AGMT Arbeitsgemeinschaft Medikamentöse Tumortherapie

# 1. TITLE PAGE

CLINICAL STUDY REPORT

**A Multicentre, Randomized Phase III Study of Rituximab as Maintenance Treatment versus Observation alone in Patients with Aggressive B-cell lymphoma – NHL-13**

Protocol Number: AGMT_NHL-13

EudraCT number: 2005-005187-90

| | |
|---|---|
| Name of Product/Test Drug/IMP: | Rituximab (MabThera®; F. Hoffmann-La Roche Ltd., Basel, Switzerland) |
| Phase of Development: | III |
| Date of First Patient In: | 16-Jun-2004 (i.e. informed consent of first patient) |
| Date of Last Patient Out: | 30-Aug-2012 (last end of study visit) |
| Indication: | Patients with Diffuse Large B-cell Lymphoma (DLBCL) or follicular NHL grade 3b who have achieved a complete remission (CR or CRu) after appropriate first-line induction therapy |
| Design: | Open-label, multi-center, randomized phase III study |
| Sponsor: | AGMT gemeinnützige GmbH<br>Prim. Univ.-Prof. Dr. Richard Greil<br>Universitätsklinik für Innere Medizin III<br>Universitätsklinikum der PMU Salzburg<br>Müllner Hauptstraße 48, 5020 Salzburg |
| Coordinating Investigator: | Univ.- Prof. Dr. Ulrich Jäger |
| Name of Sponsor Signatory: | Univ.- Prof. Dr. Ulrich Jäger<br>Univ.- Prof. Dr. Richard Greil |
| Date of Report (FINAL 1.0): | 30 July 2014 |

This study was performed in accordance with Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki and other applicable regulatory.

AGMT Arbeitsgemeinschaft Medikamentöse Tumortherapie

**AUTHOR'S NAMES AND SIGNATURES:**

**AGMT**

Univ.- Prof. Dr. Ulrich Jäger

Date: 04. Aug. 2014

Univ.- Prof. Dr. Richard Greil

Date: 31.7.2014

**Assign Data Management and Biostatistics GmbH**

Anton Klingler, PhD

Lead Biostatistician

Date: 07-Aug-2014

## 2. SYNOPSIS

| | | |
|---|---|---|
| Name of Company:<br>AGMT gemeinnützige GmbH | Individual Study Table Referring to Part of the Dossier<br><br>Volume:<br>Page: | (For National Authority Use Only) |
| Name of Finished Product:<br>MabThera® | | |
| Name of Active Ingredient:<br>Rituximab, chimeric monoclonal antibody | | |
| Title of Study:<br>A Multicentre, Randomized Phase III Study of Rituximab as Maintenance Treatment versus Observation alone in Patients with Aggressive B-cell lymphoma – NHL-13 | | |
| Principal Investigator:<br>The Principal Investigator of the study was Univ.- Prof. Dr. Ulrich Jäger from the site AKH Vienna. | | |

| | |
|---|---|
| Study Sites:<br>A list of all study sites recruiting patients for this study is available at the sponsor on request. | |
| Publication (reference):<br>Not applicable | |
| Study Dates:<br>First Patient Treated: 27-Aug-2004<br>Last Patient completed treatment: 03-Sep-2010 | Phase of Development:<br><br>Phase III |
| Objectives:<br>Primary objective:<br>To evaluate the clinical efficacy of Rituximab maintenance therapy as compared to observation in patients with aggressive B-cell Non-Hodgkins lymphoma or follicular lymphoma grade 3b who have achieved a complete remission after appropriate first-line therapy, measured by event-free survival (EFS)<br>Secondary objective:<br>To evaluate Progression-free Survival (PFS), Overall Survival (OS) and Safety. Quality of life during maintenance or observation, immunocompetence, and histological subtypes of DLBCL for Austrian patients only | |
| Methodology:<br>International, open-label, multi-center, randomized phase III study | |
| Number of Patients:<br>Planned: 600<br>Analyzed: 682 were analyzed in the Safety population and 683 were analyzed in the ITT population. | |
| Diagnosis and Main Criteria for Inclusion:<br>Patients with Diffuse Large B-cell Lymphoma (DLBCL) or follicular NHL grade 3b who have achieved a complete remission (CR or CRu) after appropriate first-line induction therapy | |
| Test Product, Dose and Mode of Administration, Batch Number:<br>Arm A: Rituximab (MabThera®; F. Hoffmann-La Roche Ltd., Basel, Switzerland) 375 mg/m$^2$ every 8 weeks for 12/24 months (6/12 infusions)<br>Arm B: Observation (no treatment)<br>No details regarding batch numbers are available since handling was not done by AGMT. | |
| Duration of Treatment:<br>Arm A, NHL-13 prior Amendment 1: 375 mg/m$^2$ every 8 weeks for 12 months (6 infusions)<br>Arm A, NHL-13 after Amendment 1: 375 mg/m$^2$ every 8 weeks for 24 months (12 infusions) | |
| Reference Therapy, Dose, and Mode of Administration, Batch Number:<br>None | |

Criteria for Evaluation:

Safety:

- Follow-up: Patients were followed-up until an event occurred or for a maximum of two years after completion of treatment/observation period

- Safety and tolerability was assessed throughout the treatment/observation period

Pharmacokinetics:

Not applicable

Efficacy:

- Relapse was evaluated with standard criteria for evaluation of response in NHL ([1])

- Quality of life was assessed during the treatment period via SF sheet (Austria only)

Statistical Methods:

Sample size calculation:

A difference in median EFS with Rituximab monotherapy vs. observation was estimated with 74.6 months (treatment arm A) vs. 46.6 months (observation arm B). Assuming exponential distribution of survival time and a recruitment ratio of 1:1 for patients, a total of 148 events if necessary to achieve 80% power with a two-sided test and significance level of 5%. 600 patients (300 per arm) with large B-cell NHL or follicular NHL Grade 3 should be recruited with a planned recruitment period of 2 years and a minimum follow-up of 2 years.

Statistical Methods:

The primary analysis population comprised all randomized patients according to the intention-to-treat principle. A secondary per-protocol analysis excluding patients with major protocol deviations was planned, if the number of patients to be excluded would exceed 10%. However, this was not the case. Analyses were planned after 1/3, 2/3 and 3/3 of the maximum necessary events had been reached (Lan-DeMets Alpha Spending Function) and were performed. Statistical tests generally were two-sided with a significance level of 5%.

The primary efficacy endpoint was analyzed using a Cox regression model with the factors geographical region and type/number of cycles of induction therapy as well as treatment group. The resulting standardized statistics were compared with the corresponding stopping boundary. Secondary endpoints were evaluated at a significance level of 5% only after the study had been terminated. Two-sided 95% confidence intervals for the treatment effect were presented.

Event-free, Progression-free and Overall survival was described using the Kaplan-Meier method and analyzed using the same model as described for the primary endpoint.

Adverse events were summarized by system organ class, preferred term and treatment arm. The absolute and percentage changes from baseline were computed. Appropriate summary statistics were provided.

Summary of Results:

Safety Results:

In general, toxicity was mild and RM was well tolerated. RM was associated with higher rates of grade 3/4 adverse events ($p$=0.0297) and infections ($p$=0.0341) in women.

Pharmacokinetic Results:

Not applicable

| |
|---|
| Efficacy Results:<br>At a median follow-up of 45 months, EFS was 80.4% for RM vs. 76.5% for observation at 3 years and 76.6% vs. 61.7% at 5 years, respectively. RM reduced relapses by 44%. The primary endpoint (EFS) was not met for the intent-to-treat population (ITT) despite a trend towards RM (Likelihood ratio *p*=0.0670).<br>Further subgroup analysis showed a lack of efficacy in female patients (3-year EFS for RM vs. observation 76.8% vs. 78.7%; HR: 1.05; 95%CI 0.67-1.66; *p*=0.8246). In contrast, RM significantly prolonged EFS in men (Likelihood ratio *p*=0.0002) with 84.1% vs. 74.4% EFS at 3 years (HR: 0.58; 95%CI 0.36-0.94; *p*=0.0267) as well as in patients with a low International Prognostic Index (IPI≤1) (Likelihood ratio *p*=0.0121). RM improved progression-free survival (PFS) of male patients (Likelihood ratio *p*=0.0122) at 3 years (89.0% vs. 77.6%; HR: 0.45; 95%CI 0.25-0.79; *p*=0.0058). Men with IPI≤1 treated with RM had a PFS of 96.1% vs. 80.5% (HR: 0.26; 95%CI 0.07-0.93; *p*=0.0388). In multivariate analysis, low IPI and RM remained independent factors influencing EFS and PFS in men. Overall survival at 3 years was not different (92.0% vs. 90.3%).<br>. |
| Conclusions:<br>RM in first remission after R-CHOP-like treatment did not significantly prolong EFS and PFS of the whole cohort. In subgroup analysis, *male* but not *female* patients with aggressive B-NHL benefitted significantly from RM. We conclude that studies addressing prolonged treatment for male patients are warranted. |
| Date of Report: FINAL 1.0, 30 July 2014 |

# 3. TABLE OF CONTENTS

List of In-text Tables

List of In-Text Figures

# 4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| AE | Adverse event |
| AGMT | Arbeitsgemeinschaft medikamentöse Tumortherapie |
| ALT | Alanin-Aminotransferase |
| AST | Aspartat-Aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| CEOP | Cyclophosphamide-Etoposide-Prednisolone-Vincristine-chemotherapy |
| CHOEP | Cyclophosphamide/Hydroxydaunorubicin/Oncovin/Etoposide/Prednisone-chemotherapy |
| CHOP | cyclophosphamide/doxorubicin/vincristine/prednisolon chemotherapy |
| CNOP | Cyclophosphamide/vincristine/mitoxantrone/prednisone-chemoterapy |
| CNS | Central nerve system |
| CR | Complete remission |
| CRO | Contract Research Organization |
| CRu | unconfirmed complete remission |
| CT | Computed tomography |
| CTC | Common Toxicity Criteria |
| CVP | Cyclophosphamide/Vincristine/Prednisone chemotherapy |
| DLBCL | Diffuse large B cell Lymphoma |
| DRM | Data review meeting |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |

| | |
|---|---|
| eCRF | electronic case report forms |
| EDC | Electronic Data Capture |
| EFS | event-free survival |
| ESHAP | Etoposide/Methylprednisolone/Cytarabine/Cisplatin-chemotherapy |
| FL | Follicular lymphoma |
| GCP | Good Clinical Practice |
| GELA | Groupe d'Etudes des Lymphomes de L'Adulte |
| GOT | Glutamat-Oxalacetat-Transaminase |
| GPT | Glutamat-Pyruvat-Transaminase |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| HIV | Human immunodeficiency virus |
| ICF | Informed consent form |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| iCHOP | Intensified CHOP |
| IEC | Independent Ethics Commitee |
| IMVP | Ifosfamid, Methotrexat und Etoposid-chemotherapy |
| IPI | International Prognostic Factor Index |
| ITT | intention to treat |
| iv | intravenous |
| LRAGS | Local reaction appearance grading scale |
| MACOP-B | methotrexate/doxorubicin/cyclophosphamide/vincristine/prednisone/bleomycin-chemotherapy |

| | |
|---|---|
| MedDRA | Medical Dictionary for Regulatory Activities |
| NaCl | Natrium Chloride |
| NCI | National Cancer Institute |
| NHL | non-Hodgkin's lymphoma |
| ORR | objective response rate |
| OS | overall survival |
| PET | Positron emission tomography |
| PFS | progression-free survival |
| PR | Partial response |
| ProMitCytaBOM | Promit+cytarabine/bleomycin/vincristine/methotrexate-chemotherapy |
| RA | Response Assessment |
| R-CHOP | CHOP+ Rituximab |
| SADR | Serious Adverse Drug Reactions |
| SAE | Serious adverse event |
| SAE | Serious adverse event |
| SAP | Statistical analysis protocol |
| SD | stable disease |
| SDV | Source Data Verification |
| SOC | system organ class |
| SOP | Standard Operating Procedure |
| TGS | Toxicity Grading Scale |
| TMF | trial master file |
| VACOP-B | etoposide/doxorubicin/cyclophosphamide/vincristine/prednisone/bleomycin- |

| | |
|---|---|
| | chemotherapy |
| WHO | World Health Association |

# 5. ETHICS

## 5.1 INDEPENDENT ETHICS COMMITTEE (IEC) OR INSTITUTIONAL REVIEW BOARD (IRB)

Prior to study initiation the protocol, the informed consent form (ICF) and any requested information were submitted to the appropriate Ethics Committees (EC). The study centers did not include subjects before approval had been obtained. The investigators were responsible for conducting the study in accordance with regulations of local regulatory authorities. Amendments to the protocol were written and approved by the sponsor in the same manner before being implemented. If necessary, amendments were submitted to the relevant ECs for approval prior to their implementation.

Details of the EC are provided by the sponsor on request.

## 5.2 ETHICAL CONDUCT OF THE STUDY

The study was conducted in accordance with Good Clinical Practice (GCP) and all applicable local laws and the Declaration of Helsinki[2], including archiving of study documents.

## 5.3 PATIENT INFORMATION AND CONSENT

It was the investigator's responsibility to obtain freely given written informed consent according to regional requirements and before the subject was exposed to any study-related procedures, including screening tests for eligibility.
The investigator explained that the subjects were completely free to refuse to enter the study or to withdraw from it at any time, without any prejudice and need for justification. The subjects were informed that representatives of the sponsor and health authority inspectors may review their source records, and that these persons are bound by confidentiality obligations.
The subjects were given a copy of the informed consent documentation. The original copy of the signed and dated informed consent was retained in the site's records, and was subject to inspection by representatives of the sponsor, or representatives from regulatory agencies.
A model ICF is available at the sponsor on request.

# 6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor:

AGMT Austria (Arbeitsgemeinschaft medikamentöse Tumortherapie)

Principal Investigator:

Ulrich JÄGER, MD
Professor of Hematology
Division of Hematology and Hemostaseology
Department of Internal Medicine I
Medical University of Vienna
Währinger Gürtel 16-18
A-1090 Vienna
Phone: +43 1 40400 4410
Fax: +43 1 40400 4030
Email: ulrich.jaeger@meduniwien.ac.at

Co-Investigators:

Marek TRNĚNÝ, M.D.
I. interni klinika LF UK
U Nemocnice 2
Praha 2
128 08
Czech Republic
Phone: +420 224962568
Fax: +420 224962061
e-mail: trneny@cesnet.cz

Michael A. FRIDRIK, M.D.
Onkologie
Allgemeines Krankenhaus der Stadt Linz GmbH
Krankenhausstraße 9
4020-Linz

Austria

Phone: +31 732 7806 1610

Fax: +31 732 7806 1940

e-mail: michael.fridrik@akh.linz.at

Randomization, Biometrics and Data management:

Anton Klingler, PhD

Assign Data Management and Biostatistics GmbH

Stadlweg 23

A-6020 Innsbruck, Austria

Phone: +43 512 890064

Fax: +43 512 281514

e-mail: anton.klingler@assigngroup.com

A list of other persons involved in the study (e.g. investigators of the different sites) is provided by the sponsor on request.

# 7. INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is an aggressive, CD20-positiv non-Hodgkin lymphoma (NHL) which is potentially curable[3,4,5]. Standard treatment consists of a combination immunochemotherapy with Rituximab (R), cyclophosphamide, doxorubicine, vincristine, and prednisone (CHOP)[6,7]. Involved field radiation treatment may also be beneficial, particularly in patients with bulky disease[8]. The number of R-CHOP cycles applied varies with prognosis dependent on clinical stage and age (younger or older than 60 years) as indicated by the International Prognostic Index (IPI)[9]. The interval between cycles may vary between 14 and 21 days (R-CHOP-14, R-CHOP-21): Current treatment guidelines recommend 6 cycles of R-CHOP for patients with low IPI (≤1), particularly under the age of 60 according to the MINT study[10,11]. Immunochemotherapy may be supplemented by radiotherapy in case of bulky disease. Some studies suggest that patients with low IPI or tumor burden can be treated with 3-4 cycles of R-CHOP plus radiotherapy[8]. Patients with intermediate or high-risk (according to IPI) are treated with 8 cycles of R-CHOP-21 or 6 cycles of R-CHOP-14[12,13]. With these risk-adapted treatment strategies 3-year progression-free survival (PFS) rates of 52-73% for elderly patients (IPI 0-5), and 85% for younger patients with IPI 0 or 1 are achieved[6]. Using intensified treatment, failure-free survival for young high-risk patients is 61-73% at 4-5 years[6].

Unfortunately, a considerable proportion of patients experience relapses (mostly during the first 3 years). Patients with 3-5 IPI risk factors only have a chance of cure in the range of 50%[7] and are treated with aggressive second-line therapy including stem cell transplantation[6]. While the addition of Rituximab to CHOP has improved long-term survival by 15 to 20%, there is still an unmet need for the prevention of the high number of relapses. Two strategies can be applied to achieve this goal:

1. Intensification of induction treatment with stronger chemotherapy, higher doses of Rituximab, or the addition of novel substances (e.g. lenalidomide or kinase inhibitors)[14,15,16,17,18,19].
2. Extended treatment with Rituximab or other drugs with acceptable toxicity in order to eradicate minimal residual lymphoma as successfully applied in follicular lymphoma.

For this NHL-13 study we chose to explore the latter possibility, initially planned for 12 months (in a pilot study with a small number of patients) and then with an extended schedule of 24 months.

Follicular lymphoma (FL) grade 3 has been alleged to exhibit an aggressive clinical behavior similar to DLBCL. While this has become disputable in recent years, at the initiation of this study FL G3 was treated with aggressive strategies (R-CHOP), particularly if classified as grade 3b[4,20,21]. Thus, this entity was included in the protocol.

## 7.1 RATIONALE FOR RITUXIMAB MAINTENANCE TREATMENT AND SCHEDULING

Rituximab maintenance after first or second-line induction treatment has considerably improved the outcome of patients with indolent NHL, particularly follicular lymphoma[22,23,24,25,26,27,28,29]. Similar results have been obtained in the treatment of mantle cell lymphoma[30]. Rituximab maintenance is therefore approved in FL and mantle cell lymphoma and is also standard of care in other indolent lymphomas. While the standard R dose is always 375 mg/m$^2$, various schedules for maintenance treatment have been applied: In relapsed FL, R is given every 3 months for 2 years[26], while in consolidation after first line induction, R is given every 2 months for 24 months [24,25,27]. Another variant is to give 4 weekly doses of R every 6 months for 2 years[23]. We have recently studied Rituximab serum concentrations in patients with untreated FL during chemoimmunotherapy induction and maintenance[31]. The following major findings emerged from this study: (1) Median R levels remained steady during 2-monthly maintenance with 375 mg/m$^2$; (2) however, serum concentrations were distributed over 1 order of magnitude dependent on tumor burden (bone marrow infiltration) and sex; (3) R levels during maintenance correlated with PFS and impending relapse. Female patients had higher serum concentrations ($C_{trough}$ and AUC), higher CR rates and longer PFS. This phenomenon was also observed in patients with DLBCL[32].This leads to the assumption that tumor burden and sex have a direct impact on the efficacy of R and their analysis should be incorporated in clinical trial protocols.

Rituximab maintenance after R-CHOP-like induction is not standard of care for DLBCL and other aggressive lymphomas (guidelines). Several studies have addressed this question albeit none of these was a prospective trial powered to answer the question whether R consolidation can prevent relapses and improve outcome of

patients with aggressive NHL: The ECOG 4494 trial studied R- maintenance with the 6-monthly, 4 times weekly schedule vs. observation in patients older than 60 years after CHOP or R-CHOP induction[33]. No beneficial of R-consolidation was found. A recently published *retrospective* Chinese study in DLBCL patients reported a positive effect on PFS in various risk groups and an advantage in OS in the high-risk IPI subgroup[34]. The analysis of R maintenance vs. observation after autologous stem cell transplantation in the CORAL study in relapsed DLBCL found a significantly improved PFS in female patients receiving Rituximab[35].

Therefore, it seems warranted to study the impact of R-maintenance in DLBCL (and FLG3) in a prospective study with planned subgroup analysis. It seems rational to include adult patients in all ages, stages and prognostic subgroups who have obtained a CR after R-CHOP like regimens. This should give an answer on whether R-maintenance has any beneficial effect, or at least as to which subgroups should be further evaluated. Based on the evidence presented, R is given in 2-monthly intervals for 2 years at a dose of 375mg/m$^2$.

Given the possibility of toxic side effects on long term maintenance, event-free survival seems to be a rational clinical endpoint.

This R-maintenance study may also serve as a paradigm for consolidation treatment with other novel drugs.

# 8. STUDY OBJECTIVES

## Primary Objective

- To evaluate the capacity of Rituximab maintenance therapy to prolong event-free survival as compared to observation alone in patients with aggressive Non-Hodgkins lymphoma.

## Secondary Objective

- To evaluate progression-free and overall survival of patients
- To evaluate the safety of Rituximab maintenance treatment
- Austrian patients only:
  - To evaluate the patients' quality of life during Rituximab maintenance therapy.
- Subgroup Analysis: Subgroup analysis was performed regarding histological subtypes according to the WHO classification. Diffuse large B-cell lymphomas were analysed regarding:
  - morphologic variants: centroblastic, immunoblastic, T-cell/histiocyte rich, anaplastic
  - subtypes: plasmablastic
  - mediastinal (thymic) large B-cell lymphoma.

  In addition, subgroups were analysed with regard to the International Prognostic Factor Index (IPI) subgroups (low, low-intermediate, intermediate-high, high).

  Histological samples (Austrian patients only) were reviewed by a Central Pathology Unit (Institute of Pathology, Medical University of Vienna, Prof. A. Chott).

# 9. INVESTIGATIONAL PLAN

## 9.1 OVERALL STUDY DESIGN AND PLAN DESCRIPTION

This was a randomized, open label, phase III study to evaluate the ability of Rituximab maintenance therapy to prolong event-free survival in aggressive NHL.

Patients in Austrian hospitals were screened after successful standard induction therapy: complete remission (CR) or unconfirmed CR (CRu) following standard R-CHOP-like therapy with 8 infusions of Rituximab plus CHOP-like chemotherapy (4-8 cycles).

Using 1:1 randomization subjects were divided into two groups, stratified for country and center as well as type and number of cycles of induction therapy (see Chapter 9.4.3). Group A received study medication (Rituximab 375 mg/m$^2$ every 8 weeks) while group B was only observed.

Subjects were monitored until an event occurred as defined in the protocol to evaluate the clinical efficacy of Rituximab maintenance therapy as compared to observation in patients with aggressive B-cell Non-Hodgkins lymphoma or follicular lymphoma grade 3b who had achieved a complete remission after appropriate first-line therapy, measured by event-free survival (EFS).

To be able to finish the study in a timely fashion, which at that time seemed unlikely to happen with Austrian sites alone, in 09-Jan-2006 (Amendment 1) it was decided to extend to other countries in order to be able to recruit more patients. The planned number of subjects could be extended from 340 to 600.

Additionally, the study medication was extended from 6 to 12 infusions (12 to 24 months) with Amendment 1. Participants that were currently in the treatment phase could agree to extend the medication in regard to Amendment 1. In this case the follow up period was shorter.

Finally 683 patients were randomized.

As planned, two interim analyses were performed.

This study started in July 2006. The last patient entered the study end of 2008. The study was completed by 2012.

Table 1 (pre-Amendment 1) and Table 2 (post Amendment 1) contain a flowchart of screening-, treatment- and follow up visits.

Patients prior Amendment 1 had 6 treatment-visits and 17 follow–up visits, while subjects after amendment 1 had to attend 12 treatment visits and only 9 follow-up visits.

**Table 1: Flowchart of assessments prior Amendment 1**

| | | Treatment period week Nr.: | | | | | | 8 wks. | follow-up first 3 years (3 monthly) | | | | | | | | | | | | f.u. yea (6 mon | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Test | SCREEN /baseline | 1 | 9 | 17 | 25 | 33 | 41 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| Informed consent | x | | | | | | | | | | | | | | | | | | | | | |
| Physical exam. | x | x | x | x | x | x | x | | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Medical history | x | x | x | x | x | x | x | | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Hematology | x | x | x | x | x | x | x | | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Blood chemistry | x | x | x | x | x | x | x | | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Immunologic comp. | x | | x | | x | | x | | | x | | x | | x | | x | | | | | | |
| HBV/HCV/HIV | x | | | | | | | | | | | | | | | | | | | | | |
| CT scan | x | | x | x | x | x | | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| IPI | x | | | | | | | | | | | | | | | | | | | | | |
| ECG | x | | | | | | | | | | | | | | | | | | | | | |
| Endoscopy[a] | x | | | | | | | x | | | | x | | | | x | | | | x | | x |
| Bone marrow[a] | x | | | | | | | x | | | | x | | | | x | | | | x | | x |
| Quality of Life | x | | x | | x | | x | | | | | | | | | | | | | | | |
| Pregnancy test[a] | x | x | x | x | x | x | x | | | | | | | | | | | | | | | |
| Adverse events | | x | x | x | x | x | x | | | | | | | | | | | | | | | |
| Rituximab[b] | | x | x | x | x | x | x | | | | | | | | | | | | | | | |
| Histology sample | x | | | | | | | | | | | | | | | | | | | | | |

[a] only if indicated
[b] only in ARM A
[c] **molecular biology optional**

**Table 2: Flowchart of assessments after Amendment 1**

| | | Treatment period (week #) | | | | | | | | | | | | | Follow-up (months) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Test | SCREEN /baseline | 1 | 9 | 17 | 25 | 33 | 41 | 49 | 57 | 65 | 73 | 81 | 89 | RA[d] | Month 3[e]; 9; 15; 21 | Month 6;12;18, 24 |
| Informed consent | x | | | | | | | | | | | | | | | |
| Physical exam. | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Medical history | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Hematology | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Blood chemistry | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Immunologic comp.[c] | x | | | x | | x | | x | | x | | x | | x | | x |
| HBV/HCV/HIV | x | | | | | | | | | | | | | x | | |
| CT scan | x | | | x | | x | | x | | x | | x | | x | | x |
| IPI | x | | | | | | | | | | | | | | | |
| ECG | x | | | | | | | x | | | | | | x | | |
| Endoscopy[a] | x | | | | x | | | x | | | x | | | x | | x |
| Bone marrow[a] | x | | | | x | | | x | | | x | | | x | | x |
| Quality of Life | x | | | x | | x | | x | | x | | x | | | | |
| Pregnancy test[a] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | | |
| Adverse events | | x | x | x | x | x | x | x | x | x | x | x | x | x | | |
| Rituximab[b] | | x | x | x | x | x | x | x | x | x | x | x | x | | | |

[a] only if indicated
[b] only in ARM A
[c] optional
[d] Final response assessment eight weeks after completion of 12th maintenance course
[e] 3 months after the 12th infusion

The Clinical Study protocol as well as its changes is summarized in this report and provided by the sponsor on request.

A sample case report form (CRF) is available and will be provided by the sponsor on request.

## 9.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

This was a randomized, open label, phase III study to evaluate the ability of Rituximab maintenance therapy to prolong event-free survival in aggressive NHL.

The maintenance dosage (one infusion every 8 weeks) has emerged as a de-facto standard for most ongoing studies with Rituximab maintenance. Clinical and pharmacokinetic data suggested that the effect of Rituximab could be improved by prolonged exposure to the drug, however, data on the optimal maintenance schedule was lacking.

The maintenance duration of 24 months was chosen to encompass the time where approximately 80-90% of all relapses in DLBCL occur.

It was anticipated that this trial would have an excellent benefit:risk ratio, as Rituximab infusions, after previous treatment with Rituximab, cause very few side effects. The treatment causes a minimal burden to patients, who receive one infusion in an ambulant setting every two months. On the contrary, most patients would even prefer to be treated for their potentially unapparent disease instead of idle waiting.

## 9.3 SELECTION OF STUDY POPULATION

### 9.3.1 Inclusion Criteria

To be eligible for inclusion, each patient had to fulfill each of the following criteria:

• Patients must have received eight infusions of Rituximab plus 4 - 8 cycles of CHOP-like chemotherapy (i.e. 12 to 24 weeks of CHOP-like schemata, including, but not limited to CEOP/IMVP, CHOEP, iCHOP, ESHAP, CNOP, MACOP-B, VACOP-B, ProMitCytaBOM) as their first-line therapy for NHL. Regimens not listed were considered by the primary investigators for inclusion on an individual basis. Induction chemotherapy had to contain an anthracycline or anthracenedione such as daunorubicin, doxorubicin, epirubicin, idarubicin, or mitoxantrone, or their liposomal forms.

• Induction treatment must have been completed with the application of the final cycle of immuno- or chemotherapy no longer than 12 weeks, and no earlier than 4 weeks before trial treatment start.

• Patients must have reached a complete remission (CR) or an unconfirmed CR (CRu) after induction therapy (according to[1]). CR or CRu must have been documented no later than four weeks prior to trial treatment start by CT scan of thorax, abdomen, and pelvis.

• Histologic diagnosis of either diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma grade 3b according to the WHO/REAL classification at time of diagnosis (prior to induction therapy).

• Confirmed CD20 positivity of the lymphoma at time of diagnosis (prior to induction therapy)

• ECOG performance status of 0, 1 or 2 at time of inclusion

• Known IPI at time of diagnosis (prior to induction therapy)

• Age 18 years or older

• Life expectancy of > 3 months

• Be willing and able to comply with the protocol for the duration of the study

• Women of child-bearing potential must have had a negative pregnancy test and must have agreed to use effective contraception for the entire treatment period and during the 12 months thereafter if randomized to maintenance treatment

• Men had to agree not to father a child if allocated to maintenance treatment during therapy and one year thereafter

• Patient's written informed consent

### 9.3.2 Exclusion Criteria

Patients who fulfilled any of the following criteria could not be included:

• First-line NHL therapy other than specified in the inclusion criteria

• More than one prior chemoimmunotherapy regimen.

• Histologies other than DLBCL and follicular lymphoma grade 3b according to the WHO/REAL classification

• Transformed lymphoma

• History of malignancy other than squamous cell carcinoma, basal cell carcinoma of the skin, surgically treated malignant melanoma or carcinoma in situ of the cervix within the last 5 years.

• Major surgery, other than diagnostic surgery, within the last 4 weeks.

• Evidence of CNS involvement. Patients with a history of uncontrolled seizures, central nervous system disorders or psychiatric disability judged by the Investigator to be clinically significant and adversely affecting compliance to study drugs.

• Clinically significant cardiac disease (e.g. congestive heart failure, symptomatic coronary artery disease and cardiac arrhythmias not well controlled with medication) or myocardial infarction within the last 6 months.

• Unacceptable hematologic status at baseline prior to study start below any of the values listed: WBC: <3 x 109/l; absolute neutrophil count (segmented + bands) <1.5 x 109/l; platelets: <100 x109/l

• Abnormal liver function tests prior to study start above any of the values listed: serum bilirubin >2 mg/dl (35 mmol/l); ALAT or ASAT >2.5 x upper limit of normal range; alkaline phosphatase > 3 x upper limit of normal range

• Abnormal renal function (serum creatinine > 2.0 mg/dl (177 µmol/l)).

• Patients with active opportunistic infections.

• HIV-positive patients.

• Intolerability to Rituximab

• Active viral hepatitis, specifically HBV or HCV infection

• Serious underlying medical conditions, which could impair the ability of the patient to participate in the trial (e.g. ongoing infection, uncontrolled diabetes mellitus, severe cardiac dysfunction or angina, gastric ulcers, active autoimmune disease)

• Life expectancy < 3 months

• Known sensitivity or allergy to murine products

• Treatment within a clinical trial within 30 days prior to trial entry

• Women who were breast feeding, were not using effective contraception, were pregnant or did not agree not to become pregnant during the treatment phase of the trial and during the 12 months thereafter, if randomized to maintenance.

• Men who did not agree not to father a child during treatment and 12 months thereafter

• Patients under tutelage

### 9.3.3 Removal of Patients from Therapy or Assessment

Patients had the right to withdraw from the trial at any time and for any reason without affecting the patient's right to treatment by the investigator. The investigator also had the right to withdraw the patients in the event of intercurrent illnesses, adverse events, treatment failure, or cure. The sponsor reserved the right to request the withdrawal of a patient due to protocol violation, administrative or other reasons.

**Premature study treatment discontinuation:**

If any of below mentioned event occurred, study treatment was discontinued, however the patient was observed until the end of the study.

Reasons for premature study treatment discontinuation:

1. Patient had missed 2 consecutive study medication infusions

2. NCI toxicity grade 4 except lymphopenia

3. Pregnancy

4. Patient withdrawed consent to recieve the study medication

5. A protocol-defined event (see Chapter 8.1 of the study protocol)

6. Other reasons that in investigator´s opinion made the premature discontinuation of the study medication the best solution for the patient

**Premature discontinuation of subject's participation in the study**

If any of below mentioned events occurred, the patient was withdrawn from the study. Reasons for withdrawal and disease status at the time of premature discontinuation were documented. If possible, final trial evaluation should have been completed. Withdrawals due to non-attendance had to be followed up by the investigator to obtain the reason for non-attendance.

Reasons for premature discontinuation of subject's participation in the study:

1. Significant protocol violations or deviations (as agreed by the investigator, sponsor and the biostatistician)

2. Patient withdraws consent

3. Death

4. Other reasons that in investigator's opinion made the premature discontinuation of subject's participation in the study the best solution for the patient

### Premature Trial Termination

After detailed consultation by the statistician, investigator and sponsor the sponsor and the investigator reserved the right to terminate the trial prematurely for persistent protocol violations, administrative, or any other valid and ethical reason. If any disadvantage of the treatment would have been published during the clinical trial, therapy would have been terminated. In this case the necessary procedures would have been arranged after review and consultation by both parties to ensure protection of the subjects' interests.

## 9.4 TREATMENTS

### 9.4.1 Treatments Administered

**ARM A:**

Treatment was carried out according to the following schedule (summarized in Table 3).

**Table 3: Treatment schedule (prior Amendment 1: 6 cycles; after Amendment 1: 12 cycles)**

| Rituximab treatment (375mg/m²) | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| | Week 1 | Week 9 | Week 17 | Week 25 | Week 33 | Week 41 |
| Rituximab treatment (375mg/m²) | 7 | 8 | 9 | 10 | 11 | 12 |
| | Week 49 | Week 57 | Week 65 | Week 73 | Week 81 | Week 89 |

Treatment (one infusion of Rituximab 375 mg/m²) started in week 1, and was repeated every eight weeks for 6 or 12 consecutive cycles.

**Dose:** 375 mg/m², Rituximab diluted in 0.9% NaCl, with a concentration of 1 mg/ml. No dose modifications were performed.

**Premedication:** Patients were supposed to be well-hydrated. Premedication with an analgetic and an antihistaminic drug was recommended.

**Infusion:** Rituximab was not supposed to be administered as an intravenous push or bolus; therefore it was received intravenously in an outpatient setting, if possible. A peripheral or central intravenous (iv) line was established and before starting the infusion, it was required that a supply of epinephrine for subcutaneous injection and diphenhydramine hydrochloride for intravenous injection, and resuscitation equipment for the emergency handling of anaphylactic reactions was ready.

The first infusion was started at an initial rate of 50 mg/hour for the first hour. During the Rituximab infusion, the patient's vital signs (blood pressure, pulse, respiration and temperature) were monitored every 15 minutes (4 times) for one hour or until stable and then hourly until the infusion was discontinued. If no toxicity was seen during the first hour, the dose rate could be escalated gradually (by increments of 50 mg/hour at 30 minute intervals) to a maximum of 300 mg/hour. If the first dose of Rituximab was well-tolerated, the starting flow rate for administration of the second and subsequent infusions was 100 mg/hour and then increased gradually (by 100 mg/hour increments at 30 minute intervals) not to exceed 400 mg/hour. If transient fever and rigors with infusion were noted the antibody infusion was temporarily discontinued, the patient was observed, and when the symptoms improved, the infusion could be continued but at half the previous rate.

**ARM B:**

No Rituximab was applied, observation only.

### 9.4.2 Identity of Investigational Product

Rituximab (MabThera®, F. Hoffmann-La Roche Ltd, Basel, Switzerland) is a chimeric human/mouse IgG1 kappa antibody that specifically reacts with the CD20 antigen found on the surface of malignant and normal B-cells. The Rituximab antibody is produced by a Chinese hamster ovary transfectoma.

Rituximab study medication for maintenance treatment was labeled by F. Hoffmann-La Roche Ltd (Basel, Switzerland) and supplied through the local Roche affiliate.

Rituximab was supplied in 10 ml or 50 ml single-dose vials containing 100 mg or 500 mg of antibody in a sodium chloride solution (pH6.5) containing polysorbate 80 and sodium citrate at a concentration of 10.0 mg/ml.

The study medication (Rituximab) was transported in shipping containers validated to maintain a temperature in transit of 2-8°C. Stability studies indicate that Rituximab is stable in its formulation when stored at 4°C for 24 months; thus, the antibody had to be stored at 2-8°C (see also Appendix 1 of the Clinical Study Protocol).

Additionally all trial medications had to be stored in a secure area.

### 9.4.3 Method of assigning Patients to Treatment Groups

Randomization was on a 1:1 basis to give 460 patients with diffuse large B-cell NHL or follicular NHL grade 3b in each of two groups:

- Arm A: treatment with one infusion of Rituximab (375 mg/m$^2$) every 8 weeks for a total of 6 (prior Amendment 1)/12 (after Amendment 1) infusions (two years).
- Arm B: observation only

Patients were randomized blocked and stratified for country as well as type and number of cycles of induction therapy:

- Type of induction therapy:
  - CHOP vs.
  - CHOEP vs.
  - CEOP/IMVP vs.
  - Other CHOP-like chemotherapy
- Number of cycles of induction chemotherapy:
  - 4-6 cycles vs.
  - 7-8 cycles

### 9.4.4 Selection of Doses in the Study

Arm A: treatment with one infusion of Rituximab (375 mg/m$^2$) every 8 weeks for a total of 6 (prior Amendment 1)/12 (after Amendment 1) infusions. This dosage was used for all treated subjects.

### 9.4.5 Selection and Timing of Dose for Each Patient

Arm A: treatment with one infusion of Rituximab (375 mg/m$^2$) every 8 weeks for a total of 6 (prior Amendment 1)/12 (after Amendment 1) infusions.

The maintenance dosage has emerged as a de-facto standard for most ongoing studies with Rituximab maintenance. Also the dosage of 375 mg/m$^2$ is recommended in the expert information.

### 9.4.6 Blinding

The study was open-label, hence no blinding was performed.

### 9.4.7 Prior and Concomitant Therapy

All concomitant medications had to be reported in the case report form.

Patients who had been tested HBV/HCV positive could receive antiviral therapy (active HBV/HCV infections as defined by elevated liver parameters were an exclusion criterion).

The use of prophylactic corticosteroids and prophylactic cytokines (e. g. CSFs, erythropoietin) was not encouraged.

Concomitant radiation therapy to areas of previously existing tumor bulk was permitted and could be completed after the time of randomization.

Premedication with an analgetic and an antihistaminic drug was recommended.

### 9.4.8 Treatment Compliance

As the treatment was accomplished in the study site by study staff, the correct application should have been guaranteed.

A preprinted drug dispensing log was provided and had to be kept current and had to identify the patient and the amount of medication dispensed to and returned/destroyed with the corresponding dates.

All medication supplies had to be available for inspection and at every monitoring visit. All unused medication had to be returned by the investigator to Roche at the end of the study.

## 9.5 EFFICACY AND SAFETY VARIABLES

### 9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

The study involved a screening visit within 14 days before the first infusion (treatment group) or the first visit in week 1 (observation subjects), during which subjects had a physical examination, additional procedures including vital signs, medical history review, evaluation of the planned infusion site and safety laboratory tests. In Week 1, entry criteria were checked and subjects were randomized to one of the groups. Subjects in Arm A received their first infusion in week 1. All subjects were required to return to the clinic every 8 weeks for infusions or observation visits, where the following investigations were performed:

<u>Every 8 weeks:</u>

- Physical examination
- Medical history / review of adverse events
- Full blood count and blood chemistry
- Pregnancy test (if applicable)

<u>At 3rd, 5th, 7th, 9th, 11th treatment or observation visit:</u>

- Immunological competence (IgA, IgG, IgM; CD3+, CD4+, CD19+, CD3+/8+, CD3+/4+, CD16+/3- lymphocytes, and NK cells), encouraged, not mandatory
- CT scan of chest, abdomen and pelvis. PET and/or MRI scans may be used additionally and/or alternatively to CT scans, if appropriate
- Quality of life questionnaire (Austria only).

<u>Every six months</u>

- Endoscopy and bone-marrow examinations if indicated

<u>Electrocardiogram (ECG)</u>

- An ECG was mandatory at baseline and was repeated at week 49 and at the time of response assessment

<u>HBV/HCV/HIV serology</u>

- Virus serology was mandatory at baseline and was repeated at the time of response assessment

<u>Within 8 weeks after the last treatment (or observation) visit:</u>

- CT scan of chest, abdomen and pelvis
- Endoscopic examination *only if these regions were affected before induction therapy* (e.g. stomach, intestine or lung localizations)
- Bone marrow aspirate and biopsy, *only if bone marrow involvement was detected before induction therapy*
- Documentation of continuing CR/CRu

After the 6th respectively 12th visit a last visit without infusion was scheduled. The follow-up controls were assessed for 2 years and were different between patients without an event and those with an event. Follow-up-visits were every 3 months after study treatment completion, until a two year/5 year follow-up after completion of maintenance therapy was reached.

**Subjects without an event:**

**Every three months after completion of maintenance:**

- Physical examination
- Medical history / review of adverse events
- Documentation of infections of grades III or IV
- Full blood count and blood chemistry

**Every six months for after completion of maintenance:**

- Immunological competence (IgA, IgG, IgM; CD3+, CD4+, CD19+, CD3+/8+, CD3+/4+, CD16+/3- lymphocytes, and NK cells), encouraged, not mandatory
- CT scan of chest, abdomen and pelvis
- Endoscopic examination as appropriate only if these regions were affected before induction therapy (e.g. stomach, intestine or lung localizations)
- Bone marrow aspirate and biopsy as appropriate, only if bone marrow involvement was detected before induction therapy

**Subjects with an event:**

Only the survival status was assessed.

Patients prior Amendment 1 had 3 years of follow up as described above and 2 further years with less frequent visits:

**4th and 5th year, every 6 months:**

- Physical examination
- Medical history
- Documentation of infections of grades III or IV

- Full blood count and blood chemistry
- CT scan of neck, chest, abdomen and pelvis

4th and 5th year, once a year:

- Endoscopic examination *only if these regions were affected before induction therapy* (e.g. stomach, intestine or lung localizations)
- Bone marrow aspirate and biopsy, *only if bone marrow involvement was detected before induction therapy*

The schedule of events is presented in Table 2.

#### 9.5.1.1 Safety assessments

Safety was assessed by the collection of adverse events.

Definitions:

An Adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Pre-existing conditions which worsen during a study are to be reported as adverse events.

They can become Serious Adverse Events if they fulfil one of the seriousness criteria described below.

A Serious adverse event (SAE) is any adverse event that at any dose fulfils at least one of the following criteria:

- is Fatal (results in death) (note: death is an outcome, not an event)
- is Life-Threatening (note: the term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which could hypothetically have caused death had it been more severe).
- required patient hospitalization or prolongation of existing hospitalization (note: "hospitalization" refers to an unplanned, overnight hospitalization).
- results in persistent or significant disability/incapacity.
- is a congenital anomaly/birth defect.
- is medically significant or requires intervention to prevent one or other of the outcomes listed above.

Note: *planned* hospitalizations and *NHL progression* was not documented as serious adverse event.

***Reporting of adverse events:***

**Treatment/observation period**

During treatment/observation period all adverse events were reported on the CRF with exception of hematological toxicity.

**Hematotoxicity during the treatment/observation period:**

Only Grade 3 and 4 hematotoxicity according to the NCI CTC had to be reported as an adverse event.

### Laboratory Test Abnormalities

Laboratory test results were recorded on the laboratory results pages of the Case Report Form, or appeared on electronically produced laboratory reports submitted directly from the central laboratory, if applicable. Laboratory test value abnormalities as such were not supposed to be reported on the AE page of the CRF as adverse events, unless there was an associated clinical condition for which the patient was given treatment or concomitant treatment altered, it was considered to be a serious adverse event, or the patient was permanently discontinued from study drug because of the abnormal test value.

A listing of standard Units used in this trial can be observed under Table 6.

### Follow-up period

Only grade III or IV infections and adverse events assessed by the investigator as related to the study medication (e.g. potential adverse drug reactions) had to be documented in the CRF.

*Treatment and Follow-up of Adverse Events:*

All adverse events had to be documented and followed up until the event was either resolved or adequately explained, even after the subject had completed his/her trial treatment.

All serious adverse events that occurred during the treatment/observation period had to be reported within one working day by the investigator to the AGMT Trial Manager/Safety desk. SAEs were reported by the AGMT to the local Roche affiliate, Roche Basel, and Genentech.

Additionally, serious adverse events had to be reported to the local ethics committee and health authorities in compliance with local laws and regulations.

Serious adverse events that occurred during the follow-up period had to be reported only if assessed by the investigator as related to the study medication.

*Severity assessment*

The intensity of adverse events was graded according to NCI Common Toxicity Criteria grading system in the toxicity categories that have recommended gradings. The NCI CTC grading system is available in the clinical study protocol. The maximum grading for each category had to be documented.

Adverse events not listed in the NCI CTC grading system were graded according to a WHO four-point system. (See W.H.O. Handbook for Reporting Results of Cancer Treatment):

**Table 4: WHO four-point scale**

| | |
|---|---|
| Mild or Grade 1 | discomfort noted, but no disruption to normal daily activities |
| Moderate or Grade 2 | discomfort sufficient to reduce or affect normal daily activities |
| Severe or Grade 3 | Inability to work or perform normal daily activities |
| Life-Threatening or Grade 4 | Substantial risk of dying at time of event |

*Causality assessment:*

Causality could be one of three possibilities:

- "NO" (definitely not drug related)
- "YES" (remotely, possibly, probably or definitely drug-related)

- "UNKNOWN"

All adverse events judged by either the investigator or Roche as being definitely not "NON DRUG-RELATED" are qualified as Adverse Drug Reactions.

*Expected toxicity of Rituximab:*

The main side effect of Rituximab is the appearance of infusion-related symptoms during the first administration; however, since Rituximab was a mandatory part of the induction therapy, no adverse reactions typical for first-time Rituximab infusion were expected to occur. Most frequent common side effects are fever and shivering (rigors); less frequent is hypotension, dyspnea and nausea.

In a few patients with a previous history of cardiac disease a sudden and unexplained worsening of the cardiac function was observed, but in patients with stable cardiac disease and an ejection fraction > 50% no such cases were described. In a previous Rituximab maintenance trial (SAKK 35/98) an incidence of 15% neutropenia was observed and an important decrease in circulating B-cells was described, but without any increased rate of infections. Sleepiness may have been caused by diphenhydraminhydrochlorid as concomitant medication.

A Data Safety Monitoring Committee was installed and reviewed the data once per year or upon unusual events.

### 9.5.1.2 Survival analysis

- **Subgroup analysis**

Subgroup analysis was performed regarding histological subtypes according to the WHO classification. Diffuse large B-cell lymphomas were analysed regarding:

- morphologic variants: centroblastic, immunoblastic, T-cell/histiocyte rich, anaplastic
- subtypes: plasmablastic
- mediastinal (thymic) large B-cell lymphoma

In addition, subgroups were analysed with regard to the International Prognostic Factor Index (IPI) subgroups (low, low-intermediate, intermediate-high, high).

Histological samples (Austrian patients only) were reviewed by a Central Pathology Unit (Institute of Pathology, Medical University of Vienna, Prof. A. Chott).

- **Progression-free survival**

Progression-free survival was defined as the period from randomization until one of the following events occurs:

- Progressive disease or relapse (according to[1])
- Death from NHL

- **Overall survival**

Death from any cause

### 9.5.1.3 Immunocompetence

Evolution of immunologic competence was an optional assessment:

Cellular level: evolution over time of the concentration of B-lymphocytes, CD3+, CD4+, CD19+, CD3+/8+, CD3+/4+, CD16+/3- lymphocytes, and natural killer cells in the patient's blood.

Humoral level: by the evolution over time of the concentration of IgG, IgA and IgM in the blood, and by monitoring of infections.

#### 9.5.1.4 Quality of life

Quality of life was assessed by quality of life patient questionnaires (SF-12v2®) for Austrian patients only.

### 9.5.2 Appropriateness of Measurements

Outcome measurements were planned and performed in accordance with international clinical guidelines.

### 9.5.3 Primary Efficacy Variable

As the primary efficacy variable the event-free survival was chosen.

Event-free was defined as the period from randomization until one of the following events occurred:

- Progressive disease or relapse (according to[1])
- Death from any cause
- Initiation of non-protocol anticancer treatment or concomitant steroids introduced because of lymphoma symptoms or concomitant radiotherapy
- Secondary malignancy
- Unacceptable toxicity (e.g. life-threatening or serious disease which is potentially due to the trial treatment; e.g. worsening of the cardiac function with ejection fraction < 50%)

### 9.5.4 Drug Concentration Measurement

Not applicable

## 9.6 DATA QUALITY ASSURANCE

### 9.6.1 Source Data and Records

The trial was monitored. A monitor contacted and visited the investigators regularly. He / she was allowed to inspect the various records of the trial (provided that patient confidentiality was maintained) in accordance with local requirements.

For this trial the expected average monitoring visit frequency was approximately every 3-6 months during treatment/observation phase.

Before enrolment of the first subject or shortly after, a trial initiation visit took place. The objective of this visit was to meet the local staff involved in the conduct of the trial (including sub-investigators, research nurse, data manager, pharmacist), to describe the main features of the protocol, the use of the electronic case report forms (eCRF), the practicalities of the trial and to distribute the trial specific trial master file (TMF).

During monitoring visits 100% Source Data Verification (SDV) was performed for the first patient at a center for all data.

If no major variations were found, source data verification could be reduced and only the following data was reviewed for every patient:

- Informed consent

- Inclusion / exclusion criteria

- Primary endpoint (event-free survival)

- Serious Adverse Drug Reactions (SADR)

- Drug inventory log

Source data entries were made in accordance with local requirements. Signed and dated copies of the laboratory result reports were kept in the subject files, eCRFs were not used as source data for any variable.

Documentation of inter-laboratory standardisation methods and quality assurance procedures is provided by the sponsor on request.

### 9.6.2 Periodic Monitoring

The trial was monitored according to SOPs, the NHL-13 A Clinical Study Protocol, NHL-13 A Monitoring Plan, ICH-GCP Guidelines and applicable regulations. A designated monitor inspected the eCRFs at regular intervals throughout the study to verify completeness, accuracy and consistency of the data, protocol adherence and adherence to GCP guidelines. The monitor had access to all source records needed to verify the entries on the CRFs. The investigator cooperated with the monitor to ensure that any discrepancies identified were resolved.

### 9.6.3 Audit and Inspection

Upon request, the investigator was to make all study-related source data and records available to a qualified quality assurance auditor mandated by the sponsor, or to regulatory inspectors. The main purposes of an audit or inspection were to confirm that the rights and welfare of the subjects had been adequately protected, and that all data relevant for the assessment of safety and efficacy of the investigational product were appropriately reported to the sponsor.

### 9.6.4 Confidentiality of Subject Data

The investigator exercised all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of subjects' identities. On CRFs or any other documents submitted to the sponsor, subjects were only identified by a subject number. Documents not for submission to the sponsor, e.g. subject identification log and original consent forms, were maintained by the investigator in strict confidence.

### 9.6.5 Electronic Case Report Forms

#### 9.6.5.1 eCase Report Form Entries

eCRF entries and corrections were only to be performed by study staff authorized by the investigator. Each user was informed by the CRO of the clinical study web-site internet address and was allocated a personal password to access the confidential web site. The personal password was kept confidentially and only used by the person to whom it was assigned. For additional authorized users at the site, a new password was requested to ensure that each entry/change could be allocated to the person who performed the entry/change.

All visit data was recorded in the database as soon as possible after each visit.

#### 9.6.5.2 Changes to eCase Report Form Data

Corrections to data on the eCRF were documented in the electronic audit trail that was 21 CFR Part 11 compliant.

Corrections were requested as follows:

- Investigators' responses were checked as they were entered and were rejected if they did not fulfill quality criteria. A message specified the type of error or syntax error and assisted in its correction.
- If required, the Clinical Research Associate (CRA) could ask for information to be corrected during monitoring.
- Computerized data-check programs and manual checks identified clinical data discrepancies for resolution. Corresponding discrepancies were loaded into the system and the site was informed about new issues to be resolved on-line.

All discrepancies were solved on-line directly by the investigator or by authorized staff.

Corrections of eCRF data were performed by the authorized staff only.

#### 9.6.5.3 eCase Report Form Entry Validation

The responsible CRA source data verified the eCRF prior to database lock. After database lock eCRF hardcopies were generated and sent to the principal investigator for sign off.

#### 9.6.5.4 Data Collection

All data that had to be collected according to the study protocol was entered into the eCRF provided by Assign Datamangement and Biostatistics GmbH. The only exception were the results from the quality of life questionnaires. These were not entered into the eCRF and not analyzed by Assign Datamangement and Biostatistics GmbH.

## 9.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

The statistical analysis was performed by Assign Data Management and Biostatistics GmbH using SAS® version 9.2. The analyses described below followed the final SAP written for Final Analysis dated 09-Jan-2012.

Data was summarized by treatment Arm, and where appropriate, by visit. Additional analyses were made separately for:

- all patients
- Patients prior Amendment1
- Patients after Amendment1

Descriptive statistics (number of observations, mean, standard deviation, minimum, median and maximum) were provided for continuous variables (e.g. age and weight). Frequency counts and percentages were presented for categorical variables (e.g. gender).

All data exclusions, including premature terminations, were detailed and tabulated. Data listings include all randomized subjects.

The analyses of baseline characteristics including demographic variables, medical history and concomitant medications have been subject to descriptive analyses.

Adverse Events and concomitant diseases have been coded using the MedDRA coding dictionary (Version 13.1); concomitant medications have been coded using the WHO Drug Dictionary (Version Q2/2010).

### 9.7.1 Statistical and Analysis Plans

A statistical analysis plan had been written for the final analysis of this Trial (provided in Section 16.1.9).

#### 9.7.1.1 Protocol Deviations

Protocol deviations were collected from the monitoring reports, protocol violation forms and identified from the study database and then tabulated in a subject listing. Protocol deviations up to study end were identified by the Data Review Meeting (DRM) attended by Assign Data Management and Biostatistics GmbH and AGMT. The DRM took place after all outstanding discrepancies for the database lock had been resolved, but before the database lock.

A Data Review Meeting Report identifies all candidates for major/minor protocol deviations until study end. A listing of the assignment of subjects to analysis populations has been prepared by Assign Data Management and Biostatistics GmbH and was approved by the sponsor before the database lock. Statistical analyses have been performed after the database lock.

Protocol deviations were classified as major or minor based on their possible impact on the study results. Major protocol deviations included but were not limited to:

• Major protocol deviations from inclusion/exclusion criteria which are possibly related to the efficacy of one of the treatment arms

- Error in treatment assignment
- Post-baseline event evaluation not available

### 9.7.1.2 Analysis Populations

The following analysis sets were used for the final analysis of this clinical study:

**Intention-To-Treat (ITT) population**

comprised all randomized patients according to the Intention-To-Treat principle and was the primary analysis population

**Per-Protocol (PP) population**

comprised all randomized patients excluding those patients with at least one major protocol deviation as defined in the DRM. The PP population was intended to be the secondary analysis population however, no secondary analysis was performed since less than 10% of patients fulfilled one of these criteria.

**Safety population**

was defined to include all randomized patients with at least one post baseline safety assessment.

### 9.7.1.3 Immunocompetence Analysis

The immunocompetence parameters (i.e. IgA, IgM, IgG, CD3+, CD4+, CD8+, CD3- CD16+, CD19+, CD3+ HLA-DR+) were evaluated on the following visits:

- Pre-amendment 1/NHL13: Screening, W9, W25, W41, End of Treatment/Observation Visit, M6, M12, M18
- Post-amendment 1: Screening, W17, W33, W49, W65, W81, End of Treatment/Observation Visit, M6, M12, M18

All immunocompetence parameters are presented in standard units in all tables (see Table 5). For conversion from study site specific units in these standard units, the conversion factors and coefficients specified in the statistical analysis plan (provided in Section 16.1.9) were used.

**Table 5: Table of standard Units**

| Parameter | Standard Unit |
|---|---|
| CD19+ | /µL |
| CD3- CD16+ | /µL |
| CD3+ | /µL |
| CD3+ HLA-DR+ | /µL |
| CD4+ | /µL |
| CD8+ | /µL |
| IgA | MG/DL |
| IgG | MG/DL |
| IgM | MG/DL |

*Inferential analysis of immunocompetence parameters*

A Wilcoxon test for paired observations was applied between the baseline values (Screening) and the end of treatment. The end of treatment is the combination of End of Treatment/Observation Visit (pre-amendment 1) and the End of Treatment/Observation Visit (RA, post-amendment 1) on imputed values according to LOCF. The same analysis was done for pre-amendment 1 and post-amendment 1 separately.

*Tables of immunocompetence parameters*

The following tables were provided stratified by amendment 1 status (all patients, pre-amendment 1, post-amendment 1). No values were imputed.

- The number of available immunocompetence samples as documented in the eCRF (item "Date of sample drawn" is available) was tabulated separately by visit (frequency statistics).
- Absolute values for all immunocompetence parameters were tabulated by visit (summary statistics).
- Relative changes from Screening (Relative change: value after Screening / value at Screening) for all immunocompetence parameters were tabulated by visit (summary statistics).
- Absolute changes from Screening (Absolute change: value after Screening – value at Screening) for all immunocompetence parameters were tabulated by visit (summary statistics).

*Listings of immunocompetence parameters*

The following listings were provided for all patients:

- A data listing was provided for all immunocompetence parameters (including unit of study site as well as standard unit) as well as the imputed values (flagged).
- A data listing was prepared for all immunocompetence parameters outside normal range.

#### 9.7.1.4 SF-12 Questionnaire

For Austrian sites only, a table whether the patient has filled in the SF-12 questionnaire (yes/no) was provided per visit (frequency statistics), separately for NHL-13 (W9, W25, W41) and NHL-13 A (W17, W33, W49, W65, W81).

A data listing of these data was provided, separately for NHL-13 and NHL-13 A.

#### 9.7.1.5 Survival analysis

Additionally to the definitions in Sections 11.3.1.1.1, 11.3.1.1.2 and 11.3.1.1.3 the event dates were defined as follows:

- Case 1: The first occurrence of one of the events (defined in 11.3.1.1.1, 11.3.1.1.2 and 11.3.1.1.3) was defined as follows: the earliest date of the documentation of one of these events was used – either from the documentation of the visits (treatment/observation period or follow-up period, eCRF "Is the patient still event-free") or from the End of study documentation (Relapse (Date of first diagnosis), Survival status (Date of death), Other anticancer treatment started (Start date), Secondary malignancy diagnosed (Date of first diagnosis), Unacceptable toxicity (Date)).

The event death as event only if from NHL was defined as the death cause "Relapse".

- Case 2: The date of last visit during the study where it was confirmed that no events (defined in 11.3.1.1.1, 11.3.1.1.2 and 11.3.1.1.3) had occurred were defined as follows: the latest date of the documentation where it was confirmed that no events had occurred were used – either from the documentation of the visits (treatment/observation period or follow-up period, eCRF "Is the patient still event-free") or from the End of study documentation (eCRF Relapse "date of last evaluation" or Survival Status "date of last observation").

- Rules for incomplete dates:
  - If the day was missing, but the month and the year were available, the day 1 of the available month was imputed if this date was after the date of randomization otherwise the date of randomization was used.

- If the day and the month were missing and the year was available, the 01 of January of the available year was imputed if this date was after the date of randomization otherwise the date of randomization was used.
- If the year was missing, the date of randomization was used.

The following parameters were statistically analysed as planned in the SAP:

- *Event-free survival (EFS) (primary endpoint)*
- *Progression-free survival (PFS)*
- *Overall survival (OS)*
- *Survival Status*
- *Diagnostics data / End of study*

### 9.7.1.6 Safety Analysis

The analyses of all safety parameters were presented for the Safety Population stratified by treatment arm and stratified by Amendment 1 status (all patients, pre-Amendment 1, post-Amendment 1), if not stated otherwise.

#### 9.7.1.6.1 Extent of Exposure

The analyses in this section were generally presented for the Safety Population stratified by treatment arm.

- *Observation time*

The observation time (in days) was calculated as follows:

– date of last observation – date of informed consent + 1

The observation time was analyzed descriptively (summary statistics). The date of last observation was the latest available date – either from the documentation of the visits (treatment/observation period or follow-up period) or from the End of study documentation.

- *Exposure to study medication / days in observation period*

The exposure to study medication (in days) / days in observation period was calculated as follows:

– date of last Treatment/Observation visit – date of W1 + 1

The exposure to study medication / days in observation period was analyzed descriptively (summary statistics).

A data listing including the observation time and the exposure to study medication as well as days in observation period was provided for all patients.

- *Rituximab infusion – for patients receiving Rituximab only*

The following tables were provided by visit.

- A table of the premedication was provided whether pain-reliever have been taken (yes/no). The same was done for antihistamine (frequency statistics).
- The Rituximab dose was tabulated (mg and mg calculated, summary statistics).
- The volume of the infusion (in ml) as well as the duration (in min) was tabulated (summary statistics).
- A table was provided presenting the information whether or not the infusion was rapid (for NHL-13 A only, frequency statistics).
- A table whether any problems or side effects have been noted during infusion (yes/no) was provided (frequency statistics).

Furthermore the following tables were presented (not by visit):

- The overall number of treatment cycles received was tabulated (frequency statistics)
- Data listings containing the Rituximab infusion details were provided for all patients

#### 9.7.1.6.2 Adverse Events

Adverse events were coded according to MedDRA (Version 13.1). Intensity grading was performed either by CTC (grade 1, 2, 3 and 4) or by clinical grading (mild, moderate, severe, life-threatening). For the analysis tables severe and life-threatening AEs were considered as AEs with grade 3 or 4, respectively. AEs with a causal relationship to study drug (probable, possible or missing) were counted as related. If classification of intensity, seriousness or causality was missing for an Adverse Event, the worst case (intensity: grade 4; seriousness: yes; causality: probable) was assumed.

Only AEs were tabulated that started on or after randomization (post-randomization AEs); an AE was considered as post-randomization AE if, and only if, the first onset or worsening was simultaneous with or after the date of randomization. AEs for which it cannot be clearly concluded that the start date was on or after the date of randomization were considered as post-randomization AEs, thus, following a worst case approach:

- If the start date was completely missing, the AE was considered as post-randomization AE.
- If only the year of the AE was available and the year was less than the year of the date of randomization, the AE was considered as AE that started prior to randomization; otherwise it was considered as post-randomization AE.
- If the year and the month of the AE were available and the year was less than the year of the date of randomization or the year of the AE was equal to the year of the date of randomization and the month of the AE was less than the month of the date of randomization, the AE was considered as AE that started prior to randomization; otherwise it was considered as post-randomization AE.

The number and proportion of patients experiencing

- at least one post-randomization AE
- at least one post-randomization AE with grade 3 or 4
- at least one related post-randomization AE
- at least one related post-randomization AE with grade 3 or 4
- at least one post-randomization AE leading to dose adjustment / interruption or discontinuation (i.e. Action taken "study drug dosage adjusted/temporarily interrupted" or "study drug permanently discontinued due to this AE")
- at least one serious post-randomization AE

were tabulated overall and grouped by primary SOC and Preferred Term (frequency statistics, including exact 95% confidence intervals) stratified by Amendment 1 status (all patients, pre-Amendment 1, post-Amendment 1).

Listings of

- all post-randomization AEs (including outcome of the Adverse Event)
- all post-randomization AEs with grade 3 or 4
- all related post-randomization AEs
- all related post-randomization AEs with grade 3 or 4

- all post-randomization AEs leading to dose adjustment / interruption or discontinuation (i.e. Action taken "study drug dosage adjusted/temporarily interrupted" or "study drug permanently discontinued due to this AE")
- all serious post-randomization AEs (including type of SAE)
- all AEs prior randomization

were provided for all patients.

#### 9.7.1.6.3 NHL diagnostics during study

The following tables were prepared:

• The results of the CT (affection yes/no) were analyzed descriptively (frequency statistics) by visit stratified by Amendment 1 status:

- NHL-13: W9, W17, W25, W33, End of Treatment/Observation Visit, M3 - M60
- NHL-13 A: W17, W33, W49, W65, W81, End of Treatment/Observation Visit, M6, M12, M18, M24

Data listings of the results of the NHL diagnostics were also listed (CT, Endoscopy, Bone marrow, Molecular biology, ECG) separately for NHL-13 and NHL-13 A.

#### 9.7.1.6.4 Infection

The following tables were prepared stratified by Amendment 1 status:

- The result whether an infection was observed since last visit (yes/no) was analyzed descriptively by visit (all follow-up visits and End of Study documentation, frequency statistics).
- In case of an infection, the CTC grading (1, 2, 3 or 4) was tabulated.
- The number and proportion of patients with at least one infection and the total number of documented infections were tabulated (frequency statistics). The same was done for CTC grading 3 and 4 (a missing grading was handled as grading 4 for this table).

A data listing was provided where the infection, the grading and the description (in case of grade 3 and 4) was provided for all patients.

#### 9.7.1.6.5 Physical Examination

A data listing of the data of the physical examination was provided for all patients (including the visit, date of examination, changes in physical examination).

Data listings were provided showing the pregnancy test results of the treatment/observation period (results of section physical examination) as well as End of Treatment/Observation Visit (if available) for female patients only, separately for NHL-13 and NHL-13 A.

#### 9.7.1.6.6 Laboratory values

##### *9.7.1.6.6.1 Hematology and chemistry laboratory*

According to study flowchart, hematology and chemistry were investigated at each visit. As agreed with the sponsor, only for the following visits the data has been entered into the eCRF.

Hematology:

- Pre-amendment 1/NHL-13: Screening, Visit W9, W25, W41, End of Treatment/Observation Visit, M6, M12, M18, M24
- Post-amendment 1: Screening, Visit W17, W33, W49, W65, W81, RA, M6, M12, M18, M24

Chemistry:

- Pre-amendment 1/NHL-13: Screening and End of Treatment/Observation Visit
- Post-amendment 1: Screening and End of Treatment/Observation Visit (RA)

Hematology and chemistry parameters were converted to the standard units provided in the Table 6 below:

**Table 6: Listing of used standard-units**

| Type | Parameter | Unit |
|---|---|---|
| Clinical Chemistry | Albumin | G/L |
| Clinical Chemistry | Alk. phosphatase | U/L |
| Clinical Chemistry | Beta-2-Microglobulin | MG/L |
| Clinical Chemistry | Creatinine | µMOL/L |
| Clinical Chemistry | Fasting blood glucose | MMOL/L |
| Clinical Chemistry | Gamma-GT | U/L |
| Clinical Chemistry | GOT (AST) | U/L |
| Clinical Chemistry | GPT (ALT) | U/L |
| Clinical Chemistry | LDH | U/L |
| Clinical Chemistry | Potassium | MMOL/L |
| Clinical Chemistry | Sodium | MMOL/L |
| Clinical Chemistry | Total bilirubin | µMOL/L |
| Clinical Chemistry | Total protein | G/L |
| Clinical Chemistry | Uric acid | µMOL/L |
| Hematology | Bands (stab cells) absolute | G/L |
| Hematology | Bands (stab cells) relative | % |
| Hematology | Basophils absolute | G/L |
| Hematology | Basophils relative | % |
| Hematology | Eosinophils absolute | G/L |
| Hematology | Eosinophils relative | % |
| Hematology | Hemoglobin | G/L |
| Hematology | Lymphocytes absolute | G/L |
| Hematology | Lymphocytes relative | % |
| Hematology | Monocytes absolute | G/L |
| Hematology | Monocytes relative | % |
| Hematology | Neutrophils (segmented+bands) absolute | G/L |
| Hematology | Neutrophils (segmented+bands) relative | % |

| Type | Parameter | Unit |
|---|---|---|
| Hematology | Platelets | G/L |
| Hematology | White blood cells (total) | G/L |

All laboratory parameters were presented in these standard units in all tables. For conversion from study site specific units in these standard units, the conversion factors and coefficients specified in statistical analysis plan were (provided in Section 16.1.9) used.

**Tables of hematology and chemistry laboratory values**

The following tables were provided stratified by Amendment 1 status. No values were imputed.

- Separate tables were provided for hematology and chemistry parameters.
- The number of available samples as documented in the eCRF (item "Date of sample drawn" was available) was tabulated separately by visit (frequency statistics).
- Absolute values for all laboratory parameters (hematology and chemistry) were tabulated by visit (summary statistics).
- Relative changes from Screening (difference: value after Screening / value at Screening) for all laboratory parameters (hematology and chemistry) were tabulated by visit (summary statistics).
- Absolute changes from Screening (difference: value after Screening – value at Screening) for all laboratory parameters (hematology and chemistry) were tabulated by visit (summary statistics).

**Tables of hematology laboratory values at end of treatment/observation period**

The following tables were provided stratified by Amendment 1 status for the end of treatment/observation period. This is the combination of the End of Treatment/Observation Visit (pre-Amendment 1/NHL-13) and End of Treatment/Observation Visit (RA, post-Amendment 1) on imputed values according to LOCF (see SAP, Chapter 2.5).

- Absolute values for all hematology laboratory parameters for Screening and at End of Treatment/Observation Visit were tabulated (summary statistics).
- Relative changes and absolute changes from Screening for all hematology laboratory parameters were tabulated (summary statistics).

**Listings of hematology and chemistry laboratory values**

The following listings were provided for all patients:

- Separate listings were provided for hematology and chemistry parameters including the imputed values (flagged).
- Data listings were prepared for all laboratory parameters outside normal range. In these listings the values were presented in the units in which they have been determined and in the standard units provided above as well as the casual relationship (if applicable, Basic disease, Adverse event, Concomitant disease, Concomitant medication, Laboratory error and No explanation).

Furthermore, the following listings were provided for NHL-13 patients:

- A data listing for the parameters Platelets, White blood cells (total) and Neutrophils (segmented+bands) relative were provided including the details whether "due to bone marrow involvement" was ticked.
- A data listing for the parameters Bilirubin, Alk. Phospatase, GOT (AST) and GPT (ALT) was provided for including the details whether "due to bone liver involvement" was ticked.

#### *9.7.1.6.6.2 Viral tests (HIV, HBV and HCV)*

A table was provided containing HIV/HBV/HCV test results (positive/negative) per visit, separately for NHL-13 (Screening) and NHL-13 A (Screening and End of Treatment/Observation Visit) (frequency statistics).

#### 9.7.1.6.7 Deaths, Serious Adverse Events and Other Significant Adverse Events

Deaths and other SAEs were listed by subject.

### 9.7.2 Determination of Sample Size

The sample size calculation was targeted on the primary comparison of interest – event-free survival. Based on previous results, the difference in median EFS with Rituximab monotherapy vs. observation was estimated with 74.6 months (Arm A) vs. 46.6 months (Arm B). Assuming exponential distribution of survival time and a recruitment ratio of 1:1 for patients, a total of 148 events would be necessary to achieve 80% power with a two-sided test and significance level of 5% (East Version 3.0, Cytel Software Cooperation). 600 patients (300 per arm) with large B-cell NHL or follicular NHL Grade 3b should be recruited with a planned recruitment period of 2 years and a minimum follow-up of 2 years.

## 9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

### 9.8.1 Changes in the Conduct of the Study

There were three amendments to the original protocol (Final Version dated 23-Mar-2004). Amendment 1 was incorporated in the study protocol Final Version dated 09-Jan-2006 and Amendment 2 was incorporated in the study protocol Final Version dated 23-Mar-2007. Amendment 3 was incorporated in the study protocol Final Version dated 01-Jul-2008.

**Amendment 1** included the following changes:

- International participation: from Amendment 1 on the study was not limited to Austrian sites any more, but was also opened for foreign countries in order to be able to recruit more subjects.
- Sponsor change: As it was deemed inappropriate for Roche Austria to handle requests and logistics from outside Austria, the AGMT now served as the overall sponsor of the study.
- Change in duration of maintenance: After evaluation of relapse patterns in Diffuse large B cell Lymphoma (DLBCL) it was considered appropriate to prolong the maintenance scheme to two years with one infusion every 8 weeks (total 12 infusions). Furthermore, emerging data from various Rituximab maintenance studies suggest that no additional significant safety hazards exist with a two-year maintenance period. Patients treated under the original protocol needed to be re-consented to continue with maintenance treatment for a total of two years.
- Change in number of CT scans: The number of CT-Scans was considered too many in a study population where the majority of patients were cured by successful induction treatment; therefore the number of required CT-Scans was reduced from 20 to 10.
- Publication policy: Was from then on included as a separate paragraph

**Amendment 2** included the following changes:

- two changes in inclusion/exclusion criterias
- one change in a misleading formulation
- two changes in possible application of Rituximab: diverse concentration changes and the possibility to execute a more rapid infusion

- Several administrative changes to ensure consistency throughout the protocol have been done.

**Amendment 3** included the following changes:

- Increase of sample size: Since actual recruitment rates were higher than it had been expected at the time of Amendment 2, the total sample size was increased in order to reduce the total study duration from 5.5 to 4 years.
- activity parameters: death from any cause corrected to death from NHL

### 9.8.2 Changes to the Planned Analyses

No changes to the SAP were performed. A total of 19 post-hoc analyses were performed. The results are also described in this report:

- Post-hoc analysis 1 (is a baseline post-hoc analysis)
- Post-hoc analysis 2 (is an efficacy post-hoc analysis)
- Post-hoc analysis 3 (is a baseline, efficacy and safety post-hoc analysis)
- Post-hoc analysis 4 (is a baseline, efficacy and safety post-hoc analysis)
- Post-hoc analysis 5 (is an efficacy post-hoc analysis)
- Post-hoc analysis 6 (is an efficacy post-hoc analysis)
- Post-hoc analysis 7 (is an efficacy post-hoc analysis)
- Post-hoc analysis 8 (is an efficacy post-hoc analysis)
- Post-hoc analysis 9 (is an efficacy post-hoc analysis)
- Post-hoc analysis 10 (is an efficacy post-hoc analysis)
- Post-hoc analysis 11 (is an efficacy post-hoc analysis)
- Post-hoc analysis 12 (is an efficacy post-hoc analysis)
- Post-hoc analysis 13 (is an efficacy post-hoc analysis)
- Post-hoc analysis 14 (is a safety post-hoc analysis)
- Post-hoc analysis 15 (is an efficacy post-hoc analysis)
- Post-hoc analysis 16 (is an efficacy post-hoc analysis)
- Post-hoc analysis 17 (is an efficacy post-hoc analysis)
- Post-hoc analysis 18 (is an efficacy post-hoc analysis)
- Post-hoc analysis 19 (is an efficacy post-hoc analysis)

Baseline post-hoc analyses are presented in Section 11.2.6, efficacy post-hoc analyses are presented in Section 11.3.1.4 and safety post-hoc analyses are presented in Section 12.8.

# 10. STUDY PATIENTS

## 10.1 DISPOSITION OF PATIENTS

683 patients were randomized into Arm A (338 patients) and Arm B (345 patients), respectively. Another 58 patients signed their informed consents, however, were not randomized (screening failures) (Table 7 and Section 14, Table 1.1.1). A table of reasons for screening failures can be obtained from Section 14, Table 1.1.2. A by-patient listing of screening failures can be obtained from Section 16, Listing 1.2.

**Table 7: Number of randomized patients by treatment arm (all patients)**

| | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=345) No. (%) | NOT RANDOMIZED (N=58) No. (%) | Total (N=741) No. (%) |
|---|---|---|---|---|
| Randomized | | | | |
| yes | 338 (100) | 345 (100) | 0 (0.0) | 683 (92.2) |
| no | 0 (0.0) | 0 (0.0) | 58 (100) | 58 (7.8) |
| Total | 338 | 345 | 58 | 741 |
| Percentages are based on the number of non-missing observations (Total) | | | | |

Section 14, Table 1.1.5 shows the number and percentage of patients attending a visit. Treatment/Observation visits W49-W89 could only be attended by subjects under Amendment 1. Follow-up visits M27-M60 could also only be attended by subjects under Amendment 1. All these visits are listed in Section 16, Listings 1.5 (Treatment/observation visits - incl. Screening) and 1.6 (Follow-up visits).

Table 8 and Section 14, Table 1.1.6 show the number and percentage of patients not completing the treatment/observation phase. 21.3% of patients in Arm A and 22.3% of patients in Arm B terminated the treatment/observation phase prematurely. The most common reason for early termination was "Event (relapse/death/therapy/malignancy/toxicity)", 58.3% of all discontinuations in group A and 58.4% of all discontinuations in group B.

**Table 8: Premature study treatment/observation period discontinuation by treatment arm (ITT Population)**

| | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=345) No. (%) |
|---|---|---|
| Treatment completed | | |
| yes | 266 (78.7) | 268 (77.7) |
| no | 72 (21.3) | 77 (22.3) |
| Total | 338 | 345 |
| Percentages are based on the number of non-missing observations (Total) | | |

A listing of patients who discontinued the treatment/observation phase prematurely can be obtained from Section 16, Listing 1.3.

Section 14, Table 1.1.7 shows the number and percentage of patients not completing the follow-up phase. 37.2% of patients in Arm A and 45.7% of patients in Arm B terminated the follow-up phase prematurely. The reasons for early Follow-up termination can be obtained from Table 9.

**Table 9: Reason for Follow-up not completed by treatment arm (ITT Population)**

| | A: RITUXIMAB (N=110) No. (%) | B: OBSERVATION (N=137) No. (%) |
|---|---|---|
| Reason for Follow-up not completed | | |
| Patient withdrew consent | 16 (14.5) | 17 (12.4) |
| Protocol violation | 7 (6.4) | 11 (8.0) |
| Event (relapse/death/therapy/malignancy/toxicity) | 19 (17.3) | 32 (23.4) |
| Other | 68 (61.8) | 77 (56.2) |
| Total | 110 | 137 |
| Percentages are based on the number of non-missing observations (Total) | | |

A listing of patients who discontinued the Follow-up phase prematurely can be obtained from Section 16, Listing 1.4.

## 10.2 PROTOCOL DEVIATIONS

All protocol deviations are tabulated in Section 14, Table 1.1.4 for the Safety as well as for the ITT population. This table was also stratified by severity.

Listings of minor as well as of all major protocol deviations are available in the data review meeting report (Final 1.0, 08-Mar-2013) which is provided in Section 16.1.9. The answers to the check of inclusion/exclusion criteria within the eCRF can be obtained from Section 16, Listings 1.7-10.

In the following only major protocol deviations observed in the ITT population are described.

Overall, 17 (2.5%) of the 683 subjects in the ITT Population had at least one major protocol deviation.

**Table 10: Major Protocol Deviations (ITT population)**

| | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=345) No. (%) | Total (N=683) No. (%) |
|---|---|---|---|
| Subjects with at least one major PD | 8 (2.4) | 9 (2.6) | 17 (2.5) |
| Total number of major PDs | 9 | 11 | 20 |
| Percentages are based on N | | | |

One subject was randomized, but is not part of the Safety population: This subject is 00705/003 (Arm B). The subjects with at least one major protocol deviation were the following:

- 45544/007

- 00102/001
- 00102/008
- 00102/012
- 00103/004
- 00105/001
- 00108/002
- 00123/002
- 00130/001
- 00601/002
- 00601/005
- 00705/003
- 01401/005
- 02104/003
- 02404/005
- 02407/003
- 02802/002

# 11. EFFICACY EVALUATION

## 11.1 DATA SETS ANALYZED

For the statistical analysis, two analysis populations were used. These were the ITT population and the Safety population. No per-protocol analysis population was used for the analysis since less then 10% had major protocol deviations (details can be obtained from the data review meeting report which is available in Section 16.1.9).

The 683 subjects who were randomized to either Arm A or Arm B were included into the ITT population. One subject with no post baseline safety assessment was excluded from the Safety population. Therefore, 682 patients were included in the Safety population (details can be obtained from the data review meeting report which is available in Section 16.1.9).

Analysis population details can be obtained from Section 16, Listing 1.1.

Wherever possible, the analysis was performed three times: Once for all patients (pre- and post-Amendment 1), once for all patients included prior Amendment 1 (pre-Amendment 1) and once for all patients included after Amendment 1 (post-Amendment 1). An overview is available in the following tables.

**Table 11: ITT Population**

| | Arm A<br>N = 338 | Arm B<br>N = 345 | All treated<br>N = 683 |
|---|---|---|---|
| **Number of Subjects:** | n | n | n |
| All Patients | 338 | 345 | 683 |
| Pre-Amendment 1 Population | 30 | 39 | 69 |
| Post-Amendment 1 Population | 308 | 306 | 614 |

**Table 12: Safety Population**

| | Arm A<br>N = 338 | Arm B<br>N = 344 | All treated<br>N = 682 |
|---|---|---|---|
| **Number of Subjects:** | n | n | n |
| All Patients | 338 | 344 | 682 |
| Pre-Amendment 1 Population | 30 | 39 | 69 |
| Post-Amendment 1 Population | 308 | 305 | 613 |

## 11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

A summary of demographic characteristics is presented in Table 13 for the ITT Population (Section 14, Tables 1.1.8-13 and 1.1.17).

**Table 13: Patient Demographics by treatment arm (ITT population)**

| Characteristic | Statistic | Arm A N = 338 | Arm B N = 345 |
|---|---|---|---|
| Gender n (%) | Female | 175 (51.8) | 163 (47.2) |
| | Male | 163 (48.2) | 182 (52.8) |
| Age [Years] | Mean (SD) | 54.8 (14.1) | 55.8 (14.7) |
| | Median | 57.0 | 58.0 |
| | Min / Max | 19.0 / 87.0 | 19.0 / 88.0 |
| Body height [cm] | Mean (SD) | 167.9 (10.0) | 168.7 (10.2) |
| | Median | 168.0 | 168.0 |
| | Min / Max | 140.0 / 194.0 | 143.0 / 196.0 |
| Body weight [kg] | Mean (SD) | 74.4 (16.2) | 74.7 (15.8) |
| | Median | 74.0 | 73.0 |
| | Min / Max | 40.0 / 135.0 | 41.0 / 125.0 |
| Body Mass Index [kg/m²] | Mean (SD) | 26.3 (4.6) | 26.1 (4.5) |
| | Median | 25.9 | 25.6 |
| | Min / Max | 15.2 / 43.4 | 17.0 / 39.5 |
| Body surface area [m², calculation according to Dubois] | Mean (SD) | 1.83 (0.23) | 1.84 (0.22) |
| | Median | 1.83 | 1.82 |
| | Min / Max | 1.30 / 2.62 | 1.28 / 2.57 |
| ECG findings (normal/abnormal) n (%) | normal | 290 (85.8) | 287 (83.4) |
| | abnormal | 48 (14.2) | 57 (16.6) |

A by-subject listing of these characteristics is provided in Section 16, Listing 1.11

In Arm A there were more female patients and in arm B there were more male patients. This and all other patient demographic characteristics were similar in both groups. Tabulations of Karnofsky performance status as well as of ECOG performance status (one of both had to be documented) are available in Table 14 and Table 15 (i.e. Section 14, Table 1.1.14). Evaluations of women`s childbearing potential and contraception are available in Table 16 (i.e. Section 14, Table 1.1.15), while tabulations of the SF-12 questionnaire can be found in Table 17 (i.e. Section 14, Table 1.1.16).

**Table 14: Karnofsky performance status per treatment Arm (ITT population)**

| | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=345) No. (%) |
|---|---|---|
| Karnofsky performance status [%] | | |
| 100 | 88 (68.2) | 102 (77.9) |

| | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=345) No. (%) |
|---|---|---|
| 90 | 35 (27.1) | 22 (16.8) |
| 80 | 3 (2.3) | 5 (3.8) |
| 70 | 2 (1.6) | 0 (0.0) |
| 60 | 0 (0.0) | 1 (0.8) |
| 50 | 1 (0.8) | 1 (0.8) |
| 40 | 0 (0.0) | 0 (0.0) |
| 30 | 0 (0.0) | 0 (0.0) |
| 20 | 0 (0.0) | 0 (0.0) |
| 10 | 0 (0.0) | 0 (0.0) |
| Total | 129 | 131 |
| Percentages are based on the number of non-missing observations (Total) | | |

**Table 15: ECOG performance status per treatment Arm (ITT population)**

| | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=345) No. (%) |
|---|---|---|
| ECOG performance status | | |
| 0 | 159 (76.1) | 156 (72.9) |
| 1 | 48 (23.0) | 52 (24.3) |
| 2 | 2 (1.0) | 6 (2.8) |
| 3 | 0 (0.0) | 0 (0.0) |
| 4 | 0 (0.0) | 0 (0.0) |
| Total | 209 | 214 |
| Percentages are based on the number of non-missing observations (Total) | | |

A by-subject listing containing the Karnofsky and the ECOG performance status is provided in Section 16, Listing 1.11.

**Table 16: Childbearing potential and contraception per treatment arm (ITT population)**

| | | Arm A | Arm B |
|---|---|---|---|

| Characteristic | Statistic | N = 175 | N = 163 |
|---|---|---|---|
| For female patients only: childbearing potential (yes/no), n(%) | yes | 48 (27.4) | 36 (22.1) |
| | no | 127 (72.6) | 127 (77.9) |
| If childbearing potential: effective contraception for the entire treatment period (yes/no), n(%) | yes | 48 (100) | 36 (100) |
| | no | 0 (0.0) | 0 (0.0) |

A by-subject listing of these characteristics is provided in Section 16, Listing 1.12

**Table 17: SF-12 questionnaire completed per treatment Arm (ITT population)**

| | | A: RITUXIMAB (N=93) No. (%) | B: OBSERVATION (N=103) No. (%) |
|---|---|---|---|
| For Austrian sites only: SF-12 questionnaire completed | yes | 85 (91.4) | 99 (96.1) |
| | no | 8 ( 8.6) | 4 ( 3.9) |
| | Total | 93 | 103 |
| Percentages are based on the number of non-missing observations (Total) | | | |

A by-subject listing of these characteristics is provided in Section 16, Listing 1.13

### 11.2.1 Current Concomitant Disease

For 68.3% of patients in group A at least one concomitant disease was documented. For group B, for 66.7% at least one concomitant disease was documented (Section 14, Table 1.1.18). Section 14, Table 1.1.19 contains the number and percentage of subjects with at least one concomitant disease by system organ class (SOC) and preferred term. Table 18 shows the results by system organ class.

**Table 18: Number of patients with at least one concomitant disease by SOC and treatment arm (ITT Population)**

| System Organ Class (MedDRA 13.1) | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=345) No. (%) |
|---|---|---|
| Vascular disorders | 125 (37.0) | 122 (35.4) |
| Metabolism and nutrition disorders | 89 (26.3) | 74 (21.4) |
| Gastrointestinal disorders | 41 (12.1) | 41 (11.9) |
| Nervous system disorders | 34 (10.1) | 41 (11.9) |
| Musculoskeletal and connective tissue disorders | 36 (10.7) | 34 ( 9.9) |

| System Organ Class (MedDRA 13.1) | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=345) No. (%) |
|---|---|---|
| Cardiac disorders | 24 (7.1) | 37 (10.7) |
| Endocrine disorders | 29 (8.6) | 28 (8.1) |
| Infections and infestations | 25 (7.4) | 24 (7.0) |
| Respiratory, thoracic and mediastinal disorders | 27 (8.0) | 17 (4.9) |
| Psychiatric disorders | 18 (5.3) | 22 (6.4) |
| Congenital, familial and genetic disorders | 18 (5.3) | 20 (5.8) |
| Reproductive system and breast disorders | 15 (4.4) | 18 (5.2) |
| Renal and urinary disorders | 11 (3.3) | 16 (4.6) |
| Hepatobiliary disorders | 10 (3.0) | 16 (4.6) |
| Blood and lymphatic system disorders | 12 (3.6) | 10 (2.9) |
| Neoplasms benign, malignant and unspecified (incl. cysts and polyps) | 10 (3.0) | 12 (3.5) |
| General disorders and administration site conditions | 4 (1.2) | 13 (3.8) |
| Immune system disorders | 8 (2.4) | 7 (2.0) |
| Skin and subcutaneous tissue disorders | 12 (3.6) | 3 (0.9) |
| Eye disorders | 6 (1.8) | 8 (2.3) |
| Injury, poisoning and procedural complications | 3 (0.9) | 5 (1.4) |
| Ear and labyrinth disorders | 3 (0.9) | 4 (1.2) |
| Investigations | 3 (0.9) | 3 (0.9) |
| Surgical and medical procedures | 3 (0.9) | 3 (0.9) |
| Social circumstances | 0 (0.0) | 2 (0.6) |
| Subjects are counted only once per System Organ Class (MedDRA 13.1), percentages are based on N | | |

The most common concomitant diseases are found in the system organ classes “Vascular disorders” (37.0% of patients in Arm A vs. 35.4% of patients in Arm B) and “Metabolism and nutrition disorders” (26.3% of patients in Arm A vs. 21.4% of patients in Arm B). All other concomitant diseases were documented for less than 20% of patients within each group.

A by-subject listing of all current concomitant diseases is provided in Section 16, Listing 1.14.

### 11.2.2 Current Concomitant Treatment / Concomitant Medication

For 77.8% of patients in group A at least one concomitant treatment/medication was documented. For group B, for 76.2% at least one concomitant treatment/medication was documented (Section 14, Table 1.1.20). Section 14, Table 1.1.21 and Table 19 contain the number and percentage of subjects with at least one concomitant treatment/medication by ATC level 2.

**Table 19: Number of patients with at least one concomitant treatment/medication by ATC level 2 and treatment arm (ITT Population)**

| ATC level 2 (WHODD Q210) | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=345) No. (%) |
|---|---|---|
| Antibacterials for systemic use | 104 (30.8) | 81 (23.5) |
| Drugs for acid related disorders | 82 (24.3) | 92 (26.7) |
| Agents acting on the renin-angiotensin system | 84 (24.9) | 80 (23.2) |
| Antithrombotic agents | 57 (16.9) | 64 (18.6) |
| Analgesics | 63 (18.6) | 49 (14.2) |
| Diuretics | 42 (12.4) | 58 (16.8) |
| Beta blocking agents | 46 (13.6) | 53 (15.4) |
| Lipid modifying agents | 45 (13.3) | 49 (14.2) |
| Antiinflammatory and antirheumatic products | 42 (12.4) | 46 (13.3) |
| Vitamins | 36 (10.7) | 38 (11.0) |
| Calcium channel blockers | 39 (11.5) | 32 (9.3) |
| Antivirals for systemic use | 37 (10.9) | 24 (7.0) |
| Psycholeptics | 32 (9.5) | 26 (7.5) |
| Drugs used in diabetes | 32 (9.5) | 24 (7.0) |
| Mineral supplements | 29 (8.6) | 27 (7.8) |
| Antihistamines for systemic use | 38 (11.2) | 17 (4.9) |
| Corticosteroids for systemic use | 36 (10.7) | 18 (5.2) |
| Antigout preparations | 23 (6.8) | 29 (8.4) |
| Psychoanaleptics | 26 (7.7) | 25 (7.2) |
| Cough and cold preparations | 31 (9.2) | 19 (5.5) |
| Antianemic preparations | 18 (5.3) | 27 (7.8) |
| Thyroid therapy | 22 (6.5) | 22 (6.4) |
| Cardiac therapy | 14 (4.1) | 22 (6.4) |
| Drugs for obstructive airway diseases | 20 (5.9) | 11 (3.2) |
| Drugs for functional gastrointestinal disorders | 15 (4.4) | 11 (3.2) |
| Ophthalmologicals | 14 (4.1) | 10 (2.9) |
| Urologicals | 9 (2.7) | 15 (4.3) |
| Antiepileptics | 13 (3.8) | 10 (2.9) |
| Unspecified herbal | 12 (3.6) | 11 (3.2) |
| Laxatives | 13 (3.8) | 8 (2.3) |

| ATC level 2 (WHODD Q210) | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=345) No. (%) |
|---|---|---|
| Drugs for treatment of bone diseases | 9 (2.7) | 11 (3.2) |
| Antiinflammatory and antirheumatic agents | 9 (2.7) | 10 (2.9) |
| Vasoprotectives | 10 (3.0) | 9 (2.6) |
| Immunostimulants | 9 (2.7) | 9 (2.6) |
| Corticosteroids, dermatological preparations | 11 (3.3) | 6 (1.7) |
| Nasal preparations | 13 (3.8) | 4 (1.2) |
| Muscle relaxants | 7 (2.1) | 8 (2.3) |
| Throat preparations | 9 (2.7) | 5 (1.4) |
| Antidiarr.,intest. Antiinfl./antiinfect. Agents | 8 (2.4) | 5 (1.4) |
| Antihypertensives | 4 (1.2) | 7 (2.0) |
| Blood substitutes and perfusion solutions | 5 (1.5) | 6 (1.7) |
| Peripheral vasodilators | 7 (2.1) | 4 (1.2) |
| Sex hormones and modulators of the genital system | 7 (2.1) | 4 (1.2) |
| Antimycotics for systemic use | 4 (1.2) | 5 (1.4) |
| Bile and liver therapy | 5 (1.5) | 4 (1.2) |
| Antiemetics and antinauseants | 4 (1.2) | 4 (1.2) |
| Immune sera and immunoglobulins | 5 (1.5) | 3 (0.9) |
| Stomatological preparations | 5 (1.5) | 3 (0.9) |
| Antifungals for dermatological use | 3 (0.9) | 4 (1.2) |
| Digestives, incl. Enzymes | 2 (0.6) | 4 (1.2) |
| Emollients and protectives | 4 (1.2) | 2 (0.6) |
| Topical products for joint and muscular pain | 0 (0.0) | 6 (1.7) |
| Anthelmintics | 4 (1.2) | 1 (0.3) |
| Antimycobacterials | 3 (0.9) | 2 (0.6) |
| Other nervous system drugs | 2 (0.6) | 3 (0.9) |
| Antibiotics and chemother. For dermatological use | 3 (0.9) | 1 (0.3) |
| Antiprotozoals | 2 (0.6) | 2 (0.6) |
| General nutrients | 2 (0.6) | 2 (0.6) |
| Anti-parkinson drugs | 1 (0.3) | 2 (0.6) |
| Antineoplastic agents | 2 (0.6) | 1 (0.3) |
| Other dermatological preparations | 1 (0.3) | 2 (0.6) |
| Other gynecologicals | 3 (0.9) | 0 (0.0) |

| ATC level 2 (WHODD Q210) | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=345) No. (%) |
|---|---|---|
| Vaccines | 2 (0.6) | 1 (0.3) |
| Antihemorrhagics | 1 (0.3) | 1 (0.3) |
| Antiobesity preparations, excl. Diet products | 1 (0.3) | 1 (0.3) |
| Antiseptics and disinfectants | 1 (0.3) | 1 (0.3) |
| Gynecological antiinfectives and antiseptics | 2 (0.6) | 0 (0.0) |
| Immunosuppressants | 1 (0.3) | 1 (0.3) |
| Other hematological agents | 2 (0.6) | 0 (0.0) |
| Otologicals | 1 (0.3) | 1 (0.3) |
| All other therapeutic products | 1 (0.3) | 0 (0.0) |
| Anesthetics | 0 (0.0) | 1 (0.3) |
| Anti-acne preparations | 1 (0.3) | 0 (0.0) |
| Antipruritics,incl antihist,anesthet,etc. | 1 (0.3) | 0 (0.0) |
| Antipsoriatics | 0 (0.0) | 1 (0.3) |
| Calcium homeostasis | 0 (0.0) | 1 (0.3) |
| Endocrine therapy | 0 (0.0) | 1 (0.3) |
| Ophthalmological and otological preparations | 1 (0.3) | 0 (0.0) |
| Subjects are counted only once per ATC level 2 (WHODD Q210), percentages are based on N | | |

The most common medications were “antibacterials for systemic use” (30.8% of patients in Arm A vs. 23.5% of patients in Arm B), “drugs for acid related disorders” (24.3% of patients in Arm A vs. 26.7% of patients in Arm B) and “agents acting on the renin-angiotensin system” (24.9% of patients in Arm A vs. 23.2% of patients in Arm B). All other concomitant diseases were documented for less than 20% of patients within each group.

By-subject listings of current concomitant medications are provided in Section 16, Listings 1.16-1.18.

### 11.2.3 NHL history

A summary of NHL-history data is presented in Table 20 and Table 21 for the ITT Population (Section 14, Tables 1.1.22-33).

**Table 20: NHL-History by treatment arm (ITT Population)**

| Characteristic | Statistic | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=345) No. (%) |
|---|---|---|---|
| Histology proven diagnosis label | Diffuse large B-cell lymphoma (DLBCL) | 329 (97.3) | 333 (96.5) |
| | Follicular NHL grade 3 | 5 (1.5) | 8 (2.3) |
| | Follicular NHL grade 3b | 4 (1.2) | 4 (1.2) |
| Stage at first diagnosis (Ann-Arbor) | 1 | 59 (17.5) | 67 (19.5) |

| Characteristic | Statistic | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=345) No. (%) |
|---|---|---|---|
| | 2 | 110 (32.5) | 116 (33.7) |
| | 3 | 83 (24.6) | 77 (22.4) |
| | 4 | 86 (25.4) | 84 (24.4) |
| Diameter of largest involved lymph node at first diagnosis | <= 5cm | 171 (50.6) | 179 (51.9) |
| | >5 and <= 7 cm | 44 (13.0) | 36 (10.4) |
| | >7 and <= 10 cm | 49 (14.5) | 44 (12.8) |
| | > 10 cm | 33 (9.8) | 44 (12.8) |
| | unknown | 41 (12.1) | 42 (12.2) |
| Number of extranodal sites of involvement at first diagnosis | 0 | 139 (41.1) | 145 (42.0) |
| | 1 | 141 (41.7) | 128 (37.1) |
| | >1 | 58 (17.2) | 72 (20.9) |
| LDH at first diagnosis by treatment arm | normal | 184 (54.4) | 182 (52.8) |
| | above upper limit | 154 (45.6) | 163 (47.2) |
| Performance status at first diagnosis | 0-1 ECOG (70-100% Karnofsky) | 298 (88.2) | 303 (87.8) |
| | 2-4 ECOG (<70% Karnofsky) | 40 (11.8) | 42 (12.2) |
| IPI score and risk arm at first diagnosis | 0 | 67 (19.8) | 69 (20.1) |
| | 1 | 94 (27.8) | 96 (27.9) |
| | 2 | 96 (28.4) | 82 (23.8) |
| | 3 | 59 (17.5) | 67 (19.5) |
| | 4 | 18 (5.3) | 26 (7.6) |
| | 5 | 4 (1.2) | 4 (1.2) |
| Risk group | low | 161 (47.6) | 165 (48.0) |
| | low intermediate | 96 (28.4) | 82 (23.8) |
| | high intermediate | 59 (17.5) | 67 (19.5) |
| | high | 22 (6.5) | 30 (8.7) |
| Bone marrow involvement present before induction therapy | yes, BM involvement | 41 (12.1) | 33 ( 9.6) |
| | no BM involvement | 297 (87.9) | 311 (90.4) |
| Number of Rituximab-infusions (prior therapy) | 5 | 1 (0.3) | 0 (0.0) |
| | 8 | 334 (98.8) | 343 (99.4) |
| | 9 | 2 (0.6) | 2 (0.6) |
| | 10 | 1 (0.3) | 0 (0.0) |
| Number of chemotherapy-cycles | 4 | 7 (2.1) | 8 (2.3) |

| Characteristic | Statistic | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=345) No. (%) |
|---|---|---|---|
| (prior therapy) | 5 | 3 (0.9) | 3 (0.9) |
| | 6 | 139 (41.1) | 150 (43.5) |
| | 7 | 10 (3.0) | 9 (2.6) |
| | 8 | 178 (52.7) | 175 (50.7) |
| | 9 | 1 (0.3) | 0 (0.0) |
| Type of chemotherapy (prior therapy) Note: The options "CHOEP", "iCHOP", "ESHAP", "CNOP", "MACOP-B", "VACOP-B" and "ProMitCytaBOM" are available for post-Amendment 1 eCRF only. In pre-Amendment 1 eCRF, these options are included in the option "other". | CEOP IMVP | 3 (0.9) | 5 (1.4) |
| | CEOP/IMVP | 7 (2.1) | 4 (1.2) |
| | CHOEP | 2 (0.6) | 2 (0.6) |
| | CHOP14 | 41 (12.1) | 39 (11.3) |
| | CHOP21 | 250 (74.0) | 268 (77.7) |
| | CNOP | 1 (0.3) | 0 (0.0) |
| | Other | 32 (9.5) | 27 (7.8) |
| | iCHOP | 2 (0.6) | 0 (0.0) |
| Response status (prior therapy, until 4 weeks prior to trial treatment start) | Complete Response (CR) | 282 (83.4) | 293 (84.9) |
| | Unconfirmed Complete Response (CRu) | 56 (16.6) | 52 (15.1) |
| Percentages are based on the number of non-missing observations (Total) | | | |

**Table 21: NHL subtypes by treatment arm (post-Amendment 1 patients only)**

| | Subtype | A: RITUXIMAB (N=291) No. (%) | B: OBSERVATION (N=289) No. (%) |
|---|---|---|---|
| Subtype if diagnosis is DLBCL | | | |
| | Centroblastic | 65 (22.3) | 58 (20.1) |
| | Immunoblastic | 8 (2.7) | 5 (1.7) |
| | T-cell/histiocyte rich | 11 (3.8) | 14 (4.8) |
| | Anaplastic | 9 (3.1) | 6 (2.1) |
| | Unknown | 198 (68.0) | 206 (71.3) |
| Mediastinal large B-cell lymphoma if diagnosis is DLBCL | | | |
| | yes | 29 (10.0) | 42 (14.5) |
| | no | 230 (79.0) | 222 (76.8) |
| | unknown | 32 (11.0) | 25 (8.7) |

| | Subtype | A: RITUXIMAB (N=291) No. (%) | B: OBSERVATION (N=289) No. (%) |
|---|---|---|---|
| Percentages are based on the number of non-missing observations | | | |

Most of the patients (97.3% in Arm A vs. 96.5% in Arm B) suffered from diffuse large B-cell lymphoma, for the most of these subjects the subtype was not known (68.0% in Arm A vs. 71.3% in Arm B). The centroblastic subtype was the most common if known (22.3% in Arm A vs. 20.1% in Arm B). The ECOG/Karnofsky-performance status was not over 1/under 70% for a major part of the study participants (88.2% in Arm A vs. 87.8% in Arm B). The distribution for risk-group was declining from low (47.6% in Arm A vs. 48.0% in Arm B) to high risk (6.5% in Arm A vs. 8.7% in Arm B). Bone marrow involvement was not common (12.1% in Arm A vs. 9.6% in Arm B).

Most patients had received 8 Rituximab infusions prior study (98.8% in Arm A vs. 99.4% in Arm B) and 6 (41.1% in Arm A vs. 43.5% in Arm B) or 8 (52.7% in Arm A vs. 50.7% in Arm B) chemotherapy cycles, which often consisted of the CHOP21-type (74.0% in Arm A vs. 77.7% in Arm B). 83.4% of patients in Arm A and 84.9% of patients in Arm B had a "Complete response" status at baseline.

A by-subject listing of NHL-History is provided in Section 16, Listings 1.19-20, 1.22 and 1.28

### 11.2.4 NHL-Diagnostics at baseline

Two NHL-diagnostics at baseline are presented in Table 22 for the ITT Population (Section 14, Tables 1.1.34-35).

**Table 22: NHL-Diagnostics at baseline by treatment Arm, (ITT Population)**

| Characteristic | Statistic | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=345) No. (%) |
|---|---|---|---|
| CT findings | yes | 2 (0.6) | 4 (1.2) |
| | no | 336 (99.4) | 341 (98.8) |
| Tumor sample (paraffin blocks) sent in for central review | yes | 38 (40.9) | 35 (34.0) |
| | no | 55 (59.1) | 68 (66.0) |
| Percentages are based on the number of non-missing observations | | | |

CT-findings were available for 0.6% of patients in Arm A vs. 1.2% of patients in Arm B, whereas only 40.9% of patients in Arm A and 34.0% of patients in Arm B had tumor samples sent in for central review.

A by-subject listing of NHL-History is provided in Section 16, Listing 1.19

### 11.2.5 Pregnancy Test

No single pregnancy test result was positive at baseline; see Table 23 below (Section 14, Table 36).

**Table 23: Female subjects only: pregnancy test result at screening by treatment arm, (ITT Population)**

| Characteristic | Statistic | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=345) No. (%) |
|---|---|---|---|
| Pregnancy test result | positive | 0 (0.0) | 0 (0.0) |
| | negative | 48 (100) | 36 (100) |
| Percentages are based on the number of non-missing observations | | | |

A by-subject listing of NHL-History is provided in Section 16, Listing 1.19

### 11.2.6 Baseline Post-hoc analyses

**Post-hoc analysis 1:**

A by-patient listing of several baseline characteristics is available under Section 16, Listing 1:

- Number of rituximab-infusions (prior therapy) by treatment arm
- Extranodal sites of involvement at first diagnosis by treatment arm
- LDH at first diagnosis by treatment arm
- Ann-Arbor Stage at first diagnosis by treatment arm
- Age [years] at screening by treatment arm (≤ or >60)
- Karnofsky/ECOG status at screening by treatment arm
- Diameter of largest involved lymph node at first diagnosis by treatment arm

Corresponding tables can be found under Section 14, Tables 1 - 8.

**Post-hoc analysis 3:**

Section 14, Tables Baseline 1 - 3 show tabulations of the factors Body weight, Body mass index and Body surface area by sex and treatment group.

**Post-hoc analysis 4:**

Post-hoc analysis 4 contains baseline tables (Section 14, Tables 1.1.1 - 1.1.36) for patients with no radiotherapy only.

## 11.3 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENT DATA

A Cox regression with factors treatment group, geographical region, type of induction therapy and number of cycles of induction therapy was applied on different survival endpoints. Furthermore, the factor IPI was added to this model for additional analysis. The geographical regions can be obtained from Table 24. The type of induction therapy can be obtained from Table 25. The number of cycles of induction therapy can be obtained from Table 26.

**Table 24: Geographical regions with region code**

| Geographical region | Region Code | Geographical region | Region Code |
|---|---|---|---|
| Austria | 1 | Czech Republic | 15 |
| Hong Kong | 2 | Croatia | 16 |
| Taiwan | 4 | South Africa | 17 |
| Serbia | 5 | Mexico | 18 |

| Geographical region | Region Code | Geographical region | Region Code |
|---|---|---|---|
| Bosnia and Herzegovina | 6 | Macedonia | 19 |
| Romania | 7 | Slovakia | 20 |
| Estonia | 8 | Thailand | 21 |
| Sweden | 9 | Malaysia | 23 |
| Russia | 10 | Israel | 24 |
| Turkey | 11 | Brazil | 25 |
| Peru | 12 | Australia | 26 |
| Slovenia | 13 | China | 28 |
| Bulgaria | 14 | | |
| Percentages are based on the number of non-missing observations | | | |

**Table 25: Types of induction therapy**

| Type of chemotherapy | Number |
|---|---|
| CHOP14 | 1 |
| CHOP21 | 1 |
| CEOP IMVP | 2 |
| CEOP/IMVP | 2 |
| CHOEP | 3 |
| CNOP | 4 |
| Other | 4 |
| iCHOP | 4 |

**Table 26: Number of cycles of induction therapy**

| Number of cycles | Number |
|---|---|
| 4 | 1 |
| 5 | 1 |
| 6 | 1 |
| 7 | 2 |
| 8 | 2 |
| 9 | 2 |

All analyses described below were performed for the ITT population.

## 11.3.1 Analysis of Efficacy

### 11.3.1.1 Survival Analysis

#### 11.3.1.1.1 Event-free survival (EFS) – primary endpoint

The event-free survival (EFS) was defined as follows:

Case 1:

One of the following events occurred between the date of randomization and the end of study:

1. Progressive disease or relapse (according to[1])
2. Death from any cause
3. Initiation of non-protocol anticancer treatment or concomitant steroids introduced because of lymphoma symptoms or concomitant radiotherapy
4. Secondary malignancy
5. Unacceptable toxicity (e.g. life-threatening or serious disease which was potentially due to the trial treatment; e.g. worsening of the cardiac function with ejection fraction < 50%)

Then the EFS was defined as the difference in days between the date of randomization and the date of the first occurrence of one of the events listed above.

Case 2:

None of the events listed above occurred till the end of study. Then the EFS was defined as the difference in days between the date of randomization and the date of the last visit during the study where it was confirmed that no events listed in Case 1 had occurred.

**Figure 1: Event Free Survival by treatment arm (ITT Population)**

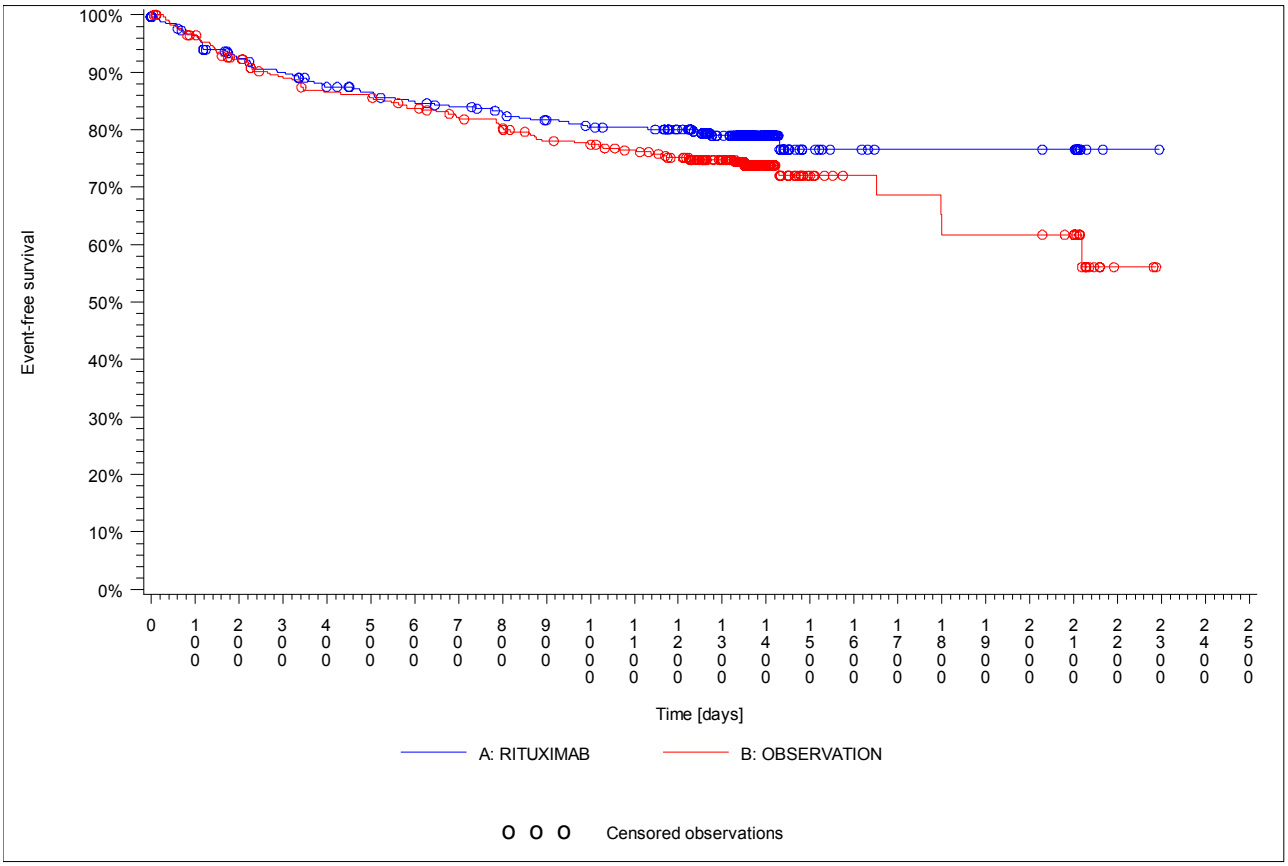


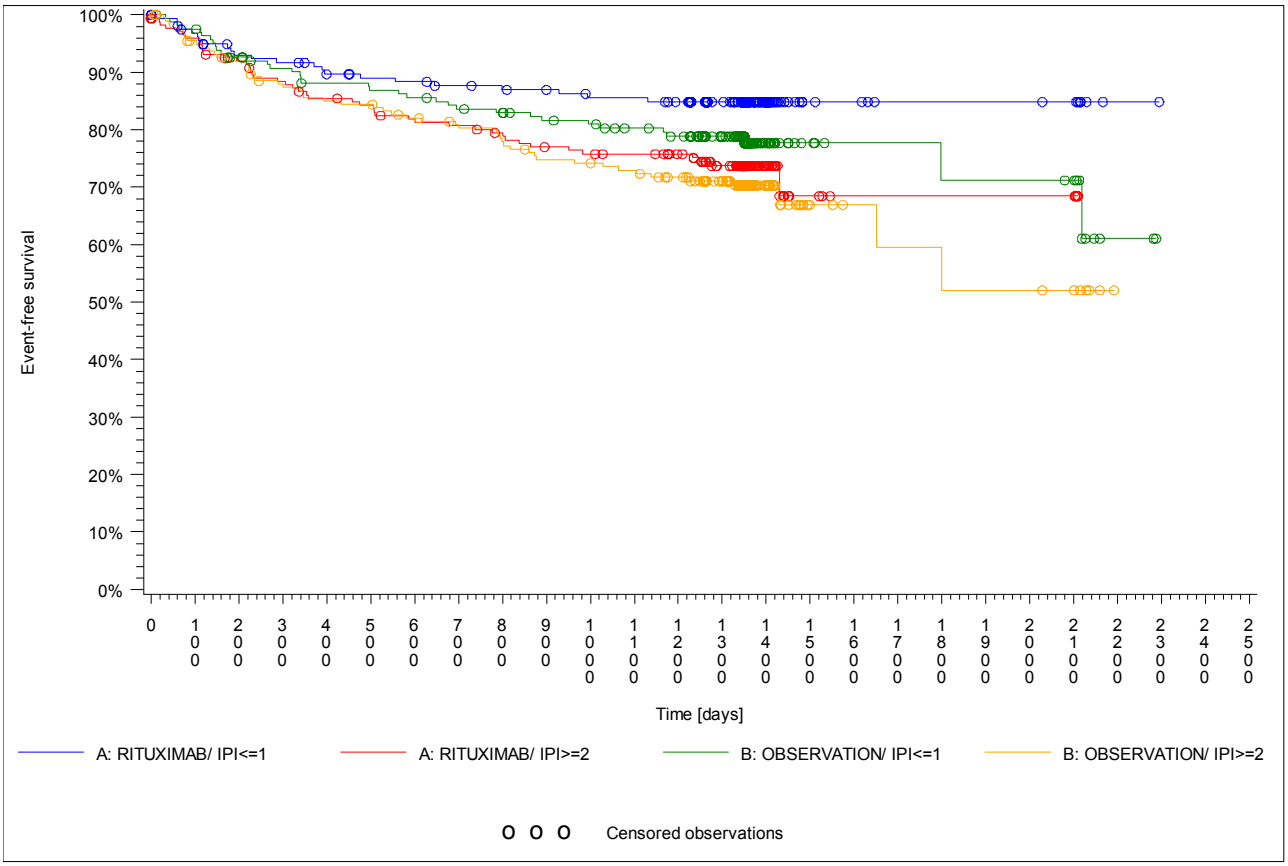

Figure 1 shows a plot of the Kaplan-Meier curve of the Event free survival by treatment arm (Section 14, Figure 1.1). Corresponding figures, also for both sexes, can be found under Section 14, Figures 1.1-3 for all patients and Section 14, Figures 2.1-3 for pre-Amendment 1- and Section 14, Figures 3.1-3 for post-Amendment 1-subjects.

A by-subject listing of event-free survival is provided in Section 16, Listing 2.1.

Section 14, Table 1.2.1 shows the outcome of the Cox regression with factors treatment group, geographical region, type of induction therapy and number of cycles of induction therapy applied on the event-free survival for all patients. The model was not significant (Likelihood ratio p = 0.0670). In Section 14, Table 1.2.2 the same model was applied to female patients only. The model also was not significant (Likelihood ratio p = 0.4638). However, the same model was significant for male patients only (Likelihood ratio p = 0.0002 in Section 14, Table 1.2.3): Differences were seen between treatment groups (A greater hazard is observed in arm B (p=0.0267)) and geographical regions (A greater hazard is observed in region 16 (p = <.0001) and 26 (p = 0.0015) as compared to region 1).

If the IPI was also included in the calculation, similar results were observed for the group (Figure 2) “all female” patients in Section 14, Table 1.2.5 (Likelihood ratio p = 0.3712) but model significance could be seen for “all patients” (Likelihood ratio p = 0.0121): patients with an IPI ≤1 had a lower hazard than those with IPI ≥2. The same difference occurred in the male group (Likelihood ratio p = <.0001) (Section 14, Tables 1.2.4 and 1.2.6).

**Figure 2: Event Free Survival by treatment arm and IPI index (ITT Population)**




Corresponding figures, also for both sexes, can be found under Section 14, Figures 1.4-6 for all patients and Section 14, Figures 2.4-6 for pre-Amendment 1- and Section 14, Figures 3.4-6 for post-Amendment 1- subjects.

The event-free survival analyses for histological subtype follicular NHL grade 3/3b by treatment arm showed a model significance (Likelihood ratio p = 0.0233), but none of the factors showed significant differences (Section 14, Tables 1.2.41).

For the event-free survival for histological subtype diffuse large B-cell lymphoma by treatment arm no significance for the model could be seen (Likelihood ratio p = 0.0759) (Section 14, Table 1.2.42).

The same could be observed for a model examining the event-free survival for all patients with an IPI ≤1 by treatment arm (Likelihood ratio p = 0.2869) and the event-free survival for all patients with IPI ≥ 2 by treatment arm (Likelihood ratio p = 0.1079) (Section 14, Tables 1.2.43 and 1.2.44, respectively).

Analyses for Pre-Amendment 1 and Post-Amendment 1-subjets separately can be found under Section 14, Tables 2.2.1-6 for the Pre-Amendment 1 population and under Section 14, Tables 3.2.1-6 and 3.2.41-48 for the post-Amendment 1 population.

#### 11.3.1.1.2 Progression-free survival (PFS)

The progression-free survival (PFS) was defined as follows:

Case 1:

One of the following events occurs between date of randomization and the end of study:

- Progressive disease or relapse

– Death from NHL

Then the PFS was defined as the difference in days between the date of randomization and the date of the first occurrence of one of the events listed above.

Case 2:

None of the events listed above occurred till the end of study. Then the PFS was defined as the difference in days between the date of randomization and the date of the last visit during the study where it was confirmed that no events listed in Case 1 had occurred.

PFS was calculated alternatively as:

- considering deaths only as events when they were caused by NHL (first calculation rule) (PFS 1)
- considering all deaths as events (second calculation rule, supportive analysis) (PFS 2).

This takes both calculation methods before and after amendment 3 of the study protocol into account (first calculation was based on the study protocol after amendment 3, second calculation was based on the study protocol prior to amendment 3). In addition, the definition of PFS as the time to progression or the death from any cause conformed to current scientific and regulatory expectations and was more conservative as the definition of PFS as described in the study protocol.

Calculating the Progression-free survival (considering death as event only if from NHL) by treatment arm, no significance of the model was observed for all patients (Likelihood ratio p = 0.2683) as well as for female patients only (Likelihood ratio p = 0.8503) (Section 14, Tables 1.2.7 and 1.2.8). Nevertheless, again the model was significant for the male group (Likelihood ratio p = 0.0195): here the treatment group had a lower hazard than the observation group (p = 0.0074). Tables can be found in Section 14, Table 1.2.9.

If for the same data not only death from NHL, but all reasons for death were included, the groups of all patients (Likelihood ratio p = 0.3646) and all females (Likelihood ratio p = 0.6816) had no significant model. Only for male patients a significance of model could be observed (Likelihood ratio p = 0.0122), in this group the observation group had a higher hazard (p=0.0058) (Section 14, Tables 1.2.10-12).

**Figure 3: Progression Free Survival (considering death as event) by treatment arm (ITT Population)**

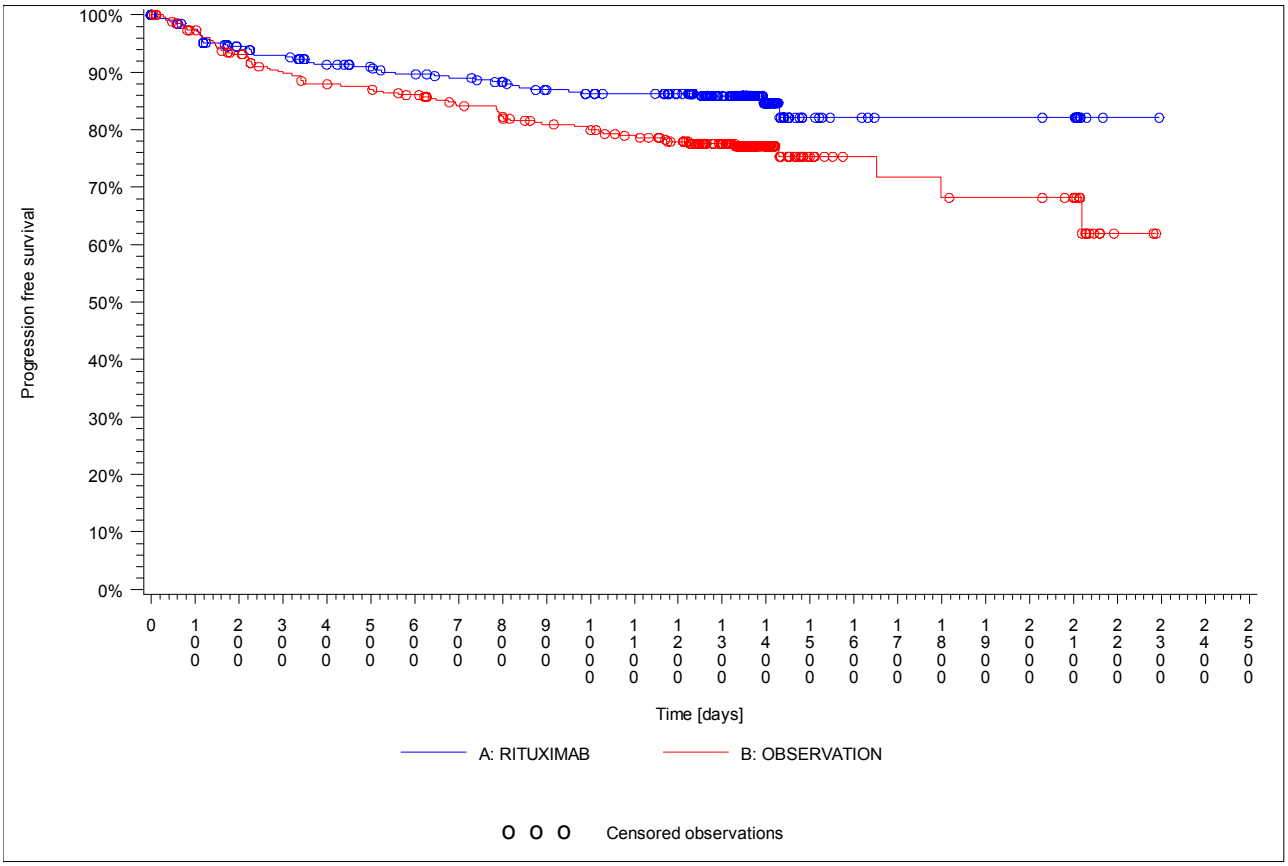
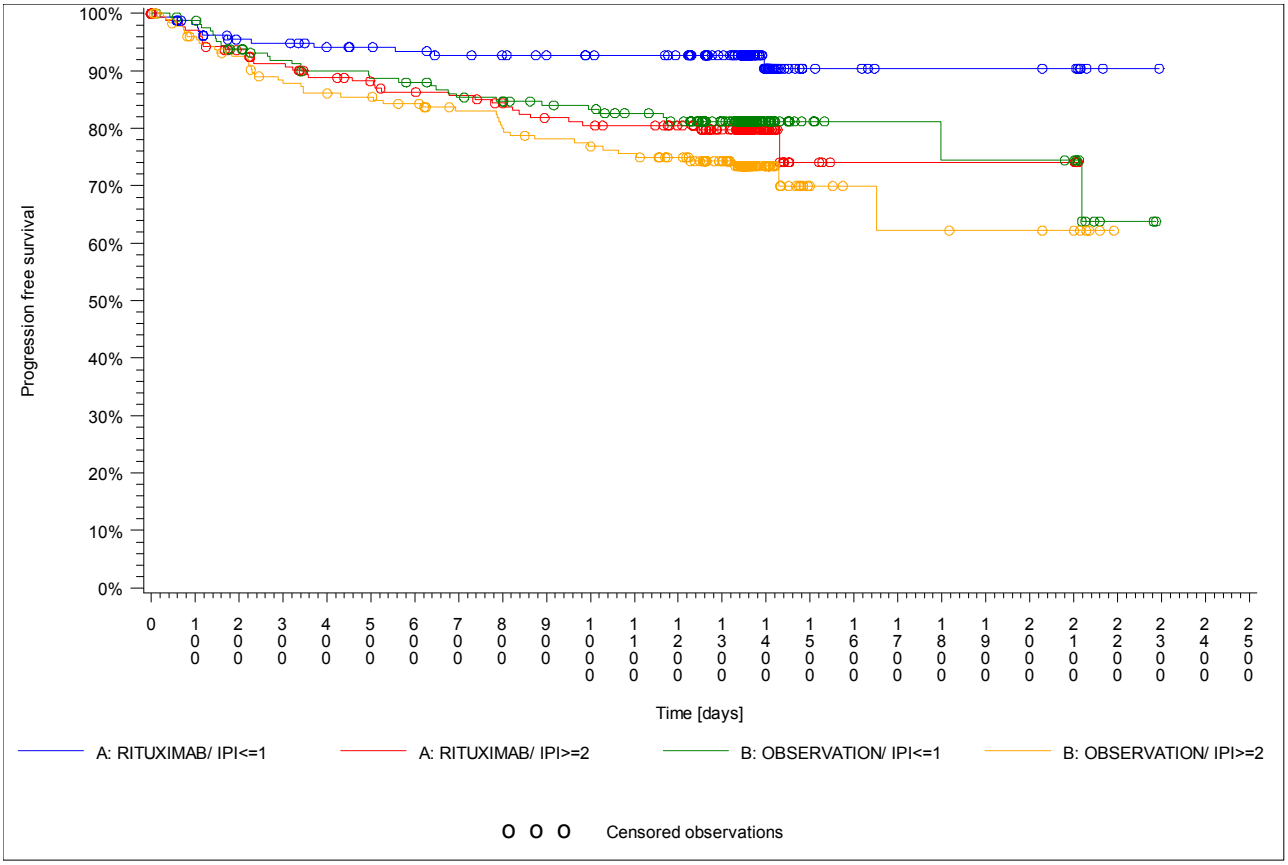



Figure 3 shows a plot of the Kaplan-Meier curve of the Progression Free Survival (considering death as event) by treatment arm.

If again the IPI, but only death from NHL is included, no model significance could be obtained for all patients (Likelihood ratio p = 0.1958) and female patients (Likelihood ratio p = 0.8241), but again for the male patient the model was significant (Likelihood ratio p = 0.0189). Here again the observation group had a higher hazard (p = 0.0052) than the treated patients as well as region 6 also showed a higher hazard than region 1 (p = 0.0008). (Section 14, Tables 1.2.13-15).

The same refers to the IPI inclusion if any deaths are considered (Figure 4): All and female patients showed no significance of the model (Likelihood ratio p = 0.0909 and 0.4923, respectively). Again the male subjects group showed significance of the model: Likelihood ratio p = 0.0042, the treatment group showed a lower hazard than the observation group (p = 0.0033) and the patients with IPI ≤1 also had a lower hazard than the group IPI ≥2 (p = 0.0254)(Section 14, Tables 1.2.16-18).

**Figure 4: Progression Free Survival (considering death as event) by treatment arm and IPI index (ITT Population)**




Analyses for Pre-Amendment 1 and Post-Amendment 1-subjets separately can be found under Section 14, Tables 2.2.7-18 for the Pre-Amendment 1 population and under Section 14, Tables 3.2.7-18 for the post-Amendment 1 population.

Corresponding figures, also for both sexes, can be found under Section 14, Figures 1.7-18 for all patients and Section 14, Figures 2.7-18 for pre-Amendment 1- and Section 14, Figures 3.7-18 for post-Amendment 1-subjects.

#### 11.3.1.1.3 Overall survival (OS)

The overall survival (OS) was defined as follows:

Case 1:

The following event occurred between date of randomization and the end of study:

- Death from any cause

Then the OS was defined as the difference in days between the date of randomization and the date of the first occurrence of the event (death from any cause).

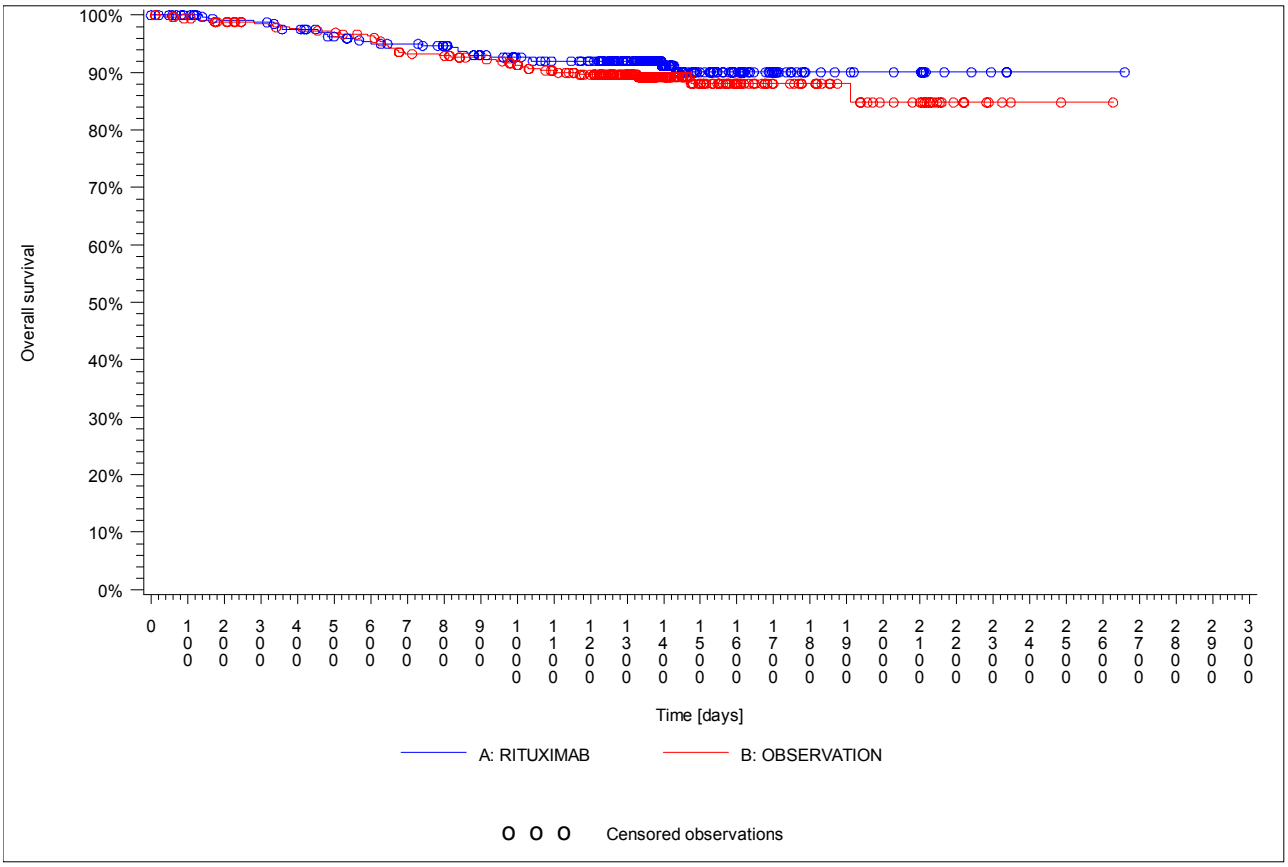
Case 2:

The event (death from any cause) did not occur till the end of study. Then the OS was defined as the difference in days between the date of randomization and the date of the last visit during the study where it was confirmed that no event (death from any cause) had occurred.

Section 14, Table 1.2.19 shows the outcome of the Cox regression with factors treatment group, geographical region, type of induction therapy and number of cycles of induction therapy applied on the Overall survival for all patients. The model was not significant (Likelihood ratio p = 0.3184). In Section 14, Table 1.2.20 the same model was applied to female patients only. The model also was not significant (Likelihood ratio p = 0.7069). The same model was not significant for male patients only (Likelihood ratio p = 0.3486) in Section 14, Table 1.2.21) either.

Figure 5 shows a plot of the Kaplan-Meier curve of the Overall survival by treatment arm:

**Figure 5: Overall survival by treatment arm (ITT Population)**




If the IPI was also included in the calculation, similar results were observed for all groups: the groups “all patients” (Likelihood ratio p = 0. 1378) (Section 14, Table 1.2.22), “all female” patients in Section 14, Table 1.2.23 (Likelihood ratio p = 0.7116) and the male group (Likelihood ratio p = 0.0870) (Section 14, Table 1.2.24) had no significant models.

**Figure 6: Overall survival by treatment arm and IPI index (ITT Population, all female patients)**

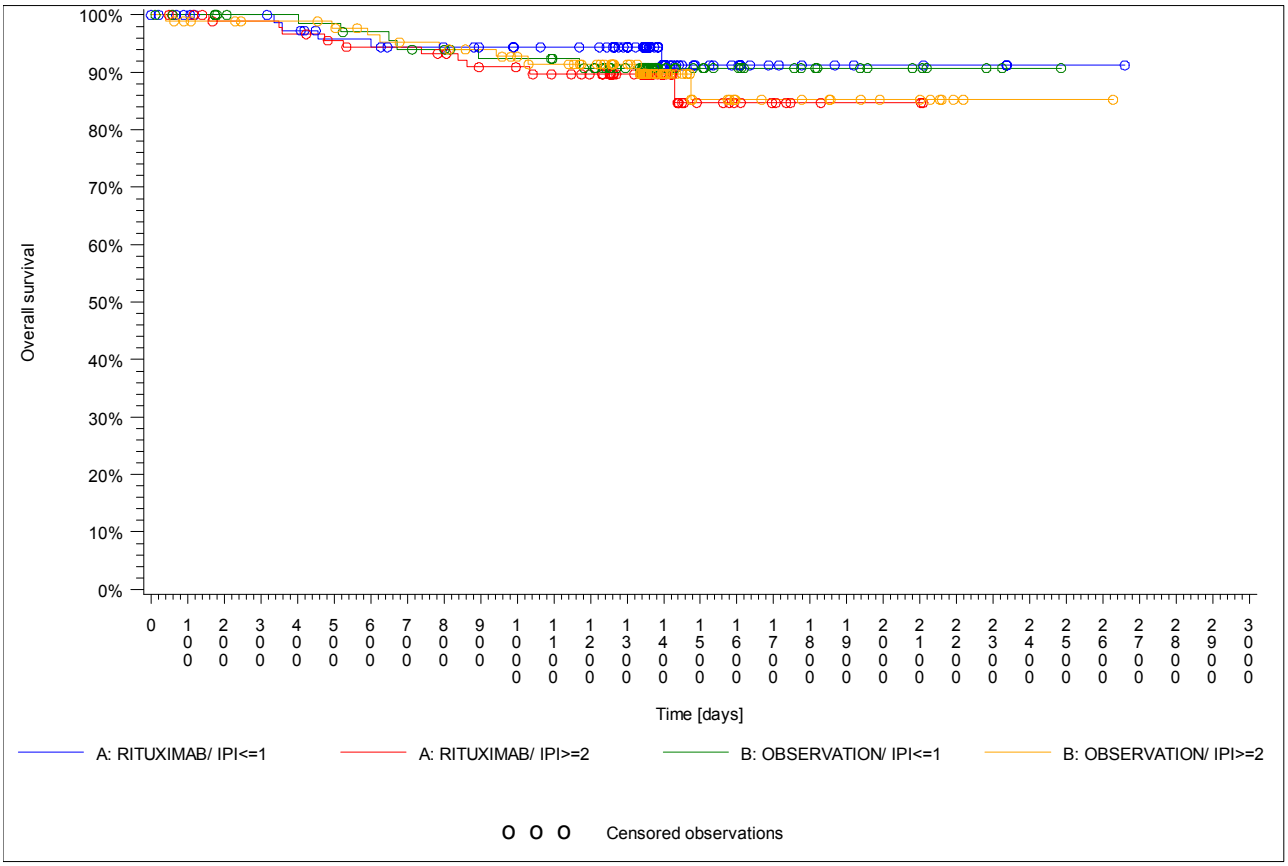



Figure 6 shows a plot of the Kaplan-Meier curve of the Overall survival by treatment arm and IPI index.

Analyses for Pre-Amendment 1 and Post-Amendment 1-subjets separately can be found under Section 14, Tables 2.2.19-24 for the Pre-Amendment1 population and under Section 14, Tables 3.2.19-24 for the post-Amendment 1 population.

Corresponding figures, also for both sexes, can be found under Section 14, Figures 1.19-24 for all patients and Section 14, Figures 2.19-24 for pre-Amendment 1- and Section 14, Figures 3.19-24 for post-Amendment 1-subjects.

#### 11.3.1.1.4 Survival Status

As it can be obtained from Section 14, Table 1.2.25 and Table 27, 8% of patients in Arm A and 10.5% of patients in Arm B died in the course of the study. Section 14, Table 1.2.26 and Table 28 show that, out of the patients who died, 48.1% in Arm A and 51.4% of patients in Arm B died due to relapse, while only 3.7% in Arm A and 2.9% in Arm B died due to a toxicity-related death cause. The remaining deaths were assessed due to other death causes. Information concerning whether an autopsy has been performed is contained in Section 14, Table 1.2.27.

**Table 27: Survival status - last known survival status by treatment arm (ITT Population)**

| | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=345) No. (%) |
|---|---|---|

| | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=345) No. (%) |
|---|---|---|
| Last survival status | | |
| alive | 311 (92.0) | 308 (89.5) |
| dead | 27 (8.0) | 36 (10.5) |
| Total | 338 | 344 |
| Percentages are based on the number of non-missing observations (Total) | | |

A by-subject listing of End-of-study survival status is provided in Section 16, Listing 2.10.

**Table 28: Survival status - death cause by treatment arm (ITT Population)**

| | A: RITUXIMAB (N=27) No. (%) | B: OBSERVATION (N=36) No. (%) |
|---|---|---|
| Death cause | | |
| Relapse | 13 (48.1) | 18 (51.4) |
| Related to toxicity | 1 (3.7) | 1 (2.9) |
| Other | 13 (48.1) | 16 (45.7) |
| Total | 27 | 35 |
| Percentages are based on the number of non-missing observations (Total) | | |

A by-subject listing of death causes is provided in Section 16, Listing 2.10.

Analyses for Pre-Amendment 1 and Post-Amendment 1-subjets separately can be found under Section 14, Tables 2.2.25-27 for the Pre-Amendment1 population and under Section 14, Tables 3.2.25-27 for the post-Amendment 1 population.

11.3.1.1.5 Diagnostics data / End of study

The following points were handled in this section:

- Treatment/observation period and follow-up: A data listing of the diagnostics data (i.e. whether patient was still event-free (yes/no) and if yes the type of event – Relapse, Death from any cause, Anticancer treatment/steroids/radiotherapy, Secondary malignancy, Unacceptable toxicity) of each visit was provided for all patients (Section 16, Listing 2.5).
- Relapse: a data listing was provided where the details of the relapse (Relapse diagnosed since study entry, date of last evaluation, Localization data, Diagnosed by and Date of fist diagnosis) was provided for all patients (Section 16, Listing 2.6).
- Other anticancer treatment: a data listing with the details of the other anticancer treatment (Other anticancer treatment started, start date, description) was provided for all patients (Section 16, Listing 2.7).

- Secondary malignancy: a data listing with the details of the secondary malignancy (Secondary malignancy diagnosed, date of first diagnosis, description) was provided for all patients (Section 16, Listing 2.8).
- Unacceptable toxicity: a data listing with the details of the Unacceptable toxicity (Unacceptable toxicity, date, description) was provided for all patients (Section 16, Listing 2.9).
- Survival status: a data listing was also provided for all patients (including: if alive: date of last observation / if not: date of death; death cause description, if other is ticked, autopsy performed) (Section 16, Listing 2.10).
- PET: a data listing was provided with the details of the Positron emission tomography (PET) (PET performed since study start, staging influenced, treatment influenced) for NHL13A only (Section 16, Listing 2.11).

### 11.3.1.2 Immunocompetence

#### 11.3.1.2.1 Inferential analysis of immunocompetence parameters

For the analysis of immunocompetence parameters, a Wilcoxon test for paired observations was applied between the baseline values (Screening) and the end of treatment values. For the following immunocompetence parameters significant changes were detected by the Wilcoxon test.

**Table 29: Immunocompetence parameter changes (ITT population)**

| | A: RITUXIMAB | | | | B: OBSERVATION | | | |
|---|---|---|---|---|---|---|---|---|
| | Kolmo-gorov-Smirnov | Shapiro-Wilk | Wilcoxon Test | Median | Kolmo-gorov-Smirnov | Shapiro-Wilk | Wilcoxon Test | Median |
| CD19+ [/µL] | - | - | - | - | 0.0100 | 0.0001 | <.0001 | 79.00 |
| CD3- CD16+ [/µL] | No significant Wilcoxon Test | | | | | | | |
| CD3+ [/µL] | No significant Wilcoxon Test | | | | | | | |
| CD3+ HLA-DR+ [/µL] | No significant test | | | | 0.0120 | 0.0020 | 0.0195 | -15.50 |
| CD4+ [/µL] | No significant test | | | | 0.0345 | 0.0210 | 0.0005 | 52.00 |
| CD8+ [/µL] | No significant Wilcoxon Test | | | | | | | |
| IgA [MG/DL] | 0.0100 | 0.0001 | 0.0006 | -0.65 | 0.0100 | 0.0001 | <.0001 | 15.00 |
| IgG [MG/DL] | No significant test | | | | 0.0100 | 0.0001 | <.0001 | 70.00 |
| IgM [MG/DL] | 0.0100 | 0.0001 | <.0001 | -4.00 | 0.0100 | 0.0001 | <.0001 | 3.00 |

For group A significant changes in immunocompetence parameters were only observed for IgA and IgM. For both parameters statistically significant drops were observed.

For group B significant changes in immunocompetence parameters were observed for CD19+, CD3+ HLA-DR+, CD4+, IgA, IgG and IgM. For CD3+ HLA-DR+ a drop was observed, all other of these parameters increased.

No significance for both groups could be observed for parameters CD3 - CD16+, CD3+ and CD8+. Reference tables can be found under Section 14, Tables 1.2.28-40.

11.3.1.2.2 Tables of immunocompetence parameters

Reference tables can be found under Section 14, Tables 1.2.28-40.

Tables of numbers of available samples by visit and treatment arm (Section 14, Tables 1.2.37), absolute values by parameter, visit and treatment arm (Section 14, Tables 1.2.38) and relative and absolute changes from Screening by parameter, visit and treatment arm (Section 14, Tables 1.2.39 and 1.2.40) were provided.

Tables of Pre-Amendment 1 and Post-Amendment 1-subject calculations separately can be found under Section 14, Tables 2.2.28-40 for the Pre-Amendment 1 population and under Section 14, Tables 3.2.28-40 for the post-Amendment 1 population.

*11.3.1.2.3* Listings of immunocompetence parameters

By-subject listings of immunocompetence parameters can be found under Section 16, Listings 2.12 and 2.13.

### 11.3.1.3 SF-12 Questionnaire

Tables whether the questionnaires were filled in and archived can be found under Section 14, Tables 2.2.41 and 3.2.49. The results contained in these questionnaires were not entered into the study database from Assign Data Management and Biostatistics GmbH and were therefore not analyzed. So, no results are available in this report.

### 11.3.1.4 Efficacy post-hoc analyses

**Post-hoc analysis 2:**

The following figures of Event Free Survival by treatment arm are available for the following subgroups:

- Patients ≤ and > 60 years (Section 14, Figures Age 1 - 12)
- Patients from Europe and from Asia (Section 14, Figures Continent 1 - 12)
- 6 vs. 8 cycles prior chemotherapy (Section 14, Figures Number of cycles 1 - 12)
- Male and female patients (Section 14, Figures Sex 1 - 12)

All figures are additionally stratified by:

- IPI
- If known by histological subtype follicular NHL grade 3/3b
- If known for histological subtype diffuse large B-cell lymphoma
- IPI ≤ 1 or ≥ 2

The same system was used for the tables in Section 14, Figures Age 1 - 12, Continent 1 - 12, Number of cycles 1 - 12 and Sex 1 - 12. Here the outcome of the Cox regression with factors treatment group, geographical region, IPI and type of induction therapy was applied on the Event free survival and one of the subgroups.

Section 14, Table Number of cycles 3 shows the outcome of the Cox regression with factors treatment group, geographical region, IPI and type of induction therapy applied on the Event-free survival for patients with 6 cycles prior chemotherapy. The model was significant (Likelihood ratio p = 0.0323): Differences were seen between the types of induction therapy (A greater hazard is observed in Arm B (p = 0.0318)) and the patients with IPI ≤1 had a lower hazard (p = 0.0028) than those with IPI ≥ 2.

The event-free survival analyses for histological subtype follicular NHL grade 3/3b by treatment arm for the patients with 6 cycles prior chemotherapy (see Section 14, Table 5) showed a model significance (Likelihood ratio p = 0.0285), but none of the factors was significant.

For the tables analyzing stratified by patients' sex, the following models showed significance:

- Event-free survival by treatment arm (male patients, Section 14, Table Sex 2): The likelihood ratio was p = 0.0002 and the Rituximab-treated group showed a lower hazard compared to the observation group (p

= 0.0267). Also for the geographical regions differences could be observed (p = 0.0449): region 16 (p <.0001) and 26 (p = 0.0015) showed a higher hazard than region 1.

- Event-free survival by treatment arm and IPI index (male patients, Section 14, Table Sex 4): The likelihood ratio for the model was p <.0001. Again the Rituximab-treated group had a lower hazard than the observation group (p = 0.0182) and the geographical regions 16 (p = 0.0001) and 26 (p = 0.0014) showed a higher hazard than region 1. Patients with IPI ≥ 2 showed a higher hazard than those with IPI ≤ 1.
- Event-free survival for histological subtype diffuse large B-cell lymphoma by treatment arm (male patients, Section 14, Table Sex 8, likelihood ratio p= 0.0002): the geographical regions (p = 0.0265) showed differences between region 16 (p = <.0001) and 26 (p = 0.0006) compared to region 1: Region 1 had a lower hazard than the regions 16 and 26.
- The Event-free survival for patients with IPI ≤ 1 by treatment arm (male patients, see Section 14, Table Sex 10) showed a model significance (Likelihood ratio p = 0.0268), but none of the factors was significant.
- The Event-free survival for patients with IPI ≥ 2 by treatment arm (male patients Section 14, Table Sex 12) showed a model significance (Likelihood ratio p = 0.0034), but none of the factors was significant.

**Post-hoc analysis 3:**

The following figures of Event Free Survival by treatment arm are available for the following subgroups and for post-Amendment 1 patients only, each was additionally stratified by sex:

- Histological subtype follicular NHL grade 3b by treatment arm (Section 14, Figures 1 and 2)
- Histological subtype diffuse large B-cell lymphoma by treatment arm (Section 14, Figures 3 and 4)
- Diffuse large B-cell lymphoma - divided by treatment arm and the histological subtypes (Section 14, Figures 5 - 16)
  - Centroblastic (Section 14, Figures 5 and 6)
  - immunoblastic (Section 14, Figures 7 and 8)
  - T-cell/histiocyte rich (Section 14, Figures 9 and 10)
  - anaplastic (Section 14, Figures 11 and 12)
  - mediastinal large B-cell lymphoma: yes or no (Section 14, Figures 13 - 16)

The same system was adapted for the tables in Section 14, Tables DLBCL 1-16.

Section 14, Tables Immunology 1.2.1 - 1.2.13 provides tables and analyses of immunocompetence parameters.

Tables of number of available samples by visit and treatment arm (Section 14, Table Immunology 1.2.10), absolute values by parameter, visit and treatment arm (Section 14, Table Immunology 1.2.11), relative changes from Screening by parameter, visit and treatment arm (Section 14, Table Immunology 1.2.12) and absolute changes from Screening by parameter, visit and treatment arm (Section 14, Table Immunology 1.2.13) were additionally provided.

**Post-hoc analysis 4:**

Post-hoc analysis 4 contains efficacy tables (Section 14, Tables 1.2.1 - 1.1.44) and efficacy figures (Section 14, Figures 1.1 - 1.28) for patients with no radiotherapy only.

**Post-hoc analysis 5:**

Post-hoc analysis 5 contains a multivariate Cox regression which was performed for the factors:

- Treatment group
- Geographical region
- Type of induction therapy
- Number of cycles of induction therapy
- Sex
- Treatment Group*Sex (Interaction)
- IPI Index

- Treatment Group*IPI Index (Interaction)

(see Section 14, Table Univariate Multivariate 1). Tables Section 14, Tables Univariate Multivariate 2 - 7 show the same analyses performed for each factor separately (except for "Treatment Group*Sex (Interaction)" and "Treatment Group*IPI Index (Interaction))".

Section 14, Tables Event overview 1 – 3 shows tabulations of the number of patients with events by treatment arm for all patients and male and female separately. Tables for relapse, death, therapy, malignancy and toxicity were additionally created.

**Post-hoc analysis 6:**

In Section 16, Listings 1 and 2 by-patient listings of CR/CRu, residual lesions, BM biopsy and endoscopy as well as events counted for Event free-survival for the ITT population are available.

In Section 14, Tables 1-86 outcomes of the Cox regression for the ITT Population (all patients) analysed for several factors (e.g. Event-free survival by treatment arm and Geographical region for, post-amendment 1 patients…) can be obtained.

**Post-hoc analysis 7:**

In Post-hoc analysis 7 figures of Progression-free survival by treatment arm (Section 14, Figure 1) and Cumulative progression rate by treatment arm (Section 14, Figure 2) were created for all patients of the ITT population.

**Post-hoc analysis 8:**

Section 14, Tables 1 - 54 show outcomes of the Cox regression for the ITT Population (all patients) with single factors (e.g. age, sex…) for the parameters:

- Event-free survival
- Progression-free survival (considering death as event only if from NHL)
- Progression-free survival (considering death as event)

Section 14, Tables 55 - 57 show outcomes of the Cox regression for the ITT Population (all patients) with more than one factor for the parameters:

- Event-free survival (factors: Treatment group, Age class, Continent, DLBCL vs. FLG3, Stage ½ vs. ¾, ENS ≤1 vs. >1, LDH normal vs. above upper limit, BM involvement vs. no BM involvement)
- Progression-free survival (considering death as event only if from NHL) (factors: Treatment group, DLBCL vs. FLG3, Stage ½ vs. ¾, ENS ≤1 vs. >1, LDH normal vs. above upper limit, BM involvement vs. no BM involvement)
- Progression-free survival (considering death as event) (factors: Treatment group, Age class, DLBCL vs. FLG3, Stage ½ vs. ¾, ENS ≤1 vs. >1, LDH normal vs. above upper limit, BM involvement vs. no BM involvement)

The factors in the models with more than one factor (Section 14, Tables 1 - 54) had been selected due to the results from the Cox regressions with single factors (Section 14, Tables 55 - 57).

**Post-hoc analysis 9:**

Under Section 14, Tables 1 - 2 outcomes of the Cox regression for Event-free survival by treatment arm (ITT population) can be observed for all patients excluding patients from Australia and all patients excluding patients with toxicity as first event.

**Post-hoc analysis 10:**

In Section 14, Figures 1 – 8 figures of the following categories are available:

- Event Free Survival
- Progression Free Survival
- Overall survival

- Cumulative progression rate

All these figures had been generated prior to post-hoc analysis 10 already, however, the unit was "months" instead of "days" this time.

**Post-hoc analysis 11:**

For the Post-hoc analysis 11 outcomes of the Cox regression with factor treatment group for the following parameters were tabulated:

- Event-free survival for different subgroups Section 14, Tables EFS 1 – 57
- Progression-free survival (considering death as event) for different subgroups Section 14, Tables PFS death as event 1 – 57
- Progression-free survival (considering death as event only if from NHL) for different subgroups Section 14, Tables PFS death as event only if from NHL 1 – 57

The numbers and percentages of patients in each subgroup used for the Cox regressions mentioned above have been tabulated prior to the Cox regressions. Examples for subgroups are: Continent, sex.

**Post-hoc analysis 12:**

In Section 14, Table 1 a tabulation of Progression-free survival by treatment arm (ITT Population, all patients) is available.

**Post-hoc analysis 13:**

For Post-hoc analysis 13, outcomes of the Cox regression with factor treatment group for the following parameters were tabulated:

- Event-free survival for different subgroups:
  - Section 14, Tables EFS all patients 1 – 57,
  - Section 14, Tables EFS female patients 1 – 54,
  - Section 14, Tables EFS male patients 1 – 54,
  - Section 14, Tables EFS IPI ≤1 1 – 54,
  - Section 14, Tables EFS >1 1 – 54
- Progression-free survival 1 (considering death as event only if from NHL) for different subgroups:
  - Section 14, Tables PFS 1 all patients 1 – 57,
  - Section 14, Tables PFS 1 female patients 1 – 54,
  - Section 14, Tables PFS 1 male patients 1 – 54,
  - Section 14, Tables PFS 1 IPI ≤1 1 – 54,
  - Section 14, Tables PFS 1 >1 1 – 54
- Progression-free survival 2 (considering death as event) for different subgroups:
  - Section 14, Tables PFS 2 all patients 1 – 57,
  - Section 14, Tables PFS 2 female patients 1 – 54,
  - Section 14, Tables PFS 2 male patients 1 – 54,
  - Section 14, Tables PFS 2 IPI ≤1 1 – 54,
  - Section 14, Tables PFS 2 >1 1 – 54

The numbers and percentages of patients in each subgroup used for the Cox regressions mentioned above have been tabulated prior to the Cox regressions. Examples for subgroups are: Continent, sex.

The outcomes of the Cox regression with different single factors were tabulated for the following parameters:

- Event-free survival for different subgroups:
  - Section 14, Tables univariate EFS all patients 1 – 18,
  - Section 14, Tables univariate EFS female patients 1 – 17,
  - Section 14, Tables univariate EFS male patients 1 – 17,
  - Section 14, Tables univariate EFS IPI ≤1 1 – 17,
  - Section 14, Tables univariate EFS >1 1 – 17
- Progression-free survival 1 (considering death as event only if from NHL) for different subgroups:

  - Section 14, Tables univariate PFS 1 all patients 1 – 18,
  - Section 14, Tables univariate PFS 1 female patients 1 – 17,
  - Section 14, Tables univariate PFS 1 male patients 1 – 17,
  - Section 14, Tables univariate PFS 1 IPI ≤1 1 – 17,
  - Section 14, Tables univariate PFS 1 >1 1 – 17
- Progression-free survival 2 (considering death as event) for different subgroups:
  - Section 14, Tables univariate PFS 2 all patients 1 – 18,
  - Section 14, Tables univariate PFS 2 female patients 1 – 17,
  - Section 14, Tables univariate PFS 2 male patients 1 – 54,
  - Section 14, Tables univariate PFS 2 IPI ≤1 1 – 54,
  - Section 14, Tables univariate PFS 2 >1 1 – 17

Examples for single factors are: Continent, Type of induction therapy.

Outcomes of the Cox regression with two factors (i.e. different single factors + treatment group) were tabulated for the following parameters:

- Event-free survival for different subgroups:
  - Section 14, Tables univariate with treatment EFS all patients 1 – 17,
  - Section 14, Tables univariate with treatment EFS female patients 1 – 16,
  - Section 14, Tables univariate with treatment EFS male patients 1 – 16,
  - Section 14, Tables univariate with treatment EFS IPI ≤1 1 – 16,
  - Section 14, Tables univariate with treatment EFS >1 1 – 16
- Progression-free survival 1 (considering death as event only if from NHL) for different subgroups:
  - Section 14, Tables univariate with treatment PFS 1 all patients 1 – 17,
  - Section 14, Tables univariate with treatment PFS 1 female patients 1 – 16,
  - Section 14, Tables univariate with treatment PFS 1 male patients 1 – 16,
  - Section 14, Tables univariate with treatment PFS 1 IPI ≤1 1 – 16,
  - Section 14, Tables univariate with treatment PFS 1 >1 1 – 16
- Progression-free survival 2 (considering death as event) for different subgroups:
  - Section 14, Tables univariate with treatment PFS 2 all patients 1 – 17,
  - Section 14, Tables univariate with treatment PFS 2 female patients 1 – 16,
  - Section 14, Tables univariate with treatment PFS 2 male patients 1 – 16,
  - Section 14, Tables univariate with treatment PFS 2 IPI ≤1 1 – 16,
  - Section 14, Tables univariate with treatment PFS 2 >1 1 – 17

Examples for single factors are: Continent, Type of induction therapy.

Multivariate analyses were performed for EFS (Section 14, Tables multivariate with treatment EFS 1 – 5), PFS 1 (Section 14, Tables multivariate with treatment PFS 1 1 – 5) and PFS 2 (Section 14, Tables multivariate with treatment PFS 2 1 – 5). For each of these parameters five tables were produced for:

- All patients
- All male patients
- All female patients
- All patients with IPI ≤1
- All patients IPI >1

Additionally to the treatment group, for the multivariate analyses factors were integrated that had a likelihood ratio of <0.1 for the model and an effect of the factor of <0.1. If one or more of the factors were used for the calculation of the IPI, two tables were performed, one with the factors and without the IPI and one with the IPI and none of the before mentioned factors.

Figures corresponding to the above mentioned analyses can be obtained from Section 14, Figures Survival figures 1.1.1 – 6.3.5 and Section 14, Figures Additional survival figures 1.1 – 3.5) for

- Event free survival (also cumulative rate)
- Progression free survival (also cumulative rate)

- Overall survival (also cumulative rate)
- Toxicity free survival (also cumulative rate)

**Post-hoc analysis 15:**

In the Post-hoc analysis 15, Cox regressions for the ITT-Population (once for the subgroup of "all male patients with IPI≤1" and once for the subgroup of "all female patients with IPI≤1") were performed on Event free-, Progression free (PFS 1 and PFS 2)- and Overall survival. The Cox regressions used the factors Treatment group, Geographical region, Type of induction therapy and Number of cycles of induction therapy and results can be found in Section 14, Tables Post-hoc 15 1-8.

Multivariate Cox regressions are available in the following Tables for EFS, PFS 1 and PFS 2:

- Section 14, Tables multivariate with treatment EFS 1-5:
- Section 14, Tables multivariate with treatment PFS1 1-5:
- Section 14, Tables multivariate with treatment PFS2 1-5:

Figures describing the Event free-, Progression free- and Overall survival for the subgroup of "all male patients with IPI≤1" and for the subgroup of "all female patients with IPI≤1"can be obtained from Section 14, Figures Post-hoc 15 1-16.

**Post-hoc analysis 16:**

In the Post-hoc analysis 16 Cox regressions for the ITT-Population were performed with the factors Treatment group, Geographical region, Type of induction therapy, Number of cycles of induction therapy and Age class for EFS and PFS 1 and PFS 2: Section 14, Tables for Age 1 - 9.

Figures and corresponding descriptive survival tables showing

- EFS by treatment arm and IPI for female patients
- EFS by treatment arm and age class for all patients
- EFS by treatment arm and age class for male patients
- EFS by treatment arm and age class for female patients

can be found in Section 14, Figures Additional survival 1.1 – 4.3. The same figures and corresponding descriptive survival tables are available for PFS 1 and for PFS 2 (Section 14, Figures Additional survival 5.1 – 12.3).

**Post-hoc analysis 17:**

Kaplan-Meier curves (once with time-axis-unit "days" and once with time-axis-unit "months") and Kaplan-Meier tables for EFS, PFS 1, PFS 2 and OS are presented for male and female patients (Section 14, Post-hoc 17, Figures 1.1 – 8.2 and Tables 1.3 – 8.3).

**Post-hoc analysis 18:**

Kaplan-Meier curves (once with time-axis-unit "days" and once with time-axis-unit "months"), Kaplan-Meier tables and Cox regressions (factors: Treatment group, Geographical region, Type of induction therapy and Number of cycles of induction therapy) for EFS, PFS 1, PFS 2 and OS were performed for

- the subgroups of patients with DLBCL, male patients with DLBCL and female patients with DLBCL (Section 14, Post-hoc 18, Figures and Tables 1.1.1-1.12.4),
- the subgroups of patients receiving CHOP14, male patients receiving CHOP14 and female patients receiving CHOP14 (Section 14, Post-hoc 18, Figures and Tables 2.1.1-2.12.4),
- the subgroups of patients receiving CHOP21, male patients receiving CHOP21 and female patients receiving CHOP21 (Section 14, Post-hoc 18, Figures and Tables 3.1.1-3.12.4),

**Post-hoc analysis 19:**

The intention of post-hoc analysis 19 was to investigate the influence of the amendment status (i.e. compare "pre-amendment patients" and "post-amendment patients").

Kaplan-Meier curves (with time-axis-unit "days") were generated for male patients in group A, female patients in group A and all patients in group A for the EFS, PFS 1, PFS 2 and OS: Curves were drawn of "pre-amendment patients" and "post-amendment patients" (Section 14, Post-hoc 19, Figures 1.1-1.12).

Cox regressions (factors: Amendment status, Geographical region, Type of induction therapy and Number of cycles of induction therapy) were performed for male patients in group A, female patients in group A and all patients in group A for the EFS, PFS 1, PFS 2 and OS: Results are presented in Section 14, Post-hoc 19, Tables 1.1-1.1.12.

## 11.3.2 Statistical/Analytical Issues

### 11.3.2.1 Adjustments for Covariates

Cox regressions were made with factor treatment group and the following factors also used for stratification of randomization:

- Geographical region
- Type of Cycles of Induction Therapy
- Number of Cycles of Induction Therapy

Additionally these Cox regressions were repeated with IPI as additional factor.

### 11.3.2.2 Handling of Dropouts or Missing Data

Missing values for EFS, PFS and OS were not imputed.

The hematology laboratory parameters as well as the immunocompetence parameters were imputed by using the Last-Observation-Carried-Forward (LOCF) approach. The last available value within the treatment/observation period was carried forward to the End of Treatment/Observation Visit. In the Follow-up period, the missing values of the laboratory parameters as well as the immunocompetence parameters were not imputed.

### 11.3.2.3 Interim Analyses and Data Monitoring

Two interim analyses had been performed for this study. The first interim analysis was performed on 27-Jan-2009 after 1/3 of the 148 events that had to be observed. The second interim analysis was performed on 30-Dec-2009 after 2/3 of the 148 events that had to be observed. Results of these interim analyses as well as other tabulations for safety purposes are not presented in this report.

### 11.3.2.4 Multicenter Studies

This was a multicenter study. However, no stratification of analyses by study site was performed. However, geographical region of the patient was considered in the efficacy analyses.

### 11.3.2.5 Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons/multiplicity were performed.

### 11.3.2.6 Use of a "Efficacy Subset" of Patients

No per-protocol population was analyzed in this study since less than 10% of patients had at least one major protocol deviation.

### 11.3.2.7 Active-Control Studies Intended to Show Equivalence

Not applicable.

### 11.3.2.8 Examination of Subgroups

For all patients in the ITT group several analyses were performed for the following subgroups:

- Female subjects
  - Event-free survival by treatment arm (Section 14, Table 1.2.2)
  - Event-free survival by treatment arm and IPI index (Section 14, Table 1.2.5)
  - Progression-free survival (considering death as event only if from NHL) by treatment arm (Section 14, Table 1.2.8)
  - Progression-free survival (considering death as event) by treatment arm (Section 14, Table 1.2.11)
  - Progression-free survival (considering death as event only if from NHL) by treatment arm and IPI index (Section 14, Table 1.2.14)
  - Progression-free survival (considering death as event) by treatment arm and IPI index (Section 14, Table 1.2.17)
  - Overall survival by treatment arm (Section 14, Table 1.2.20)
  - Overall survival by treatment arm and IPI index (Section 14, Table 1.2.23)
- Male subjects:
  - Event-free survival by treatment arm (Section 14, Table 1.2.3)
  - Event-free survival by treatment arm and IPI index (Section 14, Table 1.2.6)
  - Progression-free survival (considering death as event only if from NHL) by treatment arm (Section 14, Table 1.2.9)
  - Progression-free survival (considering death as event) by treatment arm (Section 14, Table 1.2.12)
  - Progression-free survival (considering death as event only if from NHL) by treatment arm and IPI index (Section 14, Table 1.2.15)
  - Progression-free survival (considering death as event) by treatment arm and IPI index (Section 14, Table 1.2.18)
  - Overall survival by treatment arm (Section 14, Table 1.2.21)
  - Overall survival by treatment arm and IPI index (Section 14, Table 1.2.24)
- Patients with IPI ≤1
  - Event-free survival for IPI less equal 1 by treatment arm (Section 14, Table 1.2.43)
- Patients with IPI ≥2
  - Event-free survival for IPI greater equal 2 by treatment arm (Section 14, Table 1.2.44)
- Patients with follicular NHL grade 3/3b regarding their histological subtype
  - Event-free survival for histological subtype follicular NHL grade 3/3b by treatment arm (Section 14, Table 1.2.41)
- Patients with diffuse large B-cell lymphoma regarding their histological subtype
  - Event-free survival for histological subtype diffuse large B-cell lymphoma by treatment arm (Section 14, Table 1.2.42)

Subgroup analyses were also performed in the Pre-Amendment 1 population and the Post-Amendment 1 population. Details can be obtained from the analysis.

### 11.3.3 Tabulation of Individual Response Data

Individual outcomes of event-free survival, progression-free survival, Overall survival, Survival status and immunocompetence parameters can be obtained from Section 16, Listings 2.1-2.4 and 2.1.12-13.

### 11.3.4 Drug Dose, Drug Concentration, and Relationships to Response

Not applicable.

### 11.3.5 Drug-Drug and Drug-Disease Interactions

Not applicable.

### 11.3.6 By-Patient Displays

No by-patient displays have been generated. Only by-patient listings are available.

### 11.3.7 Efficacy Conclusions

11.3.7.1. Summary:

The trial mainly aimed at the demonstration of a significant difference in EFS and PFS (death from any cause was considered an event) in patients receiving rituximab maintenance in first CR or CRu. The primary endpoint (EFS) was not met and R maintenance can therefore not be regarded as a new standard of care. However, there was a clear trend in favour of rituximab treatment (likelihood ratio p=0.067). A lower rate of relapses was observed in the treatment arm, indicating the potential of rituximab to prevent relapse to a certain extent. Subgroup analyses were subsequently performed. In univariate analysis, a positive effect of rituximab was observed. However, significance was only demonstrated for some subgroups.The most interesting result came from an unplanned analyses of sex differences. Male patients had a superior EFS and PFS, which was particularly pronounced in the low IPI subgroup. This was confirmed by multivariate analysis. Female patients had no survival benefit, but more toxic events. This result can be seen as hypothesis generating: Trials should be initiated which study R maintenance in male patients in a prospective way.

11.3.7.2 Detailed description:

Patients were balanced regarding demographics, disease characteristics at initial diagnosis, type of induction treatment, and clinical response. The median age was 57 and 58 years, respectively, with approximately half of the patients being male in both arms. The vast majority of patients had DLBCL (97.3 and 96.5%) with 47.6 and 48.0% in the low IPI group. 44.1% and 46.7% had received up to 6 cycles of R-chemo and 74.0 and 77.7% were treated with R-CHOP-21. At randomisation, 83.4% and 84.9% were in CR, while the rest was in CRu. Adherence to the study was high with a median exposure to study medication of 20.5 months.

**EFS (primary endpoint)**. After a median observation time of 45 months the overall outcome of all 683 patients was good with EFS of 80.4% in the RM arm vs. 76.5% in the observation arm at 3 years and 76.6% vs. 61.7% at 5 years, respectively.

Cox regression analysis with factors treatment group, geographical region, type of induction therapy and number of cycles of induction therapy was applied on the event-free survival for all patients. The model did not show significance (Likelihood ratio $p$=0.0670). The hazard ratio by treatment arm was 0.79; 95%CI 0.57-1.08; $p$=0.1433. Thus the primary endpoint of the study was not met for the ITT population. However, there was a clear trend towards a better outcome in the RM arm. Therefore, detailed subgroup analysis was performed.

As shown in a forest plot of univariate analyses, a shift towards RM was noted for almost all subgroups. Of note, the only major group whose EFS was not affected by RM were female patients.

The Cox regression model was not significant for female (Likelihood ratio $p$=0.4638) but highly significant for male patients (Likelihood ratio $p$=0.0002). The 3-year EFS for RM vs. observation was 76.8% vs 78.7% in female and 84.1% vs. 74.4% in male patients. RM treatment had a significant effect in men (HR: 0.58; 95%CI 0.36-0.94; $p$=0.0267), but not in women (HR: 1.05; 95%CI 0.67-1.66; $p$=0.8246).

The IPI also had a significant influence on outcome in the whole patient population (Likelihood ratio $p$=0.0121) and particularly in men (Likelihood ratio $p$<0.0001), but not women (Likelihood ratio $p$=0.3712). Patients with an IPI≤1 had a lower hazard than those with IPI>1. Men with a low IPI treated with RM had the most favourable outcome (Likelihood ratio $p$=0.0268) with an EFS of 91.2% (HR: 0.46; 95%CI 0.19-1.16; $p$=0.0993). In multivariate analysis for male patients, age≤60, RM treatment, and stage 1/2 remained independent factors. When IPI was included as a single variable, low IPI and RM remained significant.

**PFS (secondary endpoint).** PFS for RM vs. observation was 86.3 vs. 79.0% at 3 years and 82.1% vs. 68.2% at 5 years. The model was not significant (Likelihood ratio $p$=0.3646). However, RM was superior to observation when treatment arms were compared (HR: 0.62; 95%CI 0.43-0.90; $p$=0.0120). The model was not significant in female patients only (Likelihood ratio $p$=0.6816). Again, the whole model was significant for men (Likelihood ratio $p$=0.0122): the RM group in men had a lower hazard than observation (3-year PFS 89.0 vs. 77.6%; HR: 0.45; 95%CI 0.25-0.79; $p$=0.0058). When the IPI was included in the model all and female patients had no significantly different outcome (Likelihood ratio $p$=0.0909 or 0.4923, respectively). However, the model was significant for male patients (Likelihood ratio $p$=0.0042). RM had a lower hazard than observation ($p$=0.0033) and patients with IPI≤1 had a lower hazard than the IPI>1 group ($p$=0.0254). This effect was particularly pronounced in male patients with an IPI≤1 where almost no relapses occurred after RM (PFS 96.1 vs. 80.5% at 3 years, likelihood ratio $p$=0.0140) (HR: 0.26; 95%CI 0.07-0.93; $p$=0.0388). In multivariate analysis of factors potentially influencing PFS in male patients RM and low IPI remained significant.

Of note, the total number of relapses was lower in the RM arm (36 vs. 64) corresponding to a reduction by 44%.

Overall survival at 3 years was not different between RM (92.0%) and observation (90.3%) (Likelihood ratio $p$=0.3184). The best overall survival was observed in men with a low IPI receiving rituximab (97.5% vs. 93.1%) (HR: 0.35; 95%CI 0.07-1.70; $p$=0.1916).

The first 69 Austrian patients were randomized for 12 months (6 doses) of RM (N=30) vs. observation (N=39). Differences in EFS by treatment arm for the male population were significant only in the long (post-amendment 1) RM cohort (12 months RM: HR for males 0.77; 95%CI 0.22-2.65; $p$=0.6752; 24 months RM: HR for males 0.55; 95%CI 0.32-0.93; $p$=0.0270). In direct comparison between the 2 groups a trend towards the 24-months RM was noted (HR 0.27; 95%CI 0.067-1.08; $p$=0.0637) (not shown).

# 12. SAFETY EVALUATION

In this section, a brief summary of safety data is followed by a thorough presentation of these results by study endpoint. The presentation of data evaluating the safety of Rituximab infusions includes the following analyses of safety data. All tables and presentations in Chapter 12 are based on the Safety population.

## 12.1 EXTENT OF EXPOSURE

The observation times are summarized in Table 30 (Corresponding table under Section 14, Table 1.3.3). The duration of exposure to Rituximab/Observation time is summarized in Table 31 (Section 14, Table 1.3.6) with the treatment doses summarized in Table 32 (Section 14, Table 1.3.18). Tables for pre-Amendment 1 and post-Amendment 1-subjets separately can be found under Section 14, Table 2.3.6 for the pre-Amendment 1 population and under Section 14, Tables 3.3.6 for the post-Amendment 1 population.

**Table 30: Observation time in days by treatment arm (Safety Population)**

| | | A: RITUXIMAB (N=338) | B: OBSERVATION (N=344) | Total (N=682) |
|---|---|---|---|---|
| Observation time [days] | Mean | 1125 | 1118 | 1122 |
| | SD | 499.1 | 525.5 | 512.3 |
| | Median | 1352 | 1347 | 1352 |
| | Q1 / Q3 | 886.0 / 1379 | 820.5 / 1380 | 848.0 / 1379 |
| | Min / Max | 1.0 / 2299 | 1.0 / 2313 | 1.0 / 2313 |

A by-subject listing of Observation times is provided in Section 16, Listing 3.1.

Tables for Pre-Amendment 1 and Post-Amendment 1-subjets separately can be found under Section 14, Table 2.3.3 for the Pre-Amendment 1 population and under Section 14, Tables 3.3.3 for the post-Amendment 1 population.

**Table 31: Exposure to study medication / days in observation period (Safety Population)**

| | | A: RITUXIMAB (N=338) | B: OBSERVATION (N=344) | Total (N=682) |
|---|---|---|---|---|
| Time of exposure [days] | Mean | 522.8 | 519.5 | 521.1 |
| | SD | 196.7 | 194.7 | 195.6 |
| | Median | 617.0 | 617.0 | 617.0 |
| | Q1 / Q3 | 453.5 / 623.5 | 345.0 / 624.0 | 449.0 / 624.0 |
| | Min / Max | 1.0 / 731.0 | 1.0 / 727.0 | 1.0 / 731.0 |

A by-subject listing of Exposure/Observation periods is provided in Section 16, Listing 3.1.

Tables for Pre-Amendment 1 and Post-Amendment 1-subjets separately can be found under Section 14, Table 2.3.6 for the Pre-Amendment 1 population and under Section 14, Tables 3.3.6 for the post-Amendment 1 population.

The number of treatment cycles received was tabulated in Section 14, Tables 1.3.7-9.

Tables for Pre-Amendment 1 and Post-Amendment 1-subjets separately can be found under Section 14, Table 2.3.7-9 for the Pre-Amendment 1 population and under Section 14, Tables 3.3.7-9 for the post-Amendment 1 population.

**Table 32: Rituximab dose by visit (mg and mg calculated, ITT Population, patients receiving Rituximab only)**

| visit | | Actual dose (N=338) | Calculated dose (N=338) |
|---|---|---|---|
| Visit W1 | Dosage [mg] | | |
| | Mean | 683.8 | 688.0 |
| | SD | 80.9 | 85.1 |
| | Median | 697.0 | 686.0 |
| | Q1 / Q3 | 625.0 / 737.0 | 626.0 / 748.0 |
| | Min / Max | 500.0 / 900.0 | 488.0 / 982.0 |
| | Total | 336 | 336 |
| Visit W9 | Dosage [mg] | | |
| | Mean | 684.5 | 688.1 |
| | SD | 81.8 | 85.2 |
| | Median | 699.0 | 686.0 |
| | Q1 / Q3 | 626.0 / 735.0 | 626.0 / 746.0 |
| | Min / Max | 500.0 / 900.0 | 488.0 / 982.0 |
| | Total | 326 | 326 |
| Visit W17 | Dosage [mg] | | |
| | Mean | 682.9 | 687.9 |
| | SD | 91.0 | 85.2 |
| | Median | 699.0 | 686.0 |
| | Q1 / Q3 | 619.0 / 749.5 | 626.0 / 750.0 |
| | Min / Max | 0.0 / 902.0 | 488.0 / 982.0 |
| | Total | 312 | 313 |
| Visit W25 | Dosage [mg] | | |
| | Mean | 684.8 | 688.9 |
| | SD | 91.6 | 84.8 |
| | Median | 700.0 | 690.0 |
| | Q1 / Q3 | 626.0 / 750.0 | 626.0 / 750.0 |
| | Min / Max | 0.0 / 900.0 | 488.0 / 982.0 |

| visit | | Actual dose (N=338) | Calculated dose (N=338) |
|---|---|---|---|
| | Total | 302 | 303 |
| Visit W33 | Dosage [mg] | | |
| | Mean | 685.4 | 688.3 |
| | SD | 92.0 | 85.2 |
| | Median | 700.0 | 688.0 |
| | Q1 / Q3 | 625.0 / 750.0 | 626.0 / 750.0 |
| | Min / Max | 0.0 / 900.0 | 488.0 / 982.0 |
| | Total | 298 | 298 |
| Visit W41 | Dosage [mg] | | |
| | Mean | 685.4 | 689.0 |
| | SD | 90.6 | 84.3 |
| | Median | 700.0 | 690.0 |
| | Q1 / Q3 | 626.0 / 750.0 | 626.0 / 750.0 |
| | Min / Max | 0.0 / 900.0 | 488.0 / 982.0 |
| | Total | 293 | 293 |
| Visit W49 | Dosage [mg] | | |
| | Mean | 679.1 | 689.3 |
| | SD | 116.2 | 84.4 |
| | Median | 700.0 | 690.0 |
| | Q1 / Q3 | 626.0 / 750.0 | 630.0 / 750.0 |
| | Min / Max | 0.0 / 900.0 | 488.0 / 982.0 |
| | Total | 265 | 265 |
| Visit W57 | Dosage [mg] | | |
| | Mean | 682.4 | 689.6 |
| | SD | 108.6 | 84.6 |
| | Median | 700.0 | 688.0 |
| | Q1 / Q3 | 634.0 / 750.0 | 630.0 / 752.0 |
| | Min / Max | 0.0 / 920.0 | 488.0 / 982.0 |
| | Total | 260 | 260 |
| Visit W65 | Dosage [mg] | | |
| | Mean | 686.8 | 689.2 |
| | SD | 93.2 | 84.0 |

| visit | | Actual dose (N=338) | Calculated dose (N=338) |
|---|---|---|---|
| | Median | 700.0 | 688.0 |
| | Q1 / Q3 | 636.0 / 750.0 | 630.0 / 748.0 |
| | Min / Max | 0.0 / 920.0 | 488.0 / 982.0 |
| | Total | 256 | 256 |
| Visit W73 | Dosage [mg] | | |
| | Mean | 692.3 | 691.6 |
| | SD | 82.8 | 84.2 |
| | Median | 700.0 | 690.0 |
| | Q1 / Q3 | 641.0 / 750.0 | 634.0 / 754.0 |
| | Min / Max | 375.0 / 920.0 | 488.0 / 982.0 |
| | Total | 251 | 251 |
| Visit W81 | Dosage [mg] | | |
| | Mean | 689.8 | 692.2 |
| | SD | 93.5 | 84.4 |
| | Median | 700.0 | 690.0 |
| | Q1 / Q3 | 641.0 / 750.0 | 634.0 / 754.0 |
| | Min / Max | 0.0 / 920.0 | 488.0 / 982.0 |
| | Total | 245 | 247 |
| Visit W89 | Dosage [mg] | | |
| | Mean | 693.9 | 692.7 |
| | SD | 82.3 | 84.0 |
| | Median | 700.0 | 690.0 |
| | Q1 / Q3 | 645.0 / 750.0 | 638.0 / 754.0 |
| | Min / Max | 375.0 / 920.0 | 488.0 / 982.0 |
| | Total | 243 | 243 |
| In case that no Rituximab was administered at a specific visit, this visit is not displayed. | | | |

A by-subject listing of Rituximab doses is provided in Section 16, Listing 3.3.

Tables for Pre-Amendment 1 and Post-Amendment 1-subjets separately can be found under Section 14, Table 2.3.18 for the Pre-Amendment 1 population and under Section 14, Tables 3.3.18 for the post-Amendment 1 population.

Section 14, Tables 1.3.10-12 contain information regarding the pain reliver intake at Rituximab infusions. Section 14, Tables 1.3.13-15 contain information regarding the antihistamine intake at Rituximab infusions. Section 14, Tables 1.3.19-21 contain information regarding the volume and duration of Rituximab infusions.

Tables for Pre-Amendment 1 and Post-Amendment 1-subjets separately can be found under Section 14, Tables 2.3.10-15 and 2.3.19-21 for the Pre-Amendment 1 population and under Section 14, Tables 3.3.10-15 and 3.3.19-21 for the post-Amendment 1 population.

## 12.2 ADVERSE EVENTS (AES)

### 12.2.1 Brief Summary of Adverse Events

Adverse events were coded according to MedDRA (Version 13.1). Intensity grading was performed either by CTC (grade 1, 2, 3 and 4) or by clinical grading (mild, moderate, severe, life-threatening). For the analysis tables severe and life-threatening AEs were considered as AEs with grade 3 or 4, respectively. AEs with a causal relationship to the study drug (probable, possible or missing) were counted as related. If classification of intensity, seriousness or causality was missing for an Adverse Event, the worst case (intensity: grade 4; seriousness: yes; causality: probable) was assumed.

Only AEs were tabulated that started on or after randomization (post-randomization AEs); an AE was considered as post-randomization AE if, and only if, the first onset or worsening was simultaneous with or after the date of randomization. AEs for which it could not be clearly concluded that the start date was on or after the date of randomization were considered as post-randomization AEs, thus, following a worst case approach:

- If the start date was completely missing, the AE was considered as post-randomization AE.
- If only the year of the AE was available and the year was less than the year of the date of randomization, the AE was considered as AE that started prior to randomization; otherwise it was considered as post-randomization AE.
- If the year and the month of the AE were available and the year was less than the year of the date of randomization or the year of the AE was equal to the year of the date of randomization and the month of the AE was less than the month of the date of randomization, the AE was considered as AE that started prior to randomization; otherwise it was considered as post-randomization AE.

Table 33 presents an overall summary of all AEs experienced during the study, by study group (Arm A and B), AE incidence (subjects experiencing at least one event) and total number of events, for the Safety Population.

The corresponding tables can be found under Section 14, Table 1.4.1-12). Tables for Pre-Amendment 1 and Post-Amendment 1-subjets separately can be found under Section 14, Table 2.4.1-12 for the Pre-Amendment 1 population and under Section 14, Tables 3.4.1-12 for the post-Amendment 1 population.

**Table 33: Summary of adverse events (Safety population)**

| | Adverse Event | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=344) No. (%) | Total (N=682) No. (%) |
|---|---|---|---|---|
| AEs | Subjects with at least one adverse event | 232 (68.6) | 230 (66.9) | 462 (67.7) |
| | Total number of adverse events | 1003 | 830 | 1833 |
| AEs grade 3 or 4 | Subjects with at least one adverse event with grade 3 or 4 | 58 (17.2) | 56 (16.3) | 114 (16.7) |

| | Adverse Event | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=344) No. (%) | Total (N=682) No. (%) |
|---|---|---|---|---|
| | Total number of adverse events with grade 3 or 4 | 80 | 80 | 160 |
| related AEs | Subjects with at least one related adverse event | 86 (25.4) | 2 (0.6) | 88 (12.9) |
| | Total number of related adverse events | 179 | 2 | 181 |
| Related AEs grade 3 or 4 | Subjects with at least one related adverse event with grade 3 or 4 | 22 (6.5) | 2 (0.6) | 24 (3.5) |
| | Total number of related adverse events with grade 3 or 4 | 27 | 2 | 29 |
| AEs leading to dose adjustment, interruption or discontinuation | Subjects with at least one adverse event leading to dose adjustment, interruption or discontinuation | 38 (11.2) | 0 (0.0) | 38 (5.6) |
| | Total number of adverse events leading to dose adjustment, interruption or discontinuation | 43 | 0 | 43 |
| SAEs | Subjects with at least one serious adverse event | 62 (18.3) | 63 (18.3) | 125 (18.3) |
| | Total number of serious adverse events | 98 | 91 | 189 |
| Percentages are based on N | | | | |

There were 1833 AEs reported during the study by 462 (67.7%) of the 682 subjects in the Safety Population: 68.6% of patients in arm A and 66.9% of patients in arm B experienced at least one AE. By 114 (16.7%) patients of the 682 subjects in the Safety Population 160 AEs with grade 3 or 4 were reported during the study: 17.2% of patients in arm A and 16.3% of patients in arm B experienced at least one AE with grade 3 or 4.

There were 181 related AEs reported during the study by 88 (12.9%) of the 682 subjects in the Safety Population: 25.4% of patients in arm A and 0.6% of patients in arm B experienced at least one related adverse event. 29 related AEs with grade 3 or 4 were reported during the study by 24 (3.5%) of the 682 subjects in the Safety Population: 6.5% of patients in arm A and 0.6% of patients in arm B experienced at least one related AE with grade 3 or 4.

For 38 (5.6%) of the 682 subjects in the Safety Population there were 43 AEs leading to dose adjustment, interruption or discontinuation reported during the study: 11.2% of patients in arm A and 0.0% of patients in arm B experienced at least one adverse event leading to dose adjustment, interruption or discontinuation.

There were 189 SAEs reported during the study by 125 (18.3%) of the 682 subjects in the Safety Population: 18.3% of patients in arm A and 18.3% of patients in arm B experienced at least one SAE.

A by-subject listing of these AEs is provided in Section 16, Listings 3.4-9.

### 12.2.2 Display of Adverse Events

The following Adverse Event Tables were generated:

- Section 14, Table 1.4.1 shows the total number of AEs and the number and percentage of patients with at least one post-randomization AE by treatment arm.
- Section 14, Table 1.4.2 shows total number of AEs and the number and percentage of patients with at least one post-randomization AE with grade 3 or 4 by treatment arm.
- Section 14, Table 1.4.3 shows the total number of related post-randomization AEs and the number and percentage of patients with at least one related post-randomization AE by treatment arm.
- Section 14, Table 1.4.4 shows the total number of related post-randomization AEs and the number and percentage of patients with at least one related post-randomization AE with grade 3 or 4 by treatment arm.
- Section 14, Table 1.4.5 shows the total number of post-randomization AEs leading to dose adjustment and the number and percentage of patients with at least one post-randomization AE leading to dose adjustment / interruption or discontinuation by treatment arm.
- Section 14, Table 1.4.6 shows the total number of serious post-randomization AEs and the number and percentage of patients with at least one serious post-randomization AE by treatment arm.
- Section 14, Table 1.4.7 shows the total number of post-randomization AEs and the number and percentage of patients with at least one post-randomization AE by SOC, preferred term and treatment arm
- Section 14, Table 1.4.8 shows the total number of post-randomization AEs with grade 3 or 4 and the number and percentage of patients with at least one post-randomization AE with grade 3 or 4 by SOC, preferred term and treatment arm.
- Section 14, Table 1.4.9 shows the total number of related post-randomization AEs and the number and percentage of patients with at least one related post-randomization AE by SOC, preferred term and treatment arm.
- Section 14, Table 1.4.10 shows the total number of related post-randomization AEs and the number and percentage of patients with at least one related post-randomization AE with grade 3 or 4 by SOC, preferred term and treatment arm.
- Section 14, Table 1.4.11 shows the number and percentage of patients with at least one post-randomization AE leading to dose adjustment / interruption or discontinuation by SOC, preferred term and treatment arm.
- Section 14, Table 1.4.12 shows and the number and percentage of patients with at least one serious post-randomization AE by SOC, preferred term and treatment arm.

Tables for Pre-Amendment 1 and Post-Amendment 1-subjets separately can be found under Section 14, Table 2.4.1-12 for the Pre-Amendment 1 population and under Section 14, Tables 3.4.1-12 for the post-Amendment 1 population.

### 12.2.3 Analysis of Adverse Events

In the following all post-randomization AEs are tabulated by system organ class (Table 34). Further details regarding preferred term can be obtained from Section 14, Table 1.4.7.

**Table 34: At least one post-randomization AE by SOC and treatment arm (Safety Population)**

| Adverse Event | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=344) No. (%) | Total (N=682) No. (%) |
|---|---|---|---|
| Infections and infestations | 119 (35.2) | 104 (30.2) | 223 (32.7) |

| Adverse Event | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=344) No. (%) | Total (N=682) No. (%) |
|---|---|---|---|
| Gastrointestinal disorders | 67 (19.8) | 63 (18.3) | 130 (19.1) |
| Musculoskeletal and connective tissue disorders | 54 (16.0) | 72 (20.9) | 126 (18.5) |
| General disorders and administration site conditions | 50 (14.8) | 55 (16.0) | 105 (15.4) |
| Nervous system disorders | 46 (13.6) | 43 (12.5) | 89 (13.0) |
| Respiratory, thoracic and mediastinal disorders | 46 (13.6) | 35 (10.2) | 81 (11.9) |
| Skin and subcutaneous tissue disorders | 41 (12.1) | 30 (8.7) | 71 (10.4) |
| Blood and lymphatic system disorders | 38 (11.2) | 23 (6.7) | 61 (8.9) |
| Investigations | 31 (9.2) | 20 (5.8) | 51 (7.5) |
| Metabolism and nutrition disorders | 23 (6.8) | 27 (7.8) | 50 (7.3) |
| Vascular disorders | 24 (7.1) | 22 (6.4) | 46 (6.7) |
| Cardiac disorders | 20 (5.9) | 20 (5.8) | 40 (5.9) |
| Psychiatric disorders | 15 (4.4) | 20 (5.8) | 35 (5.1) |
| Injury, poisoning and procedural complications | 12 (3.6) | 18 (5.2) | 30 (4.4) |
| Eye disorders | 11 (3.3) | 13 (3.8) | 24 (3.5) |
| Reproductive system and breast disorders | 11 (3.3) | 13 (3.8) | 24 (3.5) |
| Hepatobiliary disorders | 14 (4.1) | 7 (2.0) | 21 (3.1) |
| Ear and labyrinth disorders | 10 (3.0) | 10 (2.9) | 20 (2.9) |
| Neoplasms benign, malignant and unspecified (incl. cysts and polyps) | 10 (3.0) | 10 (2.9) | 20 (2.9) |
| Surgical and medical procedures | 6 (1.8) | 8 (2.3) | 14 (2.1) |
| Endocrine disorders | 3 (0.9) | 8 (2.3) | 11 (1.6) |
| Renal and urinary disorders | 6 (1.8) | 5 (1.5) | 11 (1.6) |
| Immune system disorders | 5 (1.5) | 2 (0.6) | 7 (1.0) |
| Congenital, familial and genetic disorders | 2 (0.6) | 1 (0.3) | 3 (0.4) |
| Pregnancy, puerperium and perinatal conditions | 0 (0.0) | 1 (0.3) | 1 (0.1) |
| Social circumstances | 0 (0.0) | 1 (0.3) | 1 (0.1) |

The most common AEs in the Safety group were “Infections and infestations” (35.2% of patients in Arm A and 30.2% patients in Arm B), followed by “Gastrointestinal disorders” (19.8% of patients in Arm A and 18.3% patients in Arm B) and “Musculoskeletal and connective tissue disorders” (16.0% of patients in Arm A and 20.9% patients in Arm B). Also common were “General disorders and administration site conditions” (14.8% of patients in Arm A and 16.0% patients in Arm B), “Nervous system disorders” (13.6% of patients in Arm A and 12.5% patients in Arm B), “Respiratory, thoracic and mediastinal disorders” (13.6% of patients in Arm A and 10.2% patients in Arm B), “Skin and subcutaneous tissue disorders” (12.1% of patients in Arm A and 8.7% patients in

Arm B) and "Blood and lymphatic system disorders" (11.2% of patients in Arm A and 6.7% patients in Arm B). AEs that were observed in less than 10% in both arms are listed in the table above (Table 34).

A by-subject listing of these AEs is provided in Section 16, Listing 3.4.

Tables for Pre-Amendment 1 and Post-Amendment 1-subjets separately can be found under Section 14, Table 2.4.7 for the Pre-Amendment 1 population and under Section 14, Tables 3.4.7 for the post-Amendment 1 population.

### 12.2.4 Listing of Adverse Events by Patient

Seven listings containing Adverse Event information were generated for the Safety population:

- Section 16, Listings 3.4 shows a by-patient-listing of post-randomization Adverse Events.
- Section 16, Listings 3.5 shows a by-patient-listing of post-randomization grade 3 and 4 Adverse Events.
- Section 16, Listings 3.6 shows a by-patient-listing of related post-randomization Adverse Events.
- Section 16, Listings 3.7 shows a by-patient-listing of related post-randomization grade 3 and 4 Adverse Events by treatment arm.
- Section 16, Listings 3.8 shows a by-patient-listing of post-randomization Adverse Events leading to dose adjustment / interruption or discontinuation by treatment arm.
- Section 16, Listings 3.9 shows a by-patient-listing of serious post-randomization Adverse Events by treatment arm.
- Section 16, Listings 3.10 shows a by-patient-listing of Adverse Events prior Randomization.

## 12.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

### 12.3.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

The survival status of the patient was followed up during the study and serious Adverse Events had been reported.

#### 12.3.1.1 Deaths

All deaths that were observed during the study can be obtained from Section 16, Listing 2.10. 8% of patients in group A and 10.5% of patients in group B died during the study (Section 14, Table 1.2.25).

Tables for Pre-Amendment 1 and Post-Amendment 1-subjets separately can be found under Section 14, Table 2.2.25 for the Pre-Amendment 1 population and under Section 14, Tables 3.2.25 for the post-Amendment 1 population.

#### 12.3.1.2 Other Serious Adverse Events

A listing of all Serious AEs can be found in section Section 16, Listing 3.9. In both Arm A and B 18.3% of patients had at least one serious post-randomization AE (Section 14, Table 1.4.6).

Tables for Pre-Amendment 1 and Post-Amendment 1-subjets separately can be found under Section 14, Table 2.4.6 for the Pre-Amendment 1 population and under Section 14, Tables 3.4.6 for the post-Amendment 1 population.

#### 12.3.1.3 Significant Adverse Events

No analysis of significant AEs had been performed.

### 12.3.2 Narratives of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Narratives were not collected by Assign Data Management and Biostatistics GmbH who maintained the clinical study database. Narratives are available at the sponsor upon request.

### 12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

All serious adverse events are tabulated in Section 14, Tables 1.4.6 and listed in Section 16, Listing 3.9. This listing contains the causality assessment of the investigator. However, no table or listing of related serious adverse events was generated.

Tables for Pre-Amendment 1 and Post-Amendment 1-subjet SAEs separately can be found under Section 14, Table 2.4.6 for the Pre-Amendment 1 population and under Section 14, Tables 3.4.6 for the post-Amendment 1 population.

## 12.4 CLINICAL LABORATORY EVALUATION

### 12.4.1 Hematology and chemistry laboratory

#### 12.4.1.1 Listing of individual laboratory measurements by patient (16.2.) and each abnormal laboratory value (16.2)

Clinical hematology assessments were evaluated at Screening for all subjects and:

- For pre-Amendment 1 participants at Visit W9, W25, W41, End of Treatment/Observation Visit, Follow-up Visit M6, M12, M18 and M24
- For post-Amendment 1 participants at Visit W17, W33, W49, W65, W81, End of Treatment/Observation Visit, Follow-up Visit M6, M12, M18 and M24

Clinical chemistry assessments were evaluated at Screening and End of Treatment/Observation Visit.

By-subject listings of hematology abnormalities and serum chemistry abnormalities are provided in Section 16, Listing 3.19 and 3.20 respectively.

Hematology and serum chemistry results are provided in Section 14, Tables 1.4.17- 27 (Section 14, Table2.4.17-27 for pre-amendment 1 patients and Section 14, Table3.4.17-27 for post-Amendment 1 patients).

The following by-patient listings of Hematology and serum chemistry results were created:

- Hematology and serum chemistry results were provided in Section 16, Listing 3.17.1-15 (Hematology parameters) and 3.18 (Chemistry parameters).
- By-subject data listings for the parameters Platelets, White blood cells (total) and Neutrophils (segmented+bands) relative were provided including the details whether "due to bone marrow involvement" was ticked. They can be found in Section 16, Listing 3.21.
- A by-subject data listing for the parameters Bilirubin, Alk. Phospatase, GOT (AST) and GPT (ALT) was provided for including the details whether "due to liver involvement" was ticked. They are available in Section 16, Listing 3.22.

#### 12.4.1.2 Evaluation of Each Laboratory Parameter

No statistical comparisons between group A and group B were performed.

##### 12.4.1.2.1 Laboratory Values over Time

Tables of relative and absolute changes in laboratory values from Screening to the last follow-up-visit can be found in Section 14, Table 1.4.21-24 (by subject listings of values per visit in Section 16, Listing 3.17.1-15, 3.18

and 3.22) and relative and absolute hematology changes from Screening to the End of treatment are available in Section 14, Table 1.4.26-27 (by subject listings of values per visit in Section 16, Listing 3. 21).

Tables for Pre-Amendment 1 and Post-Amendment 1-subjets separately can be found under Section 14, Tables 2.4.21-24 and 2.4.26-27 for the Pre-Amendment 1 population and under Section 14, Tables 3.4.21-24 and 3.4.26-27 for the post-Amendment 1 population.

#### 12.4.1.2.2 Individual Patient Changes

Relative as well as absolute changes in laboratory parameters were tabulated for all patients (Section 14, Tables 21-24 and 1.4.26-27) However, no by- patient-listing was generated.

Tables for Pre-Amendment 1 and Post-Amendment 1-subjets separately can be found under Section 14, Tables 2.4.21-24 and 2.4.26-27 for the Pre-Amendment 1 population and under Section 14, Tables 3.4.21-24 and 3.4.26-27 for the post-Amendment 1 population.

#### 12.4.1.2.3 Individual Clinically Significant Abnormalities

In case of abnormality the investigator had to assess the clinical significance of the abnormality. These assessments can be obtained from Section 16, Listing 3.19 (hematology) and 3.20 (chemistry).

## 12.4.2 Viral tests (HIV, HBV and HCV)

### 12.4.2.1 HIV

Neither at screening, nor at End of treatment/Observation visit a HIV-Test was positive. The corresponding tables can be found under Table 35 and Section 14, Table 1.4.29.

**Table 35: HIV test results by visit and treatment arm (Safety Population)**

| visit | | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=344) No. (%) | Total (N=682) No. (%) |
|---|---|---|---|---|
| Screening | HIV | | | |
| | negative | 338 (100) | 343 (100) | 681 (100) |
| | positive | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Total | 338 | 343 | 681 |
| End of Treatment / Observation Visit | HIV | | | |
| | negative | 169 (100) | 141 (100) | 310 (100) |
| | positive | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Total | 169 | 141 | 310 |
| Percentages are based on the number of non-missing observations within each stratum (Total) | | | | |

A by-subject listing of the test results is provided in Section 16, Listing 3.23 and 3.24.

Tables for Pre-Amendment 1 and Post-Amendment 1-subjets separately can be found under Section 14, Tables 2.4.29 for the Pre-Amendment 1 population and under Section 14, Tables 3.4.29 for the post-Amendment 1 population.

### 12.4.2.2 HCV

At the Screening Visit, 0.9% of subjects in Arm A and 1.2% of patients in Arm B had a positive HCV test result. At the End of Treatment/Observation Visit 0.6% of remaining subjects in Arm A and 1.3% of remaining patients in Arm B had a positive HCV test result. The corresponding tables can be found under Table 36 and Section 14, Table 1.4.29.

**Table 36: HCV test results by visit and treatment arm (Safety Population)**

| visit | | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=344) No. (%) | Total (N=682) No. (%) |
|---|---|---|---|---|
| Screening | HCV | | | |
| | negative | 335 (99.1) | 339 (98.8) | 674 (99.0) |
| | positive | 3 (0.9) | 4 (1.2) | 7 (1.0) |
| | Total | 338 | 343 | 681 |
| End of Treatment / Observation Visit | HCV | | | |
| | negative | 174 (99.4) | 147 (98.7) | 321 (99.1) |
| | positive | 1 (0.6) | 2 (1.3) | 3 (0.9) |
| | Total | 175 | 149 | 324 |
| Percentages are based on the number of non-missing observations within each stratum (Total) | | | | |

A by-subject listing of the test results is provided in Section 16, Listing 3.23 and 3.24.

Tables for Pre-Amendment 1 and Post-Amendment 1-subjets separately can be found under Section 14, Tables 2.4.29 for the Pre-Amendment 1 population and under Section 14, Tables 3.4.29 for the post-Amendment 1 population.

### 12.4.2.3 HBV

At the Screening Visit, 0.9% of subjects in Arm A and 1.5% of patients in Arm B had positive HBV test results. At the End of Treatment/Observation Visit 5.1% of remaining subjects in Arm A and 6.3% of remaining patients in Arm B had a positive HBV test result. The corresponding tables can be found under Table 37 and Section 14, Table 1.4.29.

**Table 37: HBV test results by visit and treatment arm (Safety Population)**

| visit | | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=344) No. (%) | Total (N=682) No. (%) |
|---|---|---|---|---|
| Screening | HBV | | | |
| | negative | 335 (99.1) | 339 (98.5) | 674 (98.8) |
| | positive | 3 (0.9) | 5 (1.5) | 8 (1.2) |
| | Total | 338 | 344 | 682 |

| visit | | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=344) No. (%) | Total (N=682) No. (%) |
|---|---|---|---|---|
| End of Treatment / Observation Visit | HBV | | | |
| | negative | 166 (94.9) | 135 (93.8) | 301 (94.4) |
| | positive | 9 (5.1) | 9 (6.3) | 18 (5.6) |
| | Total | 175 | 144 | 319 |
| Percentages are based on the number of non-missing observations within each stratum (Total) | | | | |

A by-subject listing of the test results is provided in Section 16, Listing 3.23 and 3.24.

Tables for Pre-Amendment 1 and Post-Amendment 1-subjets separately can be found under Section 14, Tables 2.4.29 for the Pre-Amendment 1 population and under Section 14, Tables 3.4.29 for the post-Amendment 1 population.

## 12.5 VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

Results of pregnancy tests at Baseline are presented in Section 14, Table 1.1.36 (Section 14, Table 2.1.36 for pre-Amendment 1 and 3.1.36 for post-Amendment 1 separately) and in Section 16, Listing 1.28. No pregnancy test was positive at baseline.

Listings of pregnancy tests during the study are provided under Section 16, Listing 3.15 and 3.16.

## 12.6 NHL DIAGNOSTICS DURING STUDY

The results of the CTs (affection yes/no) were analyzed descriptively (frequency statistics) by visit. Visits with CT-assessments were:

- Pre-Amendment 1: Visits W9, W17, W25, W33, End of Treatment/Observation Visit, Follow-up M3- M60
- Post-Amendment 1: Visits W17, W33, W49, W65, W81, End of Treatment/Observation Visit, Follow-up M6, M12, M18, M24

The corresponding tables can be found under Section 14, Table 1.4.28 (Section 14, Table 2.4.28 for pre-Amendment 1 and 3.4.28 for post-Amendment 1 separately).

CT results as well as other NHL diagnostics (Endoscopy, Bone marrow, Molecular biology) as well as ECG results can be obtained from the by-subject listing in Section 16, Listing 3.11 and 3.12.

## 12.7 INFECTION

23.4% of patients in Arm A and 20.3% of patients in Arm B had at least one infection during follow-up (Section 14, Table 1.4.15). Of theses subjects, 3.6% of Arm A-patients and 1.2% of Arm B patients had at least one infection with grade 3 or 4 during follow-up (Section 14, Table 1.4.16).

A per-Visit tabulation of infections and CTC-of these infections can be found in Table 38 and Table 39.

**Table 38: Infection observed since last visit by visit and treatment arm (Safety Population)**

| Visit | | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=344) No. (%) | Total (N=682) No. (%) |
|---|---|---|---|---|
| Follow-up M3 | Infections observed since last visit | | | |
| | yes | 15 (6.2) | 8 (3.2) | 23 (4.7) |

| Visit | | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=344) No. (%) | Total (N=682) No. (%) |
|---|---|---|---|---|
| | no | 226 (93.8) | 242 (96.8) | 468 (95.3) |
| | Total | 241 | 250 | 491 |
| Follow-up M6 | Infections observed since last visit | | | |
| | yes | 17 (6.8) | 12 (4.7) | 29 (5.8) |
| | no | 234 (93.2) | 241 (95.3) | 475 (94.2) |
| | Total | 251 | 253 | 504 |
| Follow-up M9 | Infections observed since last visit | | | |
| | yes | 11 (4.5) | 13 (5.3) | 24 (4.9) |
| | no | 236 (95.5) | 230 (94.7) | 466 (95.1) |
| | Total | 247 | 243 | 490 |
| Follow-up M12 | Infections observed since last visit | | | |
| | yes | 14 (5.9) | 10 (4.3) | 24 (5.1) |
| | no | 225 (94.1) | 224 (95.7) | 449 (94.9) |
| | Total | 239 | 234 | 473 |
| Follow-up M15 | Infections observed since last visit | | | |
| | yes | 17 (7.2) | 19 (8.4) | 36 (7.8) |
| | no | 220 (92.8) | 207 (91.6) | 427 (92.2) |
| | Total | 237 | 226 | 463 |
| Follow-up M18 | Infections observed since last visit | | | |
| | yes | 14 (6.0) | 18 (8.1) | 32 (7.0) |
| | no | 218 (94.0) | 205 (91.9) | 423 (93.0) |
| | Total | 232 | 223 | 455 |
| Follow-up M21 | Infections observed since last visit | | | |
| | yes | 15 (6.9) | 7 (3.4) | 22 (5.2) |
| | no | 201 (93.1) | 200 (96.6) | 401 (94.8) |
| | Total | 216 | 207 | 423 |
| Follow-up M24 | Infections observed since last visit | | | |
| | yes | 9 (4.7) | 11 (6.4) | 20 (5.5) |
| | no | 181 (95.3) | 162 (93.6) | 343 (94.5) |
| | Total | 190 | 173 | 363 |
| Follow-up M27 | Infections observed since last visit | | | |

| Visit | | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=344) No. (%) | Total (N=682) No. (%) |
|---|---|---|---|---|
| | yes | 2 (13.3) | 1 (4.5) | 3 (8.1) |
| | no | 13 (86.7) | 21 (95.5) | 34 (91.9) |
| | Total | 15 | 22 | 37 |
| Follow-up M30 | Infections observed since last visit | | | |
| | yes | 0 (0.0) | 1 (5.0) | 1 (2.9) |
| | no | 15 (100) | 19 (95.0) | 34 (97.1) |
| | Total | 15 | 20 | 35 |
| Follow-up M33 | Infections observed since last visit | | | |
| | yes | 0 (0.0) | 2 (9.1) | 2 (5.9) |
| | no | 12 (100) | 20 (90.9) | 32 (94.1) |
| | Total | 12 | 22 | 34 |
| Follow-up M36 | Infections observed since last visit | | | |
| | yes | 1 (8.3) | 2 (8.7) | 3 (8.6) |
| | no | 11 (91.7) | 21 (91.3) | 32 (91.4) |
| | Total | 12 | 23 | 35 |
| Follow-up M42 | Infections observed since last visit | | | |
| | yes | 2 (15.4) | 2 (9.1) | 4 (11.4) |
| | no | 11 (84.6) | 20 (90.9) | 31 (88.6) |
| | Total | 13 | 22 | 35 |
| Follow-up M48 | Infections observed since last visit | | | |
| | yes | 0 (0.0) | 2 (11.1) | 2 (6.7) |
| | no | 12 (100) | 16 (88.9) | 28 (93.3) |
| | Total | 12 | 18 | 30 |
| Follow-up M54 | Infections observed since last visit | | | |
| | yes | 1 (8.3) | 2 (11.8) | 3 (10.3) |
| | no | 11 (91.7) | 15 (88.2) | 26 (89.7) |
| | Total | 12 | 17 | 29 |
| Follow-up M60 | Infections observed since last visit | | | |
| | yes | 1 (8.3) | 1 (5.9) | 2 (6.9) |
| | no | 11 (91.7) | 16 (94.1) | 27 (93.1) |
| | Total | 12 | 17 | 29 |

| Visit | | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=344) No. (%) | Total (N=682) No. (%) |
|---|---|---|---|---|
| End of study | Infections observed since last visit | | | |
| | yes | 16 (4.7) | 13 (3.8) | 29 (4.3) |
| | no | 322 (95.3) | 330 (96.2) | 652 (95.7) |
| | Total | 338 | 343 | 681 |
| Percentages are based on the number of non-missing observations within each stratum (Total) | | | | |

The corresponding tables can be found under Section 14, Table 1.4.13 (Section 14, Table 2.4.13 for-pre-Amendment 1 patients and 3.4.13 for post-Amendment 1 patients). By-patient listings are available in Section 16, Listing 3.13.

**Table 39: Infection observed: CTC grading by visit and treatment arm (Safety Population)**

| Visit | | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=344) No. (%) | Total (N=682) No. (%) |
|---|---|---|---|---|
| Follow-up M3 | Grade [CTC] | | | |
| | 1 | 10 (66.7) | 6 (75.0) | 16 (69.6) |
| | 2 | 4 (26.7) | 1 (12.5) | 5 (21.7) |
| | 3 | 1 (6.7) | 0 (0.0) | 1 (4.3) |
| | 4 | 0 (0.0) | 1 (12.5) | 1 (4.3) |
| | Total | 15 | 8 | 23 |
| Follow-up M6 | Grade [CTC] | | | |
| | 1 | 13 (76.5) | 4 (33.3) | 17 (58.6) |
| | 2 | 4 (23.5) | 8 (66.7) | 12 (41.4) |
| | 3 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | 4 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Total | 17 | 12 | 29 |
| Follow-up M9 | Grade [CTC] | | | |
| | 1 | 9 (81.8) | 8 (61.5) | 17 (70.8) |
| | 2 | 2 (18.2) | 5 (38.5) | 7 (29.2) |
| | 3 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | 4 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Total | 11 | 13 | 24 |
| Follow-up M12 | Grade [CTC] | | | |
| | 1 | 8 (57.1) | 4 (40.0) | 12 (50.0) |

| Visit | | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=344) No. (%) | Total (N=682) No. (%) |
|---|---|---|---|---|
| | 2 | 6 (42.9) | 6 (60.0) | 12 (50.0) |
| | 3 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | 4 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Total | 14 | 10 | 24 |
| Follow-up M15 | Grade [CTC] | | | |
| | 1 | 9 (52.9) | 12 (63.2) | 21 (58.3) |
| | 2 | 5 (29.4) | 6 (31.6) | 11 (30.6) |
| | 3 | 3 (17.6) | 1 (5.3) | 4 (11.1) |
| | 4 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Total | 17 | 19 | 36 |
| Follow-up M18 | Grade [CTC] | | | |
| | 1 | 9 (64.3) | 10 (55.6) | 19 (59.4) |
| | 2 | 5 (35.7) | 7 (38.9) | 12 (37.5) |
| | 3 | 0 (0.0) | 1 (5.6) | 1 (3.1) |
| | 4 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Total | 14 | 18 | 32 |
| Follow-up M21 | Grade [CTC] | | | |
| | 1 | 11 (73.3) | 4 (57.1) | 15 (68.2) |
| | 2 | 4 (26.7) | 3 (42.9) | 7 (31.8) |
| | 3 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | 4 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Total | 15 | 7 | 22 |
| Follow-up M24 | Grade [CTC] | | | |
| | 1 | 5 (55.6) | 8 (72.7) | 13 (65.0) |
| | 2 | 4 (44.4) | 3 (27.3) | 7 (35.0) |
| | 3 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | 4 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Total | 9 | 11 | 20 |
| Follow-up M27 | Grade [CTC] | | | |
| | 1 | 0 (0.0) | 1 (100) | 1 (33.3) |
| | 2 | 1 (50.0) | 0 (0.0) | 1 (33.3) |

| Visit | | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=344) No. (%) | Total (N=682) No. (%) |
|---|---|---|---|---|
| | 3 | 1 (50.0) | 0 (0.0) | 1 (33.3) |
| | 4 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Total | 2 | 1 | 3 |
| Follow-up M30 | Grade [CTC] | | | |
| | 1 | 0 (0.0) | 1 (100) | 1 (100) |
| | 2 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | 3 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | 4 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Total | 0 | 1 | 1 |
| Follow-up M33 | Grade [CTC] | | | |
| | 1 | 0 (0.0) | 1 (50.0) | 1 (50.0) |
| | 2 | 0 (0.0) | 1 (50.0) | 1 (50.0) |
| | 3 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | 4 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Total | 0 | 2 | 2 |
| Follow-up M36 | Grade [CTC] | | | |
| | 1 | 1 (100) | 0 (0.0) | 1 (33.3) |
| | 2 | 0 (0.0) | 2 (100) | 2 (66.7) |
| | 3 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | 4 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Total | 1 | 2 | 3 |
| Follow-up M42 | Grade [CTC] | | | |
| | 1 | 1 (50.0) | 0 (0.0) | 1 (25.0) |
| | 2 | 1 (50.0) | 2 (100) | 3 (75.0) |
| | 3 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | 4 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Total | 2 | 2 | 4 |
| Follow-up M48 | Grade [CTC] | | | |
| | 1 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | 2 | 0 (0.0) | 2 (100) | 2 (100) |
| | 3 | 0 (0.0) | 0 (0.0) | 0 (0.0) |

| Visit | | A: RITUXIMAB (N=338) No. (%) | B: OBSERVATION (N=344) No. (%) | Total (N=682) No. (%) |
|---|---|---|---|---|
| | 4 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Total | 0 | 2 | 2 |
| Follow-up M54 | Grade [CTC] | | | |
| | 1 | 0 (0.0) | 1 (50.0) | 1 (33.3) |
| | 2 | 0 (0.0) | 1 (50.0) | 1 (33.3) |
| | 3 | 1 (100) | 0 (0.0) | 1 (33.3) |
| | 4 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Total | 1 | 2 | 3 |
| Follow-up M60 | Grade [CTC] | | | |
| | 1 | 1 (100) | 0 (0.0) | 1 (50.0) |
| | 2 | 0 (0.0) | 1 (100) | 1 (50.0) |
| | 3 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | 4 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Total | 1 | 1 | 2 |
| End of study | Grade [CTC] | | | |
| | 1 | 3 (18.8) | 5 (38.5) | 8 (27.6) |
| | 2 | 7 (43.8) | 6 (46.2) | 13 (44.8) |
| | 3 | 3 (18.8) | 1 (7.7) | 4 (13.8) |
| | 4 | 3 (18.8) | 1 (7.7) | 4 (13.8) |
| | Total | 16 | 13 | 29 |
| Percentages are based on the number of non-missing observations within each stratum (Total) | | | | |

The corresponding tables can be found under Section 14, Table 1.4.14. (Section 14, Table 2.4.14 for-pre-Amendment 1 patients and 3.4.14 for post-Amendment 1 patients). By-patient listings are available in Section 16, Listing 3.13.

## 12.8 SAFETY POST-HOC ANALYSES

**Post-hoc analysis 3:**

Safety tables were created, stratified by sex and treatment arm: Section 14, Tables Safety 1 - 30.

The following tables were created, stratified by sex and treatment arm:

- Number of treatment cycles received for ITT (Section 14, Table Safety 1) and Safety population (Section 14, Table Safety 2) (Rituximab patients only).
- Rituximab infusion: pain reliever taken by visit for ITT (Section 14, Table Safety 3) and Safety population (Section 14, Table Safety 4) (Rituximab patients only).
- Rituximab infusion: antihistamine taken by visit for ITT (Section 14, Table Safety 5) and Safety population (Section 14, Table Safety 6) (Rituximab patients only).

- Rituximab dose by visit (mg and mg calculated) for ITT (Section 14, Table Safety 7) and Safety population (Section 14, Table Safety 8) (Rituximab patients only).
- Rituximab infusion: volume (in ml) and duration (in min) by visit for ITT (Section 14, Table Safety 9) and Safety population (Section 14, Table Safety 10) (Rituximab patients only).
- Rituximab infusion: any problems or side effects during infusion by visit for ITT (Section 14, Table Safety 11) and Safety population (Section 14, Table Safety 12) (Rituximab patients only).
- Tables of Safety population AEs were created for patients with:
  - At least one post-randomization AE (Section 14, Table Safety 13) and with grade 3 or 4 (Section 14, Table Safety 14).
  - At least one related post-randomization AE (Section 14, Table Safety 15) and with grade 3 or 4 (Section 14, Table Safety 1 16).
  - At least one post-randomization AE leading to dose adjustment / interruption or discontinuation (Section 14, Table Safety 17) and by SOC and preferred term (Section 14, Table Safety 23).
  - At least one serious post-randomization AE (Section 14, Table Safety 18) and by SOC and preferred term (Section 14, Table Safety 24).
  - At least one post-randomization AE by SOC and preferred term (Section 14, Table Safety 19) and with grade 3 or 4 (Section 14, Table Safety 20).
  - At least one related post-randomization AE by SOC and preferred term (Section 14, Table Safety 21) and with grade 3 or 4 by SOC, preferred term (Section 14, Table Safety 22).
- Infection observed since last visit by visit and treatment arm (Section 14, Table Safety 25) and CTC grading by visit (Section 14, Table Safety 26).
- At least one infection observed by treatment arm (Section 14, Table Safety 27) and for with grade 3 or 4 by treatment arm (Section 14, Table Safety 28).
- Unacceptable Toxicities for ITT (Section 14, Table Safety 29) and Safety population (Section 14, Table Safety 30).

**Post-hoc analysis 14:**

In the Post-hoc analysis 14 the number and percentage of patients with

- at least one post-randomization AE with grade 3 or 4
- at least one post-randomization AE by SOC and preferred term
- at least one infection (AEs in AE-section classification by Prof. Jäger on 29-Jul-2013)
- at least one infection (AEs in AE-section classification by Prof. Jäger on 29-Jul-2013) observed with grade 3 or 4
- at least one infection (Follow-up) observed
- at least one infection (Follow-up) observed with grade 3 or 4
- at least one infection (AEs in AE-section classification by Prof. Jäger on 29-Jul-2013 and FU) observed
- at least one infection (AEs in AE-section classification by Prof. Jäger on 29-Jul-2013 and FU) observed with grade 3 or 4

were tabulated for the following analysis populations:

- Safety Population, all patients by treatment and sex (Section 14, Tables by group and sex for all patients 1 – 8)
- Safety Population, all patients by treatment and sex (Section 14, Tables by group for all patients 1 - 8)
- Safety Population, all female patients by treatment (Section 14, Tables by group for female patients 1 - 8)
- Safety Population, all male patients by treatment (Section 14, Tables by group for male patients 1 - 8)
- Safety Population, all observation group patients by sex (Section 14, Tables by group for Observation patients 1 - 8)

Safety Population, all Treatment group patients by sex (Section 14, Tables by group for Rituximab patients 1 - 8)

## 12.9 SAFETY CONCLUSIONS

Adverse events were generally mild and equal between the treatment and observation arms with 17.2 and 16.3% of patients experiencing at least one CTC grade 3/4 adverse event (6.8 and 3.5% G 3/4 infections). Adverse events CTC grade 3/4 classified as related to RM were 6.5%. However, when adverse events were split into 4 groups by treatment arm and sex, a higher number of events were noted in female patients receiving RM. More women receiving RM had at least one adverse event CTC grade 3/4 (21.7 vs.12.3% in males, $p$=0.0297). Infections and infestations (all grades) occurred most frequently in female patients in the RM arm (40.6% vs. 29.4% in males with RM vs. 33.7% and 26.4% in the male and female observation arms, respectively ($p$=0.0341).

## 13. DISCUSSION AND OVERALL CONCLUSIONS

The results of this study indicate that RM treatment does not significantly prolong overall EFS or PFS of patients in CR or CRu after R-CHOP-like induction treatment for aggressive B-cell lymphoma. This is in line with the results of the ECOG 4494 trial. However, we identified a strong trend towards an improved EFS and a decrease in relapses in the RM arm in the ITT population. The most striking finding was the sex-specific outcome: While women had no benefit from RM, men had a significantly prolonged EFS and PFS. This indicates that RM is able to reverse the poor prognostic impact of male sex in DLBCL (and FLG3b), particularly in the low IPI subgroup. This is surprising since all previous evidence suggests that female lymphoma patients have a better outcome with R-containing therapy. Male sex has been identified as a poor prognostic factor in the RICOVER-60 study as well as in a recent meta-analysis of 3 major trials in R-CHOP treated DLBCL-patients older than 60 years. The clinical phenomenon is supported by pharmacokinetic data showing higher R serum concentrations in female patients. Pfreundschuh and colleagues suggested that the sex-specific difference in response is stronger because of a diminished rituximab clearance in older female patients. In our study, there was no difference in EFS between RM and observation in women of both age groups (≤60 vs. >60), while men benefitted from RM in both. On the other hand, our data confirm the observation that patients with higher body weight and higher BMI profit more from R treatment.

A possible explanation for the better outcome of men in our study is that female patients with DLBCL in CR may have deeper remissions and already saturated R serum levels after induction treatment. This hypothesis is supported by the higher number of infections in women. On the other hand, male patients may still be underdosed with the current R standard regimen of 375mg/m$^2$ in R-CHOP induction. We hypothesize that RM could eliminate residual lymphoma cells. Another possible explanation is a selection of good-risk male patients after induction as indicated by the almost equal numbers of male and female patients entering this study in CR, while there usually is a slight male predominance in DLBCL at diagnosis. Men with a low IPI had a nearly optimal outcome with a 3-year PFS of 96.1%. These patients were younger (81.5% ≤ 60 years vs. 40.2% in the IPI>1 group) and had received 6 cycles of R-CHOP instead of 8 more

frequently (46.9 vs 40.7%) compared to the IPI>1 group (34.1 vs. 62.2%). The low IPI subgroup is treated with 6 cycles of R-CHOP-21 according to current standards.

Consolidation therapy with radiation has shown a benefit for R-CHOP treated patients, particularly in limited stages. However, less than 3% of patients in NHL13 received planned radiation therapy, suggesting that RM could potentially substitute for radiotherapy. This may be important for patients with bulky disease. Future will show if other maintenance therapies (e.g. with lenalidomide) have a different effect regarding subgroups.

Overall survival was not different between RM and observation indicating that patients can be rescued by salvage treatment including autologous stem cell transplantation. This has to be weighed against the fact that RM patients can be spared exhausting second-line treatment.

There are some differences in regard to other RM studies: In the ECOG 4494 trial patients were over 60 years old, PR patients were also included, and the R regimen was different (4 x R weekly with 6 months interval). The Chinese study included patients under 60 years treated with 6 x R-CHOP-14 regardless of remission status after induction. R was administered every month for the first year and every 3 months for the second year. Numbers in subgroups (e.g. sex, IPI) were small and gender outcome was not reported. This also raises the question as to the optimal way of dosing and scheduling of R during DLBCL treatment. It will also be interesting to compare RM with intensified or extended R treatment during induction as initiated by the German study group, as well the effect of other anti-CD20 antibodies such as obinotuzumab or ofatumumab.

Our study has some weaknesses. There was no upfront stratification for gender. However, sex-specific analysis was pre-planned and the study is sufficiently large to exclude major biases. Central histopathological review was only performed for Austrian patients. The fact that there were no significant differences in outcome between the Austrian and all other patients argues for the validity of the data. FLG3b patients were included since at the time of study initiation it was believed that FLG3b behave similar to DLBCL. This has recently been questioned. However, only 3% FLG3b recruited were included. Some regional differences were seen. The response before inclusion in the study was investigator assessed and

not centrally reviewed. Nevertheless, the outcome of CR and CRu patients was not significantly different and the adherence to CT scans was high with a median number of CTs done by attended visit of 90%. These facts make it unlikely that the results of the study were significantly skewed.

*In conclusion,* the trial demonstrates that rituximab maintenance does not improve the outcome of the whole patient cohort with aggressive B-NHL in first remission. However, the results from NHL13 show that the prognosis of male patients with aggressive B-NHL is significantly improved by addition of 2-monthly RM for 2 years after R-CHOP-like first-line treatment. This finding should lead to the design of sex-specific clinical trials exploring different schedules with higher or prolonged R dosing in men.

## 14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

Section 14 is provided in a separate document.

## 15. REFERENCE LIST

References are provided as end notes to this document.

## 16. APPENDICES

Section 16 is provided in a separate document.

## Reference List


[1] Cheson et al., **1999**: Journal of Clinical Oncology Vol 17, No 4 (April), pp 1244-1253.

[2] World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Patients. Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, and amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975; 35th World Medical Assembly, Venice, Italy, October 1983; 41st World Medical Assembly, Hong Kong, September 1989.

[3] Swerdlow SH et al. (Eds.), **2008**: *WHO classification of tumours of hematopoietic and lymphoid tissues*. 4th edition Lyon, IARC press.

[4] Campo E, et al., **2011**: *The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications*. Blood 117: pp 5019-5032.

[5] Armitage JO,. **2012**: *My treatment approach to patients with diffuse large B-cell lymphoma*. Mayo Clin Proc 87: pp 161-171.

[6] Martelli M, et al., **2013**: *Diffuse large B-cell lymphoma.* Critical Rev in Oncology/Hematology 87: pp 146-171.

[7] Sehn LH., **2007**: The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood 2007 109:1857-61.

[8] Fisher RI and Shah P., **2003**: *Current trends in large cell lymphoma*. Leukemia 17: pp 1948-1960.

[9] Shipp M et al., **1993**: *The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A Predictive Model for Aggressive Non-Hodgkin's Lymphoma.* New England Journal of Medicine 329: pp 987–994.

[10] Ghielmini M et al., **2012: *ESMO guidelines consensus conference on malignant lymphoma 2011 part 1 : diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL)***. Ann Oncol 24: pp 561-576.

[11] Pfreundschuh M et.al., **2006: *CHOP-like chemotherapy plus Rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group.*** Lancet Oncology 7: pp 379–391.

[12] Coiffier B et al., **2002: *CHOP chemotherapy plus Rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma.*** New England Journal of Medicine 346: pp 235–242.

[13] Pfreundschuh M et al., **2008**: *Six versus eight cycles of bi-weekly CHOP-14 with or without Rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60).* Lancet Oncology 9: pp 105–116.

[14] Schmitz N et al., **2011**: *Conventional chemoimmunotherapy (R-CHOEP-14) or high-dose therapy (R-MEGA-CHOEP) for young, high-risk patients with aggressive B-cell lymphoma: final results of the randomized MEGA-CHOEP-Trial of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL).* Ann Oncol 22: pp 106–107.

[15] Recher C et al., **2011: *Intensified chemotherapy with ACVBP plus Rituximab versus standard CHOP plus Rituximab for the treatment of diffuse large B-cell lymphoma (LNH03-2B): an open-label randomised phase 3 trial.*** The Lancet. 378: pp 1858-1867.

[16] Reyes F et al., **2005**: *ACVBP versus CHOP plus radiotherapy for localized aggressive lymphoma.* N Engl J Med 352(12): pp 1197-1205.

[17] Murawski N et al., **2012**: *Improved outcome of elderly dLBCL patients with 6xCHOP-14 and 8 Rituximab applications given over an extended period (SMARTE-R-CHOP-14 DSHNHL trial) is due to better results of male patients.* Haematologica 97: p 109.

[18] Philip T et al., 1995: *Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive Non-Hodgkin´s lymphoma*. N Engl J Med 333: pp 1540–1545.

[19] Milpied N-J et al., 2010: *No benefit of first-line Rituximab (R)—high-dose therapy (R-HDT) over R-CHOP14 for young adults with diffuse largeB-cell lymphoma. preliminary results of the GOELAMS 075 prospective multicentre randomized trial*. ASH Annual Meeting Abstracts 116: p 685.

[20] Shustik J et al., 2011: *Follicular non-Hodgkin lymphoma grades 3A and 3B have a similar outcome and appear incurable with anthracycline-based therapy*. Ann Oncol 22: pp 1164-1169.

[21] Ganti AK et al., 2006: *Patients with grade 3 follicular lymphoma have prolonged relapse-free survival following anthracycline-based chemotherapy: the Nebraska Lymphoma Study Group experience*. Ann Oncol 17: pp 920–927.

[22] Czuczman MS et al., 1999: *Treatment of Patients with Low Grade B-Cell Lymphoma with the Combination of the Chimeric Anti CD20 Monoclonal Antibody and CHOP Chemotherapy*. J Clin Oncol, 17: pp 268-276.

[23] Hainsworth JD et al., 2002: *Rituximab as first-line and maintenance therapy for patients with indolent non-Hodgkin's lymphoma: interim follow-up of a multicenter phase II trial.* Semin Oncol. 29 (1 Suppl 2): 25-29.

[24] Ghielmini M et al., 2004: *Prolonged treatment with Rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule.* Blood. 103 (12): pp 4416-4423.

[25] Martinelli G et al., 2010: *Long-term follow-up of patients with follicular lymphoma receiving single-agent Rituximab at two different schedules in trial SAKK 35/98*. J Clin Oncol. Oct 10; 28 (29): pp 4480-4484.

[26] Van Oers MHJ et al., 2010: *Rituximab maintenance treatment of relapsed/resistant follicular Non-Hodgkin's lymphoma: long-term outcome of the EORTC 20981 phase III randomized intergroup study*. J Clin Oncol 28: pp 2853–2858.

[27] Salles G et al., 2011: *Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to Rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial.* Lancet 377: pp 42–51.

[28] Rummel MJ et al., 2013: *Bendamustine plus Rituximab versus CHOP plus Rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial.* Lancet 381: pp 1203-1210.

[29] Vidal L et al., 2009: *Rituximab maintenance for the treatment of patients with follicular lymphoma: systematic review and meta-analysis of randomized trials.* J Natl Cancer Inst 101: pp 248–255.

[30] Dreyling M et al., 2013: *ESMO Consensus conferences: guidelines on malignant lymphoma. part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma.* Ann Oncol 24: pp 857-877.

[31] Jäger U et al., 2012: *Rituximab serum concentrations during immuno-chemotherapy of follicular lymphoma correlate with patient gender, bone marrow infiltration and clinical response.* Haematologica 97: pp 1431-1438.

[32] Müller C et al., 2012: *The role of sex and weight on Rituximab clearance and serum elimination half-life in elderly patients with DLBCL*. Blood 119 (14): pp 3276-3284.

[33] Habermann TM et al., 2006: *Rituximab-CHOP versus CHOP alone or with maintenance Rituximab in older patients with diffuse large B-cell lymphoma*. Journal of Clinical Oncology 24: pp 3121–3127.

[34] Huang B-T et al., 2012: *How to determine post-RCHOP therapy for risk-tailored adult patients with diffuse large B-cell lymphoma, addition of maintenance Rituximab or observation: multicenter experience.* J Cancer Res Clin Oncol 138: pp 125–132.

[35] Gisselbrecht C et al., 2012: Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20+ diffuse large B-cell lymphoma: Final analysis of the collaborative trial in relapse aggressive lymphoma. J Clin Oncol 30: pp 4462-4469.