the log-rank test to detect an increase in the EFS long-term from 84% to 92%, corresponding to a 50% reduction in the risk of failure, i.e., an hazard ratio (HR) of 0.5. A total of 72 events were expected out of a total of 600 eligible randomized patients (300 per treatment arm). The enrollment rate for these patients was expected to be 130 to 150 patients per year, suggesting a total enrollment period (including 6 months to get to steady-state) of 4 to 5 years.

Randomisation

Randomization of patients followed the initial work-up to assign patients to relevant therapeutic groups based on their disease stage.

The 1:1 randomization is stratified on the following characteristics:

- National group: Italy, Belgium, UK, Netherlands, Hungary, Poland, Spain, France, Hong Kong, North America
- Histology: diffuse large B-Cell, Burkitt or atypical Burkitt or B-AL or aggressive mature B-cell NHL not yet specified or not specifiable
- Therapeutic group: LMB-B high risk (B), LMB-C-Cerebrospinal Fluid Negative (C1), LMB-C-Cerebrospinal Fluid Positive (C3)

For the European countries, randomization is done using TenAlea software (NKI, Amsterdam) via internet and the two arms are assigned by minimization with an alea parameter of 0.80. COG uses its existing randomization module in its eRDE system. The treatment assignment is done by stratified blocked randomization, using histology and therapeutic group as sole stratification factors.

For the statistical analysis, some randomization strata were pooled in order to avoid overfitting (approach used in the IA):

- National group: France, COG, Other small LMB groups (Belgium+Spain+UK+Netherlands), BFM groups (Italy+Hungary).
- Histology:Diffuse Large B-Cell (CRF stratum 2); Burkit or atypical Burkit or B-AL (CRF stratum 1), or aggressive mature Bcell, NHL not yet specified or not specifiable (CRF stratum 3)
- Therapeutic group: B vs C1 vs C3.

These pooled strata will be created from CRF corrected values.

Blinding (masking)

This was an open-label study. Only the reviewing members of the steering committee and IDMC were blinded to the treatment before review of each event.

Statistical methods

Interim monitoring for efficacy, toxic death, and futility based on EFS was conducted by the IDMC.

Three interim analyses were planned, they are all non-binding and the sponsor will make the final decision regarding early termination of the study. The interim analyses (IA) for efficacy were planned using the Lan-DeMets alphaspending function approach applied to an O'Brien-Fleming boundary, truncated at 3 standard deviations (SD). The overall type I error was set at 5% (1-sided).

The trial could be stopped for futility if the alternative hypothesis (HR of 0.50) was rejected. Monitoring for futility was done using the Fleming, Harrington and O'Brien approach, considering stopping for futility if the alternative hypothesis was ever rejected at a p-value below 0.005.

Table 4 Planned Analysis timings (example, depending on recruitment)

Analysis	Timing of Analysis	Number of events	Percent Information	Adjusted One-Sided Alpha Level	Cumulative One-Sided Alpha Level
First interim	2.5 years	24 events	33%	0.00135	0.00100
Second interim	3.5 years	40 events	55%	0.00764	0.00800
Third interim	4.5 years	54 events	75%	0.02099	0.02400
Final	6 years	72 events	100%	0.04249	0.05000

Due to a delay in center opening and resulting slower recruitment, the first IA occurred 3.5 years after the beginning of the study when 27 events had been observed. After this IA, randomization was stopped for efficacy, and further interim analyses were cancelled based on the IDMC recommendation. The first interim analysis was based on 27 events which corresponded to 37.5% of information and a nominal alpha error of 0.00137. The current analysis is based on 38 events, corresponding to 52.8% of information and a nominal alpha error of 0.00562. The cumulative alpha error is 0.00699.

The primary analysis was planned for when all randomized patients have been followed for at least 18 months and all single arm patients have completed their treatment - expected for 31st December 2017; final assessment of safety and pharmacokinetics were expected to also take place at this time.

The trial patients were split in 3 portions based on the date of randomization: the randomized portion, the crossover portion, and the single-arm portion.

• The randomized portion included all patients randomized prior to 27 August 2015. This date corresponds to the randomization date of the first patient who met all of the following conditions:

  o Randomized to the control group;

  o Randomized after the date of the IDMC report from which the decision to stop the randomization was made (initial interim analysis report on 14 August 2015, completed on 21 October 2015 and 03 November 2015 to answer IDMC questions, IDMC final recommendations on 09 November 2015); and

  o Received rituximab.

• The crossover portion included all patients randomized from 27 August 2015 to the interruption of enrollment (14 November 2015).

• The single-arm portion included all patients enrolled to R-Chemo after the resuming of enrollment to this only R-Chemo arm (March 2016). Patients in whom HBV serology results were positive or not available at Day 6, who were randomized and then were withdrawn (c.f. exclusion criteria in Section 6.2 of the protocol; Appendix 12.1.1) were enrolled in the intent-to-treat (ITT) population.

Intent-to-treat Set; The ITT set included all patients enrolled in the randomized portion. All efficacy analyses were produced in the ITT set, unless otherwise specified.

Modified ITT Set; The modified ITT (mITT) set included all ITT patients, except those ineligible as a result of a wrong diagnosis or risk group, or a positive or missing HBV serology at baseline. This population was to be used to conduct sensitivity analyses on the primary and secondary endpoints.

Therapeutic Group B Response Set; The therapeutic Group B response set was used to analyze CR in therapeutic Group B and included patients who met all of the following criteria: Intent-to-treat set patient; Initially treated in therapeutic Group B and Remained in therapeutic Group B after pre-phase COP treatment-response assessment, i.e., received COPADMB course(s) (COPADM course[s] that patients in

therapeutic Group B received). Patients who received COPADMB course(s) without meeting the protocol's criterion to remain in therapeutic Group B at that stage (deviation to protocol) were included.

The main analysis of the primary endpoint EFS will consist in an unadjusted analysis, comparing survival curves, and an analysis adjusted on stratification factors, comparing the adjusted HR estimate to 1. The unadjusted analysis will consist in a 1-sided non stratified log-rank test. The adjusted treatment effect size will be estimated by the HR of groups with Rituximab versus without rituximab by fitting a multivariate Cox proportional hazard model, controlling for the national group, histology, and therapeutic groups (pooled strata). The HR estimate, 90% CI of randomization group effect will be displayed, together with the type 3 analysis Wald one-sided p-value (adjusted p-value).

Patients without a reported event at the time of the clinical cut-off (31st of Dec 2017) would be censored.

Supportive analyses for the primary endpoint:

- At months 6, 12, 18, etc. … 60, the count of patients with an event observed within the previous 6 months, censored within the previous 6 months, left at risk at the time point, product-limit estimates of survival rates and 95% CI;
- The 25th and 75th quartiles and median of time to event will be also presented with their 95%CI;
- The number of events, the number at risk and the number of censored observations;
- The distributions of the earliest contributing event for EFS.
- Analyses will be repeated in the mITT set on an ITT basis and in the expanded safety set on an as-treated basis.
- Analysis will be repeated in the ITT set on an ITT basis, using the definition of EFS and earliest contribution event to EFS, as derived solely from CRF data.

The 95%CI of KM survival rates will be calculated using the Rothman formulae.

Secondary efficacy endpoint OS was analysed in the same manner as EFS. Patients without an event at the time of the clinical cut-off (31st of Dec 2017) will be censored at the latest date the patient was known to be alive, defined as the latest of all collected dates (except date of death).

Supportive analyses for OS was to be repeated using in the mITT set on an ITT basis and in the expanded safety set on an as-treated basis.

Results

Participant flow

Figure 16: Participant flow

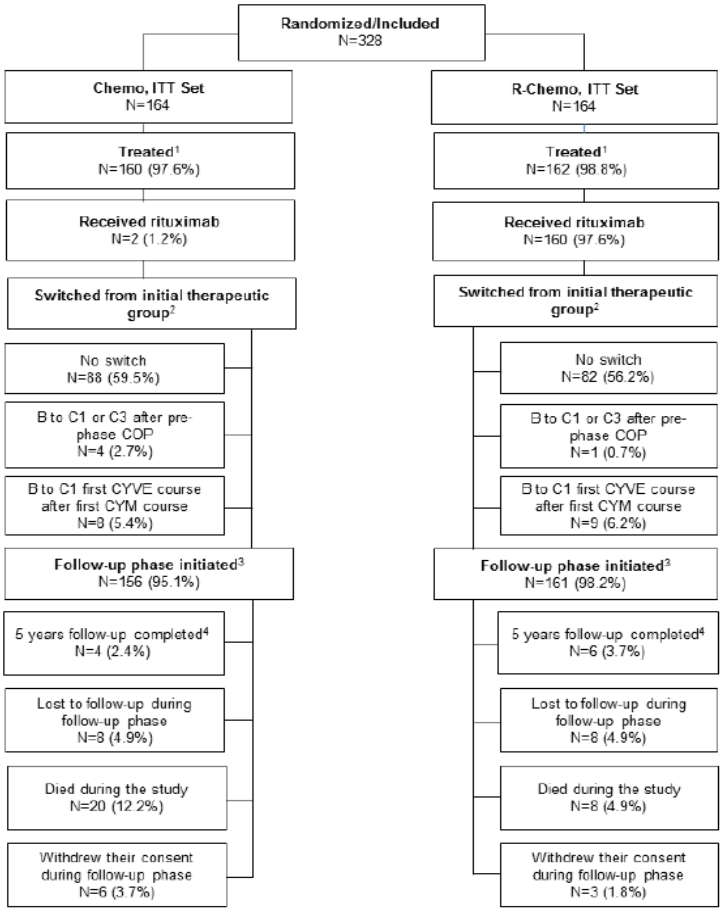
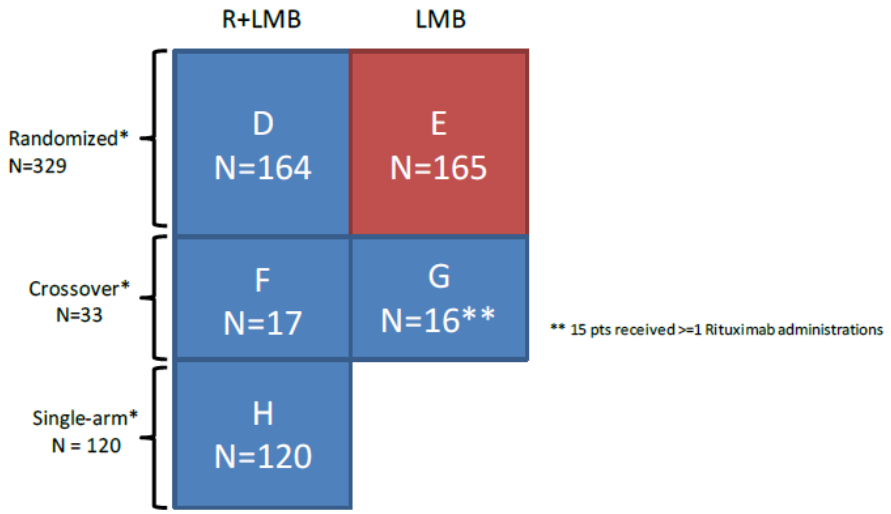


Figure 4.2-1 Trial Arms and Periods



Recruitment

The study was conducted at 141 centers in 8 European countries, in Hong Kong, and at 159 COG centres covering the US, Canada, and Australia.

First patient in: 19 December 2011

Clinical data cutoff date: 31 December 2017

A total of 484 patients were enrolled, 328 in the randomization portion before crossover, 33 in the crossover portion, and 116 in the single-arm, 7 patients were excluded due to consent and local regulatory reasons.

Conduct of the study

The original protocol was submitted as version 1.0 dated 06 July 2011. Following review by the competent authorities changes related to use contraception as an inclusion criterion /Pregnancy and lactation as an exclusion criterion and clarifications on the duration of study and the end of study and on the monitoring of acute toxicity and on the analysis of the safety data and on handling of the missing data during study analysis, were made. The Inter-B-NHL Ritux 2010 study protocol was amended twice by COG and GR and 1 additional time by GR only; the amendments were as follows:

Major changes in the protocol amendment 2 were: Adolescents included in secondary objectives; it was clarified that the MDD/MRD study was to be done only in the phase III; *Haemophilus influenzae* was added as a way to assess normal B-cell function. Some labs recognized natural killer cells using these 2 other combinations: CD3- CD56+, or CD3- CD16+CD56+; To add some clarification requested by COG. Those clarifications consisted of adding that bone marrow involvement will be defined as less than 25% of blasts in the bone marrow, and B AL will be defined as more than 25% blasts; Clarification added for the consent procedure as requested by COG, allowing registration before the start of COP at the COG sites; clarification points on posology and administration of other medication; the dose to weight was adapted in the guidance on the management of infusion related reactions; classification of DLBCL added according to Ann Arbor.

No major changes occurred in the protocol amendment 3. In amendment 4 **a**n update was included to state that the randomization was halted in November 2015 and that all remaining patients under treatment would continue treatment with rituximab and clarified that 362 patients were randomized, 181 in each arm; added that the study would continue recruitment of an additional 120 patients.

Other amendments included adjustments to the PIP and including AE's that were not initially planned to be collected in the eCRF. The first planned interim analysis was performed august 2015 and based on 310 patients and 27 events. The decision taken by the Steering Committee to stop the trial despite the fact that the results from the IA did not cross the specified significance boundary is not understood and hamper the assessment of the study. Variation in the test statistics are expected, in particular when few events are included, and therefore it is not appropriate to stop the trial if the pre-specified boundary has not been crossed, pre-specified boundaries are supposed to assure that the type I error of the study is controlled at the 5 % level.

Protocol deviations

Table 5 Major protocol Deviations by randomisation arm, ITT and rituximab safety sets

	Chemo, ITT Set N = 164	R-Chemo, ITT Set N = 164	Rituximab Safety Set N = 309
At least 1 major protocol deviation of special interest, n (%)	26 (15.9)	37 (22.6)	94 (30.4)
EC1: Patient diagnosed with PMLBL	2 (1.2)	0	1 (0.3)
EC6: Known immunodeficiency	0	0	1 (0.3)
IC1: Mature high risk B- NHL, i.e., a stage III with LDH > 2 X ULN of the adult normal value or stage IV or B-AL	1 (0.6)	0	0
IC2: Informed consent signed	7 (4.3)	16 (9.8)	28 (9.1)
IC4: Histologically or cytologically proven Burkitt lymphoma or mature B acute leukemia or diffuse large B-cell NHL or aggressive mature B-cell cell NHL not otherwise specified.	1 (0.6)	0	2 (0.6)
IC5: Complete initial work-up within 8 days prior to chemotherapy allowing a definitive staging	5 (3.0)	4 (2.4)	27 (8.7)
SC1: Patient not treated according to the treatment arm s/he was randomized to as per TenAlea software for the European countries and as per the eRDE system in the United States, Canada, and Australia.	1 (0.6)	0	1 (0.3)
SC2a: Patient switched to more intensive regimen without protocol's conditions met.	3 (1.8)	5 (3.0)	8 (2.6)
SC2b: Patient not treated according to the protocol's therapeutic group (other cases).	3 (1.8)	6 (3.7)	12 (3.9)
SC4: Treatment response not available between Days 5 and 10 of first pre-phase COP course (Group B or C1).	3 (1.8)	8 (4.9)	16 (5.2)
SC5: Treatment response not available after the 1st CYM course (Group B patients)	1 (0.6)	1 (0.6)	3 (1.0)
SC6: Treatment response not available after the 2nd CYVE course (C1, including patients switched from group B, and C3).	1 (0.6)	1 (0.6)	3 (1.0)
SC7: In the Rituximab arm, less than 4 Rituximab administrations.	0	0	1 (0.3)

Baseline data

Table 6 Demographic characteristics by randomisation arm, ITT and rituximab safety sets

	Chemo, ITT Set (N = 164) n (%)	R-Chemo, ITT Set (N = 164) n (%)	Rituximab Safety Set (N = 309) n (%)
Sex, n (%)			
Male	137 (83.5)	135 (82.3)	250 (80.9)
Female	27 (16.5)	29 (17.7)	59 (19.1)
Age at randomization (years)			
N	164	164	309
Mean	8.1	8.7	8.5
Standard deviation	4.35	3.96	4.05
Minimum	1	2	1
1st quartile	4.5	5.0	5.0
Median	7.0	8.0	8.0
3rd quartile	11.5	12.0	12.0
Maximum	17	17	17
Range	16	15	16
Age group, n (%)			
6 months to < 3 years	7 (4.3)	1 (0.6)	6 (1.9)
3 to < 12 years	116 (70.7)	116 (70.7)	219 (70.9)
12 to 18 years	41 (25.0)	47 (28.7)	84 (27.2)
BSA (m^2)			
N	164	164	309
Mean	1.098	1.140	1.126
Standard deviation	0.4276	0.4150	0.3957
Minimum	0.47	0.57	0.55
1st quartile	0.760	0.815	0.820
Median	0.970	1.025	1.030
3rd quartile	1.370	1.430	1.390
Maximum	2.70	2.32	2.32
Range	2.23	1.75	1.77
Karnofsky/Lansky performance status[1], n (%)			
10	1 (0.6)	2 (1.2)	7 (2.3)
20	2 (1.2)	2 (1.2)	6 (2.0)
30	4 (2.4)	6 (3.7)	15 (5.0)
40	15 (9.1)	8 (4.9)	17 (5.6)
50	13 (7.9)	10 (6.1)	16 (5.3)
60	13 (7.9)	7 (4.3)	17 (5.6)
70	18 (11.0)	22 (13.4)	52 (17.2)
80	36 (22.0)	43 (26.2)	63 (20.8)
90	29 (17.7)	39 (23.8)	60 (19.8)
100	33 (20.1)	25 (15.2)	50 (16.5)

Table 7 Disease characteristics by randomisation arm, ITT and rituximab safety sets

	Chemo, ITT Set (N = 164)	R-Chemo, ITT Set (N = 164)	Rituximab Safety Set (N = 309)
Primary site of disease, n (%)			
Thorax	6 (3.7)	6 (3.7)	11 (3.6)
Abdomen and/or retroperitoneum	95 (57.9)	96 (58.5)	176 (57.0)
Head and neck (except skin and nodes)	9 (5.5)	20 (12.2)	32 (10.4)
Peripheral lymph node	6 (3.7)	2 (1.2)	13 (4.2)
Cerebral lymphoma	3 (1.8)	2 (1.2)	5 (1.6)
Other tumor site	10 (6.1)	7 (4.3)	14 (4.5)
B-AL (L3-AL) (clinical presentation)	34 (20.7)	30 (18.3)	56 (18.1)
Not specified	1 (0.6)	1 (0.6)	2 (0.6)
Murphy's stage[1], n (%)			
Stage III, LDH > 2 ULN	75 (45.7)	71 (43.3)	130 (42.1)
Stage IV, CNS negative (bone marrow < 25%)	11 (6.7)	9 (5.5)	23 (7.4)
Stage IV, CNS positive, CSF negative	14 (8.5)	18 (11.0)	35 (11.3)
Stage IV, CNS positive, CSF positive	5 (3.0)	5 (3.0)	10 (3.2)
B-AL, CNS negative	35 (21.3)	40 (24.4)	69 (22.3)
B-AL, CNS positive, CSF negative	11 (6.7)	10 (6.1)	16 (5.2)
B-AL, CNS positive, CSF positive	12 (7.3)	11 (6.7)	26 (8.4)
BL[1]	1 (0.6)	0	0
Has the patient bone marrow involvement, n (%)			
Yes	74 (45.1)	74 (45.1)	143 (46.3)
No	90 (54.9)	90 (54.9)	166 (53.7)
Bone marrow aspirates: maximum blast % in sample			
N	73	73	142
Mean	56.4	63.5	60.7
Standard deviation	36.48	32.05	33.93
Bone marrow biopsy, n (%)			
Not done	48 (29.3)	49 (29.9)	106 (34.3)
Done	116 (70.7)	115 (70.1)	203 (65.7)
If done, results, n (%)			
Negative	69 (59.5)	71 (61.7)	127 (62.6)
Positive focal	6 (5.2)	1 (0.9)	7 (3.4)
Positive diffuse	41 (35.3)	43 (37.4)	69 (34.0)
If positive focal, n (%)			
< 5 foci	3 (50.0)	0	3 (42.9)

≥ 5 foci	3 (50.0)	1 (100)	4 (57.1)
If bone marrow involvement, blasts in blood, n (%)			
No	40 (52.6)	44 (57.9)	77 (52.0)
Yes	28 (36.8)	29 (38.2)	63 (42.6)
Not done	8 (10.5)	3 (3.9)	8 (5.4)
CNS involvement, n (%)			
Yes	44 (26.8)	44 (26.8)	87 (28.2)
No	119 (72.6)	120 (73.2)	222 (71.8)
Not tested	1 (0.6)	0	0
If yes, CSF blasts, n (%)			
No	27 (61.4)	28 (63.6)	51 (58.6)
Yes	17 (38.6)	15 (34.1)	34 (39.1)
Not tested	0	1 (2.3)	2 (2.3)
Pre-therapeutic lumbar puncture done, n (%)			
Yes	164 (100)	162 (98.8)	305 (98.7)
No	0	2 (1.2)	4 (1.3)
If yes, contamination by blood, n (%)			
No	133 (81.1)	139 (85.8)	257 (84.3)
Yes	31 (18.9)	23 (14.2)	48 (15.7)
Corticosteroids received during the week before staging, n (%)			
Yes	33 (20.1)	35 (21.3)	67 (21.7)
No	131 (79.9)	129 (78.7)	242 (78.3)
Pre-therapeutic PET done, n (%)			
Yes	68 (41.5)	78 (47.6)	116 (37.5)
No	96 (58.5)	86 (52.4)	193 (62.5)
Hepatitis B immunized, n (%)			
Yes	115 (71.0)	110 (67.1)	181 (58.6)
No	47 (29.0)	54 (32.9)	128 (41.4)
Hepatitis B serology results			
HBsAg, n (%)			
Negative	163 (100)	163 (100)	307 (100)
Positive	0	0	0
Anti-HBs antibody, n (%)			
Negative	103 (63.6)	105 (65.6)	206 (69.1)
Positive	59 (36.4)	55 (34.4)	93 (30.9)
Anti-HBc antibody, n (%)			
Negative	163 (100)	160 (100)	302 (100)
Positive	0	0	0

Numbers analysed

Table 8 Patient disposition in the study by randomisation arm, ITT and rituximab safety sets

	Chemo, ITT Set n (%)	R-Chemo, ITT Set n (%)	Rituximab Safety Set n (%)
Randomized/included, n	164	164	309
Treated[1], n (%)	160 (97.6)	162 (98.8)	309 (100)
In pre-phase COP	160 (97.6)	162 (98.8)	308 (99.7)
In induction phase	155 (94.5)	160 (97.6)	308 (99.7)
In consolidation phase	145 (88.4)	155 (94.5)	300 (97.1)
In maintenance phase[2]	74 (91.4)	82 (92.1)	164 (93.2)
Received rituximab, n (%)	2 (1.2)	160 (97.6)	309 (100)
Number of waiting COP courses received, n (%)			
1	6 (3.7)	8 (4.9)	14 (4.5)
2	2 (1.2)	1 (0.6)	2 (0.6)
3	0	1 (0.6)	1 (0.3)

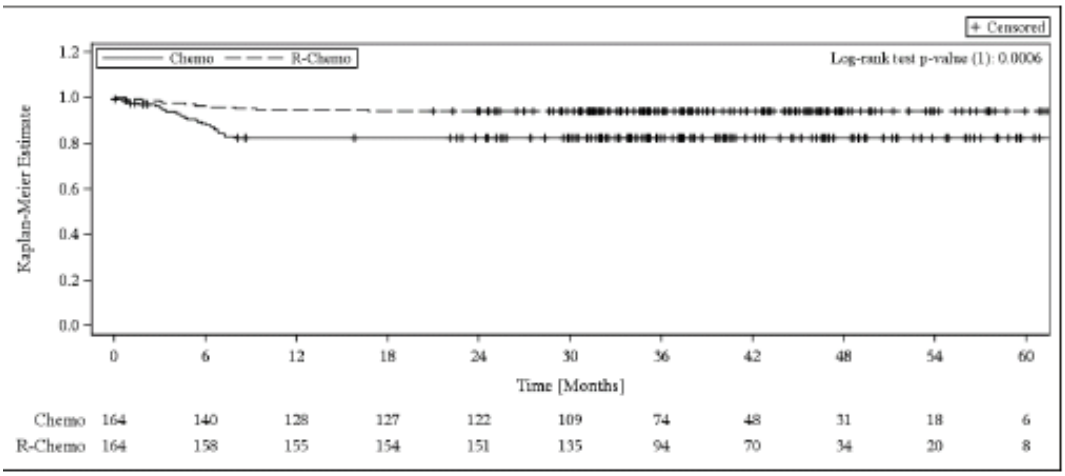
Outcomes and estimation

Table 9: An overview of efficacy until the cutoff date 31 December 2017

Analysis	Chemo	R-Chemo
EFS	28 events	10 events
	One-sided log-rank test p-value 0.0006	
	Adjusted Cox HR 0.32 (90% CI: 0.17, 0.58); p-value 0.0010	
3-year EFS rates[1]	82.3% (95% CI: 75.7%, 87.5%)	93.9% (95% CI: 89.1%, 96.7)%)
OS	20 deaths	8 deaths
	1-sided log-rank test p-value 0.0061	
	Adjusted Cox model HR 0.36 (95% CI: 0.16; 0.81)	
3-year OS[2]	87.3% (95% CI: 81.2%, 91.6%)	95.1% (95% CI: 90.5%, 97.5)%)
CR rate	93.6% (95% CI: 88.15%; 97.02%)	94.0% (95% CI: 88.84%, 97.20%)

Primary endpoint:

Figure 17: One-sided log-rank test and K-M plot of EFS, ITT set



Chemo = Chemotherapy; CYVE = Cytarabine, Vepeside; ITT = Intent-to-Treat; R-Chemo = Rituximab + Chemotherapy.

The event of interest was progressive disease/relapse, second malignancy, death from any cause or nonresponse as evidenced by detection of viable cells in residue after second CYVE course (for therapeutic Group C patients and therapeutic Group B patients switched to therapeutic Group C), whichever event occurred first as confirmed by the steering committee. In the absence of event, censor applied at latest date out of the latest follow-up visit date, the latest late effect start date and the date of the last dose of protocol therapy if this latest date was before the cutoff date and cutoff date otherwise.

Source: Figure 14.2.1.1.1

(1) One-sided log-rank test, testing null hypothesis of equality of survivorships in randomization arms R-Chemo and Chemo against alternative hypothesis "survivorship in group R-Chemo is higher than in Chemo."

Event-free survival as determined by a 1-sided treatment-effect test using a multivariate Cox model with 90% CI reported is summarized in Table 19 for the ITT set.

Table 10 Key primary analysis of EFS – One sided treatement effect by multivariate cox model, ITT

Effects	Parameter Estimate	Standard Error	Hazard Ratio (90% CI)[1]	P-value[2]
Randomization arm effect size[3]	-1.1463	0.3696	0.32 (0.17; 0.58)	0.0010

CI = Confidence interval; CYVE = Cytarabine, Vepeside; ITT = Intent-to-Treat; kg = Kilogram.

Source: Table 14.2.1.1.2

The event of interest was progressive disease/relapse, second malignancy, death from any cause or nonresponse as evidenced by detection of viable cells in residue after second CYVE course (for therapeutic Group C patients and therapeutic Group B patients switched to therapeutic Group C), whichever event occurred first as confirmed by the steering committee. In the absence of event, censor applied at latest date out of the latest follow-up visit date, the latest late effect start date and the date of the last dose of protocol therapy if this latest date was before the cutoff date and cutoff date otherwise. An event observed after the cutoff date was regarded as censored at cutoff date too.

(1) Wald CI.

(2) One-sided type 3 Wald Chi2 test of null hypothesis of randomization arm HR = 1 against alternative hypothesis of HR < 1. Obtained by fitting a multivariate non stratified Cox model with randomization arm and post-randomization corrected values of strata as effects (pooled national group, histologic group and therapeutic group) Mistakenly randomized PMLBL ITT patients 3-C-2 and 3-E-70 were assigned to therapeutic group as entered at time of randomization (C1 and B respectively).

(3) The reference category is the arm "Chemo."

Table 11 Supportive KM analyses of EFS- ITT set and rituximab safety set (KM probabilities)

	Chemo, ITT Set (N = 164)	R-Chemo, ITT Set (N = 164)	Rituximab Safety Set (N = 309)
Day 365 (Month 12)[1]			
Survival probability [95% CI][2]	82.3 [75.67; 87.50]	94.5 [89.90; 97.09]	93.4 [90.04; 95.70]
Number at risk	128	155	252
Number of events	10	3	8
Day 730 (Month 24)[1]			
Survival probability [95% CI][2]	82.3 [75.67; 87.50]	93.9 [89.14; 96.65]	92.5 [88.83; 95.00]
Number at risk	122	151	168
Number of events	0	0	1
Day 1095 (Month 36)[1]			
Survival probability [95% CI][2]	82.3 [75.67; 87.50]	93.9 [89.14; 96.65]	92.5 [88.83; 95.00]
Number at risk	74	94	91
Number of events	0	0	0
Day 1460 (Month 48)[1]			
Survival probability [95% CI][2]	82.3 [75.67; 87.50]	93.9 [89.14; 96.65]	92.5 [88.83; 95.00]
Number at risk	31	34	33
Number of events	0	0	0

Table 12: Supportive KM analyses of EFS - ITT set and rituximab safety set (KM statistics)

	Chemo, ITT Set (N = 164)	R-Chemo, ITT Set (N = 164)	Rituximab Safet Set (N = 309)
Number at risk	164	164	309
Number of events	28	10	22
Number censored	136	154	287
Earliest contributing EFS event, n (%)			
Overall			
Progression/relapse	21 (75.0)	3 (30.0)	13 (59.1)
Second malignancy	0	2 (20.0)	2 (9.1)
Death due to lymphoma	2 (7.1)	0	0
Toxic death	3 (10.7)	3 (30.0)	5 (22.7)
Viable cells after CYVE2	2 (7.1)	2 (20.0)	2 (9.1)
Therapeutic Group B[1]			
Progression/relapse	10 (71.4)	3 (60.0)	7 (77.8)
Second malignancy	0	1 (20.0)	1 (11.1)
Death due to lymphoma	1 (7.1)	0	0
Toxic death	2 (14.3)	0	0
Viable cells after CYVE2	1 (7.1)	1 (20.0)	1 (11.1)
Therapeutic Group C1[1]			
Progression/relapse	8 (80.0)	0	2 (25.0)
Second malignancy	0	0	0
Death due to lymphoma	0	0	0
Toxic death	1 (10.0)	3 (75.0)	5 (62.5)
Viable cells after CYVE2	1 (10.0)	1 (25.0)	1 (12.5)
Therapeutic Group C3[1]			
Progression/relapse	3 (75.0)	0	4 (80.0)
Second malignancy	0	1 (100)	1 (20.0)
Death due to lymphoma	1 (25.0)	0	0
Toxic death	0	0	0
Viable cells after CYVE2	0	0	0

Sensitivity analyses

Event-Free Survival in mITT Set

In the KM plot of EFS sensitivity analysis performed for the mITT set the adjusted HR was 0.32 (95% CI: 0.15, 0.66). Kaplan-Meier EFS probabilities over time showed that the EFS probability for patients receiving R-Chemo was higher than for those receiving Chemo at Year 1 (94.5% vs. 82.7%) and remained higher at Years 2, 3, and 4 (93.9% vs. 82.7% for each time point). For the Chemo mITT set, 27 EFS events were reported vs. 10 for R-Chemo mITT set. Progression/relapse was the earliest contributing event for 20 patients (74.1%) in the Chemo mITT set and 3 patients (30.0%) in the R-Chemo mITT set.

Figure 18

Fig 14.2.4.1.1.1
First RFS Sensitivity Analysis - One-Sided Log-rank Test and Kaplan-Meier Curve, Modified ITT Set

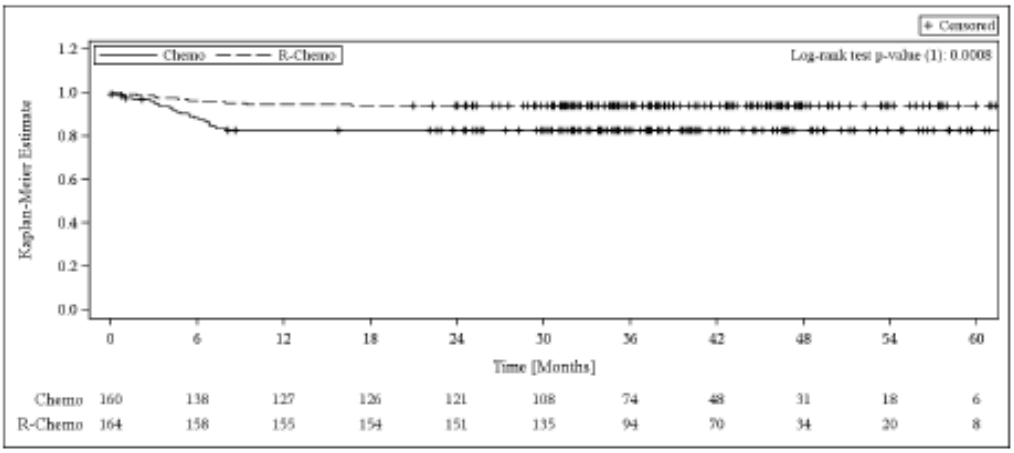


Table 14.2.4.1.1.2
First RFS Sensitivity Analysis - Treatment Effect Size By Multivariate Cox Model, Modified ITT Set

Effect	Parameter estimate	Standard Error	Hazard Ratio (95% CI) (1)
Randomization Arm Effect Size (2)	-1.1375	0.3713	0.32 (0.15, 0.66)

Event-Free Survival in Expanded Safety Set

Figure 19 Results of the second EFS sensitivity analyses performed for the expanded safety set

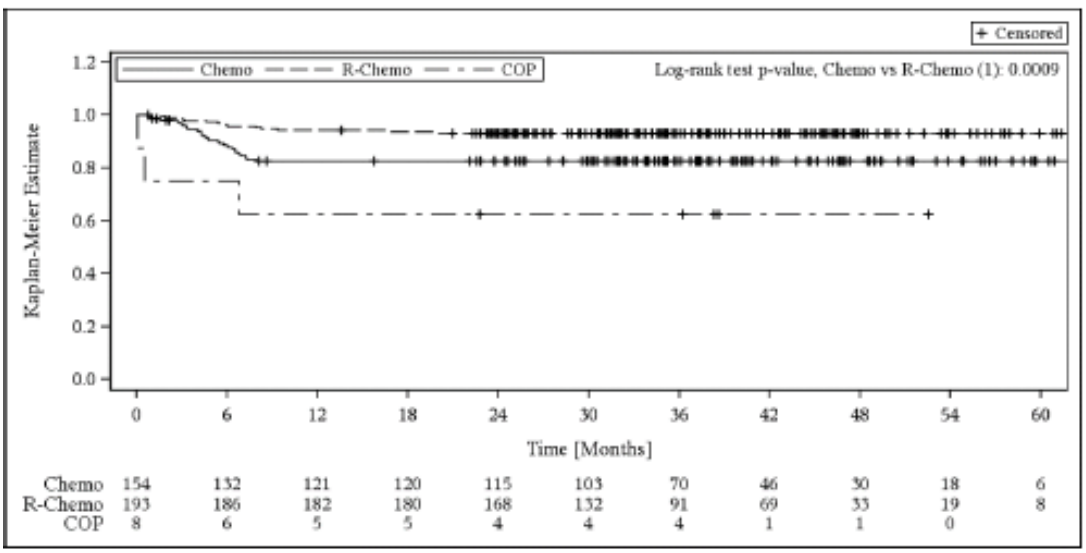


Table 14.2.4.1.2.2
Second EFS Sensitivity Analysis - Treatment Effect Size By Multivariate Cox Model, Expanded Safety Set As Treated

Effect	Parameter estimate	Standard Error	Hazard Ratio [95% CI] (1)
Actual Treatment Effect Size (2)	-1.0310	0.3405	0.36 [0.18; 0.70]

Figure 20: Kaplan-Meier plot of overall survival (OS)

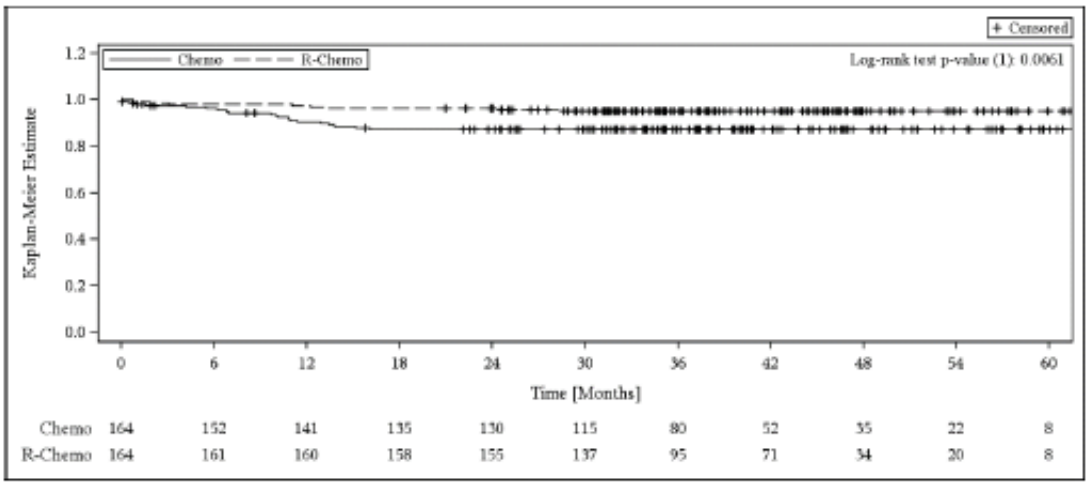


Table 13 OS treatment effect size by multivariate cox model, ITT set

Effect	Parameter Estimate	Standard Error	Hazard Ratio (95% CI)[1]
Randomization arm effect size[2]	-1.0286	0.4197	0.36 (0.16; 0.81)

CI = Confidence Interval; ITT = Intent-to-Treat.

OS in mITT

The first OS sensitivity analysis KM plot for the mITT set showed consistent results. Twenty patients in the Chemo mITT arm and 8 patients in the R-Chemo mITT arm had died, and the survival probability was higher for patients in the R-Chemo mITT arm vs. the Chemo mITT arm at Year 1 (97.6% vs. 90.4%), Year 2 (96.3% vs. 87.1%), and Years 3 and 4 (95.1% vs. 87.1% for both time points). The hazard ratio was 0.35 (95% CI: 0.15, 0.79).

OS in Expanded Safety Set

The OS sensitivity analysis KM plot for the expanded safety set showed consistent results. Seventeen patients in the Chemo set and 10 patients in the R-Chemo set had died, and the survival probability was higher for patients receiving R-Chemo than for patients receiving Chemo at Year 1 (97.4% vs. 91.9%), Year 2 (95.9% vs. 88.5%), and Years 3 and 4 (94.6% vs. 88.5% at both time points). The hazard ratio is 0.43 (95% CI:0.20, 0.94).

Secondary endpoint – CR

Most patients achieved CR, 93.6% (95% CI: 88.15%, 97.02%) of patients in the Chemo ITT set, 94.0% (95% CI: 88.84%, 97.20%) of patients in the R-Chemo ITT set, and 95.4% (95% CI: 92.19%, 97.51%) of patients of the rituximab safety set.

CR rate at the reference assessment time is summarized by randomization arm for the ITT set and the rituximab safety set in Table 14.2.2.2. More than half of the patients in the Chemo ITT set (106 patients [75.7%]), R-Chemo ITT set (103 patients [69.1%]), and the rituximab safety set (207 patients [73.9%]) achieved CR at the reference assessment time.

Sensitivity Analyses for Complete Remission Rate

Results of sensitivity analyses of the CR response status performed for the mITT set and for the expanded safety set are summarized in Table 14.2.4.3.1 and Table 14.2.4.3.2, respectively.

In the mITT set, most patients achieved CR: 93.6% of patients of in the Chemo arm and 94.0% of patients in the R-Chemo arm. For the expanded safety set, most patients achieved CR: 93.5% of patients receiving Chemo and 94.4% of patients receiving R-Chemo.

Additional sensitivity analyses were performed as follows:

• Response status by randomization arm, using CRF data only (ITT set), is summarized in Table 14.2.4.3.4. This analysis showed 130 patients (92.9%) and 139 patients (93.3%) achieved CR in the Chemo and R-Chemo arms, respectively. The evaluation of remission at treatment-response assessment times is listed by patient in Listing 16.2.6.2.1. Details of the calculation of CR are listed for the ITT set and the rituximab safety set in Listing 16.2.6.2.4.

Therapeutic Group B

Exploratory endpoint CR in therapeutic Group B is summarized by randomization arm for the therapeutic Group B response set in Table 14.2.3.1. For therapeutic Group B, the majority of patients achieved CR (97.0% for patients receiving Chemo, 97.2% for patients receiving R-Chemo) as follows:

• For patients in the Chemo arm: 91.0% early CR, 6.0% slow CR, and 3.0% no CR

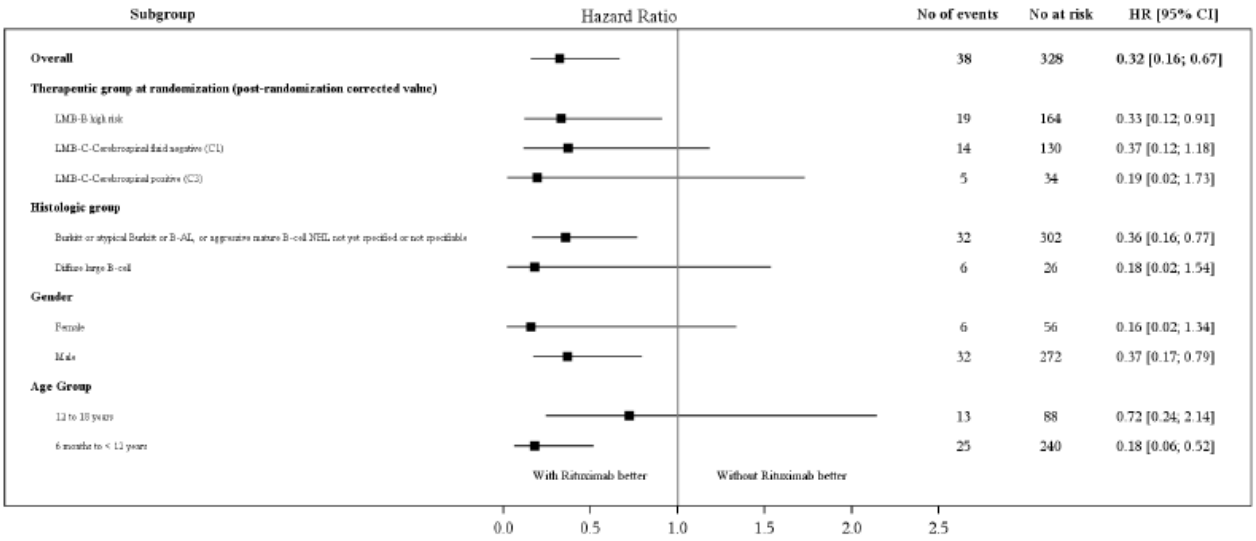
• For patients in the R-Chemo arm: 88.7% early CR, 8.5% slow CR, and 2.8% no CR

Results of a sensitivity analysis using eCRF data only were the same as in the main analysis.

Ancillary analyses

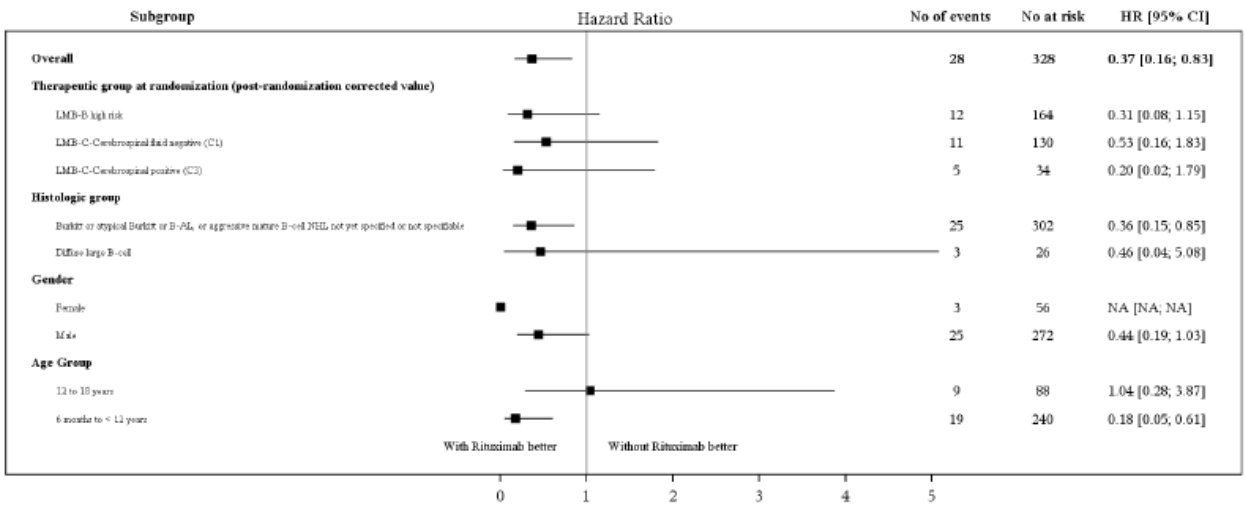
Subgroup analyses

Fig 14.2.5.1
Forest Plot of Randomization Arm Effect Sizes on EFS by Subgroup, ITT Set



CI = Confidence Interval; EFS = Event-Free survival; HR = Hazard Ratio; ITT = Intent To Treat
HRs obtained by fitting univariate Cox models with EFS as endpoint and the randomization arm as effect in each subgroup separately.
Arm "Chemo" used as reference category.
PROGRAM: F14_2_5_fplot.sas, OUTPUT: F14_2_5_1_fplot.rtf Date/time of run: 20DEC2018, 14:42

Fig 14.2.5.2
Forest Plot of Randomization Arm Effect Sizes on OS by Subgroup, ITT Set



CI = Confidence Interval; OS = Overall survival; HR = Hazard Ratio; ITT = Intent To Treat
HRs obtained by fitting univariate Cox models with OS as endpoint and the randomization arm as effect in each subgroup separately.
Arm "Chemo" used as reference category.
PROGRAM: F14_2_5_fplot.sas, OUTPUT: F14_2_5_2_fplot.rtf Date/time of run: 20DEC2018, 14:42

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for study BO25380

Title: A Phase III multicentre, open-label, randomized study evaluating the benefit of addition of rituximab to the standard LMB chemotherapy regimen in untreated pediatric and adolescent patients presenting with advanced stage B-cell NHL/B-AL, except PMLBL			
Study identifier	BO25380		
Design	An open-label, 1:1 randomized phase III study evaluating the benefit of the addition of 6 injections of rituximab to the standard LMB chemotherapy regimen		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		6 years not applicable not applicable
Hypothesis	Superiority		
Treatments groups	R-chemo		Rituximab with standard LMB chemotherapy, 3.5-5.5 months, 164 patients
	Chemo		Standard LMB chemotherapy, 3.5-5.5 months, 164 patients
Endpoints and definitions	Primary endpoint	EFS	Event-Free Survival (EFS) is defined as the time between randomization and occurrence of progressive disease, relapse, second malignancy, death from any cause or nonresponse as evidenced by detection of viable cells in residue after the second CYVE course (for therapeutic Group C patients and therapeutic Group B patients who switched to therapeutic Group C), whichever event occurred first.
	Secondary Endpoint	CR rate	Complete Remission (CR) was defined as the complete disappearance of all measurable or evaluable lesions (except bone), no L3 blasts in the bone marrow nor in the CSF.
	Secondary Endpoint	OS	Overall survival (OS) is defined as time from randomization to death due to any cause.
Database lock	28 September 2018		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Intent to treat population Data up to 31 December 2017		
Descriptive statistics and estimate variability	Treatment group	Chemo	R-Chemo
	Number of subject	164	164
	EFS 3-year rate (%)	82.3	93.9
	95% CI	75.7 - 87.5	89.1 - 96.7

	OS 3-year rate (%)	87.3	95.1
	95% CI	81.2, 91.6	90.5, 97.5
	CR rate* (%) 95% CI	93.6 88.2 - 97.0	94.0 88.8 - 97.2
Effect estimate per comparison	EFS	Comparison groups	R-Chemo vs Chemo
		Hazard Ratio	0.32
		90% CI	0.17-0.58
		P-value	0.0006
	OS	Comparison groups	R-Chemo vs Chemo
		Hazard Ratio	0.36
		95% CI	0.16 - 0.81
		P-value	0.0061
Notes	Hazard ratios provided are from an adjusted multivariate Cox model. P-values provided are from an un-adjusted one-sided log rank test. * CR rates were only calculated from patients where response was evaluable.		

Supportive study(ies)

Of 122 patients enrolled in the single-arm portion of the study, data were available for 166 patients. The majority of patients achieved CR: 97.0% (95% CI: 91.48%, 99.38%), but neither median EFS or median OS was reached.

2.4.3. Discussion on clinical efficacy

A multicenter, open-label, randomized study of Lymphome Malin B (LMB) chemotherapy (corticosteroids, vincristine, cyclophosphamide, high-dose methotrexate, cytarabine, doxorubicin, etoposide and triple drug [methotrexate/cytarabine/ corticosteroid] intrathecal therapy) alone or in combination with MabThera was conducted in paediatric patients with previously untreated advanced stage CD20 positive DLBCL/BL/BAL/BLL.

Design and conduct of clinical studies

The application is based on one pivotal randomized phase 3 open label multicenter study BO 25380, where rituximab was added to standard chemotherapy in untreated pediatric patients with advanced-stage B-NHL/B-AL (stage III and LDH > ULN × 2, any stage IV, or B-AL). The in – and exclusion criteria adequately define the population covered by the proposed indication. Patients included in the trial were Stage III or more at diagnosis. Overall the study was well conducted, however some concerns were raised, which have all been addressed. The design of the study, treatments and backbone therapy as well as efficacy endpoints are endorsed, no sites were inspected by any regulatory agency.

Advanced stage is defined as Stage III with elevated LDH level ("B-high"), [LDH > twice the institutional upper limit of the adult normal values (> Nx2)] or any stage IV or BAL. Patients were randomized to receive either LMB chemotherapy or six IV infusions of MabThera at a dose of 375mg/m^2 BSA in combination with LMB chemotherapy (two during each of the two induction courses and one during each of the two consolidation courses) as per the LMB scheme. A total of 328 randomized patients were

included in the efficacy analyses, of which one patient under 3 years of age received MabThera in combination with LMB chemotherapy.

The two treatment arms, LMB (LMB chemotherapy) and R-LMB (LMB chemotherapy with MabThera), were well balanced with regards to baseline characteristics. Patients had a median age of 7 and 8 years in the LMB arm and R-LMB arm, respectively. Approximately half of patients were in Group B (50.6% in the LMB arm and 49.4% in the R-LMB arm), 39.6% in Group C1 in both arms, and 9.8% and 11.0% were in Group C3 in the LMB and R-LMB arms, respectively. Based on Murphy staging, most patients were either BL stage III (45.7% in the LMB arm and 43.3% in the R-LMB arm) or BAL, CNS negative (21.3% in the LMB arm and 24.4% in the R-LMB arm). Less than half of the patients (45.1% in both arms) had bone marrow involvement, and most patients (72.6% in the LMB arm and 73.2% in the R-LMB arm) had no CNS involvement. The primary efficacy endpoint was EFS, where an event was defined as occurrence of progressive disease, relapse, second malignancy, death from any cause, or non-response as evidenced by detection of viable cells in residue after the second CYVE course, whichever occurs first. The secondary efficacy endpoints were OS and CR (complete remission).

Only one patient below the age of 3 was included in the R-Chemo group. Nonetheless the MAH is proposing the use of rituximab in paediatric patients from 6 months and forward. Simulations have been conducted with the updated model to predict exposure in children < 3 years. Ctrough and cumulative $AUC_{1\text{-}4\ cycles}$ are comparable across age groups, but Cmax higher in the youngest population. It is agreed that the higher Cmax (over) predicted with the model not is expected to have clinical relevance. Randomization 1:1 to chemotherapy with or without rituximab was stratified by National group, histology and therapeutic group, the stratification factors are considered acceptable from a clinical point of view, but the MAH was asked to clarify whether 6 block randomization were implemented in for the EU countries, The MAH explained, that in the EU countries the treatment arms were assigned by minimization using the TenAlea software. The minimization factors were: national group, histology, and chemotherapy group. An alea parameter of 0.80 was used, this method prevents the physicians from guessing the assigned treatment arm. If a potential error in the randomization strata was detected, patients were not re-randomized.

For the statistical analysis, the corrected values were used. The MAH was asked to clarify how many of those values were corrected, and whether using the corrected stratification values instead of the original ones could affect the results. Four patients in the ITT Chemo arm and 1 patient in R-Chemo arm in the ITT set (1.5%) had post-randomization corrections to their stratification values. The MAH presented sensitivity analysis for OS and EFS were the uncorrected stratification values were used. The results are consistent with those presented in the primary analyses.

The MAH defined two primary analyses for EFS: an unadjusted analysis, comparing survival curves, and an analysis adjusted on stratification factors, comparing the adjusted HR estimate to 1. The unadjusted analysis will consist in a 1-sided non-stratified log-rank test. The adjusted treatment effect size will be estimated by fitting a multivariate Cox proportional hazard model, controlling for the national group, histology, and therapeutic groups (pooled strata). The censoring rule is defined as all patients without a reported event at the time of the clinical cut-off (31st of Dec 2017) will be censored. As supportive analyses, the EFS will be analysed using the m-ITT population and the safety population. Additionally, an analysis will be performed using the investigator's EFS values. Although the definition of EFS is endorsed, it is not quit understood which analyses will be considered the main analysis: the one from the adjusted or unadjusted model., The MAH clarified that in the PIP and the SAP the results from the (unadjusted) log-rank analysis are considered the main analysis for regulatory purposes. In the protocol, the primary efficacy endpoint was to be analysed using the adjusted Cox modelling. The interim analysis was performed using this multivariate Cox model adjusting for national group, histology, and therapeutic group.

The Steering Committee decided which events were to be considered EFS events. The MAH did not discuss how intercurrent events (e.g. initiation of another therapy, early discontinuation of investigational product,

early discontinuation of the trial) could affect the EFS analysis. In this analysis, all patients who did not have a recorded EFS event at the cut-off date were censored. The assumption of non-informative censoring has not been justified. The MAH was asked to: 1) define intercurrent events of interest; 2) disclose how many patients had an intercurernt event; 3) present additional sensitivity analyses where the assumption of non-informative censored is not used for patients who had an intercurrent event (administrative censoring is acceptable). The MAH was also asked to justify the assumptions made during the analysis and compare the results with those presented in the primary analyses. The potential intercurrent events of interest include early discontinuation of the treatment due to investigator-assessed progression (without steering committee confirmation), physician decision, non-response, or intolerable toxicity. A total of 12 patients (6 in each arm) in the ITT set experienced a potential intercurrent event. The MAH performed several sensitivity analyses:

Composite strategy 1: The investigator-assessed progression was considered as an EFS event. The HR from the adjusted Cox model was 0.35 (90% CI, 0.20 – 0.64).

Composite strategy 2: All potential intercurrent events, as defined above, were considered as EFS events. The Cox HR from this analysis was 0.42 (90% CI, 0.26 – 0.70).

Treatment policy strategy, all 362 randomized patients were incorporated, including those allowed to cross-over from Chemo arm to Rituximab arm; the Cox HR from this analysis was 0.4 (90% CI, 0.23 – 0.70).

All the supplementary / sensitivity analyses gave similar results to those obtained in the primary analysis.

The secondary endpoints OS and CR are endorsed although they were not controlled for multiplicity. The definitions used for the analysis of CR were created based on combination presented in the eCRF, and in some cases it was not possible to translate a value registered in the eCRF to a "yes / no" variable.

It is considered problematic that the CR status could not be clearly obtained from the eCRF and therefore a table with correspondence between values was created. The clarified the correspondence table between values was created at the time of SAP writing and before CSR analyses. The study was a open-label study, hence the results should be interpreted with caution. The MAH provided information about the functioning of the steering committee. Data from the clinical database were provided to members of the Steering Committee without the allocated arms to ensure they were blinded to efficacy.

In November 2015 the randomization was stopped due to the results from the first IA, although they did not cross the specified significance boundary. The results were provided to an independent data monitoring committee, who recommended the Sponsor to halt the trial. The Sponsor then made the decision to stop the trial.

The MAH provided details from the IDMC meetings how the decision of stopping the trial despite the lack of crossing of the statistical boundary was made. The MAH also provided information about the simulations performed to calculate the probability that the trial would have a significant result in several scenarios. Conditional power calculations indicated that if the true HR was in the range 0.33-0.73 the trial would be expected to stop for efficacy with a probability of 87-100 %. If the true HR was 1 (no difference), the probability to stop the trial for efficacy at the final analysis was 60 %. These arguments are acknowledged, although the halt of the trial have limited the possibility to obtain a precise estimate of rituximab treatment. However, taking into account the limitations of the current trial, the results obtained seem to indicate a positive effect of the R-chemo treatment.

A number of patients switched from their initial treatment group to another, from B to C1 or C1 to C3, this was mainly due to lack of response to the pre-phase chemotherapy.

For therapeutic group C1, the MAH states, that 36.9% to 43.1% had B-AL, i.e. > 25% blasts, but BM involvement was reported in 75.4% to 76.9

Efficacy data and additional analyses

A total of 328 randomized patients were included in the efficacy analyses, of which one patient under 3 years of age received MabThera in combination with LMB chemotherapy.

The two treatment arms, LMB (LMB chemotherapy) and R-LMB (LMB chemotherapy with MabThera), were well balanced with regards to baseline characteristics. Patients had a median age of 7 and 8 years in the LMB arm and R-LMB arm, respectively. Approximately half of patients were in Group B (50.6% in the LMB arm and 49.4% in the R-LMB arm), 39.6% in Group C1 in both arms, and 9.8% and 11.0% were in Group C3 in the LMB and R-LMB arms, respectively. Based on Murphy staging, most patients were either BL stage III (45.7% in the LMB arm and 43.3% in the R-LMB arm) or BAL, CNS negative (21.3% in the LMB arm and 24.4% in the R-LMB arm). Less than half of the patients (45.1% in both arms) had bone marrow involvement, and most patients (72.6% in the LMB arm and 73.2% in the R-LMB arm) had no CNS involvement. The primary efficacy endpoint was EFS, where an event was defined as occurrence of progressive disease, relapse, second malignancy, death from any cause, or non-response as evidenced by detection of viable cells in residue after the second CYVE course, whichever occurs first. The secondary efficacy endpoints were OS and CR (complete remission).

Primary efficacy analyses were performed in 328 randomized patients with a median follow-up of 3.1 years. At the pre-specified interim analysis with approximately 1 year of median follow-up, clinically relevant improvement in the primary endpoint of EFS was observed, with 1-year rate estimates of 94.2% (95% CI, 88.5% - 97.2%) in the R-LMB arm vs. 81.5% (95% CI, 73.0% - 87.8%) in the LMB arm, and adjusted Cox HR 0.33 (95% CI, 0.14 – 0.79). Upon IDMC (independent data monitoring committee) recommendation based on this result, the randomization was halted and patients in the LMB arm were allowed to cross over to receive MabThera. The study met its primary endpoint with a statistically significant difference in favour of R-Chemo, 3 year EFS rate was 93.9% in the R-Chemo ITT group compared with 82.3% in the Chemo ITT group, (HR 0.32, 90% CI: 0.17, 0.58; p = 0.0010). Median EFS was not reached in either treatment group and Kaplan-Meier analyses of EFS were supportive.

The results of the second EFS sensitivity analysis were consisted with the primary efficacy endpoint analysis results with an adjusted HR = 0.36 (95% CI: 0.18, 0.70). Both investigator and the Steering Committee reported 28 EFS events in the R-Chemo arm, but number of events in the Chemo arm was 11 by investigator and 10 according to the Steering Committee Central Review, this did not affect the HR in a meaningful way.

Progression/relapse was reported in 21 patients (75.0%) in the Chemo group vs. 3 patients (30.0%) in the R-Chemo group. Two patients had secondary malignancies in the R-Chemo arm vs. none in the Chemo arm. No difference was reported for number of toxic deaths.

Overall survival showed a clinical meaningful benefit for patients in the R-Chemo group compared with the Chemo group, adjusted HR being 0.36 (95% CI: 0.16, 0.81).

At the clinical cutoff, 20 and 8 patients had died in the Chemo and R-Chemo group respectively. Lymphoma was the most frequently reported cause of death, 14 patients died in the Chemo ITT arm and 3 in the R-Chemo ITT arm. In the safety section, Table 32, the number of patients who died of lymphoma in the Chemo arm is reported to be 13, this table only concerns deaths per actual treatment received. Overall survival in mITT and the Expanded Safety Set were consistent.

About 94% of the patients in both treatment groups, achieved CR, overall no major difference in numbers of patients achieving CR was noted between the two treatment groups. Considering the difference in EFS favouring the R-Chemo arm it would be expected, that more patients in the R-Chemo arm achieved CR. In clinical practice it is considered important to achieve CR, since these patients usually are better off than patients who do not achieve CR.

The unmet medical need in this rare condition is clear for the entire paediatric population. In clinical practice, rituximab is used in the EU paediatric community in paediatric B-NHL and the proposed dose of 375 mg/m2 is the dose referred to in the various published papers. However, only one patient below 3 years was included in the study, but the MAH har adequately provided an extrapolation, updated the adult NHL model and included a maturation factor to the constant clearance component to take into account the effect of the FcRn variation with age. The time independent clearance component is mostly dependent on B-cell count and tumour size and these are not expected to be linked to maturation. Values for covariates have been taken from the literature. The Applicant has adequately justified why a PBPK model not would be expected to provide additional information compared to the updated population PK mode (see discussion on Clinical Pharmacology). Simulations have been conducted with the updated model to predict exposure in children < 3 years. A BSA adjusted rituximab dose is appropriate also in children < 3 years of age and an extension of the indication B-NHL indication to the age group 6 months to 3 years can be accepted despite lack of clinical PK data in the age group.

As CD20 negative patients were excluded from the study, the wording of the indication was amended to reflect this - this is consistent with the adult indication.

The following indication is agreed: MabThera in combination with chemotherapy is indicated for the treatment of paediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated advanced stage CD20 positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukaemia (mature B-cell acute leukaemia) (BAL) or Burkitt-like lymphoma (BLL).

The recommended initial rate for infusion is 0.5 mg/kg/h (maximum 50 mg/h); it can be escalated by 0.5 mg/kg/h every 30 minutes if there is no hypersensitivity or infusion-related reactions, to a maximum of 400 mg/h. Subsequent doses of MabThera can be infused at an initial rate of 1 mg/kg/h (maximum 50 mg/h); it can be increased by 1 mg/kg/h every 30 minutes to a maximum of 400 mg/h.

2.4.4. Conclusions on the clinical efficacy

Overall the study met its primary endpoint with a clinical meaningful and statistically significant effect of rituximab in combination with chemotherapy on EFS in paediatric patients with advanced NHL.

2.5. Clinical safety

Introduction

For completeness, AE data (including tabulations) provided in Section 7 of this CSR also summarize AEs that occurred in patients who received any dose of rituximab, including those who crossed-over from the Chemo treatment group following the interim analysis. However, given the variable exposure to rituximab among patients in this group, AE counts for the "Rituximab safety set" should not be compared with those shown in the "Chemo safety set" and "R-Chemo safety set." For the evaluation of safety, the following defines each group presented.

- Chemo safety set, N = 153, patients from the randomized portion of the trial who received chemotherapy courses beyond initial COP course and no doses of rituximab
- R-Chemo safety set, N = 162, patients from the randomized portion of the trial only, this excludes any patient who crossed over to R therapy when crossover was permitted
- Initial COP only safety set, N = 7, patients withdrawn from study treatment scheme before initiation of induction course.

- Rituximab safety set, N = 309, this was any patient who received at least one dose of rituximab, which includes patients from the randomized portion of the trial (R-Chemo safety set 162 patients), plus the 31 patients who were eligible to cross over (2 patients of the crossover over part did not receive rituximab) and 116 patients from the single-arm open- label portion of the study.

Table 25 Brief Summary of Adverse Events by Actual Treatment Arm, Safety and Rituximab Safety Sets

	Chemo, Safety Set (N = 153)	R-Chemo, Safety Set (N = 162)	Initial COP(s) Only, Safety Set (N = 7)	Rituximab Safety Set (N = 309)
Patients who experienced reportable AEs[1]				
At least 1 event	148 (96.7)	158 (97.5)	5 (71.4)	300 (97.1)
At least 1 event of Grade ≥ 4[2]	57 (37.3)	69 (42.6)	4 (57.1)	128 (41.4)
A fatal event[3]	6 (3.9)	5 (3.1)	2 (28.6)	8 (2.6)
A toxic fatal event[4]	2 (1.3)	3 (1.9)	0	5 (1.6)
Subsequent malignancy	0	2 (1.2)	0	2 (0.6)
At least 1 acute event[5]	148 (96.7)	158 (97.5)	2 (28.6)	300 (97.1)
At least 1 acute event of Grade ≥ 4[2]	53 (34.6)	69 (42.6)	2 (28.6)	128 (41.4)
A fatal acute event[3]	2 (1.3)	3 (1.9)	1 (14.3)	5 (1.6)
A toxic acute fatal event[4]	2 (1.3)	2 (1.2)	0	4 (1.3)
Subsequent malignancy	0	0	0	0
At least 1 late effect[5]	5 (3.3)	11 (6.8)	3 (42.9)	18 (5.8)
At least 1 late effect of Grade ≥ 4[2]	4 (2.6)	3 (1.9)	2 (28.6)	5 (1.6)
A fatal late event[3]	4 (2.6)	2 (1.2)	1 (14.3)	3 (1.0)
A toxic late fatal event[4]	0	1 (0.6)	0	1 (0.3)
Subsequent malignancy	0	2 (1.2)	0	2 (0.6)
Patients with events reported to pharmacovigilance units[6]				
At least 1 SAE[7]	35 (39.3)	47 (49.5)	0	169 (54.7)

AE = Adverse Event; Chemo = Chemotherapy; COP = Cyclophosphamide, Oncovin, Prednisone; R-Chemo = Rituximab + Chemotherapy; SAE = Serious Adverse Event.

Source: Table 14.3.2.1

Patient exposure

Table 26 Extent of Exposure to Rituximab, Safety Set

	1st(R-) COPADM (N = 162)	2nd(R-) COPADM (N = 159)	1st(R-) CYM (N = 74)	2nd(R-) CYM (N = 65)	1st(R-) CYVE[1] (N = 83)	2nd(R-) CYVE[2] (N = 91)	Waiting COP (N = 10)	Overall (N = 162)
Number of doses received, n (%)								
0	0	0	0	0	0	0	0	0
1	2 (1.3)	7 (4.4)	74 (100)	64 (100)	80 (98.8)	88 (100)	0	1 (0.6)
2	157 (98.7)	151 (95.6)	0	0	1 (1.2)	0	0	3 (1.9)
3	0	0	0	0	0	0	0	1 (0.6)
4	0	0	0	0	0	0	0	5 (3.1)
5	0	0	0	0	0	0	0	4 (2.5)
6	0	0	0	0	0	0	0	147 (90.7)
7	0	0	0	0	0	0	0	1 (0.6)
Cumulative dose received (mg/m^2)[3]	159	158	74	64	81	88	0	162
N	738.6	710.6	361.3	364.7	365.6	364.4		2121.6
Mean	71.18	82.08	15.78	16.36	41.87	16.73		310.08
Standard deviation	56	335	310	328	326	323		56
Minimum	732.6	705.9	354.4	355.4	350.6	355.7		2145.5
1st Quartile	744.7	726.4	360.5	364.0	362.3	364.1		2195.1
Median	752.9	743.4	370.9	374.5	369.0	374.0		2224.0
3rd Quartile	1054	843	403	407	708	431		2596
Maximum	998	508	93	80	382	108		2541
Range	159	158	74	64	81	88	0	162
Extent of exposure (days)[4]								
N	159	158	74	64	81	88	0	162
Mean	3.5	3.0	1.0	1.0	1.4	1.0		71.5
Standard deviation	2.87	0.70	0.00	0.00	3.22	0.00		16.99
Minimum	1	1	1	1	1	1		1
1st Quartile	3.0	3.0	1.0	1.0	1.0	1.0		66.0
Median	3.0	3.0	1.0	1.0	1.0	1.0		72.5
3rd Quartile	3.0	3.0	1.0	1.0	1.0	1.0		79.0
Maximum	29	9	1	1	30	1		112
Range	28	8	0	0	29	0		111
Any dose modification or additions/omissions of rituximab, n (%)								
N	159	158	74	64	81	88	0	162
Mean	0.3	0.5	0.3	0.3	0.2	0.2		1.3
No	136 (84.5)	116 (73.4)	49 (66.2)	45 (70.3)	64 (79.0)	70 (78.7)	5 (83.3)	147 (70.0)
Unknown	0	0	0	0	0	0	0	0
Yes, planned	23 (14.3)	39 (24.7)	24 (32.4)	18 (28.1)	13 (16.0)	16 (18.0)	1 (16.7)	55 (26.2)
Yes, unplanned	2 (1.2)	3 (1.9)	1 (1.4)	1 (1.6)	4 (4.9)	3 (3.4)	0	8 (3.8)
Reason for 375 mg/m^2 per infusion not administered, n (%)								
Infusion-related reaction	2 (12.5)	1 (3.4)	0	0	1 (9.1)	1 (7.7)	0	2 (4.0)
Other adverse event	0	1 (3.4)	0	0	0	1 (7.7)	0	1 (2.0)
Medication error	0	0	0	1 (8.3)	0	0	0	1 (2.0)
Patient/parent refusal	0	0	0	0	0	0	0	0
Other	14 (87.5)	27 (93.1)	18 (100)	11 (91.7)	10 (90.9)	11 (84.6)	1 (100)	46 (92.0)

BSA = Body Surface Area; COPADM = Cyclophosphamide, Oncovin, Prednisolone, Adriamycin, Methotrexate; CYM = Cytarabine, Methotrexate; CYVE = Cytarabine, Vepeside; HD = High-Dose; IT = Intrathecal; MTX = Methotrexate.

Source: Table 14.3.1.1.1.1

Note: Patients who were to receive rituximab but withdrew from the protocol therapy during/after initial COP course(s) could not be included in this summary.

(1) CYVE +/- IT & HD MTX in Group C1, IT-CYVE-MTX in Group C3.

(2) CYVE in Group C1, IT-CYVE in Group C3.

(3) Calculated as the sum of all doses received during the different courses, divided by the BSA, further rounded to 1 decimal place.

(4) Last date of rituximab intake - first date of rituximab intake + 1.

Table 14.3.1.2.1
Exposure to Chemotherapy IV Doxorubicin By Actual Treatment Arm Over Time, Safety and Rituximab Safety Sets

	Chemo, Safety Set (N=153)	R-Chemo, Safety Set (N=162)	Rituximab Safety Set (N=309)
First COPADM course			
Type of course, n(%)			
First COPADM B	74 (48.4)	78 (48.1)	141 (45.8)
First COPADM C1	64 (41.8)	66 (40.7)	125 (40.6)
First COPADM C3	15 (9.8)	18 (11.1)	42 (13.6)
IV Doxorubicin received, n(%)			
Yes	153 (100)	161 (99.4)	305 (99.0)
No	0	1 (0.6)	3 (1.0)
If yes, dose reduction ≥ 25%, n(%)			
Yes	0	0	0
No	152 (100)	161 (100)	305 (100)
Second COPADM course			
Type of course, n(%)			
Second COPADM B	69 (47.3)	76 (47.8)	140 (46.2)
Second COPADM C1	62 (42.5)	65 (40.9)	122 (40.3)
Second COPADM C3	15 (10.3)	18 (11.3)	41 (13.5)
IV Doxorubicin received, n(%)			
Yes	146 (100)	159 (100)	302 (99.7)
No	0	0	1 (0.3)
If yes, dose reduction ≥ 25%, n(%)			
Yes	0	1 (0.6)	2 (0.7)
No	146 (100)	158 (99.4)	300 (99.3)
First maintenance course (1)			
Type of course, n(%)			
First M1 C1	60 (82.2)	66 (79.5)	127 (77.4)
First M1 C3	13 (17.8)	17 (20.5)	37 (22.6)
IV Doxorubicin received, n(%)			
Yes	73 (100)	82 (98.8)	163 (99.4)
No	0	1 (1.2)	1 (0.6)
If yes, dose reduction ≥ 25%, n(%)			
Yes	1 (1.4)	0	1 (0.6)
No	72 (98.6)	82 (100)	162 (99.4)

COP = Cyclophosphamide, Oncovin, Prednisolone; COPADM = Cyclophosphamide, Oncovin, Prednisolone, Adriamycin, Methotrexate; IV = Intravenous. Note: Patients withdrawn from the protocol therapy during/after initial COP course(s) could not be included in this summary.
(1) Group C responder patients only.

Table 14.3.1.2.2
Exposure to Chemotherapy IV Methotrexate By Actual Treatment Arm Over Time, Safety and Rituximab Safety Sets

	Chemo, Safety Set (N=153)	R-Chemo, Safety Set (N=162)	Rituximab Safety Set (N=309)
First COPADM course			
Type of course, n(%)			
1st COPADM B	74 (48.4)	78 (48.1)	141 (45.8)
1st COPADM C1	64 (41.8)	66 (40.7)	125 (40.6)
1st COPADM C3	15 (9.8)	18 (11.1)	42 (13.6)
IV methotrexate received, n(%)			
Yes	153 (100)	161 (99.4)	306 (99.4)
No	0	1 (0.6)	2 (0.6)
If yes, dose reduction ≥ 25%, n(%)			
Yes	1 (0.7)	3 (1.9)	5 (1.6)
No	151 (98.7)	158 (98.1)	301 (98.4)
NA	1 (0.7)	0	0
Second COPADM course			
Type of course, n(%)			
2nd COPADM B	69 (47.3)	76 (47.8)	140 (46.2)
2nd COPADM C1	62 (42.5)	65 (40.9)	122 (40.3)
2nd COPADM C3	15 (10.3)	18 (11.3)	41 (13.5)
IV methotrexate received, n(%)			
Yes	146 (100)	159 (100)	303 (100)
No	0	0	0
If yes, dose reduction ≥ 25%, n(%)			
Yes	1 (0.7)	2 (1.3)	4 (1.3)
No	145 (99.3)	157 (98.7)	299 (98.7)

Administration of 8 mg/m² MTX as a 24h-infusion, n(%)			
Yes	16 (88.9)	17 (85.0)	34 (81.0)
No	2 (11.1)	3 (15.0)	8 (19.0)
If yes, time from start of MTX infusion to start of folinic acid (hours)			
N	16	17	34
Mean	34.1	32.5	32.0
Standard Deviation	5.14	5.94	5.80
Minimum	24	24	24
1st Quartile	36.0	24.0	24.0
Median	36.0	36.0	36.0
3rd Quartile	36.0	36.0	36.0
Maximum	41	40	40
Range	17	16	16
If no, MTX dose received(g/m²)			
N	2	3	8
Mean	4.70	4.40	5.08
Standard Deviation	2.404	3.143	3.065
Minimum	3.0	2.2	0.0
1st Quartile	3.00	2.20	2.60
Median	4.70	3.00	5.70
3rd Quartile	6.40	8.00	8.00
Maximum	6.4	8.0	8.0
Range	3.4	5.8	8.0

COP = Cyclophosphamide, Oncovin, Prednisolone; COPADM = Cyclophosphamide, Oncovin, Prednisolone, Adriamycin, Methotrexate; CYM = CYtarabine, Methotrexate; CYVE = CYtarabine, VEposide; HD = High density; IT = Intra Thecal; IV = Intravenous; MTX = methotrexate.
Note: Patients withdrawn from the protocol therapy during/after initial COP course(s) could not be included in this summary.
(1) Group C responder patients only.
(2) Applies to course 1st IT-CYVE-MTX and M1 C3 only.

PROGRAM: T14_3_1_2_2_exmot.sas, OUTPUT: T14_3_1_2_2_exmot.rtf Date/time of run: 19DEC2018, 14:59

Table 14.3.1.2.3
Exposure to Chemotherapy Intrathecal Drugs In CNS pos CSF neg C1 Patients Consolidation Courses By Actual Treatment Arm Over Time, Safety and Rituximab Safety Sets

	Chemo, Safety Set (1) (N=153)	R-Chemo, Safety Set (1) (N=162)	Rituximab Safety Set (1) (N=309)
First CYVE C1			
Administration of 2 drugs intrathecal a D1, n(%)			
Yes	22 (71.0)	22 (78.6)	41 (82.0)
No	9 (29.0)	6 (21.4)	9 (18.0)
Administration of HD-MTX (8 g/m²) and 3 drugs IT at about D18 D20, n(%)			
Yes	23 (79.3)	22 (78.6)	40 (80.0)
No	6 (20.7)	6 (21.4)	10 (20.0)
Second CYVE C1			
Administration of 2 drugs intrathecal at D1, n(%)			
Yes	24 (85.7)	24 (80.0)	44 (83.0)
No	4 (14.3)	6 (20.0)	9 (17.0)

CSF = Cerebro Spinal Fluid; CNS = Central Nervous System; CYVE = CYtarabine, VEposide; D1 = Day 1; HD = High density; IT = Intra Thecal; MTX = methotrexate.
Note: Patients who withdrew from the protocol therapy during/after initial COP course(s) or induction courses could not be included in this summary.
(1) Applies to patients with CNS positive and CSF negative only (subgroup of group C1 patients)

Adverse events

Common AEs

Table 28 Reportable Acute Adverse Events Observed in ≥ 10% of Patients by System Organ Class and Preferred Term, Safety and Rituximab Safety Sets

	Chemo, Safety Set (N = 153)	R-Chemo, Safety Set (N = 162)	Rituximab Safety Set (N = 309)
Any reportable AE,[1] n (%)	147 (96.1)	154 (95.1)	296 (95.8)
Blood and lymphatic system disorders	139 (90.8)	150 (92.6)	286 (92.6)
Febrile neutropenia	139 (90.8)	150 (92.6)	286 (92.6)
Gastrointestinal disorders	117 (76.5)	131 (80.9)	246 (79.6)
Stomatitis	115 (75.2)	129 (79.6)	242 (78.3)
Enteritis	24 (15.7)	39 (24.1)	84 (27.2)
Infections and infestations	54 (35.3)	67 (41.4)	127 (41.1)
Sepsis	20 (13.1)	29 (17.9)	52 (16.8)
Device related infection	19 (12.4)	21 (13.0)	43 (13.9)
Lung infection	15 (9.8)	21 (13.0)	44 (14.2)
Enterocolitis infectious	18 (11.8)	16 (9.9)	28 (9.1)
Investigations	22 (14.4)	32 (19.8)	51 (16.5)
Alanine aminotransferase increased	22 (14.4)	32 (19.8)	48 (15.5)
Aspartate aminotransferase increased	11 (7.2)	18 (11.1)	26 (8.4)
Metabolism and nutrition disorders	22 (14.4)	32 (19.8)	54 (17.5)
Hypokalemia	21 (13.7)	26 (16.0)	45 (14.6)
Decreased appetite	7 (4.6)	18 (11.1)	23 (7.4)

AE = Adverse Event; Chemo = Chemotherapy; COP = Cyclophosphamide, Oncovin, Prednisone; CRF = Case Report Form; LVEF = Left Ventricular Ejection Fraction; LVSF = Left Ventricular Shortening Fraction; MedDRA = Medical Dictionary for Regulatory Activities; R-Chemo = Rituximab + Chemotherapy; SAE = Serious Adverse Event.

Adverse events CRF reporting requirements included all Grade 2-5 cardiac events, LVEFLV-EF / /LV-SFLVSF cardiac abnormalities and other nonhematological Grade 3-5 events, except fatigue and anorexia. During COP courses, only Grade 4-5 events had to be reported. Acute targeted toxicities found with grade 'No' or 'Grade 0 or Grade 1 or Grade 2' were not regarded as events in this summary.

Adverse events coded using MedDRA dictionary version 20.1.

(1) For the initial COP only safety set, 1 or 2 patients had reported AEs observed in ≥ 10% of patients (n =7). Details are provided in Table 14.3.2.2.3.

Source: Table 14.3.2.2.3

Table 29 Reportable Acute Adverse Events by Actual Treatment Arm and Course, Excluding Waiting COPs, Safety and Rituximab Safety Sets

	Chemo, Safety Set (N = 153)	R-Chemo, Safety Set (N = 162)
Initial COPs		
Therapeutic Group B	12 (15.8)	21 (26.3)
Therapeutic Group C1	15 (24.6)	12 (18.2)
Therapeutic Group C3, n (%)	5 (31.3)	1 (6.3)
First COPADM course		
First COPADM B, n (%)	66 (89.2)	66 (84.6)
First COPADM C1, n (%)	63 (96.4)	62 (93.9)
First COPADM C3, n (%)	12 (80.0)	16 (88.9)
Second COPADM course		
Second COPADM B, n (%)	48 (69.6)	52 (68.4)
Second COPADM C1, n (%)	56 (90.3)	58 (89.2)
Second COPADM C3, n (%)	12 (80.0)	18 (100)
First consolidation course		
First CYM-B, n (%)	21 (30.9)	31 (41.9)
First CYVE-C1, n (%)	51 (85.0)	62 (95.4)
First IT-CYVE-MTX C3, n (%)	14 (93.3)	16 (88.9)
Second consolidation course[1]		
Second CYM-B, n (%)	10 (16.1)	23 (35.4)
Second CYVE-C1, n (%)	48 (75.0)	53 (72.6)
Second CYVE-MTX C3, n (%)	15 (100)	18 (100)
Third consolidation course[1]		
Second CYVE-C1, n (%)	0	1 (14.3)
First maintenance course[2]		
M1-C1, n (%)	35 (58.3)	36 (54.5)
M1-C3, n (%)	9 (69.2)	7 (41.2)
Second maintenance course		
M2-C1, n (%)	14 (24.6)	21 (31.8)
M2-C3, n (%)	1 (7.7)	4 (23.5)

AE = Adverse Event; Chemo = Chemotherapy; COP = Cyclophosphamide, Oncovin, Prednisolone; COPADM = Cyclophosphamide, Oncovin, Prednisolone, Adriamycin, Methotrexate; CRF = Case Report Form; CYM = Cytarabine, Methotrexate; CYVE = Cytarabine, Vepeside; IT = Intrathecal; LVEF = Left Ventricular Ejection Fraction; LVSF = Left Ventricular Shortening Fraction; MedDRA = Medical Dictionary for Regulatory Activities; MTX = Methotrexate; R-Chemo = Rituximab + Chemotherapy.

Source: Table 14.3.2.2.1

Adverse events CRF reporting requirements included all Grade 2-5 cardiac events, LVEF/LVSF cardiac abnormalities and other nonhaematological Grade 2-5 events, except fatigue and anorexia. During COP courses, only Grade 4-5 events had to be reported. Acute targeted toxicities found with grade 'No' or 'Grade 0 or Grade 1 or Grade 2' were not regarded as events in this summary.

Adverse events coded using MedDRA dictionary version 20.1.

(1) In Group B patients switching from first CYM-B course to first CYVE C1 course, the second and third consolidation courses are the first and second CYVE C1 courses.

(2) The maintenance phase applies to patients in Group C at end of consolidation phase and in complete remission after 2nd CYVE course.

Grade 4-5 AEs

Table 14.3.2.2.5.1
Reportable Acute Grade 4-5 Adverse Events By System Organ Class and Preferred Term, Safety and Rituximab Safety Sets

	Chemo, Safety Set (N = 153)	R-Chemo, Safety Set (N = 162)	Initial COP(s) Only, Safety Set (N = 7)	Rituximab Safety Set (N = 309)
Any reportable AE, n(%)	53 (34.6)	69 (42.6)	2 (28.6)	128 (41.4)
Infections and infestations	19 (12.4)	31 (19.1)	0	57 (18.4)
Sepsis	18 (11.8)	26 (16.0)	0	48 (15.5)
Lung infection	4 (2.6)	2 (1.2)	0	6 (1.9)
Appendicitis	0	2 (1.2)	0	2 (0.6)
Device related infection	0	2 (1.2)	0	2 (0.6)
Enterocolitis infectious	1 (0.7)	1 (0.6)	0	2 (0.6)
Candida infection	0	1 (0.6)	0	1 (0.3)
Chorioretinitis	0	1 (0.6)	0	1 (0.3)
Douglas' abscess	0	1 (0.6)	0	1 (0.3)
Encephalitis	0	1 (0.6)	0	1 (0.3)
Endocarditis	1 (0.7)	0	0	0
Meningitis	0	1 (0.6)	0	1 (0.3)
Peritonitis	0	1 (0.6)	0	1 (0.3)
Streptococcal infection	0	1 (0.6)	0	1 (0.3)
Bacteraemia	0	0	0	1 (0.3)
Bacterial sepsis	0	0	0	1 (0.3)
Investigations	16 (10.5)	24 (14.8)	0	36 (11.7)
Alanine aminotransferase increased	9 (5.9)	13 (8.0)	0	17 (5.5)
Neutrophil count decreased	4 (2.6)	9 (5.6)	0	11 (3.6)
Platelet count decreased	5 (3.3)	6 (3.7)	0	12 (3.9)
Aspartate aminotransferase increased	1 (0.7)	7 (4.3)	0	8 (2.6)
White blood cell count decreased	4 (2.6)	4 (2.5)	0	4 (1.3)
Investigations (cont.)				
Lymphocyte count decreased	0	4 (2.5)	0	4 (1.3)
Lipase increased	0	1 (0.6)	0	1 (0.3)
Transaminases increased	1 (0.7)	0	0	0
Blood bilirubin increased	0	0	0	1 (0.3)
Gastrointestinal disorders	12 (7.8)	21 (13.0)	0	43 (13.9)
Stomatitis	7 (4.6)	13 (8.0)	0	28 (9.1)
Colitis	1 (0.7)	3 (1.9)	0	3 (1.0)
Ascites	1 (0.7)	1 (0.6)	0	2 (0.6)
Jejunal perforation	1 (0.7)	1 (0.6)	0	1 (0.3)
Diarrhoea	1 (0.7)	0	0	1 (0.3)
Enteritis	0	1 (0.6)	0	6 (1.9)
Gastric perforation	0	1 (0.6)	0	1 (0.3)
Ileal perforation	0	1 (0.6)	0	1 (0.3)
Ileus	0	1 (0.6)	0	1 (0.3)
Intestinal haemorrhage	0	1 (0.6)	0	1 (0.3)
Pancreatic haemorrhage	0	1 (0.6)	0	1 (0.3)
Proctitis	0	1 (0.6)	0	1 (0.3)
Small intestinal obstruction	0	1 (0.6)	0	1 (0.3)
Small intestinal perforation	1 (0.7)	0	0	0
Anal haemorrhage	0	0	0	1 (0.3)
Impaired gastric emptying	0	0	0	1 (0.3)
Intestinal perforation	0	0	0	1 (0.3)
Intussusception	0	0	0	1 (0.3)
Blood and lymphatic system disorders	10 (6.5)	22 (13.6)	0	41 (13.3)
Febrile neutropenia	10 (6.5)	20 (12.3)	0	33 (10.7)
Anaemia	1 (0.7)	1 (0.6)	0	3 (1.0)
Thrombocytopenia	0	1 (0.6)	0	2 (0.6)
Methaemoglobinaemia	0	0	0	1 (0.3)
Neutropenia	0	0	0	2 (0.6)
Metabolism and nutrition disorders	13 (8.5)	9 (5.6)	0	14 (4.5)
Hypokalaemia	6 (3.9)	6 (3.7)	0	9 (2.9)
Tumour lysis syndrome	4 (2.6)	2 (1.2)	0	4 (1.3)
Hypocalcaemia	3 (2.0)	1 (0.6)	0	3 (1.0)
Hypophosphataemia	2 (1.3)	0	0	0
Acidosis	0	1 (0.6)	0	1 (0.3)
Hyperuricaemia	1 (0.7)	0	0	0
Hypoalbuminaemia	0	1 (0.6)	0	1 (0.3)
Hyponatraemia	1 (0.7)	0	0	0
Hyperkalaemia	0	0	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders	4 (2.6)	3 (1.9)	1 (14.3)	6 (1.9)
Acute respiratory distress syndrome	2 (1.3)	1 (0.6)	1 (14.3)	1 (0.3)
Respiratory failure	2 (1.3)	2 (1.2)	0	4 (1.3)
Hypoxia	0	1 (0.6)	0	1 (0.3)
Pleural effusion	0	0	0	2 (0.6)

Renal and urinary disorders	4 (2.6)	1 (0.6)	2 (28.6)	3 (1.0)
Acute kidney injury	4 (2.6)	1 (0.6)	2 (28.6)	3 (1.0)
Nervous system disorders	3 (2.0)	3 (1.9)	0	6 (1.9)
Encephalopathy	2 (1.3)	0	0	0
Cerebellar syndrome	0	1 (0.6)	0	1 (0.3)
Cerebral artery embolism	1 (0.7)	0	0	0
Headache	0	1 (0.6)	0	1 (0.3)
Status epilepticus	0	1 (0.6)	0	1 (0.3)
Cerebrospinal fluid leakage	0	0	0	1 (0.3)
Posterior reversible encephalopathy syndrome	0	0	0	1 (0.3)
Seizure	0	0	0	1 (0.3)
Vascular disorders	3 (2.0)	2 (1.2)	0	3 (1.0)
Hypotension	2 (1.3)	2 (1.2)	0	3 (1.0)
Hypertension	1 (0.7)	0	0	0
Cardiac disorders	2 (1.3)	1 (0.6)	0	1 (0.3)
Cardiac arrest	0	1 (0.6)	0	1 (0.3)
Cardiac failure	1 (0.7)	0	0	0
Cardiac failure acute	1 (0.7)	0	0	0
Hepatobiliary disorders	0	2 (1.2)	0	5 (1.6)
Hepatocellular injury	0	2 (1.2)	0	2 (0.6)
Hepatotoxicity	0	0	0	2 (0.6)
Hepatobiliary disorders (cont.)				
Hyperbilirubinaemia	0	0	0	1 (0.3)
Immune system disorders	1 (0.7)	1 (0.6)	0	1 (0.3)
Anaphylactic reaction	0	1 (0.6)	0	1 (0.3)
Hypersensitivity	1 (0.7)	0	0	0
Injury, poisoning and procedural complications	2 (1.3)	0	0	0
Stomal hernia	1 (0.7)	0	0	0
Wrong drug administered	1 (0.7)	0	0	0
General disorders and administration site conditions	0	1 (0.6)	0	3 (1.0)
Multiple organ dysfunction syndrome	0	1 (0.6)	0	1 (0.3)
Pyrexia	0	0	0	2 (0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (14.3)	0
Neoplasm progression	0	0	1 (14.3)	0
Psychiatric disorders	0	1 (0.6)	0	2 (0.6)
Confusional state	0	1 (0.6)	0	1 (0.3)
Personality change	0	0	0	1 (0.3)
Skin and subcutaneous tissue disorders	0	1 (0.6)	0	1 (0.3)
Stevens-Johnson syndrome	0	1 (0.6)	0	1 (0.3)

AE = Adverse event; COP = Cyclophosphamide, Oncovin, Prednisolone; CRF = Case Report Form; LV-EF = Left Ventricular Ejection Fraction; LV-SF = Left Ventricular Shortening Fraction.
Adverse events CRF reporting requirements included all grade 2-5 cardiac events, LV-EF / LV-SF cardiac abnormalities and other non haematological grade 2-5 events, except fatigue and anorexia. During COP courses, only grade 4-5 events had to be reported. Acute targeted toxicities found with grade 'No' or 'Grade 0 or Grade 1 or Grade 2' were not regarded as events in this summary.
Adverse events coded using MedDRA dictionary version 20.1

Table 11: All Patients who Reported AEs of AST/ALT Increased and Bilirubin Increased:

Arm	Pt ID	AE term	CTC Grade	Other Hepatobiliary AEs
Rituximab	3-C-115	AST increased* ALT increased AST increased Blood bilirubin increased	3 4 3 3	None
Rituximab	3-E-320	ALT increased ALT increased ALT increased Blood bilirubin increased	3 2 2 3	Ggt increased (G2)
Chemo	3-C-14	ALT increased* Blood bilirubin increased*	3 3	None
Chemo	3-C-66	ALT increased* AST increased* ALT increased ALT increased ALT increased/ Blood bilirubin increased Blood bilirubin increased	4 3 4 3 3 3 3	None

Chemo	3-C-79	ALT increased* AST increased* ALT increased ALT increased AST increased Blood bilirubin increased	4 3 4 3 3 3	None

None of the events were serious. * Event occurred during initial COP.

Table 12: Acute AEs Categorized in the Hepatobiliary Disorders SOC

	Chemo Safety Set (n=153)	R-Chemo Safety Set (n=162)
Hepatocellular injury	0	2 (1.2)
Cholestasis	1 (0.7)	0
Hepatitis toxic	1 (0.7)	0
Jaundice	1 (0.7)	0

Late AEs

The large majority of patients did not experience a late AE. Five patients (3.3%) in the Chemo safety set and 11 patents (6.8%) in the R-Chemo safety set experienced at least 1 late AE, and 18 patients (5.8%) in the rituximab safety set experienced at least 1 late AE. In the Initial COP(s) only safety set, 3 patients (42.9%) experienced at least 1 late AE. Four patients in the R-Chemo set experienced late effects in the SOC of infections and infestations vs. none in the Chemo set. Three patients in the Chemo set and 1 patient in the R-Chemo set were diagnosed with neoplasm. All of these events corresponded to the deaths of these 4 patients related to lymphoma progression. Two patients in the RChemo set experienced second malignancy (reported as "uncoded" term in Table 30) vs. none in the Chemo set. The remaining late effects were observed in only 1 or 2 patients in the Chemo and R-Chemo safety sets.

Table 30 Reportable Late Effects by System Organ Class and Preferred Term, Safety and Rituximab Safety Sets

	Chemo, Safety Set (N = 153)	R-Chemo, Safety Set (N = 162)	Initial COP(s) Only, Safety Set (N = 7)	Rituximab Safety Set (N = 309)
Any reportable AE, n (%)	5 (3.3)	11 (6.8)	3 (42.9)	18 (5.8)
Infections and infestations	0	4 (2.5)	2 (28.6)	5 (1.6)
Lung infection	0	2 (1.2)	0	2 (0.6)
Bacterial infection	0	1 (0.6)	0	1 (0.3)
Enterobacter sepsis	0	1 (0.6)	0	1 (0.3)
Epstein-Barr virus infection	0	0	1 (14.3)	0
Pseudomonal sepsis	0	1 (0.6)	0	1 (0.3)
Sepsis	0	0	1 (14.3)	0
Staphylococcal sepsis	0	1 (0.6)	0	1 (0.3)
Adenovirus infection	0	0	0	1 (0.3)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	3 (2.0)	1 (0.6)	0	1 (0.3)
Neoplasm	3 (2.0)	1 (0.6)	0	1 (0.3)
Blood and lymphatic system disorders	0	2 (1.2)	0	3 (1.0)
Febrile neutropenia	0	1 (0.6)	0	1 (0.3)
Lymphopenia	0	1 (0.6)	0	2 (0.6)
Cardiac disorders	1 (0.7)	0	1 (14.3)	0
Cardiac arrest	0	0	1 (14.3)	0
Left ventricular dysfunction	1 (0.7)	0	0	0
Uncoded	0	2 (1.2)	0	2 (0.6)
Uncoded[1]	0	2 (1.2)	0	2 (0.6)
Eye disorders	0	1 (0.6)	0	2 (0.6)
Corneal epithelial microcysts	0	1 (0.6)	0	1 (0.3)
Dry eye	0	0	0	1 (0.3)
Nervous system disorders	0	1 (0.6)	0	2 (0.6)
Encephalopathy	0	1 (0.6)	0	1 (0.3)
Dystonic tremor	0	0	0	1 (0.3)
Respiratory, thoracic, and mediastinal disorders	1 (0.7)	0	0	0
Respiratory failure	1 (0.7)	0	0	0
Investigations	0	0	0	2 (0.6)
Ejection fraction decreased	0	0	0	1 (0.3)
Neutrophil count decreased	0	0	0	1 (0.3)

Table 31 Reportable Late Grade 4-5 Effects by System Organ Class and Preferred Term, Safety and Rituximab Safety Sets

	Chemo, Safety Set (N = 153)	R-Chemo, Safety Set (N = 162)	Initial COP(s) Only, Safety Set (N = 7)	Rituximab Safety Set (N = 309)
Any reportable AE, n (%)	4 (2.6)	3 (1.9)	2 (28.6)	5 (1.6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	3 (2.0)	1 (0.6)	0	1 (0.3)
Neoplasm	3 (2.0)	1 (0.6)	0	1 (0.3)
Infections and infestations	0	1 (0.6)	1 (14.3)	2 (0.6)
Enterobacter sepsis	0	1 (0.6)	0	1 (0.3)
Pseudomonal sepsis	0	1 (0.6)	0	1 (0.3)
Sepsis	0	0	1 (14.3)	0
Staphylococcal sepsis	0	1 (0.6)	0	1 (0.3)
Adenovirus infection	0	0	0	1 (0.3)
Cardiac disorders	0	0	1 (14.3)	0
Cardiac arrest	0	0	1 (14.3)	0
Respiratory, thoracic, and mediastinal disorders	1 (0.7)	0	0	0
Respiratory failure	1 (0.7)	0	0	0
Uncoded	0	1 (0.6)	0	1 (0.3)
Uncoded[1]	0	1 (0.6)	0	1 (0.3)
Investigations	0	0	0	1 (0.3)
Neutrophil count decreased	0	0	0	1 (0.3)

AE = Adverse Event; Chemo = Chemotherapy; COP = Cyclophosphamide, Oncovin, Prednisone; CRF = Case Report Form; LVEF = Left Ventricular Ejection Fraction; LVSF = Left Ventricular Shortening Fraction; MedDRA = Medical Dictionary for Regulatory Activities; R-Chemo = Rituximab + Chemotherapy; SAE = serious adverse event.

Source: Table 14.3.2.3.2

Adverse events CRF reporting requirements included all Grade 3-5 cardiac events, LVEF/LVSF cardiac abnormalities and other nonhematological Grade 3-5 events, except fatigue and anorexia. During COP courses, only Grade 4-5 events had to be reported. Acute targeted toxicities found with grade 'No' or 'Grade 0 or Grade 1 or Grade 2' were not regarded as events in this summary.

Adverse events coded using MedDRA dictionary version 20.1.

(1) The uncoded term is Subsequent Malignancy for patient 3-E-113.

Table 13 Patients in R-Chemo Safety Set with Late AEs

Pt ID	Treatment Group/age[1]/sex	Late AE term/Grade/outcome	Time from Last R infusion to AE onset (days)[2]	Further details
3-E-3	C1/9M	Lung infection/3/unk	85	lowB cell count on 18Dec12
3-E-9	B/6M	Febrile neutropenia/2/unk	82	
3-E-57	C1/6M	Encephalopathy/1/ unk	27	Sequelae of previous acute AE of encephalitis
3-C-58	B/2M	Enterobacter sepsis/4/resolving Pseudomomal sepsis/4/ resolving staphylococcal sepsis/4/ resolving	67	low B cell count on 18Aug14 and 16Feb15
3-E-83	C1/4M	Lung infection/3/unk	271	Sepsis and other infections reported as acute AEs. Low B cell count on 24Jun15
3-C-93	B/13M	Neoplasm/5/fatal	245	Disease progression

3-E-90	C1/5M	Bacterial infection/3/unk	156	Enterocolitis infection (x3) reported as acute AEs
3-E-95	C1/3M	Corneal epithelial microcysts/2/unk	398	
3-E-113	C3/11M	Histiocytic sarcoma/5/fatal	450	
3-E-122	B/15F	Melanoma/4/resolving	65	
3-E-161	B/13M	Lymphopenia/3/unk	140	

1. Age at randomization. 2. Based on new output L999_10_2_leffect.rtf.

Adverse events of special interest (AESI)

Cardiotoxicity

Table 39 Cardiac Abnormalities and Toxicities by Actual Treatment Arm Over Time, Safety and Rituximab Safety Sets

	Chemo, Safety Set (N = 153)	R-Chemo, Safety Set (N = 162)	Rituximab Safety Set (N = 309)
Cardiotoxicity[1]			
At any time during the trial, n (%)			
Yes	4 (2.7) [0.7; 6.7]	16 (10.0) [5.8; 15.7]	25 (8.2) [5.4; 11.8]
No	145 (97.3) [93.3; 99.3]	144 (90.0) [84.3; 94.2]	281 (91.8) [88.2; 94.6]
Before first doxorubicin administration[2]			
Yes	2 (1.4) [0.2; 5.0]	4 (2.5) [0.7; 6.4]	8 (2.7) [1.2; 5.2]
No	139 (98.6) [95.0; 99.8]	153 (97.5) [93.6; 99.3]	291 (97.3) [94.8; 98.8]
Within 2 months before first M1 course[3]			
Yes	0 (0.0) [0.0; 7.9]	4 (7.3) [2.0; 17.6]	5 (5.1) [1.7; 11.4]
No	45 (100) [92.1; 100]	51 (92.7) [82.4; 98.0]	94 (94.9) [88.6; 98.3]
12±3 months after the end of treatment[4]			
Yes	2 (3.4) [0.4; 11.9]	5 (7.6) [2.5; 16.8]	7 (7.3) [3.0; 14.4]
No	56 (96.6) [88.1; 99.6]	61 (92.4) [83.2; 97.5]	89 (92.7) [85.6; 97.0]
60±6 months after the initiation of treatment[5]			
Yes	0 (0.0) [0.0; 70.8]	0 (0.0) [0.0; 70.8]	0 (0.0) [0.0; 70.8]
No	3 (100) [29.2; 100]	3 (100) [29.2; 100]	3 (100) [29.2; 100]
Abnormal echocardiography			
At any time during the trial, n (%)			
Yes	12 (8.0)	22 (13.8)	34 (11.1)
No	138 (92.0)	138 (86.3)	272 (88.9)
If yes,			
Wall motion abnormalities, n (%)			
Yes	1 (8.3)	1 (4.5)	5 (14.7)
No	11 (91.7)	21 (95.5)	29 (85.3)
Structural or functional abnormalities, n (%)			
Yes	4 (33.3)	14 (63.6)	19 (55.9)
No	8 (66.7)	8 (36.4)	15 (44.1)
Other abnormalities, n (%)			
Yes	8 (66.7)	11 (50.0)	17 (50.0)
No	4 (33.3)	11 (50.0)	17 (50.0)
Before first doxorubicin administration[2]			
Yes	9 (6.1)	17 (10.8)	25 (8.3)
No	138 (93.9)	140 (89.2)	275 (91.7)

If yes,			
Wall motion abnormalities, n (%)			
Yes	0	0	0
No	9 (100)	17 (100)	25 (100)
Structural or functional abnormalities, n (%)			
Yes	3 (33.3)	11 (64.7)	16 (64.0)
No	6 (66.7)	6 (35.3)	9 (36.0)
Other abnormalities, n (%)			
Yes	7 (77.8)	10 (58.8)	15 (60.0)
No	2 (22.2)	7 (41.2)	10 (40.0)
Within 2 months before first M1 course[3]	1 (2.2)	4 (7.0)	4 (4.0)
Yes	1 (2.2)	4 (7.0)	4 (4.0)
No	44 (97.8)	53 (93.0)	97 (96.0)
If yes,			
Wall motion abnormalities, n (%)	0	0	0
Yes	0	0	0
No	1 (100)	4 (100)	4 (100)
Structural or functional abnormalities, n (%)	1 (100)	2 (50.0)	2 (50.0)
Yes	1 (100)	2 (50.0)	2 (50.0)
No	0	2 (50.0)	2 (50.0)
Other abnormalities, n (%)	0	3 (75.0)	3 (75.0)
Yes	0	3 (75.0)	3 (75.0)
No	1 (100)	1 (25.0)	1 (25.0)
12±3 months after the end of treatment[4]			
Yes	3 (4.9)	5 (7.6)	6 (6.3)
No	58 (95.1)	61 (92.4)	90 (93.8)
If yes,			
Wall motion abnormalities, n (%)			
Yes	0	1 (20.0)	2 (33.3)
No	3 (100)	4 (80.0)	4 (66.7)
Structural or functional abnormalities, n (%)			
Yes	1 (33.3)	4 (80.0)	4 (66.7)
No	2 (66.7)	1 (20.0)	2 (33.3)
Other abnormalities, n (%)			
Yes	2 (66.7)	1 (20.0)	1 (16.7)
No	1 (33.3)	4 (80.0)	5 (83.3)
60±6 months after the initiation of treatment[5]			
Yes	0	0	0
No	3 (100)	3 (100)	3 (100)

Secondary malignancies

There were 2 secondary malignancies reported in the study, both in the R-Chemo arm (melanoma and histiocytic sarcoma). The event of melanoma was reported in a therapeutic Group B patient who had a pre-existing skin nevus which rapidly progressed after the patient started study treatment. The event of melanoma was reported in a therapeutic Group B patient who had a pre-existing skin nevus which rapidly progressed after the patient started study treatment. The histiocytic sarcoma was diagnosed 16.6 months after randomization in a therapeutic Group C3 patient and was fatal (death occurred 1 year after diagnosis).

Infusion-related reactions

Table 40 Rituximab Infusion-Related Reactions by Actual Treatment Arm, Safety Set

	R-Chemo, Safety Set (N = 162)	Rituximab Safety Set (N = 309)
Total number of infusion-related reactions,[1] n (%)		
0	98 (60.5)	200 (64.9)
1	45 (27.8)	81 (26.3)
2	11 (6.8)	14 (4.5)
3	3 (1.9)	4 (1.3)
4	1 (0.6)	4 (1.3)
5	1 (0.6)	1 (0.3)
6	3 (1.9)	4 (1.3)
Total number of infusion-related reactions		
N	162	308
Mean	0.6	0.5
Standard deviation	1.11	1.02
Minimum	0	0
1st Quartile	0.0	0.0
Median	0.0	0.0
3rd Quartile	1.0	1.0
Maximum	6	6
Range	6	6
Worst grade of infusion-related reactions,[2] n (%)		
0	50 (52.6)	143 (61.6)
1	19 (20.0)	34 (14.7)
2	21 (22.1)	43 (18.5)
3	5 (5.3)	11 (4.7)
4	0	1 (0.4)
Maximum grade of IRR First infusion,[2] n (%)		
0	57 (60.0)	156 (67.2)
1	15 (15.8)	28 (12.1)
2	19 (20.0)	40 (17.2)
3	4 (4.2)	8 (3.4)
Second infusion,[2] n (%)		
0	85 (89.5)	215 (93.9)
1	7 (7.4)	11 (4.8)
2	2 (2.1)	2 (0.9)
3	1 (1.1)	1 (0.4)
Third infusion,[2] n (%)		
0	87 (92.6)	214 (95.1)
1	5 (5.3)	8 (3.6)
3	2 (2.1)	3 (1.3)
Fourth infusion,[2] n (%)		
0	86 (91.5)	212 (94.2)
1	5 (5.3)	9 (4.0)
2	1 (1.1)	1 (0.4)
3	2 (2.1)	3 (1.3)

Fifth infusion,[2] n (%)		
0	85 (93.4)	200 (93.5)
1	4 (4.4)	8 (3.7)
2	1 (1.1)	3 (1.4)
3	1 (1.1)	2 (0.9)
4	0	1 (0.5)
Sixth infusion,[2] n (%)		
0	80 (89.9)	197 (93.8)
1	7 (7.9)	8 (3.8)
2	2 (2.2)	4 (1.9)
3	0	1 (0.5)

IRR = Infusion-related Reaction; R-Chemo = Rituximab + Chemotherapy.

Source: Table 14.3.4.2

(1) Obtained by summing up the number of infusion-related reactions reported in each course. For studies managed by Gustave Roussy, patient defined as having experienced an infusion-related reaction if highest grade of reaction for the infusion > 0. For studies managed by Children's Oncology Group, whether a patient experienced an infusion-related reaction is collected as such. If grade was collected as "0," this means there was no infusion-related reaction.

(2) Information collected in studies managed by Gustave Roussy only.

Table 14. Frequency of All Acute AEs by Safety Set and Treatment Group

	Group B		Group C1		Group C3	
	Chemo (n=78)	R-Chemo (n=79)	Chemo (n=60)	R-Chemo (n=66)	Chemo (n=15)	R-Chemo (n=17)
Any reportable AE, n (%)	68 (87.2)	70 (88.6)	60 (100)	65 (98.5)	15 (100)	17 (100)
SOCs with ≥ 25% of patients in either set or treatment group						
Blood and lymphatic system disorders	62 (79.5)	66 (83.5)	58 (96.7)	63 (95.5)	15 (100)	17 (100)
Gastrointestinal disorders	51 (65.4)	55 (69.6)	54 (90.0)	63 (95.5)	14 (93.3)	17 (100)
Infections and infestations	26 (33.3)	30 (38.0)	38 (63.3)	50 (75.8)	12 (80.0)	12 (70.6)
Investigations	10 (12.8	11 (13.9)	18 (30.0)	22 (33.3)	5 (33.3)	8 (47.1)
Metabolism and nutrition disorders	10 (12.8)	16 (20.3)	9 (15.0)	18 (27.3)	3 (20.0)	6 (35.3)
Selected Other SOCs						
Respiratory, Thoracic and Mediastinal Disorders	3 (3.8)	4 (5.1)	2 (3.3)	8 (12.1)	2 (13.3)	3 (17.6)

Source: T14_3_2_2_2_2_aesoc.rtf, T14_3_2_2_2_3_aesoc.rtf, T14_3_2_2_2_4_aesoc.rtf in final CSR.

Table 15. Frequency of Grade 4-5 Acute AEs by Safety Set and Treatment Group

	Group B		Group C1		Group C3	
	Chemo (n=78)	R-Chemo (n=79)	Chemo (n=60)	R-Chemo (n=66)	Chemo (n=15)	R-Chemo (n=17)
Any reportable AE, n (%)	16 (20.5)	20 (25.3)	18 (30.0)	32 (48.5)	5 (33.3)	7 (41.2)
SOCs with ≥ 10% of patients in either set or treatment group						
Infections and infestations	5 (6.4)	8 (10.1)	9 (15.0)	15 (22.7)	3 (20.0)	3 (17.6)

Investigations	2 (2.6)	6 (7.6)	6 (10.0)	12 (18.2)	3 (20.0)	3 (17.6)
Gastrointestinal disorders	5 (6.4)	5 (6.3)	6 (10.0)	10 (15.2)	1 (6.7)	2 (11.8)
Blood and lymphatic system disorders	4 (5.1)	4 (5.1)	6 (10.0)	11 (16.7)	0	5 (29.4)
Selected Other SOCs						
Respiratory, Thoracic and Mediastinal Disorders	1 (1.3)	1 (1.3)	1 (1.7)	1 (1.5)	0	0

Source: T14_3_2_2_5_2_aesoc.rtf, T14_3_2_2_2_3_aesoc.rtf, T14_3_2_2_2_4_aesoc.rtf in final CSR.

Table 16. Frequency of Late Effects per Treatment Group and Arm

	Group B		Group C1		Group C3	
	Chemo (n=78)	R-Chemo (n=79)	Chemo (n=60)	R-Chemo (n=66)	Chemo (n=15)	R-Chemo (n=17)
Patients with late effect(s), n (%)	1 (1.3)	5 (6.3)	3 (5.0)	5 (7.6)	1 (6.7)	1 (5.9)

Source: review of L16_2_4_1_demo.rtf and L16_2_7_1_2_1_leffect.rtf in final CSR.

Table 17. Frequency of Protocol-defined Cardiotoxicity per Treatment Group and Arm

Cardiotoxicity n (%)	Group B		Group C1		Group C3	
	Chemo (n=78)	R-Chemo (n=79)	Chemo (n=60)	R-Chemo (n=66)	Chemo (n=15)	R-Chemo (n=17)
Cardiotoxicity at any time	2 (2.7)	5 (6.3)	2 (3.4)	9 (13.8)	0	2 (12.5)
cardiotoxicity at baseline	1 (1.4)	2 (2.6)	1 (1.8)	1 (1.6)	0	1 (6.3)

Source: NEW outputs T99_8_1_carditox.rtf, T99_8_2_carditox.rtf, T99_8_3_carditox.rtf.

Note that percentage values for cardiotoxicity data are based on the number of patients per safety set with cardiotoxicity data reported (n=149, n=160, n=306 for the Chemo, R-Chemo and Rituximab safety sets, respectively).

Table 18. Frequency of IRRs per Treatment Group and Arm

IRRs, n (%)	Group B	Group C1	Group C3
	R-Chemo (n=79)	R-Chemo (n=66)	R-Chemo (n=17)
Total number of IRRs			
0	52 (65.8)	38 (57.6)	8 (47.1)
1	21 (26.6)	18 (27.3)	6 (35.3)
>1	6 (7.6)	10 (15.2)	3 (17.6)
Worst Grade IRR[1]			
1	8 (17.0)	9 (24.3)	2 (18.2)

2	9 (19.1)	8 (21.6)	4 (36.0)
3	2 (4.3)	3 (8.1)	0

Source: NEW outputs T99_6_1_infusion.rtf, T99_6_2_infusion.rtf, T99_6_3_infusion.rtf. IRR Grade only collected in countries handled by GR only. No G3+ IRRs were reported in the Rituximab Safety Set. 1. Percentages are percentage of pts who had IRR grade reported.

Serious adverse event/deaths/other significant events

Deaths

Seventeen deaths were reported in the Chemo safety set, of which 13 were due to lymphoma, 2 were due to toxicity of first-line inter B-NHL trial treatment, 1 was due to toxicity of subsequent treatment, and 1 was unknown. For the R-Chemo safety set, 8 deaths were reported as follows: 3 due to lymphoma, 2 due to toxicity of first-line inter B-NHL trial treatment, 1 due to toxicity of subsequent treatment, 1 due to second malignancy, and 1 due to "other" (patient 3-C-23: sepsis during chemotherapy) that was also considered by the steering committee review a toxic death related to the first-line inter B-NHL trial treatment. Narratives for toxic deaths are provided in Section 10.3.3. In the Initial COP only safety set, 3 deaths were reported: 2 related to lymphoma and 1 due to "other" cause (patient 3-C-68: sepsis during chemotherapy) that was considered by the steering committee review a toxic death related to the first-line inter B-NHL trial treatment. All these 3 patients were initially randomized to the Chemo arm.

Table 32 Death Reports by Actual Treatment Arm, Safety and Rituximab Safety Sets

	Chemo, Safety Set (N = 153)	R-Chemo, Safety Set (N = 162)	Initial COP(s) Only, Safety Set	Rituximab Safety Set (N = 309)
Autopsy performed, n (%)				
Yes	0	0	2 (66.7)	1 (7.1)
No	16 (94.1)	8 (100)	1 (33.3)	13 (92.9)
Unknown	1 (5.9)	0	0	0
Primary cause of death, n (%)				
Complications of lymphoma prior to treatment	0	0	1 (33.3)	0
Lymphoma	13 (76.5)	3 (37.5)	1 (33.3)	6 (42.9)
Acute tumor lysis syndrome	0	0	0	0
Toxicity of first line Inter B-NHL trial treatment	2 (11.8)	2 (25.0)	0	4 (28.6)
Toxicity of subsequent treatment	1 (5.9)	1 (12.5)	0	2 (14.3)
Not determinable, whether lymphoma or toxicity	0	0	0	0
Late effect of first line treatment	0	0	0	0
Second malignancy	0	1 (12.5)	0	1 (7.1)
Other disease[1]	0	1 (12.5)	1 (33.3)	1 (7.1)
Suicide	0	0	0	0
Unrelated to any disease	0	0	0	0
Unknown	1 (5.9)	0	0	0

AE = Adverse Event; B-NHL = B-cell non-Hodgkin lymphoma; Chemo = Chemotherapy; COP = Cyclophosphamide, Oncovin, Prednisone; R-Chemo = Rituximab + Chemotherapy; SAE = serious adverse event.

(1) "Other disease" = "sepsis."

Source: Table 14.3.2.5.1

Table 33 Fatal Adverse Events by System Organ Class and Preferred Term, Safety and Rituximab Safety Sets

	Chemo, Safety Set (N = 153)	R-Chemo, Safety Set (N = 162)	Rituximab Safety Set (N = 309)
Any reportable AE, n (%)	6 (3.9))	5 (3.1)	8 (2.6)
Infections and infestations	2 (1.3)	3 (1.9)	6 (1.9)
Sepsis	2 (1.3)	3 (1.9)	5 (1.6)
Endocarditis	1 (0.7)	0	0
Lung infection	1 (0.7)	0	0
Adenovirus infection	0	0	1 (0.3)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	3 (2.0)	2 (1.2)	2 (0.6)
Neoplasm	3 (2.0)	1 (0.6)	1 (0.3)
Histiocytic sarcoma	0	1 (0.6)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	3 (2.0)	0	0
Acute respiratory distress syndrome	2 (1.3)	0	0
Respiratory failure	1 (0.7)	0	0
Blood and lymphatic system disorders	1 (0.7)	1 (0.6)	1 (0.3)
Febrile neutropenia	1 (0.7)	1 (0.6)	1 (0.3)
Nervous system disorders	1 (0.7)	1 (0.6)	1 (0.3)
Cerebellar syndrome	0	1 (0.6)	1 (0.3)
Cerebral artery embolism	1 (0.7)	0	0
Cardiac disorders	1 (0.7)	0	0
Cardiac failure acute	1 (0.7)	0	0
Gastrointestinal disorders	0	1 (0.6)	1 (0.3)
Intestinal haemorrhage	0	1 (0.6)	1 (0.3)
Psychiatric disorders	0	1 (0.6)	1 (0.3)
Confusional state	0	1 (0.6)	1 (0.3)

AE = Adverse Event; Chemo = Chemotherapy; COP = Cyclophosphamide, Oncovin, Prednisolone; CRF = Case Report Form; LVEF = Left Ventricular Ejection Fraction; LVSF = Left Ventricular Shortening Fraction; MedDRA = Medical Dictionary for Regulatory Activities; R-Chemo = Rituximab + Chemotherapy.

Source: Table 14.3.2.5.2

Adverse events CRF reporting requirements included all Grade 3-5 cardiac events, LVEF/LVSF cardiac abnormalities and other nonhaematological Grade 3-5 events, except fatigue and anorexia. During COP courses, only Grade 4-5 events had to be reported. Acute targeted toxicities found with grade 'No' or 'Grade 0 or Grade 1 or Grade 2' were not regarded as events in this summary.

Adverse events coded using MedDRA dictionary version 20.1

Toxic fatal AEs defined as Grade 5 acute or late events or 2nd cancer in patients whose reason for death was reported as "acute tumor lysis syndrome (TLS)", "toxicity of first line Inter B-NHL trial treatment", "Not determinable whether lymphoma or toxicity" or "second malignancy."

Table 34 Toxic Fatal Adverse Events by System Organ Class and Preferred Term, Safety and Rituximab Safety Sets

	Chemo, Safety Set (N = 153)	R-Chemo, Safety Set (N = 162)	Rituximab Safety Set (N = 309)
Any reportable AE, n (%)	2 (1.3)	3 (1.9)	5 (1.6)
Infections and infestations	2 (1.3)	2 (1.2)	4 (1.3)
Sepsis	2 (1.3)	2 (1.2)	4 (1.3)
Endocarditis	1 (0.7)	0	0
Lung infection	1 (0.7)	0	0
Blood and lymphatic system disorders	1 (0.7)	1 (0.6)	1 (0.3)
Febrile neutropenia	1 (0.7)	1 (0.6)	1 (0.3)
Nervous system disorders	1 (0.7)	1 (0.6)	1 (0.3)
Cerebellar syndrome	0	1 (0.6)	1 (0.3)
Cerebral artery embolism	1 (0.7)	0	0
Respiratory, thoracic, and mediastinal disorders	2 (1.3)	0	0
Acute respiratory distress syndrome	2 (1.3)	0	0
			0
Cardiac disorders	1 (0.7)	0	0
Cardiac failure acute	1 (0.7)	0	
Gastrointestinal disorders	0	1 (0.6)	1 (0.3)
Intestinal haemorrhage	0	1 (0.6)	1 (0.3)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	1 (0.6)	1 (0.3)
Histiocytic sarcoma	0	1 (0.6)	1 (0.3)
Psychiatric disorders	0	1 (0.6)	1 (0.3)
Confusional state	0	1 (0.6)	1 (0.3)

AE = Adverse Event; Chemo = Chemotherapy; COP = Cyclophosphamide, Oncovin, Prednisolone; CRF = Case Report Form; LVEF = Left Ventricular Ejection Fraction; LVSF = Left Ventricular Shortening Fraction; MedDRA = Medical Dictionary for Regulatory Activities; R-Chemo = Rituximab + Chemotherapy.

Adverse events CRF reporting requirements included all Grade 2-5 cardiac events, LVEF/LVSF cardiac abnormalities and other nonhaematological Grade 3-5 events, except fatigue and anorexia. During COP courses, only Grade 4-5 events had to be reported. Acute targeted toxicities found with grade 'No' or 'Grade 0 or Grade 1 or Grade 2' were not regarded as events in this summary.

Adverse events coded using MedDRA dictionary version 20.1.

Toxic fatal AEs defined as Grade 5 acute or late events or 2nd cancer in patients whose reason for death was reported as "acute tumor lysis syndrome (TLS)", "toxicity of first line Inter B-NHL trial treatment", "Not determinable whether lymphoma or toxicity" or "second malignancy."

Source: Table 14.3.2.5.3

Table 35 Toxic Deaths by Treatment Arm

Treatment Arm	Safety Set	Patient Number	Primary Cause of Death
R-Chemo	R-Chemo, safety set and Rituximab safety set	3-C-23	Other disease
Chemo	Initial COP(s) only, safety set	3-C-68[1]	Other disease
R-Chemo	R-Chemo, safety set and Rituximab safety set	3-C-86	Toxicity of first line Inter B-NHL trial treatment
R-Chemo	R-Chemo, safety set and Rituximab safety set	3-E-14	Toxicity of first line Inter B-NHL trial treatment
Chemo	Chemo, safety set	3-E-38	Toxicity of first line Inter B-NHL trial treatment
Chemo	Chemo, safety set	3-E-56	Toxicity of first line Inter B-NHL trial treatment
R-Chemo	R-Chemo, safety set and Rituximab safety set	3-E-113	Histiocytic sarcoma
R-Chemo	Rituximab safety set	3-E-286	Toxicity of first line Inter B-NHL trial treatment
R-Chemo	Rituximab safety set	3-E-290	Toxicity of first line Inter B-NHL trial treatment

Chemo = Chemotherapy Treatment Arm; R-Chemo = Chemotherapy Plus Rituximab Treatment Arm.

(1) Patient 3-C-68 was discontinued from the study prior to randomization; however rituximab was received as off-study treatment.

Source: CSR toxic narratives (Section 10.3.3).

Serious Adverse Events

Table 36 Serious Adverse Events Reported by ≥ 5% of Patients in the Chemo or R-Chemo Arm, Safety and Rituximab Safety Sets

	Chemo, Safety Set (N = 88)	R-Chemo, Safety Set (N = 86)	Initial COP(c) Only, Safety Set (N = 1)	Rituximab Safety Set (N = 308)
Any SAE, n (%)	35 (39.3)	47 (49.5)	0	169 (54.7)
Infections and infestations	16 (18.0)	30 (31.6)	0	97 (31.4)
Sepsis	1 (1.1)	6 (6.3)	0	24 (7.8)
Device-related infection	0	4 (4.2)	0	15 (4.9)
Gastrointestinal disorders	5 (5.6)	12 (12.6)	0	70 (22.7)
Stomatitis	0	0	0	33 (10.7)
Blood and lymphatic system disorders	9 (10.1)	9 (9.5)	0	53 (17.2)
Febrile neutropenia	8 (9.0)	8 (8.4)	0	45 (14.6)
Uncoded[1]	0	0	0	18 (5.8)
Uncoded	0	0	0	18 (5.8)

Chemo = Chemotherapy; COG = Children's Oncology Group; COP = Cyclophosphamide, Oncovin, Prednisone; MedDRA = Medical Dictionary for Regulatory Activities; R-Chemo = Rituximab + Chemotherapy; SAE = Serious Adverse Event.

Adverse events coded using MedDRA dictionary version 20.1.

COG's data are only included in the rituximab safety set column.

Source: Table 14.3.2.4.1

(1) Uncoded: SAEs related to infections/infestations were noted for 18 of the 18 patients.

Table 37 Safety Data for Rituximab Identified Risks

Identified Risk (for Rituximab in Adult Oncology Patients)	Chemo N = 163		R-Chemo N = 162		Rituximab Safety Set (N = 308)	
	Acute AEs	Late AEs	Acute AEs	Late AEs	Acute AEs	Late AEs
Infusion related reactions	Please refer to Section 7.8.3					
Infections[1]	80 (52.3)	0	101 (62.3)	4 (2.5)	182 (58.9)	18 (5.8)
Impaired immunization response	Please refer to Section 7.7.1					
Progressive multifocal leukoencephalopathy[2]	3 (2.0)	0	0	1 (0.6)	2 (0.6)	1 (0.3)
Hepatitis B reactivation[3]	0	0	0	0	0	0

AEs = Adverse Events; Chemo = Chemotherapy; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R-Chemo = Rituximab + Chemotherapy; SOC = System Organ Class.

Source: Table 14.3.2.2.2.1 and Table 14.3.2.3.1

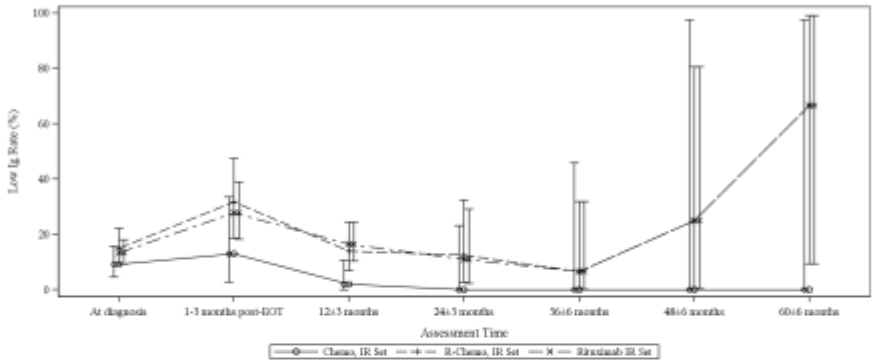
1. Infections and infestations MedDRA SOC.
2. Progressive multifocal leukoencephalopathy was summarized manually by combining the following MedDRA PTs in the source tables: Demyelination, Encephalitis viral, Encephalopathy, JC virus granule cell neuropathy, JC virus infection, JC virus test, JC virus test positive, Human polyomavirus infection, Leukoencephalopathy, Progressive multifocal leukoencephalopathy; AE reporting terms containing: PML, Leukoencephalopathy, JC virus, JCV, Polyoma.
3. Hepatitis B reactivation was summarized manually by combining the following MedDRA PTs in the source tables: Asymptomatic viral hepatitis, Hepatitis, Hepatitis acute, Hepatitis B, Hepatitis B antibody abnormal, Hepatitis B antibody positive, Hepatitis B antigen positive, Hepatitis B core antibody positive, Hepatitis B core antigen positive, Hepatitis B DNA assay positive, Hepatitis B DNA increased, Hepatitis B e antibody positive, Hepatitis B e antigen positive, Hepatitis B reactivation, Hepatitis B surface antigen positive, Hepatitis B virus test positive, Hepatitis fulminant, Hepatitis viral, hepatitis infectious, herpes simplex hepatitis. Infections and infestations MedDRA SOC.

Laboratory findings

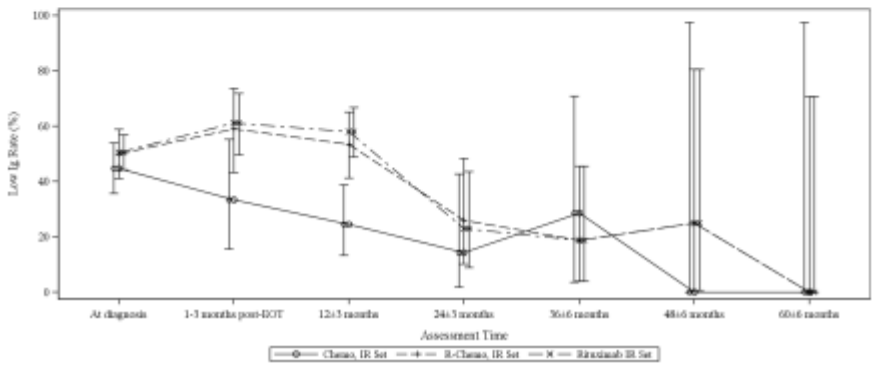
Immune reconstitution analyses

Figure 13 Line Plot of Low Immunoglobulin Levels Rates Over Time by Randomization Arm, IR and Rituximab IR Set (IgA, IgG, and IgM)

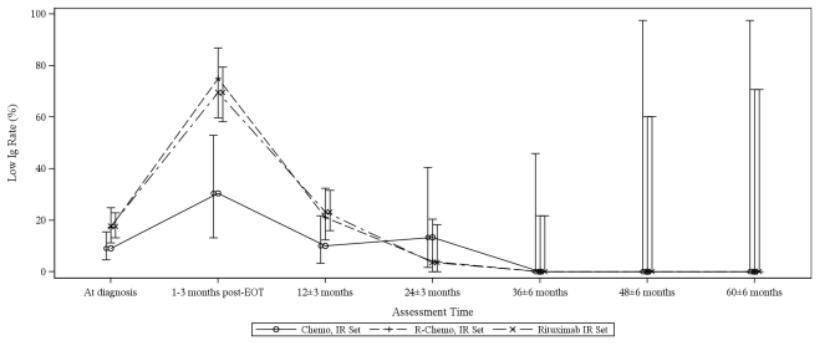
IgA



IgG



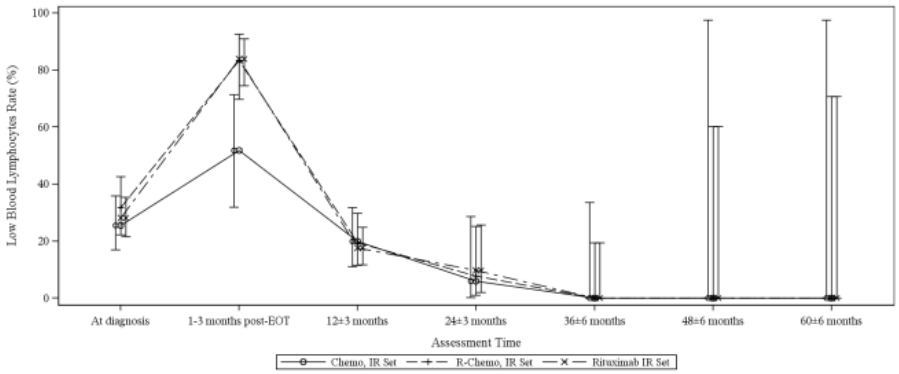
IgM



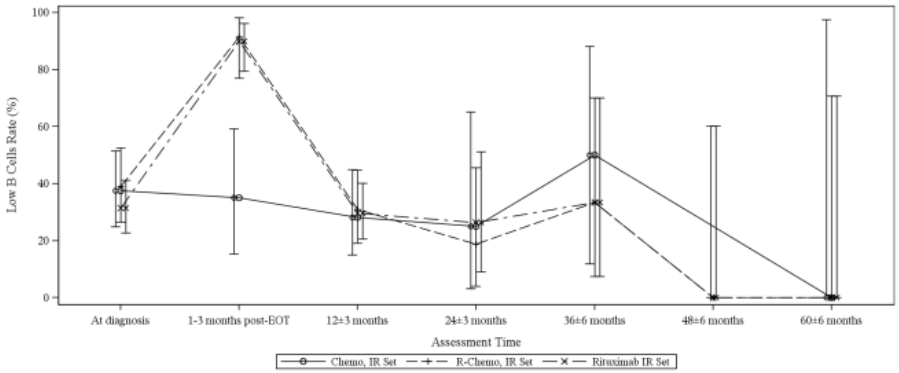
Lymphocytes and B cells

Figure 14 Line Plots of Low Blood Lymphocytes and B-Cell Levels Over Time by Randomization Arm, IR and Rituximab IR Set

Blood lymphocytes



B cells



Chemo = Chemotherapy; CI = Confidence Interval; COP = Cyclophosphamide, Oncovin, Prednisone; EOT = End of Treatment; IR = Immune Response; R-Chemo = Rituximab + Chemotherapy.

High-Low bars correspond to Clopper-Pearson Exact 95% CI.

Source: Figure 14.2.7.2.2.

Safety in special populations

There is only one patient below the age of 3 in the R-chemo group (see discussion on Clinical Pharmacology).

Safety related to drug-drug interactions and other interactions

See clinical pharmacology.

Discontinuation due to adverse events

No summary of patients who had AEs that led to rituximab dose reduction is provided as this data were not collected on the study case report forms. However, a review of individual SAE cases was done to identify SAEs that led to rituximab withdrawal. This review identified 7 patients with SAEs that led to rituximab withdrawal.

Post marketing experience

Company Global Safety Database

A total of 371 cases reporting 851 AEs in pediatric patients (<18 years of age) across all oncology indications from the company global safety database were analyzed. The majority of the AEs were reported in children

(>2 years to >12 years of age [48.4%]) and adolescents (>12 years to <18 years of age [48.3%]), and the safety profile of MabThera/Rituxan was comparable between these two age groups. Only 3.3% of AEs

were reported in infants and neonates (<2 years of age).

A total of 203 cases (54.7%) reporting 427 AEs (50.2%) were from the NHL indication. Of these 427 AEs, 263 (61.6%) were known ADRs for MabThera/Rituxan in the adult population, such as IRRs and related signs/symptoms, infections, and hypogammaglobulinemia (immunoglobulins below the lower limit of normal). Of the remaining 164 AEs (bone marrow failure, death, product use issue, drug ineffective etc.) not known as ADRs in adult patients, 137 (83.5%) were associated with clear alternative explanations and risk factors and the remaining 27 (16.5%) had insufficient information for an adequate assessment.

From the total of 851 AEs analyzed, 77 (9.0%) fatal AEs were reported, of which one was in CLL, and 38 each were in NHL and other oncology indications (i.e., posttransplant lymphoproliferative disorder, Epstein-Barr virus associated lymphoproliferative disorder, acute lymphocytic leukemia, Hodgkin's disease etc.). Approximately 25% of these fatal events were related to infections (sepsis, aspergillus infection, unspecified infection etc.).

The safety profile of MabThera/Rituxan observed in the pediatric population was overall consistent with the well-established safety profile in the adult population for the approved oncology indications as provided in the Core Data Sheet (CDS) Version 31.0. The AEs that were not known ADRs of MabThera/Rituxan either had alternative explanations and risk factors or had insufficient information for an adequate assessment.

Overall, the reporting ratio of AEs was highest from the SOC Infections and infestations (N=72, 16.9%), and was followed by:

- General disorders and administration site conditions (N=62, 14.5%)
- Blood and lymphatic system disorders (N=49, 11.5%)
- Gastrointestinal disorders (N=42, 9.8%)
- Nervous system disorders (N=36, 8.4%)
- Respiratory, thoracic and mediastinal disorders (N=29, 6.8%)
- Skin and subcutaneous tissue disorders (N= 27, 6.3%)

The PTs reported in these SOCs were either in line with an identified risk or ADR (as per the Undesirable Effects listed in CDS Version 31.0) of MabThera/Rituxan in adult patients (IRRs, infections and hypogammaglobulinemia) or were related to the underlying condition and/or associated to the potential effects of past/concomitant immunosuppressant therapy.

Literature Review

Overall, review of the relevant literature did not provide new safety findings or any new safety information to what is already known for the safety profile of rituximab in adult patients. Of the 683 articles retrieved from the literature search, 33 were found to be relevant (i.e., articles that provided safety findings in pediatric patients exposed to rituximab) for inclusion. The majority of the reported AEs (e.g. infections, hypogammaglobulinemia, IRRs) were consistent with the safety findings from the data retrieved from the company global safety database for pediatric patients, and with the known safety profile of MabThera/Rituxan in adults for the approved oncology indications.

The comparisons between the pediatric safety data in Study BO25380 to the rituximab adult oncology population were limited by the relatively small size of the pediatric population compared with the adult population, the AE reporting requirements in Study BO25380, and the differences in disease biology and background treatments between populations. Additionally, the analyses in the DSR were not based on actual exposure data, there were differences in the source of adult and pediatric data (largely clinical trials in adults versus largely post-marketing data in the pediatric population).

However, despite this, the safety profile of MabThera/Rituxan observed in the pediatric population was overall consistent with the well-established safety profile in the adult populations for the approved oncology indications as provided in the CDS Version 31.0.

The AEs that were not known ADRs of MabThera/Rituxan either had alternative explanations and risk factors or had insufficient information for an adequate assessment.

Therefore, based on the analysis of the data in the company global safety database in pediatric oncology patients treated with MabThera/Rituxan, it was concluded that observed safety profile of MabThera/Rituxan in the pediatric population appeared to be consistent with that in adult patients.

2.5.1. Discussion on clinical safety

A multicenter, open-label randomized study of Lymphome Malin B chemotherapy (LMB) with or without MabThera was conducted in paediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated advanced stage CD20 positive DLBCL/BL/BAL/BLL.

Overall, a significant number of paediatric patients with NHL have been exposed to R-chemo for a significant period of time. This should enable a thorough assessment of the safety aspects of this combination in the proposed patient population.

A total of 309 paediatric patients received MabThera and were included in the safety analysis population. Paediatric patients randomized to the LMB chemotherapy arm with MabThera, or enrolled in the single arm part of the study, were administered MabThera at a dose of 375mg/m2 BSA and received a total of six IV infusions of MabThera (two during each of the two induction courses and one during each of the two consolidation courses of the LMB scheme).

The most common AEs occurred in the SOC "blood and lymphatic system disorders", where febrile neutropenia was the most common AE. Furthermore, the addition of rituximab to chemotherapy leads to an increased risk of AEs, especially in terms of gastrointestinal disorders (stomatitis, enteritis), infections (sepsis), metabolism and nutrition disorders (hypokalemia and decreased appetite), and investigations (ALAT and ASAT increase). The increased risk of infection in children is now reflected in the SmPC.

It is clearly seen that the addition of rituximab to chemotherapy also leads to an increased risk of Grade 4-5 AEs in terms of sepsis, liver enzyme increase (ALAT/ASAT), stomatitis and febrile neutropenia. Unfortunately, laboratory data were not collected on the study eCRF, and thus it is not possible to confirm if any of the patients fulfilled the criteria for Hy's law. However, there no clinical signs or symptoms that would seem to indicate that a given patient have experienced DILI.

There were two secondary malignancies in the study, both in the R-chemo arm. The MAH has provided brief case narratives. As mentioned by the MAH, NHL patients are known to be at higher risk for secondary malignancies. There have been case reports of melanoma in adult patients, while the case of histocytic sarcoma shoed identical clonal anomaly with regards to the initial cancer (IGH-MYC fusion). No firm conclusions can be drawn from such a small number of patients.

There were fewer deaths in the R-chemo arm compared to the chemo arm, 8 vs 17. Although the numbers are small and should be interpreted with caution, it is nonetheless clinically encouraging to see this numerical difference in favor of R-chemo.

It is clearly seen that the addition of rituximab to chemo leads to a significant increase in SAEs, 49.5% vs. 39.3%. As discussed previously, the differences are mainly seen in terms of infections and gastrointestinal disorders. There was only one (late) case of PML in the R-chemo arm compared to 3 acute cases in the chemo arm. Furthermore, there were no cases of Hepatitis B reactivation in any of the arms. This is reassuring, since approximately 35% of the patients had Anti-HBs antibody at baseline.

Data on post-treatment vaccination and persistence of previous antibodies is limited. However, given that the disease setting is very serious, in the clinical setting, patient are usually closely monitored and vaccinated post-treatment, if they haven't got all their vaccines. Children that are transplanted are usually closely monitored and re-vaccinated after approximately 6 months. Relevant recommendations in the SmPC are sufficient.

In summary, the safety profile of MabThera in paediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated advanced stage CD20 positive DLBCL/BL/BAL/BLL was generally consistent in type, nature and severity with the known safety profile in adult NHL and CLL patients. Addition of MabThera to chemotherapy did result in an increased risk of some events including infections (including sepsis) compared to chemotherapy only.

2.5.2. Conclusions on clinical safety

Overall, the safety profile of rituximab in combination with chemotherapy in a paediatric NHL population is as expected, thus in line with previous knowledge and experience. There were no new safety findings. However, there is only one patients below the age of 3 in the R-chemo group.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 21.1 is acceptable. The CHMP endorsed this advice without changes. The CHMP endorsed the Risk Management Plan version 21.1 with the following content:

Safety concerns

Table 14 Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Infections, including serious infections (All Indications) • Progressive multifocal leukoencephalopathy (All Indications) • Hepatitis B reactivation (All Indications) • Hypogammaglobulinemia (non-oncology indications)
Important potential risks	• Malignant events (non-oncology indications) • Impact on cardiovascular disease (non-oncology indications) • Relapses (GPA/MPA only) • Off-label use of the subcutaneous formulation (NHL/CLL, SC formulations) • Administration route error (NHL/CLL, SC formulations)

Missing information	• Use in pregnancy and lactation (All Indications) • Long term use in GPA/MPA patients (GPA/MPA only)

Pharmacovigilance plan

Table 15 On-going and planned additional pharmacovigilance activities

Study **Status**	**Summary of Objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
There are no planned or ongoing category 1 studies				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
There are no planned or ongoing category 2 studies.				
Category 3 - Required additional pharmacovigilance activities				
MA28150 (RITAZAREM): An international, open label, randomized controlled trial comparing rituximab with azathioprine as maintenance therapy in relapsing ANCA-associated vasculitis (RITAZAREM)-Phase III, interventional, randomized, open-label, comparative trial Ongoing	Time to relapse / the primary endpoint is the time to disease relapse (either minor or major relapse) from randomization. Proportion of patients who maintain remission at 24 and 48 months	Relapses	Estimated study completion date	Estimated CSR availability September 2020
BE29950 (RIVAS): Prospective, single center, secondary data use, long-term surveillance, non-interventional PASS. Ongoing	Registry to collect serious adverse event data over 5 years to determine the long-term safety of rituximab for the treatment of GPA/MPA.	Long term use in GPA/MPA patients	Study start: Interim analyses: Final CSR is due	Q4 2016 Annual reporting of cumulative data in PBRER 31 Dec 2021

ANCA= Anti-Neutrophil Cytoplasmic Antibody, BVAS= Birmingham Vasculitis Activity Score, CLL= Chronic Lymphocytic Leukemia, CSR=Clinical study report, GPA= Granulomatosis with polyangiitis, SC =Subcutaneous

Risk minimisation measures

Table 16 Summary table of risk minimization activities by safety concern

Safety concern	**Risk minimization measures**
Infections, including serious infections **All Indications**	**Routine risk communication:** EU SmPC section 4.4: Special warnings and precautions for use EU SmPC Section 4.8: Undesirable Effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** Patient Alert Card (non oncology indications) Educational Material for Healthcare Professionals and Patients (non-oncology indications)
Progressive Multifocal Leukoencephalopathy	**Routine risk communication:** EU SmPC section 4.4: Special warnings and precautions for use **Routine risk minimization activities recommending specific clinical measures to address the risk:** Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. Further evaluations, including Magnetic Resonance Imaging scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments, should be considered. If a patient develops PML, the dosing of MabThera must be permanently discontinued. **Other risk minimization measures beyond the Product Information:**

	Medicine's legal status: Medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** Patient Alert Card (non oncology indications) Educational Material for Healthcare Professionals and Patients (non-oncology indications)
Hepatitis B Reactivation All Indications	**Routine risk communication:** EU SmPC section 4.4: Special warnings and precautions for use **Routine risk minimization activities recommending specific clinical measures to address the risk:** Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with MabThera. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with MabThera. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation. **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** None
Hypogammaglobulinemia **non-oncology indications**	**Routine risk communication:** EU SmPC section 4.4: Special warnings and precautions for use **RA** EU SmPC Section 4.8: Undesirable effects **GPA/MPA** EU SmPC Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:**

	Immunoglobulin levels are recommended to be determined prior to initiating treatment with MabThera **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** None
Malignant Events **(Non-oncology indications)**	**Routine risk communication:** EU SmPC Section 4.4: Special warnings and precautions for use **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None
Impact on Cardiovascular Disease **(Non-oncology indications)**	**Routine risk communication:** EU SmPC section 4.4: Special warnings and precautions for use **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** None
Relapses	**Routine risk communication:**

(GPA/MPA only)	EU SmPC Section 5.1: Pharmacodynamic properties **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None
Off-label Use of the Subcutaneous Formulation **(NHL/CLL, SC formulations)**	**Routine risk communication:** EU SmPC section 4.1 Therapeutic indications Separate EU SmPCs are available for the IV (100 mg and 500 mg) and SC formulations (1400 mg for NHL and 1600 mg for CLL). EU SmPC (for SC formulation) section 4.4: Special warnings and precautions for use EU SmPC (IV and SC) section 4.2: Posology and method of administration **Routine risk minimization activities recommending specific clinical measures to address the risk:** Separate SmPCs are available for the IV (100 mg and 500 mg) and SC formulations (1400 mg for NHL and 1600 mg for CLL). **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** Educational Material for Healthcare Professionals
Administration route error (NHL/CLL, SC formulations)	**Routine risk communication:** The IV and SC formulations are covered by separate EU SmPCs to reinforce the difference between the IV and SC formulations. EU SmPC (IV and SC) section 1: Name of the Medicinal Product EU SmPC (IV and SC) section 4.2: Posology and method of administration

	Routine risk minimization activities recommending specific clinical measures to address the risk: The IV and SC formulations are covered by separate SmPCs to reinforce the difference between the IV and SC formulations. **Other risk minimization measures beyond the Product Information:** **Packaging: Clear package differentiation** • Color differentiation (distinct colored bands) • Unique cap colors for the vials matching the colored bands • Clear statements on both the primary and secondary packaging i.e., words "*subcutaneous*", "*solution for subcutaneous injection*" and "Only *for subcutaneous use*" in red font. Peel-off sticker is included on the individual vials of the subcutaneous formulations specifying the strength, the route of administration and the indication. SC and IV formulations are covered by separate SmPCs, which include specific warning against incorrect route of administration. *Medicine's legal status*: Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** Educational Material for Healthcare Professionals

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The treatment of paediatric patients (aged ≥6 months to <18 years old) with previously untreated advanced stage CD20 positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukaemia (mature B-cell acute leukaemia) (BAL) or Burkitt-like lymphoma (BLL).

3.1.2. Available therapies and unmet medical need

Despite a high cure rate in children and adolescents with NHL, there is an unmet need for improving the EFS in paediatric patients with advanced stage NHL.

3.1.3. Main clinical studies

A multicenter, open-label, randomized study of Lymphome Malin B (LMB) chemotherapy (corticosteroids, vincristine, cyclophosphamide, high-dose methotrexate, cytarabine, doxorubicin, etoposide and triple drug [methotrexate/cytarabine/ corticosteroid] intrathecal therapy) alone or in combination with MabThera was conducted in paediatric patients with previously untreated advanced stage CD20 positive DLBCL/BL/BAL/BLL. Advanced stage is defined as Stage III with elevated LDH level ("B-high"), [LDH > twice the institutional upper limit of the adult normal values (> Nx2)] or any stage IV or BAL. Patients were randomized to receive either LMB chemotherapy or six IV infusions of MabThera at a dose of 375mg/m^2 BSA in combination with LMB chemotherapy (two during each of the two induction courses and one during each of the two consolidation courses) as per the LMB scheme. A total of 328 randomized patients were included in the efficacy analyses, of which one patient under 3 years of age received MabThera in combination with LMB chemotherapy.

3.2. Favourable effects

At the pre-specified interim analysis with approximately 1 year of median follow-up, clinically relevant improvement in the primary endpoint of EFS was observed, with 1-year rate estimates of 94.2% (95% CI, 88.5% - 97.2%) in the R-LMB arm vs. 81.5% (95% CI, 73.0% - 87.8%) in the LMB arm, and adjusted Cox HR 0.33 (95% CI, 0.14 – 0.79). Upon IDMC (independent data monitoring committee) recommendation based on this result, the randomization was halted and patients in the LMB arm were allowed to cross over to receive MabThera. The study met its primary endpoint, a statistically significant and clinically relevant improvement of 3-year EFS was shown in favour of R-Chemo, 3-year EFS rate was 93.9% in the R-Chemo ITT group compared with 82.3% in the Chemo ITT group, (HR 0.32, 90% CI: 0.17, 0.58; p = 0.0010). Median EFS was not reached in either treatment group and Kaplan-Meier analyses of EFS were supportive.

The results of the second EFS sensitivity analysis were consisted with the primary efficacy endpoint analysis results with an adjusted HR = 0.36 (95% CI: 0.18, 0.70).

Progression/relapse was reported in 21 patients (75.0%) in the Chemo group vs. 3 patients (30.0%) in the R-Chemo group. Two patients had secondary malignancies in the R-Chemo arm vs. none in the Chemo arm.

Overall survival showed a clinical meaningful benefit for patients in the R-Chemo group compared with the Chemo group, adjusted HR being 0.36 (95% CI: 0.16, 0.81)

3.3. Uncertainties and limitations about favourable effects

There are no uncertainties about the favourable effects.

3.4. Unfavourable effects

The most common AEs occurred in the SOC "blood and lymphatic system disorders", where febrile neutropenia was the most common AE. The addition of rituximab to chemotherapy also leads to an increased risk of AEs, especially in terms of gastrointestinal disorders (stomatitis, enteritis), infections (sepsis), metabolism and nutrition disorders (hypokalemia and decreased appetite), and investigations (ALAT and ASAT increase).

The addition of rituximab to chemotherapy also leads to an increased risk of Grade 4-5 AEs in terms of sepsis, liver enzyme increase (ALAT/ASAT), stomatitis and febrile neutropenia.

The addition of rituximab to chemo leads to a significant increase in SAEs, 49.5% vs. 39.3%. As discussed previously, the differences are mainly seen in terms of infections and gastrointestinal disorders. There was only one (late) case of PML in the R-chemo arm compared to 3 acute cases in the chemo arm. Furthermore, there were no cases of Hepatitis B reactivation in any of the arms. This is reassuring, since approximately 35% of the patients had positive Anti-HBs antibody at baseline.

3.5. Uncertainties and limitations about unfavourable effects

There are no uncertainties about the unfavourable effects.

3.6. Effects Table

Table 2. Effects Table for Mabthera in paediatric B-NHL

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
EFS	Event free survival	%	93.9	82.3	HR = 0.32 (90% CI: 0.17, 0.58); p= 0.001	
3 year OS	3 year overall survival	%	95.1	87.3	HR = 0.36 (95% CI: 0.16, 0.81)	
CR	Complete response	%	94.9	93.6		
Unfavourable Effects						
Febrile neutropenia		%	92.6	90.8		
Infections		%	41.4	35.3		
SAE		%	49.5	39.3		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Adding rituximab to standard chemotherapy in advanced B-NHL results in a significant and clinically relevant increase of 3-year EFS. These results are important, although assessment of the study was hampered by the fact that the study was stopped at the first interim analysis, despite it did not cross the specified significance boundary. The safety profile of rituximab is well known from the use in the adult population and considered manageable. Overall the safety profile of rituximab was consistent with the known safety profile in adults, no new safety signals were raised. Only one patient below the age of 3 was included in the R-Chemo group, this has adequately been reflected in the SmPC.

The proposed indication is intended to be in children from 6 months of age, however, no PK data are available in children in the age group 6 month to 3 years of age to support or justify the 375 mg/m2 dose in this age group. The MAH has performed simulations using a model to predict exposure in children <3 years. Ctrough and cumulative $AUC_{1\text{-}4\ cycles}$ are comparable across age groups, but Cmax higher in the youngest population. It is agreed that the higher Cmax (over) predicted with the model not is expected to have clinical relevance. This is supported by paediatric rituximab data from other indications.

3.7.2. Balance of benefits and risks

Despite a high cure rate in children and adolescent with B-NHL, a further improvement of EFS is needed especially in the advanced-stage NHL, therefore the benefit of adding rituximab to standard chemotherapy in advanced B-NHL results in a significant and clinically relevant increase of 3-year EFS is significant.

The safety profile of rituximab is well known from the use in the adult population and considered manageable. Overall the safety profile of rituximab was consistent with the known safety profile in adults, no new safety signals were raised. Only one patient below the age of 3 was included in the R-Chemo group, this has adequately been reflected in the SmPC.

3.7.3. Additional considerations on the benefit-risk balance

3.8. Conclusions

The overall B/R of Mabthera in combination with chemotherapy for the treatment of paediatric patients (aged ≥6 months to <18 years old) with previously untreated advanced stage CD20 positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukaemia (mature B-cell acute leukaemia) (BAL) or Burkitt-like lymphoma (BLL), is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of paediatric patients (aged ≥6 months to <18 years old) with previously untreated advanced stage diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukaemia (mature B-cell acute leukaemia) (BAL) or Burkitt-like lymphoma (BLL) in combination with chemotherapy for MabThera; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 21 of the RMP has also been submitted.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0064/2019 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that MabThera is not similar to Kymriah, Yescarta and Polivy within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular, the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'MabThera-H-C-165-II-0168'