**DPTLDSG**
**Deutsche PTLD Studiengruppe e.V.**

TRIAL PROTOCOL

# RISK-STRATIFIED SEQUENTIAL TREATMENT OF POST-TRANSPLANT LYMPHOPROLIFERATIVE DISEASE WITH 4 COURSES OF RITUXIMAB SC FOLLOWED BY 4 COURSES OF RITUXIMAB SC, 4 COURSES OF RITUXIMAB SC COMBINED WITH CHOP-21 OR 6 COURSES OF RITUXIMAB SC COMBINED WITH ALTERNATING CHOP-21 AND DHAOX: THE PTLD-2 TRIAL


Sponsor:

DIAKO Ev. Diakonie-Krankenhaus Bremen gemeinnützige GmbH
Gröpelinger Heerstrasse 406-408
28239 Bremen
Germany

Principal Coordinating Investigator:

Prof. Dr. med. Ralf Ulrich Trappe
DIAKO Ev. Diakonie-Krankenhaus Bremen gemeinnützige GmbH
Gröpelinger Heerstrasse 406-408
28239 Bremen
Germany



Trial protocol code: DPTLDSG-IIT-PTLD-2

NCT: NCT02042391

DRKS: DRKS00005380

EudraCT number: 2013-004479-11

Version of 30 September 2017, Version 3-0

## I. Signatures

Prof. Dr. med. Ralf Ulrich Trappe
(Principal Coordinating Investigator [PCI, LKP])

30.09.17

On behalf of the sponsor — Signature — Date
DIAKO Bremen gGmbH
Medical contact of the sponsor
Director Department of Hematology and Oncology, DIAKO Bremen gGmbH

Prof. Dr. med. Hanno Riess
(Protocol Committee)

Head Department of Oncology, Hematology and — Signature — Date
Tumor Immunology, Charité Campus Mitte, Charité-Universitätsmedizin Berlin

Prof. Dr. med. Martin Dreyling
(Protocol Committee)

Director Lymphoma Program, Medical Department III — Signature — Date
University Medical Center Munich - Campus Grosshadern

Prof. Dr. med. Ulrich Dührsen
(Protocol Committee)

Director Department of Hematology — Signature — Date
University of Duisburg-Essen

Priv.-Doz. Dr. med. Mathias Witzens-Harig
(Protocol Committee)

Director Lymphoma Program, Department of Hematology, Oncology and Rheumatology — Signature — Date
University of Heidelberg

Prof. Dr. med. Peter Schlattmann
(Statistics)

Statistician — Signature — Date
Deputy Head Institute of Medical Statistics, Computer Sciences and Documentation, University of Jena

# I. Signatures

Prof. Dr. med. Ralf Ulrich Trappe
(Principal Coordinating Investigator [PCI, LKP])

On behalf of the sponsor
DIAKO Bremen gGmbH
Medical contact of the sponsor
Director Department of Hematology and Oncology, DIAKO Bremen gGmbH

Signature _____ Date _____

Prof. Dr. med. Hanno Riess
(Protocol Committee)

Head Department of Oncology, Hematology and Tumor Immunology, Charité Campus Mitte, Charité-Universitätsmedizin Berlin

Signature _____ Date 11.10.17

Prof. Dr. med. Martin Dreyling
(Protocol Committee)

Director Lymphoma Program, Medical Department III
University Medical Center Munich - Campus Grosshadern

Signature _____ Date _____

Prof. Dr. med. Ulrich Dührsen
(Protocol Committee)

Director Department of Hematology
University of Duisburg-Essen

Signature _____ Date _____

Priv.-Doz. Dr. med. Mathias Witzens-Harig
(Protocol Committee)

Director Lymphoma Program, Department of Hematology, Oncology and Rheumatology
University of Heidelberg

Signature _____ Date _____

Prof. Dr. med. Peter Schlattmann
(Statistics)

Statistician
Deputy Head Institute of Medical Statistics, Computer Sciences and Documentation, University of Jena

Signature _____ Date _____

# I. Signatures

Prof. Dr. med. Ralf Ulrich Trappe
(Principal Coordinating Investigator [PCI, LKP])

On behalf of the sponsor
DIAKO Bremen gGmbH
Medical contact of the sponsor
Director Department of Hematology and Oncology, DIAKO Bremen gGmbH

Signature _____ Date _____

Prof. Dr. med. Hanno Riess
(Protocol Committee)

Head Department of Oncology, Hematology and Tumor Immunology, Charité Campus Mitte, Charité-Universitätsmedizin Berlin

Signature _____ Date _____

Prof. Dr. med. Martin Dreyling
(Protocol Committee)

Director Lymphoma Program, Medical Department III
University Medical Center Munich - Campus Grosshadern

Signature _____ Date 30.9.2017

Prof. Dr. med. Ulrich Dührsen
(Protocol Committee)

Director Department of Hematology
University of Duisburg-Essen

Signature _____ Date _____

Priv.-Doz. Dr. med. Mathias Witzens-Harig
(Protocol Committee)

Director Lymphoma Program, Department of Hematology, Oncology and Rheumatology
University of Heidelberg

Signature _____ Date _____

Prof. Dr. med. Peter Schlattmann
(Statistics)

Statistician
Deputy Head Institute of Medical Statistics, Computer Sciences and Documentation, University of Jena

Signature _____ Date _____

# I. Signatures

Prof. Dr. med. Ralf Ulrich Trappe
(Principal Coordinating
Investigator [PCI, LKP])

On behalf of the sponsor
DIAKO Bremen gGmbH
Medical contact of the sponsor
Director Department of Hematology and Oncology, DIAKO Bremen gGmbH

Signature _____ Date _____

Prof. Dr. med. Hanno Riess
(Protocol Committee)

Head Department of Oncology, Hematology and
Tumor Immunology, Charité Campus Mitte, Charité-Universitätsmedizin Berlin

Signature _____ Date _____

Prof. Dr. med. Martin Dreyling
(Protocol Committee)

Director Lymphoma Program, Medical Department III
University Medical Center Munich - Campus Grosshadern

Signature _____ Date _____

Prof. Dr. med. Ulrich Dührsen
(Protocol Committee)

Director Department of Hematology
University of Duisburg-Essen

Signature _____ Date 30 OCT-2017

Priv.-Doz. Dr. med. Mathias Witzens-Harig
(Protocol Committee)

Director Lymphoma Program, Department of
Hematology, Oncology and Rheumatology
University of Heidelberg

Signature _____ Date _____

Prof. Dr. med. Peter Schlattmann
(Statistics)

Statistician
Deputy Head Institute of Medical Statistics, Computer Sciences and Documentation, University of Jena

Signature _____ Date _____

# I. Signatures

Prof. Dr. med. Ralf Ulrich Trappe
(Principal Coordinating Investigator [PCI, LKP])

On behalf of the sponsor
DIAKO Bremen gGmbH
Medical contact of the sponsor
Director Department of Hematology and Oncology, DIAKO Bremen gGmbH

Signature _____ Date _____

Prof. Dr. med. Hanno Riess
(Protocol Committee)

Head Department of Oncology, Hematology and Tumor Immunology, Charité Campus Mitte, Charité-Universitätsmedizin Berlin

Signature _____ Date _____

Prof. Dr. med. Martin Dreyling
(Protocol Committee)

Director Lymphoma Program, Medical Department III
University Medical Center Munich - Campus Grosshadern

Signature _____ Date _____

Prof. Dr. med. Ulrich Dührsen
(Protocol Committee)

Director Department of Hematology
University of Duisburg-Essen

Signature _____ Date _____

Priv.-Doz. Dr. med. Mathias Witzens-Harig
(Protocol Committee)

Director Lymphoma Program, Department of Hematology, Oncology and Rheumatology
University of Heidelberg

Signature M. Witzens-Harig Date 10.10.2017

Prof. Dr. med. Peter Schlattmann
(Statistics)

Statistician
Deputy Head Institute of Medical Statistics, Computer Sciences and Documentation, University of Jena

Signature _____ Date _____

# I. Signatures

Prof. Dr. med. Ralf Ulrich Trappe
(Principal Coordinating Investigator [PCI, LKP])

On behalf of the sponsor
DIAKO Bremen gGmbH
Medical contact of the sponsor
Director Department of Hematology and Oncology, DIAKO Bremen gGmbH

Signature _____ Date _____

Prof. Dr. med. Hanno Riess
(Protocol Committee)

Head Department of Oncology, Hematology and Tumor Immunology, Charité Campus Mitte, Charité-Universitätsmedizin Berlin

Signature _____ Date _____

Prof. Dr. med. Martin Dreyling
(Protocol Committee)

Director Lymphoma Program, Medical Department III
University Medical Center Munich - Campus Grosshadern

Signature _____ Date _____

Prof. Dr. med. Ulrich Dührsen
(Protocol Committee)

Director Department of Hematology
University of Duisburg-Essen

Signature _____ Date _____

Priv.-Doz. Dr. med. Mathias Witzens-Harig
(Protocol Committee)

Director Lymphoma Program, Department of Hematology, Oncology and Rheumatology
University of Heidelberg

Signature _____ Date _____

Prof. Dr. med. Peter Schlattmann
(Statistics)

Statistician
Deputy Head Institute of Medical Statistics, Computer Sciences and Documentation, University of Jena

Signature _____ Date 30.3.2017

## II. Synopsis

| | |
|---|---|
| Sponsor: | DIAKO Ev. Diakonie-Krankenhaus Bremen gGmbH<br>Gröpelinger Heerstrasse 406-408<br>28239 Bremen, Germany<br><br>Represented by:<br>Walter Eggers, General Manager [Geschäftsführer] |
| Principal Coordinating Investigator: | Prof. Dr. med. Ralf Ulrich Trappe<br>Department of Hematology and Oncology<br>DIAKO Ev. Diakonie-Krankenhaus Bremen gGmbH<br>Gröpelinger Heerstrasse 406-408<br>28239 Bremen, Germany |
| Title of the clinical trial: | Risk-stratified sequential treatment of post-transplant lymphoproliferative disease (PTLD) with 4 courses of rituximab SC* followed by 4 courses of rituximab SC, 4 courses of rituximab SC combined with CHOP-21 or 6 courses of rituximab SC combined with alternating CHOP-21 and DHAOx: The PTLD-2 trial |
| Indication: | Previously untreated CD20-positive lymphoproliferative disorder (PTLD) following solid organ transplantation |
| Phase: | Phase II clinical trial |

* the first application of rituximab is IV, all subsequent applications are SC

| | |
|---|---|
| Type of trial, trial design, methodology: | Multicenter clinical trial<br>One arm, open label survival study |
| Number of subjects: | 60 (≥15 evaluable patients in the rituximab monotherapy arm) |

Primary trial objective:

To determine the safety and the efficacy of first-line risk stratified* sequential treatment with 4 weekly courses of rituximab SC** followed by

- 4 courses of rituximab SC monotherapy ever 3 weeks in low-risk patients,
- 4 cycles of rituximab SC plus CHOP (+GCSF) ever 3 weeks in high-risk patients,
- 6 alternating cycles of rituximab SC plus CHOP+GCSF or DHAOx+GCSF applied ever 3 weeks in very high-risk patients

diagnosed with CD20-positive post-transplant lymphoproliferative disorder following solid organ transplantation

---

* risk stratification is by response to the first 4 courses of rituximab, IPI and type of transplant

** the first application of rituximab is IV, all subsequent applications are SC

Study end points:

Primary end point:

- Event free survival (EFS) of low-risk patients in the intention to treat population defined as time from start of treatment to event with following definitions for low-risk and event:

*1. Low-risk:*

- all patients in complete remission at interim staging, i.e. 4 weeks after the four weekly courses of rituximab SC monotherapy
- all patients in partial remission at interim staging with an initial international prognostic index (IPI) of 0,1 or 2

*2. Events:*

- any grade III or IV infection during the 20-week treatment period
- treatment discontinuation for any reason
- disease progression at any time
- death (any cause)

Secondary end points:

- Overall survival, time to progression, progression free survival, response and overall response at interim staging, response and overall response after full treatment, duration of response, treatment related mortality in the ITT and PP population
- Secondary end points will be analyzed in the total trial cohort and by treatment group

Other variables:

- Frequency of grade III and IV leucocytopenia and grade III and IV infections by treatment group

Criteria for evaluation:

Efficacy:

- Response to treatment will be determined according to the response criteria for malignant lymphoma *(Cheson et al., 1999)* (Appendix 11.10). CT scans chest, abdomen and pelvis, bone marrow biopsy, blood laboratory information and disease related symptom assessment will be performed and constitute the primary source for response / progression determination. Details are given in Table 13.
- Primary source data for efficacy parameters will be sent to the DPTLDSG study office for central review.

Safety:

- Adverse events will be evaluated each treatment visit, at interim and final staging
- Primary source data for any grade 3 and 4 infection during the treatment period will be sent to the DPTLDSG study office for review.

Medical Condition and Principal inclusion and exclusion criteria:

Medical condition or disease to be investigated:

- CD20-positive post-transplant lymphoproliferative disorder (PTLD) following solid organ transplantation

Principal inclusion criteria:

- CD20-positive PTLD with or without EBV association, confirmed after biopsy or resection of tumor
- Measurable disease of > 2 cm in diameter and/or bone marrow involvement
- Patients having undergone heart, lung, liver, kidney, pancreas, small intestine transplantation or a combination of the organ transplantations mentioned

- ECOG ≤ 2
- Clinically insufficient response to an upfront reduction of immunosuppression with or without antiviral therapy
- Age at least 18 years
- Not legally incapacitated
- Written informed consent from the trial subject has been obtained
- Negative pregnancy test (females with child-bearing potential only; not required in postmenopausal women and permanently sterilised women)
- Use of highly-effective contraceptive methods during treatment and for 12 months following study therapy (this applies to female trial participants as well as female partners of male participants: females with child-bearing potential only)

Principal exclusion criteria:

- Complete surgical extirpation of the tumor or irradiation of residual tumor masses
- Missing data for IPI stratification
- Upfront treatment with rituximab or chemotherapy
- Known hypersensitivity to rituximab, murine proteins or to any of the excipients
- Concomitant diseases which exclude the administration of therapy as outlined by the study protocol, in particular: severe heart failure (New York Heart Association Class IV), severe uncontrolled cardiac disease; HIV infection; other active, severe infections such as tuberculosis or Hepatitis B
- Meningeal and CNS involvement
- Pregnant women and nursing mothers
- Persons held in an institution by legal or official order
- Persons with any kind of dependency on the investigator or employed by the sponsor or investigator
- Life expectancy less than 6 weeks

| | |
|---|---|
| Name of investigational medicinal product (IMP): | Mabthera SC® |
| Investigational medicinal product – dosage and method of administration: | 1400 mg fixed dose, subcutaneous injection (SC) |
| IMP or therapy used as a comparator – dosage and method of administration: | Historical survival of patients treated with 4 courses of Mabthera IV (375 mg/m$^2$) followed by four cycles of CHOP-21 + GCSF (PTLD-1 trial) |
| Duration of treatment: | Low-risk patients: 4 weekly applications of rituximab SC monotherapy (4 weeks), 4 weeks without treatment, 4 applications of rituximab SC every 3 weeks (12 weeks).<br>High-risk patients: 4 weekly applications of rituximab SC monotherapy (4 weeks), 4 weeks without treatment, 4 cycles of rituximab SC plus CHOP+GCSF every 3 weeks (12 weeks).<br>Very high-risk patients: 4 weekly applications of rituximab SC monotherapy (4 weeks), 4 weeks without treatment, 3 alternating cycles of rituximab SC plus CHOP-21+GCSF and 3 cycles of rituximab SC and DHAOx+GCSF (18 weeks).<br>Follow-up until the trial is officially closed; minimal follow-up one year. |

| | | |
|---|---|---|
| Schedule: | First patient first visit (FPFV): | 1 October 2014 |
| | Last patient first visit (LPFV): | 31 March 2021 |
| | Last patient last visit (LPLV): | 31 July 2022 |
| | Final study report: | 31 December 2022 |

| | |
|---|---|
| Statistician: | Prof. Dr. med. Peter Schlattmann<br>Institute of Medical Statistics, Computer Sciences and Documentation<br>University of Jena<br>Bachstrasse 18<br>07743 Jena<br>Germany |
| Statistical methods: | This phase II study compares historical survival with rituximab IV followed by CHOP+GCSF (PTLD-1 trial, ST cohort) with rituximab SC monotherapy in the low-risk patient cohort using a one-arm survival study. For the historical control group from the PTLD-1 trial the event free survival probability at 24 months is known to be 0.51. For a similar risk group the event free survival probability at 24 months in the PTLD-2 trial is assumed to be 0.82. Log-rank statistics to Kaplan-Meier analysis will be used to compare the event free-survival in the two patient cohorts. |
| GCP conformance: | The present trial will be conducted in accordance with the valid versions of the trial protocol and the internationally recognized Good Clinical Practice Guidelines (ICH-GCP), including archiving of essential documents. |
| Financing: | Roche Pharma AG<br>German PTLD Study Group |

## III. Synopse in deutscher Sprache

| | |
|---|---|
| Sponsor: | DIAKO Ev. Diakonie-Krankenhaus Bremen gGmbH<br>Gröpelinger Heerstraße 406-408<br>28239 Bremen<br>Deutschland<br><br>Vertreten durch:<br><br>Walter Eggers, Geschäftsführer |
| Leiter der klinischen Prüfung: | Prof. Dr. med. Ralf Ulrich Trappe<br>Medizinische Klinik II für Hämatologie und Onkologie<br>DIAKO Ev. Diakonie-Krankenhaus Bremen gGmbH<br>Gröpelinger Heerstraße 406-408<br>28239 Bremen<br>Deutschland |
| Studientitel: | Risikostratifizierte sequentielle Therapie der post-transplantations-assoziierten lymphoproliferativen Erkrankung (PTLD) mit 4 Zyklen Rituximab SC*, gefolgt von 4 Zyklen Rituximab SC, 4 Zyklen Rituximab SC plus CHOP-21 oder 6 Zyklen Rituximab SC kombiniert mit alternierend CHOP-21 oder DHAOx: Die PTLD-2 Studie |
| Indikation | Unbehandelte CD20-positive post-transplantations-assoziierte lymphoproliferative Erkrankung (PTLD) nach Transplantation solider Organe |
| Phase: | Phase II |

* die erste Applikation Rituximab ist IV, alle folgenden Gaben sind SC

| | |
|---|---|
| Studiendesign | Offene, einarmige Multizenter-Studie |
| Patientenzahl: | 60 Patienten insgesamt (≥15 im Rituximab-Monotherapie Arm) |

Primäres Studienziel: Beurteilung der Sicherheit und Wirksamkeit einer Risiko–strati–fizierten* sequentiellen Erstlinientherapie mit 4 wöchentlichen Gaben von Rituximab SC Monotherapie** gefolgt von

- 4 weiteren Gaben Rituximab SC alle 3 Wochen bei niedrigen Risiko
  oder
- 4 Zyklen Rituximab SC kombiniert mit CHOP-21+GCSF bei hohem Risiko
  oder
- 6 Zyklen Rituximab SC kombiniert mit alternierenden Zyklen CHOP-21+GCSF und DHAOx+GCSF bei sehr hohem Risiko

bei Patienten mit CD20-positiver post-transplantations-asso–ziierter lymphoproliferativer Erkrankung (PTLD) nach Trans–plantation solider Organe

* die Risikostratifikation erfolgt auf der Grundlage des Ansprechens auf die ersten vier Gaben Rituximab SC, des IPI und des transplantierten Organs

** die erste Applikation Rituximab ist IV, alle folgenden Gaben sind SC

Studienendpunkte:

Primärer Studienendpunkt:

- Ereignisfreies Überleben (EFS) der Niedrig-Risiko-Gruppe in der Intention-to-treat-Population definiert als Zeit von Therapiebeginn bis Ergeigniseintritt mit folgenden Definitionen für niedriges Risiko und Ereignis:

  *1. Niedriges Risiko:*
  - Patienten in kompletter Remission 4 Wochen nach der letzten der 4 wöchentlichen Gaben von Rituximab
  - Patienten mit einem initialen IPI von 0, 1 oder 2 in partieller Remission 4 Wochen nach der letzten der insgesamt 4 wöchentlichen Gaben von Rituximab

  *2. Ereignis:*
  - jegliche Grad III oder IV Infektion während der 20-wöchigen Behandlungsphase
  - jeglicher Therapieabbruch, unabhängig von der Ursache
  - jeglicher Erkrankungsprogress
  - Tod, unabhängig von der Ursache

Sekundäre Studienendpunkte:

- Ansprechen und Gesamtansprechen auf die 4 initialen Gaben Rituximab-Monotherapie, Ansprechen und Gesamtansprechen auf die Gesamttherapie, Dauer des Ansprechens, Zeit bis zum Progress, progressionsfreies Überleben, Gesamtüberleben und therapiebedingte Mortalität in der intention-to-treat- und der per-protocol-Kohorte
- Alle sekundären Endpunkte werden in der Gesamtpatientenpopulation und in den jeweiligen Therapiegruppen untersucht

Weitere Variablen:

- Häufigkeit von Grad III und IV Leukopenien und von Grad III und IV Infektionen in den jeweiligen Therapiegruppen

Analysekriterien:

Wirksamkeit:

- das Therapieansprechen wird anhand der internationalen Response-Kriterien für maligne Lym–phome (Cheson et al., 1999) ermittelt (Appendix 11.10). Die primäre Datenbasis für die Responsebeurteilung sind die klinische Untersuchung mit Erfassung krank–heitsspezifischen Symptome, CT Untersuchungen von Thorax, Abdomen und Becken, Knochenmarksunter–suchungen und laborchemische Untersuchungen an peripherem Blut wie in Tabelle 13 spezifiziert

- es erfolgt ein zentrales Monitoring des Therapiean–sprechens: hierzu werden alle Quelldaten der zur Responsebeurteilung notwendigen Untersuchungen an die Studienzentrale der DPTLDSG übermittelt

Sicherheit:

- unerwünschte Ereignisse werden zu allen Therapievisits und zum Zeitpunkt des Zwischen- und Abschluss–stagings erfasst

- alle Grad 3 und 4 Infektionen unter Therapie unterliegen einem zentralen Monitoring: hierzu werden die entsprechenden Quelldaten zu einem Infektionsereignis vom Studienzentrum an die DPTLDSG Studienzentrale weitergeleitet

Indikation und Ein- und Ausschlusskriterien:

Indikation und Erkrankung die untersucht werden soll:

- Unbehandelte CD20-positive post-transplantations-assoziierte lymphoproliferative Erkrankung (PTLD) nach Transplantation solider Organe

<u>Einschlusskriterien:</u>

- CD20-positive PTLD mit oder ohne EBV- Assoziation, histopatho-logisch bestätigt durch eine Biopsie oder Tumorresektion

- Mindestens eine messbare Läsion mit > 2 cm im Durchmesser und/oder Knochenmarkbeteiligung
- Patienten nach Herz-, Lungen-, Leber-, Nieren-, Bauchspeicheldrüsen- oder Dünndarmtransplantation oder einer Kombination der genannten Transplantate
- ECOG ≤ 2
- Klinisch unzureichendes Ansprechen auf vorausgegangene Reduktion der Immunsuppression mit oder ohne antiviraler Therapie
- Alter **≥** 18 Jahre
- Einwilligungsfähigkeit
- Vorliegen der schriftliche Einwilligungserklärung sowie Fähigkeit und Bereitschaft den Visitenplan und die Erfordernisse des Studienprotokolls einzuhalten
- Negativer Schwangerschaftstest (nur bei Frauen in gebärfähigem Alter; nicht notwenig bei Frauen nach der Menopause oder permanenter Sterilisierung)
- Empfängnisverhütung für die Dauer der Therapie und die darauf folgenden 12 Monate (Studienteilnehmerinnen sowie weibliche Partner von männlichen Studeinteilnehmern; nicht notwenig bei Frauen nach der Menopause oder permanenter Sterilisierung)

<u>Ausschlußkriterien:</u>

- Komplette chirurgische Resektion des Tumor oder Bestrahlung aller verbliebenen Tumorläsionen
- Frühere Behandlung mit Rituximab oder Chemotherapie
- Bekannte Überempfindlichkeit gegen Rituximab, Mausproteine, oder einen sonstigen Bestandteil des PrüfmedikamentesBegleiterkrankungen, welche eine Behandlung in einer klinischen Studie ausschließen, insbesondere
  - schweres Herzversagen (New York Heart Association Klasse IV); schwere, unkontrollierte Herzerkrankungen,
  - HIV Infektion,
  - Andere aktive, schwere Infektionen wie Tuberkulose oder Hepatitis B.
- Meningiosis und ZNS-Befall
- Schwangere und stillende Frauen

| | |
|---|---|
| | • Lebenserwartung von weniger als 6 Wochen<br>• Patienten in einer psychiatrischen Unterbringung und Gefängnis–insassen<br>• Kollegen oder Angestellte der Studienärzte oder einer involvierten Institution, einschließlich des Sponsors der Studie |
| Name der Prüfsubstanz: | Mabthera SC® |
| Dosierung und Applikationsmethode der Prüfsubstanz: | 1400 mg, subkutane Injektion (SC) |
| IMP or therapy used as a comparator – dosage and method of administration: | Historische Überlebensdaten einer sequentiellen Therapie mit 4 intravenösen Gaben Rituximab (375 mg/$m^2$) gefolgt von 4 Zyklen CHOP-21+GCSF (PTLD-1 Studie, ST Kohorte) |
| Dauer der Behandlung: | Patienten mit niedrigem Risiko: 4 wöchentliche Gaben Rituximab SC (4 Wochen), 4 Wochen ohne Therapie, 4 weitere Applikationen Rituximab SC in dreiwöchentlichem Abstand (12 Wochen)<br><br>Patienten mit hohem Risiko: 4 wöchentliche Gaben Rituximab SC (4 Wochen), 4 Wochen ohne Therapie, 4 Zyklen Rituximab SC plus CHOP-21+GCSF (12 Wochen)<br><br>Patienten mit sehr hohem Risiko: 4 wöchentliche Gaben Rituximab SC (4 Wochen), 4 Wochen ohne Therapie, 6 Zyklen Rituximab SC kombiniert mit CHOP-21+GCSF alternierend mit DHAOx+GCSF (18 Wochen)<br><br>Die Nachbeobachtung läuft bis zum offiziellen Abschluss der Studie, mindestestens jedoch für ein Jahr. |

| | | |
|---|---|---|
| Rekrutierungsbeginn und Rekrutierungsende | Erster Patient, erste Behandlung (FPFV): | 1. Oktober 2014 |
| | Letzter Patient, erste Behandlung (LPFV): | 31. März 2021 |
| | Letzter Patient, letzte Behandlung (LPLV): | 31. März 2022 |
| | Abschlußbericht: | 31. Dezember 2022 |

| | |
|---|---|
| Statistik: | Prof. Dr. med. Peter Schlattmann<br>Institut für Medizinische Statistik, Informatik und Dokumentation<br>Universitätsklinikum Jena<br>Bachstrasse 18<br>07743 Jena<br>Deutschland |
| Statistikmethode: | Diese Phase II Studie vergleicht Überlebensdaten mit Rituximab SC Monotherapie bei Patienten mit niedrigem Risiko mit den historischen Überlebensdaten einer sequentiellen Therapie mit 4 Gaben Rituximab IV gefolgt von 4 Zyklen CHOP-21+GCSF (PTLD-1 Studie, ST Kohorte) als einarmige Überlebensstudie. Für die historische Kontrollgruppe beträgt die Wahrscheinlichkeit des ereignisfreien Überlebens nach 2 Jahren 0.51. Für eine vergleichbare Patientengruppe wird in der PTLD-2 Studie ein ereignisfreies Überleben nach 2 Jahren von 0.82 angenommen. |
| GCP Konformität: | Die vorliegende Studie wird durchgeführt in Übereinstimmung mit der gültigen Version des Prüfprotokolls, den international anerkannten Regeln der guten klinischen Praxis (ICH-GCP) und den Archivierungsrichtlinien |

Finanzierung der Studie: Roche Pharma AG

Deutsche PTLD Studiengruppe

## IV. Table of contents

## IV.a) List of tables



## IV.b) List of figures

## V. Abbreviations

| Abbreviation | Meaning |
|---|---|
| AE | Adverse Event |
| AESI | Adverse event of special interest |
| ASCT | Autologous stem cell transplantation |
| BfArM | Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte) |
| CHOP | Chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone |
| CRF | Case Report Form |
| DHAOx | Chemotherapy with dexamethasone, oxaliplatin and high-dose cytarabine |
| DMC | Data Monitoring Committee |
| EBV | Epstein-Barr virus |
| EPN | European PTLD Network |
| EFS | Event free survival |
| G-CSF | Granulocyte colony stimulating factor |
| GPTLDSG | German PTLD Study Group |
| IPI | International prognostic index |
| IV | Intravenous |

| | |
|---|---|
| LKP | Leiter der klinischen Prüfung (Principal Coordinating Investigator) |
| PCI | Principal Coordinating Investigator (Leiter der klinischen Prüfung) |
| PEI | Paul-Ehrlich-Institut |
| PFS | Progression free survival |
| PTLD | Post-transplant lymphoproliferative disorder |
| RSST | Risk stratified sequential treatment with rituximab and R-CHOP as described in the PTLD-1 RSST trial |
| SAE | Serious Adverse Event |
| SC | Subcutaneous |
| ST | Sequential treatment with rituximab and CHOP as described in the PTLD-1 ST trial |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TTP | Time to Progression |
| TRM | Treatment related mortality |
| ORR | Overall response rate |
| OS | Overall survival |

# 1. Introduction

Post-transplant lymphoproliferative disorder (PTLD) is a spectrum of lymphoid or plasmacytic proliferations associated with the use of potent immunosuppressive drugs after solid organ transplantation (Penn et al., 1969) and covers a wide morphological spectrum ranging from early lesions and polymorphic lymphoproliferations to monomorphic lymphomas (Swerdlow et al., 2008).

The incidence of PTLD in solid organ transplant recipients is significantly higher than that of lymphoma in the immunocompetent (Quinlan et al., 2010). Similar to the increased incidence of malignancy in other immunodeficiency states, impaired immunological surveillance is believed to play a key role in the pathogenesis of PTLD (Waldmann et al., 1972). In addition, the concept of an antigenic drive in lymphomagenesis (Fisher and Fisher, 2006) has recently been reinforced by the discovery of stereotyped B-cell receptors in chronic lymphocytic leukemia (Stamatopoulos et al., 2007) and diffuse large B-cell lymphoma (Sebastián et al., 2012). Solid organ transplantation provides a chronic antigenic stimulus and this could potentially contribute to the pathogenesis of PTLD – however, this hypothesis has not been tested so far.

In keeping with the concept of decreased immunological surveillance, primary infection with Epstein-Barr virus (EBV) or reactivation after solid organ transplantation confers a high risk of developing PTLD. Whereas the former is more frequent in children (Smets et al., 2002), EBV-associated PTLD in adults is usually the consequence of EBV reactivation. We and others have found evidence for a bimodal distribution of the incidence of PTLD. Whereas EBV-positive PTLD are common early after transplantation, the incidence of EBV-negative PTLD peaks around ten years after transplantation (Quinlan et al., 2010; Trappe et al., 2012a). Epidemiological analyses have shown distinct sets of risk factors for early and late PTLD (Quinlan et al., 2011) so that other (i.e. non-viral) etiological factors must also be considered.

For more than 30 years, immunosuppression reduction has been the cornerstone of PTLD treatment and high response rates have been reported particularly in early lesions and polymorphic PTLD (Reshef et al., 2011). However, the only prospective study specifically

addressing this issue suggests that the efficacy of immunosuppression reduction has been overestimated retrospectively (Swinnen et al., 2008).

In CD20-positive B-cell PTLD, the most frequent subtype, both rituximab monotherapy (Choquet et al., 2006; Oertel et al., 2005) and combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) (Choquet et al., 2007a) have efficacy; however, the latter is associated with significant treatment related mortality (TRM). To improve long-term efficacy after rituximab monotherapy and to avoid the toxicity of CHOP seen in first-line treatment, we initiated an international phase II trial combining first-line rituximab and CHOP in sequence, demonstrating efficacy and safety (Trappe et al., 2012a). We have successfully tested risk-stratification based on response to rituximab in a phase II trial to reduce the number of patients requiring chemotherapy and could demonstrate the efficacy and safety of this approach (Trappe et al., 2017).

In summary, PTLD are clinically different from lymphoma in the immunocompetent due to their higher incidence (Quinlan et al., 2010), their frequent association with Epstein Barr virus and their good response to immunotherapy and chemotherapy (Trappe et al., 2012a; Zimmermann et al., 2012a). Epidemiology and histological data suggest several pathways to PTLD. PTLD is a prime example of carcinogenesis in an (iatrogenic) immunological niche. Due to the toxicity of chemotherapy in already immunosuppressed patients, early identification of those patients who will profit from this therapy is paramount.

The German PTLD study group (GPTLDSG) and the European PTLD Network (EPN) have conducted prospective clinical trials in the field for over 10 years and have set international standards in the treatment of PTLD (Choquet et al., 2006; Oertel et al., 2005; Trappe et al., 2012a, 2017). In addition, the German PTLD registry has been collecting data from patients with rare subtypes of PTLD and those ineligible for inclusion in clinical trials. This has allowed the clinical characterization of rare entities such as plasmacytoma-like, plasmablastic and Burkitt PTLD (Trappe et al., 2011; Zimmermann et al., 2012a, 2012b). International collaborations have made it possible to assemble the largest cohort of patients with primary CNS PTLD (Evens et al., 2013) and to study expression of miRNAs in PTLD (Nourse et al., 2012). In addition, the head of the German PTLD Study Group, Prof. Dr. Ralf Ulrich Trappe, is a board member of the German Competence Network Malignant Lymphoma, which has

been involved in coordinating the system of reference pathology in Germany, clinical trials as well as molecular research in lymphoma.

All GPTLDSG studies included central review of pathology samples by reference pathologists, to ensure stringent diagnostic criteria were met. Tumor material was archived centrally whenever possible to allow for further molecular characterization. There is a proven collaboration record with Prof. Siebert at the Institute of Medical Genetics through the malignant mechanisms in malignant lymphoma project (supported by the Deutsche Krebshilfe, (Klapper et al., 2012; Martin-Subero et al., 2009; Richter et al., 2012). Rainer Siebert is also the Coordinator of the International Cancer Genome Consortium (ICGC) Malignant Lymphoma sequencing project. Further established cooperations include Maher Gandhi from Brisbane, Australia, who has long been on the forefront of the molecular characterization of EBV-associated lymphoma entities. This combined expertise recently gained in large-scale multi-center research efforts for the molecular characterization of PTLD.

Results from the PTLD-1 trial (sequential treatment, ST):

In 2003, the European Study Groups on PTLD started a cooperative, multicenter, prospective, phase II trial to investigate the efficacy and safety of sequential treatment with rituximab and CHOP-21 in PTLD unresponsive to immunosuppression reduction. Treatment-naïve adult solid organ transplant recipients diagnosed with CD20-positive PTLD who had failed to respond to upfront immunosuppression reduction received four courses of rituximab (375 mg/m2 IV) once a week followed by four weeks without treatment and four cycles of three-weekly CHOP. In case of disease progression during rituximab monotherapy CHOP was commenced immediately. Supportive therapy with granulocyte-colony stimulating factor (G-CSF) after chemotherapy was mandatory and antibiotic prophylaxis was recommended. The primary endpoint was treatment efficacy measured as response rates and response duration. Recruitment to the protocol was stopped after inclusion of 70 patients.

From December 12 2002 until May 5 2008, 70 patients were assigned to sequential treatment. PTLD was of late type in 53/70 (76%), monomorphic in 67/70 (96%) and histologically EBV-associated in 29/66 (44%) of cases. The overall response rate was 53/59 (90%, 95% CI: 79-96%) with 40/59 (67%, 95% CI: 55-78%) complete responses. Median

response duration was not yet reached (>79.1 months) and 74% (95% CI: 62-86%) of responders were progression-free at 3 and 5 years. Median time to progression in the ITT population was 77·4 months (95% CI 10·8–148·8): 69% (95% CI 57–80) of patients were progression-free at 3 years and 66% (54–78) at 5 years. Main adverse events were grade 3 and 4 leukopenia in 42/62 (68%, 95% CI 55-78%) and grade 3 and 4 infections in 26/64 patients (41%, 95% CI 29-53%). CHOP-associated TRM was 7/66 (10.6%, 95% CI 5-21%). Median overall survival was 6.6 years (95% CI: 2.8-10.4 years).

This trial demonstrated that sequential treatment with rituximab and CHOP results in excellent disease control and overall survival in adults with PTLD (Trappe et al., 2012a). It also shows that CHOP is associated with a significant treatment related toxicity including grade III/IV infections in 42% of patients.

Results from the PTLD-1 RSST trial (risk stratified sequential treatment, RSST):

As the response to rituximab predicted overall survival (OS), the PTLD-1 trial was amended in 2007 introducing risk-stratified sequential treatment (RSST) according to the response to rituximab. Following rituximab on days 1, 8, 15 and 22, RSST consisted of 4 3-weekly courses of rituximab monotherapy for patients in complete remission (CR, low risk) while all others (high risk) received 4 cycles of R-CHOP-21 + G-CSF.

152 patients were enrolled in the PTLD-1 RSST trial. Median age was 56·4 years. 69 out of 152 patients were kidney, 40 liver, 18 lung, 15 heart, 5 heart/kidney, 3 kidney/pancreas and 2 heart/lung transplant recipients. Median time from transplantation to PTLD was 9·0 years. Most cases (112/152, 74%) were of the diffuse large B-cell (DLBCL) type, 67/144 (47%) were EBV-associated, and 101/151 (67%) were Ann Arbor stage III or IV. 37/148 patients (25%) achieved a CR at interim staging and were allocated to rituximab monotherapy consolidation in the low-risk group. At final staging, 111 of 126 patients had a complete or partial response (88%, 95% CI 81–93) of which 88 were complete responses (70%, 95% CI 61–77). Median response duration was not reached; the 3-year estimate was 82% (95% CI 74–90). Median overall survival was 6·6 years (95% CI 5·5–7·6). The frequency of grade 3/4 infections and of treatment-related mortality were 34% (95% CI 27–42) and 8% (95% CI 5–14), respectively. Response to rituximab induction remained a prognostic factor for overall survival despite treatment stratification. The TTP estimate in the low-risk rituximab

consolidation group was 89% (95% CI 76–100) at three years compared to 69% (95% CI 44–95) in the 14 patients in PTLD-1 ST who had reached CR with rituximab induction and continued ST with CHOP chemotherapy (Trappe et al., 2017).

The analysis of further risk factors suitable for early treatment stratification identified the IPI (0,1,2 versus 3,4,5) and the thoracic transplant (i.e. patients with heart or lung transplantation) as new, independent and strong predictors of progression free and overall survival after sequential treatment of PTLD. Thus, “response to rituximab at interim staging”, IPI (0,1,2 versus 3,4,5) and “type of transplant” can be combined to stratify treatment more accurately in order to reduce treatment toxicity and to increase treatment efficacy in appropriate risk groups (Trappe et al., 2015).

In summary, the recently published PTLD-1 trial defined a new standard of care in the treatment of PTLD demonstrating superiority of sequential immunochemotherapy with 4 courses of rituximab IV followed by 4 cycles of standard CHOP (+GCSF) over 4 to 8 courses of rituximab monotherapy extending median overall survival from 2.4 to 6.5 years. The PTLD-1 RSST trial introduced risk stratification in sequential treatment according to the response to the first 4 courses of rituximab monotherapy. It demonstrated that it is safe to restrict chemotherapy to the 76% of patients who do not achieve a complete remission within 4 weeks after upfront rituximab monotherapy.

Going forward with risk stratified sequential treatment strategies, the objective of the PTLD-2 trial is to determine the safety and efficacy of risk stratified sequential treatment with 4 courses of rituximab SC followed by either 4 courses of rituximab SC monotherapy, four cycles of rituximab SC plus CHOP (+GCSF) or four cycles of rituximab SC plus alternating CHOP/DHAOx (+GCSF) in low-, high-risk- and very-high-risk patients. Results from the SABRINA trial have shown that rituximab SC results in increased $c_{trough}$ and AUC levels early during treatment and a non-inferior CR rate as compared to rituximab IV.(Davies et al., 2014) In addition to “response to rituximab monotherapy at interim staging” the PTLD-2 trial introduces stratification by IPI and “type of transplant” to define distinct risk groups. The major advantage of this new stratification is an extended low-risk group that is considered to be eligible for rituximab SC monotherapy.

In the PTLD-2 trial patients with a low risk of disease progression, defined as those who achieve a complete remission after the first four courses of rituximab SC monotherapy (expected patient population 24%) and those with an IPI of 0 to 2 who achieve a partial remission at interim staging (14%), will go on with rituximab SC monotherapy. Patients with an IPI of 3 to 5 who achieve a partial remission (21%), patients with stable disease at interim staging (18%) and non-thoracic transplant recipients with progressive disease at interim staging (15%) will be considered high risk. These patients will go on with 4 cycles of rituximab SC plus CHOP (+GCSF) similar to the PTLD-1 RSST protocol. Thoracic transplant recipients refractory to rituximab SC (8%) will be considered very high risk and will go on with rituximab SC followed by alternating rituximab SC plus CHOP/DHAOx (+GCSF).

We expect to improve outcome in all patient subgroups; however, the type of improvement will be different for the three risk groups. While data from the rituximab monotherapy trials, the PTLD-1 ST and PTLD-1 RSST trial suggest that rituximab monotherapy is at least as effective as sequential treatment with rituximab followed by CHOP in low-risk patients, CHOP is much more toxic. Thus, extending the low-risk group will result in less toxicity. As a result of an impaired renal function due to chronic immunosuppression, volume overload is a considerable problem in patients with PTLD. Rituximab SC has the advantage of a small volume SC application. This applies to all patients, but low-risk patients will further benefit from the fact that there is no IV therapy at all. In addition, increasing the total dose of rituximab by administering 1400mg SC instead of 375 mg/m$^2$ IV might improve efficacy.

In very high-risk patients data from the PTLD-1 ST and PTLD-1 RSST trial have shown that the current treatment is not sufficient to control the disease. Death due to disease progression was observed in more than 80% of patients. Here, rituximab SC combined with alternating chemotherapy cycles of CHOP and DHAOx (+GCSF) may increase treatment efficacy with an acceptable toxicity profile.

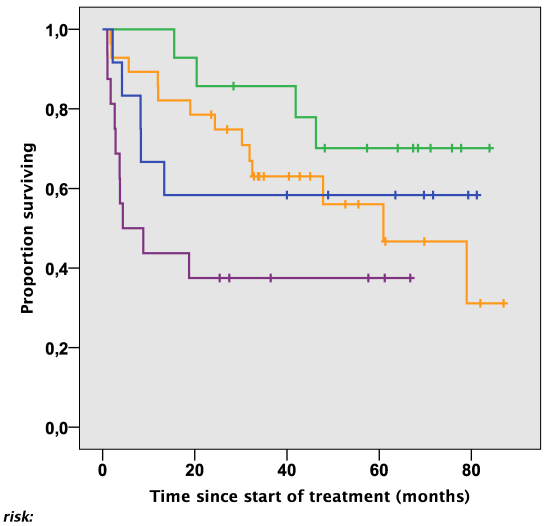
# 2. Objectives of the clinical trial

## 2.1. Rationale for the clinical trial

Sequential treatment with rituximab followed by CHOP results in an improved median overall survival of 6.5 years compared to 2.4 years with rituximab monotherapy. However, due to the high risk of chemotherapy-associated complications, particularly infections in chronically immunosuppressed transplant recipients, tailoring treatment to patients according to their risk profile might improve outcome even further.

*→ Response to rituximab at interim staging is a prognostic marker in PTLD*

The PTLD-1 trial demonstrated that response to 4 courses of rituximab monotherapy at interim staging is a strong prognostic marker for time to progression (p=0.028) and overall survival (p=0.035).




| Number at risk: | | | | | |
|---|---|---|---|---|---|
| CR at interim staging: | 14 | 13 | 11 | 7 | 1 |
| PR at interim staging: | 28 | 22 | 12 | 6 | 2 |
| SD at interim staging: | 12 | 7 | 6 | 5 | 2 |
| PD at interim staging: | 16 | 6 | 3 | 2 | 0 |

**Figure 1: Overall survival by response to 4 courses of rituximab at interim staging (PTLD-1 trial):**

Patients with CR (green) vs. PR (orange) vs. SD (blue) vs. disease progression (purple) after rituximab monotherapy All

patients received sequential treatment with 4 courses rituximab followed by 4 cycles of CHOP chemotherapy (+GCSF). Patients in CR, PR, SD or PD at interim staging had a significantly different OS although all of them received 4 courses of CHOP-21 chemotherapy+GCSF. Reprinted from The Lancet Oncology **(Trappe et al., 2012a)**.

*→ Patients in complete remission at interim staging do not need chemotherapy: results from the PTLD-1 RSST trial*

Based on the results of the PTLD-1 trial, the PTLD-1 RSST trial tested whether it is safe to treat patients in complete remission at interim staging with rituximab monotherapy. The two-year TTP of 97% (95% CI 92–100) in the "low-risk" rituximab consolidation group confirmed the key hypothesis of this protocol: A complete response to rituximab induction identifies a group of patients with B-cell PTLD who do not need chemotherapy. This was further supported by the observation that response to rituximab monotherapy remained a predictive marker for OS and TTP. (Trappe et al., 2017)

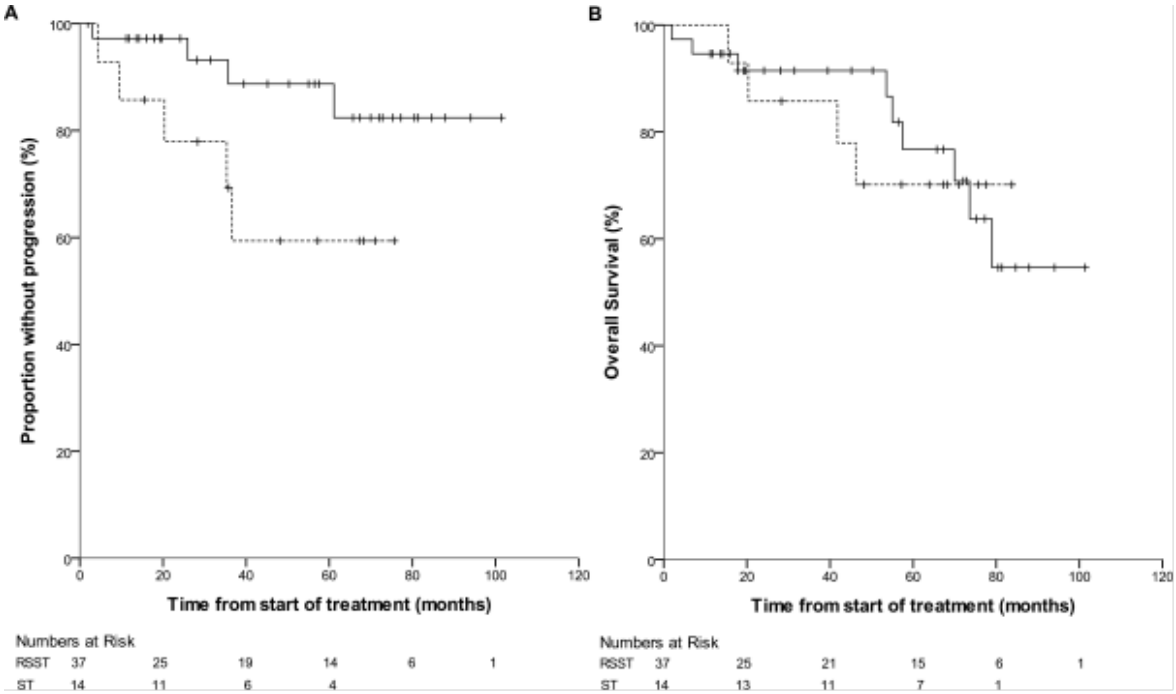



**Figure 2: Patients in complete response after rituximab induction (low-risk group)**

Time to progression and overall survival in in the PTLD-1 RSST trial low-risk cohort treated with rituximab monotherapy (n=37, solid line) and the PTLD-1 trial low-risk cohort treated with rituximab followed by CHOP (n=14, dashed line). A: Time

to progression B: Overall survival. (Trappe et al., 2017).

*→ IPI as a prognostic marker in PTLD*

PTLD are clinically different from lymphoma in the immunocompetent due to their higher incidence (Quinlan et al., 2010), their frequent association with Epstein Barr virus and their good response to immunotherapy and chemotherapy (Trappe et al., 2012a; Zimmermann et al., 2012a). Furthermore, extranodal disease and advanced stage, two of the risk factors included in the international prognostic index (IPI) (The International Non-Hodgkin's Lymphoma Prognostic Factors Project, 1993), are very common in PTLD (Trappe et al., 2012a). In an attempt to take these differences from lymphoma in the general population into account, a steadily growing number of prognostic indices have been put forward in PTLD by groups in Australia, Europe and the US (Caillard et al., 2012; Choquet et al., 2007a; Dierickx et al., 2013; Evens et al., 2010; Ghobrial et al., 2005; Hourigan et al., 2008; Leblond et al., 2001). The differences in the selection criteria of the underlying cohorts and the changes in treatment over time are reflected in different results. Due to the rarity of PTLD, the majority of these studies have been limited by either their retrospective or single-institution design (Dierickx et al., 2013; Evens et al., 2010; Ghobrial et al., 2005; Hourigan et al., 2008; Leblond et al., 2001), or non-standardized treatment (Caillard et al., 2012; Dierickx et al., 2013; Evens et al., 2010; Ghobrial et al., 2005; Leblond et al., 2001). Furthermore, while some included PTLD both after solid organ transplantation (SOT) and hematopoietic stem cell transplantation (Dierickx et al., 2013), others included all solid organ transplantation (Choquet et al., 2007a; Evens et al., 2010; Ghobrial et al., 2005; Leblond et al., 2001) or only kidney transplant recipients (Caillard et al., 2012; Hourigan et al., 2008). Despite different results and numerous scoring systems, there were some trends across cohorts:

- poor ECOG performance status was repeatedly identified as a prognostic factor for OS in univariate (Choquet et al., 2007a; Dierickx et al., 2013; Evens et al., 2010; Ghobrial et al., 2005; Hourigan et al., 2008; Leblond et al., 2001) and multivariable analysis (Choquet et al., 2007a; Ghobrial et al., 2005; Leblond et al., 2001);
- age (Caillard et al., 2012; Choquet et al., 2007a; Dierickx et al., 2013) and

- elevated LDH (Caillard et al., 2012; Choquet et al., 2007a; Hourigan et al., 2008) were similarly prognostic in multivariable analyses in three publications each.
- Extranodal disease (Dierickx et al., 2013; Evens et al., 2010; Ghobrial et al., 2005) and
- CNS involvement (Caillard et al., 2012; Evens et al., 2010; Leblond et al., 2001) were significant predictors of OS in three studies in univariate analysis.

Regarding prognostic scoring systems, the international prognostic index (IPI) was a significant predictor of OS in four cohorts (Choquet et al., 2007a; Dierickx et al., 2013; Ghobrial et al., 2005; Hourigan et al., 2008) whereas the Leblond prognostic index (Hourigan et al., 2008; Leblond et al., 2001) and the PTLD prognostic index (Choquet et al., 2007a; Hourigan et al., 2008) remained significant in two cohorts. The biggest change in treatment over time has been the introduction of treatment of CD20-positive PTLD with the monoclonal antibody rituximab (Choquet et al., 2006; Gonzalez-Barca et al., 2007; Oertel et al., 2005) - some authors have therefore published subgroup analyses of those patients treated with rituximab (Evens et al., 2010)

In contrast to earlier analyses, the cohort of 70 patients treated in the PTLD-1 trial is the largest prospectively treated trial cohort in this disease entity to date and due to uniform diagnostic criteria and treatment optimally suited to determine the clinical relevance of prognostic factors in PTLD under sequential immunochemotherapy with rituximab and CHOP. We therefore tested the prognostic value of previously characterized prognostic indices for PTLD in the patient cohort of the PTLD-1 trial.

From the different established prognostic indices the international prognostic index (IPI), the PTLD prognostic index and Ghobrial score reached significance for progression free and overall survival. The IPI high-risk criteria characterized two groups of similar size with significantly different OS and PFS. Our analysis further confirmed ECOG performance status, age, and lack of response to therapy as prognostic factors for overall survival. In addition, thoracic organ SOT was identified as a new prognostic factor for progression free and overall survival in both, univariate and multivariable analysis. Ghobrial score and PTLD prognostic index were arguably superior to IPI predicting overall survival. However,

given the rarity of PTLD with only few cases per year even at specialized hematological centers, applying the high risk criteria according to IPI (IPI ≥ 3) due to the common risk factors extranodal disease and advanced stage has practical advantages over the use of disease-specific prognostic indices (Trappe et al., 2015).

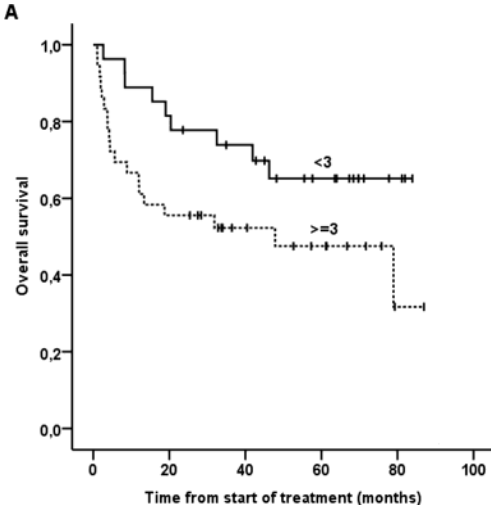



**Figure 3: Overall survival by IPI in the PTLD-1 trial (N=70)**

All patients received 4 courses of rituximab followed by 4 cycles of CHOP-21 chemotherapy (+GCSF). Patients with an IPI<3 (solid line) have a significant better outcome than patients with an IPI ≥3 (dashed line). Similar results were observed for PFS.

*→ Can we combine "response to rituximab at interim staging" and IPI for risk stratification?*

The results obtained in the patient cohort of the PTLD-1 ST trial were confirmed in the PTLD-1 RSST trial cohort by univariable and multivariable analysis. Multivariable analysis taking into account "response to rituximab at interim staging" and IPI (<3 versus ≥3) revealed likelihood ratio test p-values of <0.001 for both, PFS and OS. Results maintained significance when the subgroup of patients in partial remission at interim staging was stratified by IPI. Thus combining "response to rituximab at interim staging" and IPI (<3 versus ≥3) likely is a valuable approach to tailor chemotherapy.

*→ Can we combine "response to rituximab at interim staging" and "type of transplant" for*

*risk stratification?*

Recipients of thoracic (heart, lung and combinations such as heart/lung or heart/kidney) solid organ transplantation (SOT) have an increased risk of PTLD (Engels et al., 2011) and poor overall survival has been described in patients with PTLD after lung transplantation in particular (Muchtar et al., 2013; Zimmermann et al., 2013). In our PTLD-1 trial, thoracic organ SOT was significantly correlated with a poor overall survival ($p=0.043$). Multivariable analysis for overall survival revealed a HR of 7.827 for thoracic organ SOT ($p<0.001$) and a HR of 0.322 for "response to rituximab at interim staging" ($p=0.017$). Similar results were obtained in a Cox-regression analysis accessing the risk of disease progression with an HR of 2.983 for thoracic SOT ($p=0.008$) and an HR of 0.213 for "response to rituximab" ($p=0.075$). Most importantly: current treatment strategies result in a OS survival probability at 2 years of only 20% in thoracic SOT recipients not responding to 4 courses of rituximab monotherapy. Thus, salvage treatment is not effective in these very high-risk patients and therefore early treatment intensification is a must.

→ *What are our strategies to improve treatment efficacy in very-high-risk patients?*

There is no starting point for a more aggressive first-line treatment other than CHOP in PTLD. Thus, we will use a less aggressive modification of R-DHAP, one of the two standard salvage line treatments in DLBCL: R-ICE and R-DHAP. (Gisselbrecht et al., 2010). While R-ICE has been proven equally effective than R-DHAP (Gisselbrecht et al., 2010), retrospective subgroup analyses from this trial have suggested that the molecular subtype of germinal center derived DLBCL is better treated with R-DHAP than with R-ICE (Thieblemont et al., 2011). Because EBV induces a germinal center like reaction, most PTLD can be assumed to be germinal center derived DLBCL, making R-DHAP the more rational choice. For reasons of toxicity cisplatin will be substituted by oxaliplatin in PTLD, resulting in a less toxic (Hanada et al., 2010) but similarly effective (Lignon et al., 2010) variant (R-DHAOx). As a second-line treatment does-reduced platinum-based treatments (R-CE) can rescue about 55% of patients refractory to CHOP (Oertel et al., 2003), but this was associated with significant treatment related mortality (22%) (Oertel et al., 2003).

However, this still compares well with the treatment-related mortality of first-line CHOP (20-30%) (Choquet et al., 2007b).

The European Mantle Cell Lymphoma Network recently evaluated the potential superiority of first-line high-dose Ara-C-containing regimens over standard R-CHOP in mantle cell lymphomas in a randomized trial comparing standard R-CHOP followed by myeloablative radiochemotherapy (12 Gy total body irradiation [TBI], 2 × 60 mg/kg cyclophosphamide) and ASCT (control arm A) versus alternating courses of 3 × CHOP and 3 × DHAP (high-dose Ara-C, cisplatin, dexamethasone) plus rituximab followed by a high-dose Ara-C-containing myeloablative regimen (10 Gy TBI, 4 × 1.5 g/m2 Ara-C, 140 mg/m2 melphalan) and ASCT (experimental arm B). After induction, the overall response was similarly high in both arms, but the CR rate and combined CR/complete response unconfirmed (CRu) rate were significantly higher in arm B. Accordingly, after a median follow-up of 27 months, patients in arm B experienced a significantly longer time to treatment failure, mainly due to a lower number of relapses. Safety after induction was comparable in both arms, except for increased grades 3 and 4 hematological toxicity, a slight excess of renal toxicity and more frequent grades 1 and 2 nausea and vomiting in arm B. Thus, high-dose Ara-C in addition to R-CHOP significantly increased complete response rates and TTF without a clinically relevant increase of toxicity (Witzens-Harig et al., 2012) in non-transplant recipients when used first-line.

We therefore decided to test 3 cycles of R-CHOP combined with three alternating cycles of R-DHAOx (high-dose Ara-C, oxaliplatin, dexamethasone) plus GCSF in very high-risk patients (this is 8% of the total patient population) in order to improve treatment efficacy.

→ *What are our strategies to improve treatment safety in low-risk patients?*

While the interim analysis of the SABRINA trial has shown that rituximab SC results in increased $c_{trough}$ and AUC levels early during treatment and a non-inferior CR rate in follicular lymphoma (Davies et al., 2014), we assume that results with rituximab SC will be at least as good as with rituximab IV.

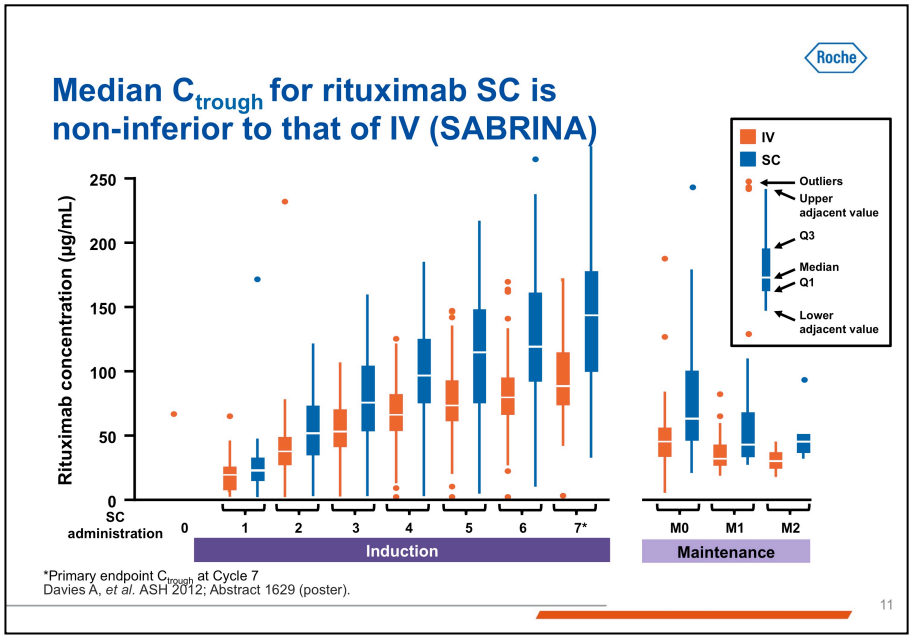



**Figure 4: Rituximab serum levels after IV and SC application**

Moreover, rituximab SC will considerably increase treatment tolerability in the post-transplant population where renal impairment and volume overload is a major problem. While more than 38% of patients will be treated with 8 courses of rituximab monotherapy, treatment convenience and compliance will increase, especially in this subgroup of patients where there is no need of any IV therapy any more. The “no chemotherapy” strategy in the low-risk patient cohort will considerably reduce the probability of treatment related infections. The PTLD-1 trial demonstrated a grade III/IV infection rate of 42% with CHOP+GCSF. 10% of patients prematurely stopped chemotherapy due to infectious toxicity. Although grade III/IV infections were less frequent in the corresponding low-risk patient population, the rate still was 30%. Both the rituximab monotherapy trials (Choquet et al., 2006; Oertel et al., 2005) as well as the PTLD-1 RSST trial demonstrated a grade III/IV infection rate with rituximab monotherapy of less than 5%. Restricting chemotherapy to high-risk and very-high-risk patients will reduce the grade III/IV infection rate in the 38% low-risk patients from 30% to about 5%.

→ *What is the expected number of patients in the low-risk group?*

With 70 patients recruited to the PTLD-1 trial and 152 patients recruited to the PTLD-1 RSST trial the complete remission rate after 4 courses of rituximab IV is known to be 22%. The partial remission rate is known to be 32%. 50% of the latter patients are known to be IPI 0 to 2. Thus, at least 38% of patients in the PTLD-2 trial are assumed to fulfill the criteria for low risk patients.

→ *What is the progression free survival of low-risk patients with current treatment strategies?*

The progression free survival probability at 24 months of the corresponding low-risk patient cohort in the PTLD-1 ST trial (N=24) and the PTLD-1 RSST trial (N=49) is known to be 0.79 and 0.87, respectively.

→ *What are our expectations for event free survival of low-risk patients in the PTLD-2 trial?*

The trial aims to prove the superiority of rituximab SC monotherapy in low-risk patients over sequential immunochemotherapy by demonstrating an improved event free survival probability at 2 years. Based on a lower rate of grade III/IV infections with rituximab monotherapy (5% with rituximab alone in the PTLD-1 RSST trial versus 30% with CHOP ± rituximab) and a similar efficacy of rituximab monotherapy in low-risk patients, an event free survival probability at 24 months of at least 0.82 is assumed.

→ *What is the event free survival of low-risk patients in the control group?*

This is a one-arm, prospective phase II trial. Therefore, a historical control group will be used. The PTLD-1 trial ST cohort is an ideal historical control group due to the identical inclusion criteria, identical reporting procedures and a high overlap in recruitment centers. In the PTLD-1 ST trial all patients were treated with sequential immunochemotherapy, i.e. 4 courses of rituximab monotherapy followed by 4 cycles of CHOP chemotherapy

2012a). The event free survival probability at 24 months of the corresponding low-risk patient cohort in this trial is known to be 0.51. The difference in the 2-year event free and progression free survival probabilities in the PTLD-1 trial (PFS: 0.79, EFS: 0.51) is due to CHOP-related grade III/IV infections.

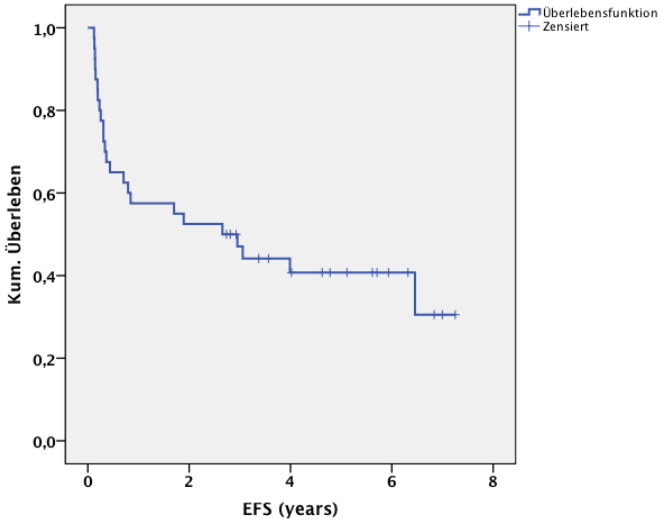



**Figure 5: Event free survival for the corresponding low-risk population in the PTLD-1 ST trial**

All patients received sequential treatment with 4 courses rituximab followed by 4 cycles of CHOP chemotherapy + GCSF).

Low risk is defined as
- complete remission at interim staging
- partial remission at interim staging in patients with IPI 0 to 2

Event is defined as:
- treatment-related infections grade III or IV
- treatment discontinuation from any reason
- disease progression
- death from any reason

## 2.2. Primary objective

The primary objective is to determine the safety and the efficacy of first-line risk stratified sequential treatment with 4 weekly courses of rituximab SC followed by 4 courses of rituximab SC monotherapy ever 3 weeks in low-risk patients, 4 cycles of rituximab SC plus CHOP (+GCSF) ever 3 weeks in high-risk patients and 6 alternating cycles of rituximab SC plus CHOP+GCSF or DHAOx+GCSF applied ever 3 weeks in very high-risk patients diagnosed with CD20-positive post-transplant lymphoproliferative disorder

following solid organ transplantation. Using extended risk-stratification based on interim staging data and IPI about 40% of patients will be stratified to the low-risk group and receive rituximab SC monotherapy. Superiority of rituximab monotherapy over sequential immunochemotherapy in these patients will be demonstrated using a combined efficacy and toxicity endpoint, integrating PFS data and the frequency of grade 3 and 4 infections during treatment (EFS). EFS in the low-risk population at two years will be compared to the 2-year EFS of a corresponding historical control group from the PTLD-1 trial (ST cohort).

### 2.3. Secondary and other objectives

The PTLD-2 trial intends to improve treatment in all patient subgroups. Descriptive statistics will be used to evaluate efficacy and safety by treatment group. All data will be compared to the current standard of care, i.e. sequential treatment with 4 courses of rituximab IV followed by 4 cycles of R-CHOP (PTLD-1 trial, ST cohort) and risk-stratified sequential immunochemotherapy with 4 courses of rituximab IV followed by consolidation with rituximab IV or by 4 cycles of R-CHOP (PTLD-1 trial, RSST cohort).

Following target variables will be analyzed:

- Response after full treatment
- Duration of response
- Time to progression
- Progression free survival
- Disease free survival
- Overall survival
- Treatment related mortality
- The frequency of grade III and IV leucocytopenia with R-CHOP and alternating R-CHOP/DHAOx
- the frequency of grade III and IV infections in all predefined risk groups
- the frequency of local reactions after subcutaneous injection of rituximab

- the impact of EBV-association and type of transplant on treatment outcome
- the impact of baseline variables on outcome and toxicity

To assess potential differences in the response to rituximab IV monotherapy response at interim staging will be compared to combined data from the PTLD-1 ST and PTLD-1 RSST trial. Additionally, potential gender specific differences will be analyzed. All analyses will be performed both in the ITT and PP populations.

# 3. Organizational and administrative aspects of the trial

## 3.1. Sponsor

Sponsor: DIAKO Ev. Diakonie-Krankenhaus Bremen gGmbH
Gröpelinger Heerstrasse 406-408
28239 Bremen
Germany

Represented by: Walter Eggers, General Manager [Geschäftsführer]

## 3.2. Principal Coordinating Investigator

Principal Coordinating Investigator (PCI): Prof. Dr. med. Ralf Ulrich Trappe
Department of Hematology and Oncology
DIAKO Ev. Diakonie-Krankenhaus Bremen gGmbH
Gröpelinger Heerstrasse 406-408
28239 Bremen
Germany

## 3.3. Statistics

Statistician: Prof. Dr. med. Peter Schlattmann
Institute of Medical Statistics, Computer Sciences and Documentation
University of Jena
Bachstrasse 18
07743 Jena
Germany

## 3.4. Data Monitoring Committee

A Data Monitoring Committee made up of independent experts will be set up. It consists of two physicians who are not involved in the conduct of the trial (see Section 11.4). The task of the DMC is to oversee the safety of the trial subjects in the clinical trial by periodically assessing the safety and efficacy of the trial therapy, and to monitor the integrity and validity of the data collected and the conduct of the clinical trial. Treatment with DHAOx in very high-risk patients might exhibit severe toxicity. The DMC therefore will evaluate response and safety data in very high-risk patients with special attention.

Throughout this process of surveillance, the DMC provides the sponsor with recommendations with regard to continuing the trial (e.g. termination or modification) based on the data collected. The data necessary for the DMC to fulfill this function is provided by the sponsor as determined by the DMC. Amongst other datasets, these must include listings providing information on serious adverse events and further variables that the DMC considers necessary at least every 12 months and when formal interim analyses are conducted.

Data from patients treated with DHAOx will be sent to the DMC as soon as they become available at the central study office. As soon as the first 3 patients with DHAOx have finished treatment, the DMC will provide the sponsor with a recommendation how to continue this treatment (e.g. termination, modification or unchanged).

## 3.5. Further committees

### 3.5.1. Steering Committee

A list of the members of the Steering Committee is given in Appendix 11.2.

### 3.5.2. Advisory Committee

A list of the members of the Advisory Committee is given in Appendix 11.5.

## 3.6. Study laboratories and other technical services

This trial includes reference pathology and reference tissue cytogenetics as well as reference flow cytometry and reference EBV load measurements in peripheral blood samples by experts in the field. Reference pathology ensures histopathological confirmation of the diagnosis and is obligatory in this trial, while reference cytogenetics, flow cytometry and EBV load measurement are used to identify the extent of disease, patients at risk for relapse and/or prognostic factors in PTLD. Central tissue and peripheral blood banking for associated research projects will be performed at these institutions for all patients included in this trial that consent to additional research projects.

The names and addresses of the providers are given in Appendix 11.6.

## 3.7. Central organization units

| | |
|---|---|
| Project management: | German PTLD Study Group<br>Central Study Office<br>Department of Hematology and Oncology<br>DIAKO Ev. Diakonie-Krankenhaus Bremen gGmbH<br>Gröpelinger Heerstrasse 406-408<br>28239 Bremen<br>Germany |
| Monitoring: | Kompetenznetz Maligne Lymphome<br>Kerpener Str. 62 D<br>50937 Köln |
| Data management: | Institute of Medical Statistics, Computer Sciences and Documentation<br>University of Jena<br>Bachstrasse 18<br>07743 Jena |

SAE management: German PTLD Study Group
Central Study Office
Department of Hematology and Oncology
DIAKO Ev. Diakonie-Krankenhaus Bremen gGmbH
Gröpelinger Heerstrasse 406-408
28239 Bremen
Germany

## 3.8. Investigators and trial sites

This clinical trial will be carried out as a multicenter, open label trial at 23 trial sites in Germany. If necessary, further qualified trial sites may be recruited to the trial.

A list of the trial sites with names of the principal investigators is given in appendix 11.1. The listing of trial sites, principal investigators, subinvestigators, and further trial staff, will be kept and continuously updated in a separate list. The final version of this list will be attached to the final report of the clinical trial.

Requirements for investigators and trial sites

The proof of knowledge of regulatory procedures, experience with the conduct of clinical trials and special experience in the trial indication will be assessed by a trial site questionnaire (included in the trial master file, a copy is available on request).

While PTLD is a rare disease, special experience in the trial indication is anticipated in all trial sites that contributed to the PTLD-1 trial and in those treating ≥2 PTLD patients a year assuming that at least one patient per year can be included in this trial. Trial sites not qualified as a hematology department (i.e. transplant centers) need to send patients to cooperating trial sites for chemotherapy application if this is indicated according to the treatment protocol.

Adequate knowledge of regulatory procedures and experience with the conduct of clinical trials is assumed in all trial sites with ≥2 active clinical trials regardless of the trial indication, in qualified clinical trial sites and in clinical trial sites that successfully were inspected or audited within the last 5 years not showing unsolved major findings.

Clinical trial sites must have access to a radiology department or cooperate with a radiologist that is equipped and qualified to perform standard CT scanning to ensure adequate staging and restaging examinations. Laboratory examinations also must not necessarily be done in-house but the laboratory must be certified to perform at least differential blood count and LDH measurements. FACS and EBV-load measurement can either be done in-house (then the laboratory needs to be certified for these analyses) or samples can be sent to the DPTLDSG's reference laboratories (appendix 11.6). Biopsy samples always have to be sent to one of the two reference pathologists. In-house pathology is therefore not necessary to participate in this trial.

All trial sites' principal investigators must have at least 2 years of experience in the clinical testing of pharmaceutical preparations.

## 3.9. Financing

This clinical trial will be financed by a restricted grant from Roche Pharma AG (Grenzach-Wyhlen). Roche will also provide Mabthera SC and IV. Further financial and personal support is available from the German PTLD Study Group.

# 4. Trial conduct

## 4.1. General aspects of trial design

This phase II study compares historical survival with rituximab IV followed by CHOP (PTLD-1 trial, ST cohort) with rituximab SC monotherapy in low-risk patients using a one-arm, open label survival study. Patients are risk-stratified after 4 initial cycles of rituximab monotherapy according to their response to rituximab, IPI and type of transplant. Low-risk patients continue with rituximab monotherapy SC. High-risk patients and very-high-risk patients will be treated with rituximab SC plus chemotherapy (either CHOP or DHAOx). The primary endpoint is event free survival in the low-risk population (treated with rituximab SC monotherapy) which is expected to be improved over event free survival in the corresponding patient cohort from the PTLD-1 ST trial. Statistics is descriptive for any other endpoint. Reference diagnostics are included to ensure high data quality with respect to diagnosis (reference pathology, reference tumorcytogenetics and molecular genetics) and safety (monitoring of EBV-load as a marker for patients at risk for PTLD relapse during follow-up, monitoring of cellular immunity to guide pneumocystis jirovecii prophylaxis and immunosuppression). Remaining blood and tissue samples from consenting subjects will be included in the GPTLDSG clinical repository (section 4.10). Diagnostic laboratories are not allowed to use patient samples from this trial without the PCI's written permission.

### 4.1.1. Schedule

After staging examinations and an initial attempt to treat the lymphoma with reduction of immunosuppression only, patients start treatment with 4 courses of rituximab monotherapy once a week on days 1, 8, 15, and 22. The first application of rituximab is IV. All subsequent applications are SC.

Interim restaging examinations will be performed between days 45 and 50. At this point, patients will be stratified to three risk groups. Risk groups will be defined by response to the initial 4 courses of rituximab, the type of transplant (non-thoracic versus thoracic) and by IPI (<3 versus ≥3).

Patients in complete remission at interim staging and patients in partial remission at interim staging with an IPI of 0-2 will be considered low-risk. These patients will go on with 4 additional doses of rituximab SC monotherapy given in three-week intervals.

Patients in partial remission at interim staging with an initial IPI of 3 to 5 and patients with stable disease at interim staging will go on with 4 courses CHOP + GCSF plus rituximab SC given in three-week intervals.

Non thoracic transplant recipients with disease progression at interim staging or at any time during rituximab SC monotherapy will go on with rituximab SC plus CHOP-21 chemotherapy + GCSF.

Thoracic organ transplant recipients with disease progression at interim staging or at any time during rituximab SC monotherapy will go on with alternating cycles of rituximab SC plus CHOP-21 + GCSF (3 cycles) and DHAOx + GCSF (3 cycles).

Final staging will be performed 4 weeks after the last treatment or at any time when disease progression is suspected.

The minimal follow-up of individual trial subjects in the trial is one year. The minimal median follow-up for the whole trial cohort is two years. All patients will be followed up according to international standards until the trial is officially closed. During the first two years of follow-up, examinations will be performed every 3 months. Follow-up data beyond the second year should be included in the trial's analysis when they are in line with the international standards for follow-up in malignant lymphoma, i.e. have been performed at least every six months in the third to fifth year and once yearly thereafter.

Reference pathology and reference tumorcytogenetics will be performed at diagnosis and at time of relapse. Serial flow cytometry-monitoring and serial EBV-PCR will be performed at diagnosis, interim staging, final staging and during follow-up as indicated in Table 3 and Table 13. Detailed information on treatment is given in section 4.6.

**Table 1: Schedule of the trial**

| | |
|---|---|
| First patient first visit (FPFV): | 1 October 2014 |

| | |
|---|---|
| Last patient first visit (LPFV): | 31 March 2021 |
| Last patient last visit (LPLV): | 31 July 2022 |
| Final study report: | 31 December 2022 |

**Table 2: Schedule of interim analyses**

| | |
|---|---|
| After inclusion of ≥20 patients: 1st interim analysis on efficacy and safety of 4 courses of rituximab SC in the total study population | 1 November 2017 |
| After inclusion of ≥40 patients: 2nd interim analysis on efficacy and safety of 4 courses of rituximab SC monotherapy in the total study population and on efficacy and safety in the high-risk and very-high-risk patient population | 1 July 2019 |

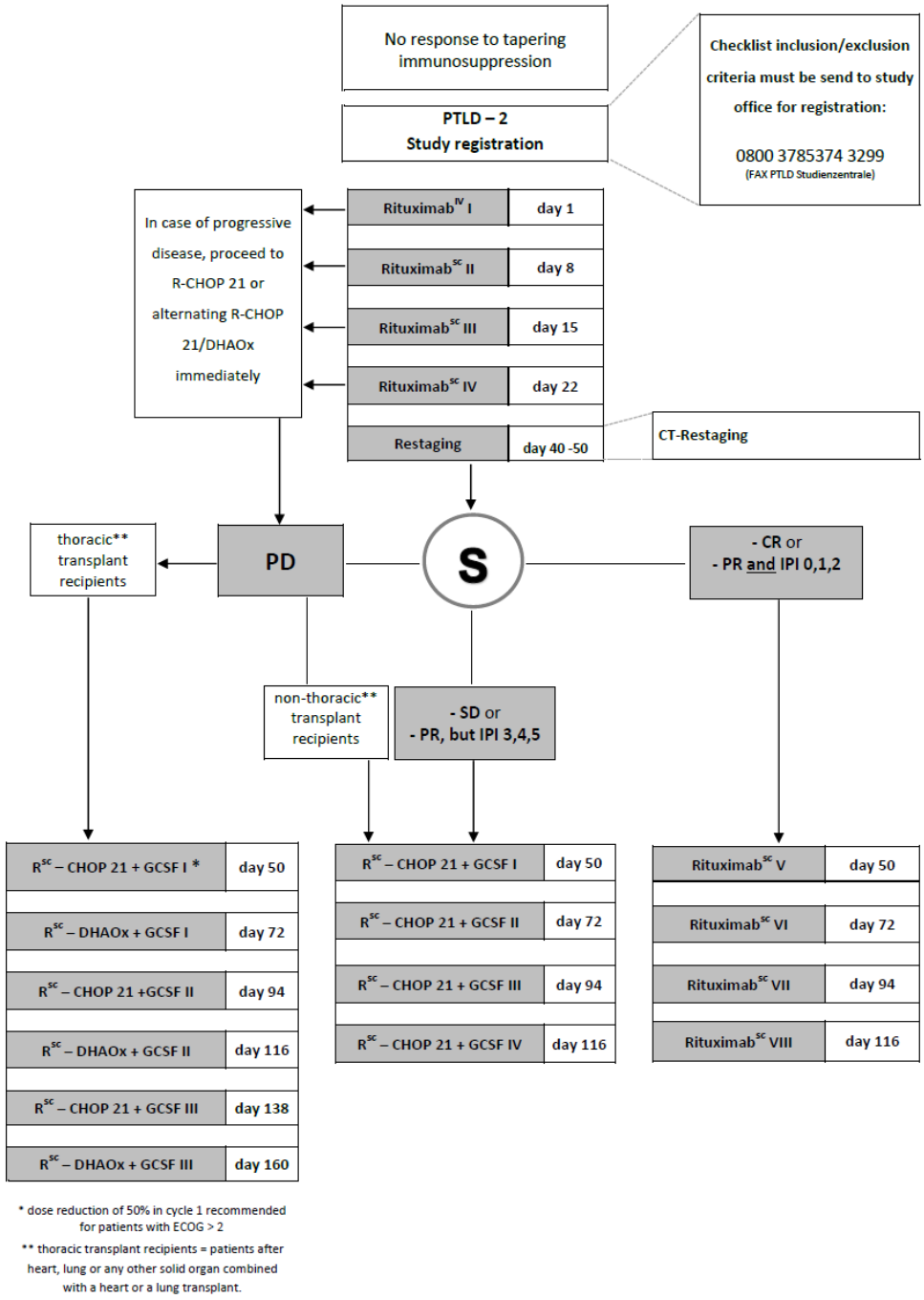
**Table 3: Schedule of reference diagnostics**

| | |
|---|---|
| Reference pathology | At enrollment |
| Reference tumor-cytogenetics | At enrollment |
| Reference flow-cytometry of malignant B-cells and non-malignant T-cells | • Before first application of rituximab<br>• At interim staging<br>• At final staging |
| EBV load measurements | • Before the first application of rituximab<br>• At interim staging<br>• At final staging<br>• During follow-up at month 3, 6, 9, 12, 18 and 24 |

End of the clinical trial

The clinical trial will end 31 July 2022. Database closure is scheduled for 30 September 2022. Finalization of biometric analyses is scheduled for 31 October 2022. The final study report will be ready 31 December 2022.

**Figure 6: Trial flowchart**



## 4.2. Discussion of trial design

Due to the rarity of the disease conducting clinical trials in PTLD is difficult. 1st-line chemotherapy in PTLD (mainly CHOP) has only been evaluated in retrospective analyses so far. While CHOP was effective in the treatment of PTLD, treatment-related mortality of 1st-line CHOP was at 20-30% (Choquet et al., 2007b). Using 4 courses of rituximab monotherapy the German PTLD study group conducted the world´s first prospective clinical trial in PTLD at the beginning of the last decade (Oertel et al., 2005). This trial included a total of 17 patients. Two other rituximab monotherapy trial were subsequently done in France (Choquet et al., 2006) (N=43) and Spain (Gonzalez-Barca et al., 2007) (N=38). These three trials built the body of the evidence for rituximab monotherapy in PTLD. Rituximab monotherapy can cure up to 40% of patients without the risk of chemotherapy-associated toxicity. However, many patients experience disease progression with rituximab monotherapy and median progression free survival is only 6 months (Choquet et al., 2007a). The PTLD-1 ST trial, the second largest clinical trial in the field of PTLD, recruited patients from 2003 to 2007. Using sequential treatment with rituximab IV followed by CHOP, the trial successfully demonstrated increased progression-free and overall survival. CHOP applied from day 50 after rituximab monotherapy had a much lower toxicity than 1st-line CHOP or 1st-line R-CHOP. The trial included a total of 75 patients and today serves as a reference in the treatment of PTLD, because it demonstrated considerably better overall survival with sequential immuno-chemotherapy (median OS: 6.6 years versus 2.4 years for rituximab monotherapy) (Trappe et al., 2012a). In 2007, the PTLD-1 RSST trial introduced risk-stratified sequential treatment according to the response to rituximab monotherapy at interim staging in order to restrict chemotherapy to those with a need for chemotherapy and showed that about 25% of patients can safely be treated without chemotherapy. The PTLD-1 RSST trial, the largest clinical trial in the field of PTLD, has recruited 152 patients and median OS was again 6.6 years (Trappe et al., 2017). Almost all German study centers that contributed to the PTLD-1 ST and PTLD-1 RSST trial will also contribute to the PTLD-2 trial, while new centers were welcome. The incidence of PTLD in Germany is about 40/year and about 30 patients/year might be eligible for the PTLD-2 trial. Expected recruitment in the PTLD-2 trial in Germany is 12 patients per year. With a recruitment period of 6 years, 60 patients is reasonable target recruitment.

Even in an international setting, the recruitment rate is too small to perform a phase III clinical trial in this disease entity within a reasonable timeframe. The recruitment period for a phase III trial, would probably be up to 10 years. Because emerging concepts in the treatment of aggressive lymphoma such as PI3K- and BCL-2 inhibitors might become available for the treatment of PTLD in some years, the trial results would most likely be outdated once they are available.

Due to these limitations, the PTLD-2 trial is a phase II one-arm survival study refining the stratification concept developed by the German PTLD Study Group: The introduction of rituximab SC will increase treatment convenience especially for low-risk patients. Clinical data have shown that rituximab SC is as at least as effective as rituximab IV (Shpilberg and Jackisch, 2013). Interim data from the SABRINA trial comparing rituximab IV and rituximab SC in combination with chemotherapy for the treatment of follicular lymphoma have proven non-inferior serum levels of the 1400 mg SC formulation compared to the 375 mg/m$^2$ IV formulation associated with a non-inferior treatment response, but absolute numbers for complete remission rates were even higher in the rituximab SC arm (Davies et al., 2014). Risk-stratification is now in three groups (low-, high and very high-risk groups, as identified in the PTLD-1 trial cohort): These are formed not only based on the response to rituximab, but also based on the international prognostic index (IPI) and the transplanted organ. This trial tests if the proportion of PTLD patients treated without chemotherapy can safely be increased to up to 40% - and if a small portion of patients at very-high risk for disease progression (up to 10%) can benefit from a more intensive chemotherapy protocol.

Comparison of event free survival in the rituximab monotherapy group is with historical survival in the corresponding patient cohort from the PTLD-1 ST trial (an ideal historical control group due to the identical inclusion criteria) using Kaplan-Meier statistics. For the historical control group the event free survival probability at 24 months is known to be 0.51. For a similar risk group the event free survival probability at 24 months in the PTLD-2 trial is assumed to be 0.82. This is reached in case of a non-inferior risk of disease progression associated with less treatment-related toxicity events with rituximab monotherapy compared to CHOP+GCSF.

With a total of 15 patients within the low-risk group superiority of rituximab SC monotherapy over sequential treatment with rituximab IV and CHOP can be shown with a 0.050 two-sided

significance level and a 90% power. This corresponds to a minimum of 40 patients in total. With a calculated drop-out rate and a safety margin of 33%, the total number of patients to perform the trial is 60.

## 4.3. Selection of trial population

Adult female or male patients with biopsy confirmed diagnosis of lymphoproliferative disorders after solid organ transplantation (e.g. heart, lung, liver, kidney etc.) with stage I-IV disease and ECOG ≤2 will be included.

Patients with ECOG ≥3 are excluded because of their very high risk of treatment related mortality with chemotherapy and their low probability to achieve a response qualifying for rituximab monotherapy.

Patients with CNS-involvement are excluded, because neither rituximab monotherapy nor CHOP is an effective treatment for pCNS-PTLD and PTLD with CNS-involvement.

Patients with PTLD after bone marrow and peripheral stem cell transplantation are excluded because of their different clinical prognosis and only limited experience with sequential treatment and risk stratified sequential treatment post bone marrow/peripheral stem cell transplantation.

Reasons for gender distribution

No patient selection by gender will be performed. The expected gender distribution in the trial will be a reflection of the gender distribution of solid organ transplantation with a predominance of males (60-70%). As the gender distribution is different for the different transplant types, the distribution of transplant types within the trial will affect gender distribution. However, the numbers of the females included appear adequate to detect major gender-specific differences in efficacy and safety of treatment.

### 4.3.1. Inclusion criteria

- Diagnosis of CD20-positive post-transplant lymphoproliferative disorder (PTLD) with or without EBV association, confirmed after biopsy or resection of a tumor

- Measurable disease of > 2 cm in diameter and/or bone marrow involvement
- Patients having undergone heart, lung, liver, kidney, pancreas, small intestine transplantation or a combination of the organ transplantations mentioned
- ECOG ≤ 2
- Clinically insufficient response to an upfront reduction of immunosuppression with or without antiviral therapy; clinically insufficient response is defined as partial remission with unacceptable toxicity from reduction of immunosuppression or stable disease after a minimum of 2 weeks or as progressive disease at any time; evaluation of response is assessed by clinical evaluation of involved regions and/or serum LDH; CT scanning is performed only in patients with a clinically suspected partial response
- Age at least 18 years
- Not legally incapacitated
- Written informed consent from the trial subject has been obtained
- Negative pregnancy test (females with child-bearing potential only; not required in postmenopausal women [for > 2 years] and permanently sterilised women [e.g. tubal occlusion, hysterectomy, bilateral salpingectomy])
- Use of highly-effective contraceptive methods during treatment and for 12 months following study therapy (this applies to female trial participants as well as female partners of male participants: females with child-bearing potential only; not required in postmenopausal women [for > 2 years] and permanently sterilised women [e.g. tubal occlusion, hysterectomy, bilateral salpingectomy]). The following contraceptive methods are regarded as highly-effective:
  - Abstinence
  - Long-acting injectable contraceptives
  - Tubal ligation (female sterilization)
  - Intrauterine devices that release hormones (hormone spiral)

#### 4.3.2. Exclusion criteria

- Complete surgical extirpation of the tumor or irradiation of the only residual tumor masses without measurable bone marrow involvement

- Missing data for IPI stratification
- Upfront treatment with rituximab or chemotherapy
- Known hypersensitivity to rituximab, murine proteins or to any of the excipients (sodium citrate, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid, water; recombinant human hyaluronidase, L-Histidine, L-Histidine monohydrate, α,α-Trehalose-Dihydrat, L-Methionin)
- Concomitant diseases which exclude the administration of therapy as outlined by the study protocol, in particular:
    - severe heart failure (New York Heart Association Class IV), severe uncontrolled cardiac disease;
    - HIV infection;
    - other active, severe infections such as tuberculosis or Hepatitis B.
- Meningeal and CNS involvement
- Participation in other interventional trials with the exception of clinical trials addressing immunosuppression following solid organ transplantation (patients must disclose involvement in other clinical trials in the informed consent form)
- Pregnant women and nursing mothers
- Persons with any kind of dependency on the investigator or employed by the sponsor or investigator
- Persons held in an institution by legal or official order
- Life expectancy less than 6 weeks

### 4.4. Withdrawal of trial subjects after trial start

Subjects have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw subjects from the study in the event of intercurrent illness, adverse events, treatment failure after a prescribed procedure, protocol violation,

cure, administrative reasons or for other reasons. An excessive rate of withdraws can render the study uninterpretable; therefore unnecessary withdrawal of subjects should be avoided.

Should a subject decide to withdraw, all efforts will be made to complete and report the observations a thoroughly as possible.

#### 4.4.1. Procedures for premature withdrawal from treatment

The investigator should contact the subject or a responsible relative by telephone or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the subject`s withdrawal should be made with an explanation of why the subject is withdrawing from the study. This information should be documented on the “withdrawn from study” CRF. If the reason for removal of a subject from the study is an adverse event the principal specific event will be recorded on the “adverse event” CRF.

In the case that the subject decides to prematurely discontinue study treatment (“refuses treatment”), he/she should be asked if he/she can still be contacted for further information. The outcome of that discussion should be documented in the medical records and on the “withdrawn from study” CRF.

### 4.5. Closure of trial sites/Premature termination of the clinical trial

#### 4.5.1. Closure of trial sites

A center may be replaced for the following administrative reasons:

- Poor protocol adherence

#### 4.5.2. Premature termination of trial

The sponsor has the right to terminate the trial prematurely if there are any relevant medical or ethical concerns, or if completing the trial is no longer practicable. If such action is taken, the reasons for terminating the trial must be documented in detail. All trial subjects still under

treatment at the time of termination must undergo a final examination, which must be documented. The PCI must be informed without delay if any investigator has ethical concerns about continuation of the trial.

Premature termination of the trial will be considered if:

- The risk-benefit balance for the trial subjects changes markedly
- The sponsor considers that the trial must be discontinued for safety reasons (e.g. on the advice of the DMC)
- It is no longer practicable to complete the trial (e.g. slow accrual)

The sponsor decides on whether to discontinue the trial in consultation with the PCI, DMC, SC, Advisory Committee and/or statistician.

## 4.6. Treatment

### 4.6.1. Treatment to be given

#### *4.6.1.1. Treatment cycles 1-4*

Rituximab will be administered as a single therapeutic agent at a standard dosage of 375 mg/m$^2$ infused intravenously at day 1, as per institutional practice (table 4). Rituximab infusions should be administered under the close supervision of an experienced physician, and in an environment where full resuscitation facilities are immediately available. The recommended initial rate for infusion is 50 mg/h; after the first 30 minutes, it can be escalated in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h. Further instructions on IV administration are provided in Mabthera IV medicinal products professional information included in the investigator's site file.

Three subsequent single therapeutic agent applications of rituximab will be administered subcutaneously at a fixed dose of 1400 mg once a week for 3 weeks at days 8, 15 and 22 (table 4). The 1400 mg SC dose of rituximab translates into 11.7 mL solution that must be withdrawn from the vial. Rituximab SC will be administered subcutaneously at an injection

rate of approximately 2 mL/min. Detailed instructions on subcutaneous administration are provided in Mabthera SC medicinal product's professional information included in the investigator's site file.

**Table 4: Cycles 1-4: rituximab monotherapy**

| Medication | Dose | Mode | D1 | D8 | D15 | D22 |
|---|---|---|---|---|---|---|
| **Rituximab** | 375 mg/m$^2$ | IV | x | | | |
| **Rituximab** | **1400 mg fixed dose** | SC | | x | x | x |

#### *4.6.1.2. Four weeks treatment free interval and risk stratification*

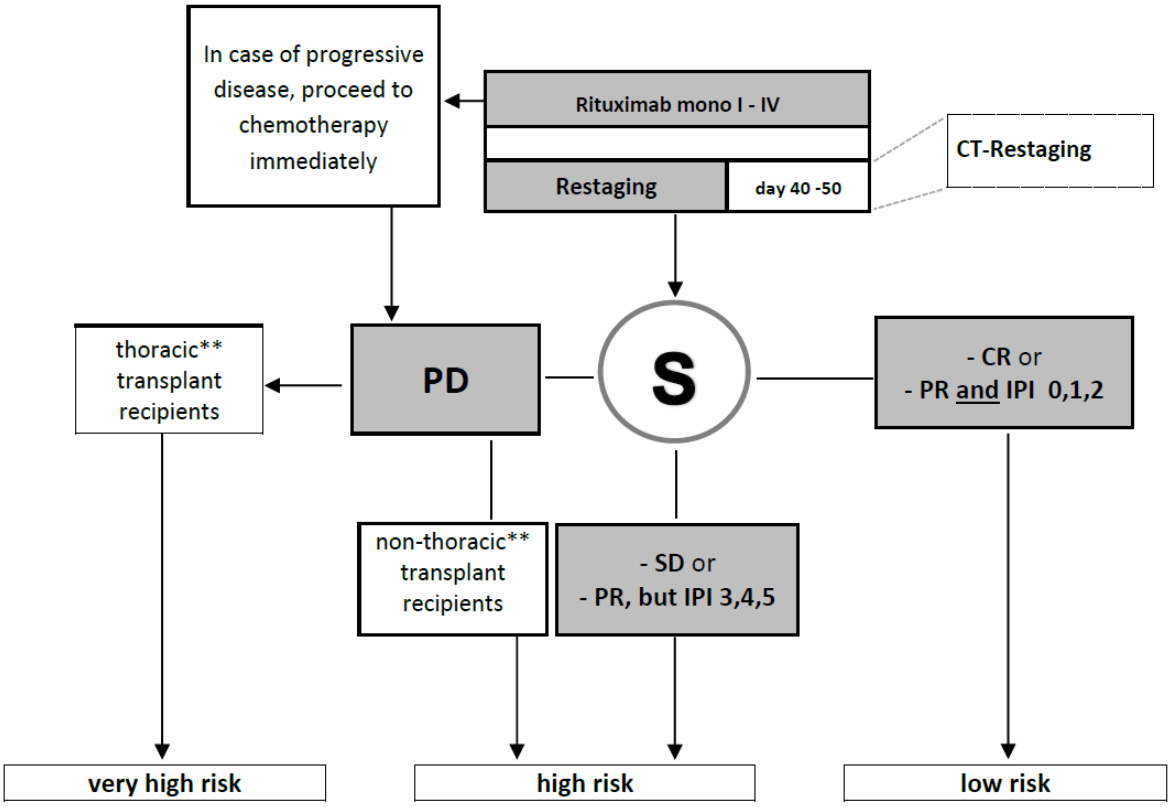
After the 4$^{th}$ application of rituximab there are four weeks without treatment. In case of disease progression during rituximab monotherapy or at any time during the 4 weeks interval without treatment patients start subsequent treatment immediately. Details on procedures for response assessment and examinations to be performed at interim staging are given in section 4.7.1 of this protocol.

Patients will be considered low-risk if they reached a complete remission with the first 4 applications of rituximab monotherapy or if they reached a partial remission and had a baseline IPI of 0, 1 or 2.

Patients will be considered high-risk if they reached a partial remission 4 weeks after the 4$^{th}$ application of rituximab monotherapy and had an IPI of 3, 4 or 5 at the start of PTLD treatment or if they show stable disease 4 weeks after the 4$^{th}$ application of rituximab monotherapy.

Heart and lung transplant recipients and patients with a combination of organs transplanted including a heart or lung transplant who show disease progression during rituximab monotherapy, the 4 weeks interval without treatment or at staging 4 weeks after the 4$^{th}$ application of rituximab monotherapy will be considered very high-risk, while all other transplant recipients (i.e. the non-heart- and non-lung-transplant recipients) will be considered high-risk in this situation.

**Figure 7: Risk stratification**




#### *4.6.1.3. Risk-stratified treatment*

Treatment is according to the patient's risk profile.

(1) Low-risk patients:

Patients considered low-risk will receive four more single therapeutic agent applications of rituximab administered subcutaneously at a fixed dose of 1400 mg once every three weeks at days 50, 71, 92 and 113.

**Table 5: Cycles 5-8: rituximab monotherapy**

| Medication | Dose | Mode | D50 | D71 | D92 | D113 |
|---|---|---|---|---|---|---|
| **Rituximab** | **1400 mg fixed dose** | SC | x | x | x | x |

(2) High-risk patients:

Patients considered high-risk will receive four more applications of rituximab administered subcutaneously at a fixed dose of 1400 mg combined with CHOP chemotherapy every 3 weeks at days 50, 71, 92 and 113. CHOP chemotherapy will be administered at standard doses: cyclophosphamide 750 mg/m$^2$ day 1, adriamycine 50 mg/m$^2$ day 1, vincristine 1.4 mg/m$^2$ day 1 (maximum dose per cycle: 2 mg; for patients >70 years the maximum dose per cycle is 1 mg) and prednisone 100mg (at day 1 to 5 of each cycle). Cyclophosphamide, adriamycine and vincristine will be infused intravenously. Prednisone will be administered orally in a single dose. At day 3-4 of each treatment cycle, recombinant G-CSF treatment is obligatory, either as a PEGylated formulation (single dose) or repetitive dosing until recovery of WBC, as per institutional practice.

**Table 6: Cycles 5-8: R$^{SC}$-CHOP-21 + GCSF**

| **Medication** | **Dose** | **Mode** | **D 50*** | **D 50-54** | **D 71*** | **D 71-75** | **D 92*** | **D 92-96** | **D 113*** | **D 113-117** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Rituximab** | **1400 mg fixed dose** | SC | x | | x | | x | | x | |
| **Cyclophosphamide** | **750 mg/m$^2$** | IV | x | | x | | x | | x | |
| **Adriamycin** | **50 mg/m$^2$** | IV | x | | x | | x | | x | |
| **Vincristine** | **1,4 mg/m$^2$** maximum total dose: 2mg | IV | x | | x | | x | | x | |
| **Prednisolone** | **100 mg** | PO | | x | | x | | x | | x |

***** At day 3-4 of each treatment cycle, recombinant G-CSF treatment is obligatory, either as a PEGylated formulation (single dose) or repetitive dosing until recovery of WBC, as per institutional practice.

(3) Very high-risk patients:

Patients considered very high-risk will receive six more applications of rituximab administered subcutaneously at a fixed dose of 1400 mg combined with chemotherapy every 3 weeks at days 50, 71, 92, 113, 134 and 155. Chemotherapy is CHOP at days 50, 92 and 134 that is administered at standard doses of cyclophosphamide 750 mg/m$^2$ day 1, adriamycine 50 mg/m$^2$ day 1, vincristine 1.4mg/m$^2$ day 1 (maximum dose per cycle: 2 mg; for patients >70 years the maximum dose per cycle is 1 mg) and prednisone 100mg (at day 1 to

5 of each cycles), as per institutional practice. Cyclophosphamide, adriamycine and vincristine will be infused intravenously. Prednisone will be administered orally.

Chemotherapy is DHAOx at days 71, 113 and 155 and will be administered at standard doses of oxaliplatin (130 mg/m$^2$, day 1) and cytarabine (ARA-C, 2x 1000 mg/m$^2$ at day 2), but a reduced dose of dexamethasone (40 mg/m$^2$, only at day 1), as per institutional practice. Oxaliplatin is a single dose administered the day before the first dose of cytarabine. The dose of cytarabine (ARA-C) will be given in an interval of 12 hours on day two. Cytarabine (ARA-C) and oxaliplatin will be infused intravenously. Dexamethasone will be administered orally 1 hour before administration of oxaliplatin. At day 3-4 of each treatment cycle, recombinant G-CSF treatment is obligatory, either as a PEGylated formulation (single dose) or repetitive dosing until recovery of WBC, as per institutional practice.

**Table 7: Cycles 5-10: Alternating R$^{SC}$-CHOP-21 / R$^{SC}$-DHAOx-21 + GCSF**

| **Medication** | **Dose** | **Mode** | **D 50*** | **D 50 - 54** | **D 71*** | **D 72** | **D 92*** | **D 92 - 96** | **D 113*** | **D 114** | **D 134*** | **D 134 - 138** | **D 155 *** | **D 156** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Rituximab** | **1400 mg fixed dose** | SC | x | | x | | x | | x | | x | | x | |
| **Cyclophosphamide** | **750 mg/m$^2$** | IV | x | | | | x | | | | x | | | |
| **Adriamycin** | **50 mg/m$^2$** | IV | x | | | | x | | | | x | | | |
| **Vincristine** | **1,4 mg/m$^2$,** maximum total dose: 2mg | IV | x | | | | x | | | | x | | | |
| **Predni-solone** | **50 mg/m$^2$** | PO | | x | | | | x | | | | x | | |
| **Dexa-methasone#** | **40 mg/m$^2$** | PO | | | x | | | | x | | | | x | |
| **Oxaliplatin** | **130 mg/m$^2$** | IV | | | x | | | | x | | | | x | |
| **Cytarabine** | **1000 mg/m$^2$** | IV | | | | x x | | | | x x | | | | x x |

***** At day 3-4, recombinant G-CSF treatment is obligatory, either as a PEGylated formulation (single dose) or repetitive dosing until recovery of WBC, as per institutional practice.

# Please note: this is a dose reduction of dexamethasone. There is no dexamethasone on days 2 to 4 of a treatment cycle!

For very-high risk patients who are in a very good general condition, an optional restaging can be performed around day 130 (i.e. before the final two cycles of the protocol). If CR is not reached by that time, peripheral blood stem cell mobilization and apheresis with the goal of autologous transplantation may be attempted. These patients remain in the per-protocol population. The Data Monitoring Committee must be informed about this procedure as soon as possible.

#### *4.6.1.4. Follow-up*

All trial subjects will be followed up until the trial is officially closed. After the end of an initial 1-year follow-up period subjects will be followed according to institutional practice. Restaging results assessed during the follow-up period beyond 1 year will be used to determine time to event outcomes if the minimal restaging examinations given in table 9 have been performed. Of note, vaccination with live virus vaccines is not recommended for four half-lives (approximately 5 months) following rituximab therapy.

### 4.6.2. Concomitant medication during rituximab therapy

Premedication with oral acetaminophen (up to 1000 mg) and diphenhydramine hydrochloride (up to 100 mg) prior to IV or SC rituximab administration is allowed, as per institutional practice and does not need to be documented. Premedication with oral corticosteroids (up to 100 mg prednisolone) prior to IV administration of rituximab at day 1 also is allowed, as per institutional practice and does not need to be documented.

### 4.6.3. Concomitant medication during immunochemotherapy

<u>Prophylaxis of Nausea and Vomiting:</u>

Premedication to prevent nausea and vomiting is allowed, as per institutional practice. This does include glucocorticoids (e.g. dexamethasone). If glucocorticoids are part of the anti-emetics regimen, they should be administered prior to the rituximab administration.

Please note that additional administrations of high-dose glucocorticoids in lymphoma-therapeutic doses given outside of the CHOP and DHAOx regimes are not allowed.

Prophylaxis of Neutropenic Infections:

The use of recombinant G-CSF after CHOP and DHAOx chemotherapy is obligatory, either as a PEGylated formulation (single dose) or repetitive dosing until recovery of WBC, as per institutional practice. The administration of G-CSF or PEG-GCSF must be documented on the treatment CRFs.

#### 4.6.4. Other concomitant medication during treatment

TLS prophylaxis:

Prophylaxis against Tumor-Lysis Syndrome (TLS), e.g., allopurinol or rasburicase treatment, may be given as per institutional practice and does not need to be documented in the CRF.

Pneumocystis jirovecii prophylaxis:

Prophylactic medication with co-trimoxazole (trimethoprim/sulfamethoxazole) to prevent pneumocystis jirovecii pneumonia (e.g. 960mg two to three times a week, according to institutional practice) is obligatory. Pneumocystis jirovecii pneumonia prophylaxis must be continued until peripheral B-cells have adequately recovered. If a patient does not tolerate prophylactic administration of co-trimoxazole, prophylaxis with pentacarinat (300 mg, every 3 to 4 weeks) is allowed. The administration of pneumocystis jirovecii prophylaxis must be documented on the treatment CRFs.

#### 4.6.5. Guidance on management of AESIs

The following adverse events have been defined to be of special interest:

- Local skin reactions at injection site (Rituximab sc) are usually mild and do not require specific treatment
- Severe Infusion related reactions (Rituximab IV) – Rituximab should be administered under the close supervision of an experienced physician, and in an environment where full resuscitation facilities are immediately available: The management of

severe infusion related reactions involves stopping the rituximab infusion, IV fluids, steroids and antihistamines and all other resuscitation measures required.

- Serious infections require urgent in-patient care, in particular early diagnosis and treatment
- Progressive multifocal Leukencephalopathy requires the cessation of rituximab treatment – the Deutsche AIDS-Gesellschaft has issued a guideline on the management of opportunistic infections in HIV patients which can provide a starting point for further management: http://www.awmf.org/uploads/tx_szleitlinien/055-006l_S2k_Opportunistische_Infektionen_bei_HIV_infizierten_Patienten_2011-11.pdf
- Pneumocystis jirovecei pneumonia – requires antibiotic treatment based on cotrimoxazole and specialist supportive care - the Deutsche AIDS-Gesellschaft has issued a guideline on the management of opportunistic infections in HIV patients which can provide a starting point for further management: http://www.awmf.org/uploads/tx_szleitlinien/055-006l_S2k_Opportunistische_Infektionen_bei_HIV_infizierten_Patienten_2011-11.pdf
- Skin reactions such as Toxic Epidermal Necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome – these require cessation of rituximab treatment and specialist care – the following review can provide a starting point: http://www.ojrd.com/content/pdf/1750-1172-5-39.pdf

### 4.6.6. Dose modification for toxicity

The NCI-CTC (version 4.0) will be used to grade toxicity. Before starting a new treatment cycle, toxicity must have resolved.

#### *4.6.6.1. Delay of chemotherapy*

Patients who experience delay exceeding 21 days in the initiation of the next planned treatment cycle of R-monotherapy, R-CHOP or R-DHAOx will be removed from receiving study treatment.

No dose modification should be done for rituximab IV or rituximab SC. If chemotherapy is delayed, rituximab administration must also be delayed.

#### *4.6.6.2. Hematological toxicity*

Modification of treatment with rituximab IV or SC in combination with CHOP/DHAOx because of hematological toxicity will be determined according to institutional practice. It is recommended that cycles be delayed in 1-week increments for a maximum of 14 days until hematological parameters allow the next cycle of induction treatment to be administered (*e.g.*, ANC ≥ 1x $10^9$/L, platelets ≥ 75x$10^9$/L)

If Grade 3 or Grade 4 granulocytopenia or thrombocytopenia persists until the next planned cycle, the following reduction of chemotherapy doses may be implemented for all subsequent treatment cycles. The next cycle must be delayed until the granulocyte and platelets counts return to an acceptable level (*e.g.*, ANC ≥ 1x $10^9$/L, platelets ≥ 75x$10^9$/L).

**Table 8: Dose reduction of chemotherapy in case of hematological toxicity PERSISTING UNTIL THE NEXT PLANNED CYCLE**

| **NCI** | **Granulocytes (x$10^9$/L)** | | **Platelets (x$10^9$/L)** | **Cyclophosphamide** | **Doxorubicin** | **Oxaliplatin** | **Ara-C** |
|---|---|---|---|---|---|---|---|
| **grade** | | | | **dose reduction** | **dose reduction** | **dose reduction** | **dose reduction** |
| 3 | 0,5 - 1,0 | and/or | 25-50 | -25% | -25% | -25% | -25% |
| 4 | <0,5 | and/or | <25 | -50% | -50% | -50% | -50% |

**If myelosuppression is thought to be mainly caused by lymphoma infiltration of bone marrow, the study site investigator may decide not to reduce the chemotherapy doses.**

#### *4.6.6.3. Non-hematological toxicity*

Patients who develop clinically relevant non-hematological adverse events of CTC grade 2 or higher should have their next cycle of treatment delayed in 1-week increments for up to a maximum of 14 days. Specific exceptions are listed in the following subsections (4.6.6.3.1. to 4.6.6.3.6.).

#### *4.6.6.3.1. Hemorrhagic Cystitis*

Patients should be adequately hydrated prior to and after cyclophosphamide administration and should be instructed to void frequently. Mesna may be used as prophylaxis according to institutional practice. If gross hematuria develops, cyclophosphamide should be withheld until resolution of cystitis. A dose reduction of 50% cyclophosphamide may be considered for the next cycle. Re-escalation of cyclophosphamide to the initial full dose is strongly recommended if symptoms do not recur.

#### *4.6.6.3.2. Hepatotoxicity*

If the bilirubin level is between 1,5 and 2,0 mg/dL, doxorubicin and Ara-C dose should be reduced by 25% of baseline to avoid myelotoxicity. If the bilirubin level is between 2,0 mg/dL and 3,0 mg/dL doxorubicin and Ara-C doses should be reduced by 50%. With subsequent courses of treatment and with improved hepatic function, full doses may be given again.

#### *4.6.6.3.3. Nephrotoxicity*

If the renal function is impaired chemotherapy doses should be reduced according to table 9.

**Table 9: Impaired renal function: dose reduction of chemotherapy**

| Substance | Creatine-Clearance | Dose reduction |
|---|---|---|
| Cyclophosphamide | <10 ml/min | -25 % |
| Adriamycin | | no dose reduction recommended |
| Vincristine | | no dose reduction recommended |
| Steroids | | no dose reduction recommended |
| Oxaliplatin | >20 ml/min | no dose reduction recommended* |
| Oxaliplatin | <20 ml/min | no dose reduction, but hemodialysis 3 to 6 hours after the end of the oxaliplatin infusion recommended* |
| Ara-C | <60 ml/min | -40%# |
| Ara-C | <45 ml/min | -50%# |
| Ara-C | <30 ml/min | reduce the Ara-C dose by 50% and split the dose into two portions infused within 3 hours in an interval of 24 hours, hemo-dialysis should be initiated 6 hours after the end of each Ara-C infusion# |

* In patients with mild-to-moderate renal impairment, as defined by measured creatinine clearance >20ml/min, full doses of oxaliplatin at 130 mg/m$^2$ are well tolerated with no increase in drug-related toxicity (Takimoto et al., 2003). According to current evidence, in the first hour following oxaliplatin treatment, the active drug is cleared rapidly from plasma ultrafiltrate via protein binding, tissue distribution, cellular sequestration, and reaction with plasma constituents, ultimately forming inactive platinum adducts. These processes are independent of renal function and represent the alpha-phase half-life (Takimoto et al., 2007). Although data on oxaliplatin-related toxicity is scarce in patient with severe renal impairment, as defined by a creatinine clearance <20/ml/min, we recommend no dose reduction, but hemodialysis 3-6 hours after application.

# Renal insufficiency is believed to play a key role in the neurotoxicity of cytarabine. Ara-C pharmacokinetics in patients with severe renal insufficiency was shown to be comparable to patients with normal renal function. Peak plasma levels as well as intracellular Ara-CTP kinetics were also not found to be significantly influenced by renal function. However, Ara-U serum levels were shown to accumulate during high dose Ara-C treatment with Ara-U levels being 12-fold higher in patients with renal impairment compared to patients with normal renal function (Lindner et al., 2008). While the only significant altered parameter in Ara-C pharmacokinetics is the elimination of Ara-U and excessive plasma levels of Ara-U have been found especially in the cerebrospinal fluid of patients with impaired renal function, dose

reduction of Ara-C is advisable in patients with impaired renal function to prevent neurotoxicity. While Ara-C and its metabolite Ara-U can be effectively be cleared by hemodialysis (Radeski et al., 2011), a reduction of Ara-C doses by 50% and subsequent dialysis is recommended in patients with a creatinine clearance <30 ml/min.

#### *4.6.6.3.4. Cardiotoxicity*

We recommend measurement of left ventricular ejection fraction (LVEF) before the start of doxorubicin treatment and reevaluation after cycles 6b, 8b (high risk group) and 7c (very high risk group). In patients with normal LVEF (> 50%) prior to the start of treatment, a decrease by 10% or below 50% indicates a deterioration of cardiac function. In this case, the continuation of doxorubicin treatment should be carefully re-evaluated.

#### *4.6.6.3.5. Neurotoxicity*

In the case of moderate/severe neurotoxicity related to vincristine (grade 2-3), after recovery to grade ≤ 1, the dose of **vincristine** will be reduced by 50% for all subsequent courses of therapy until the end of the combined immunochemotherapy treatment. The dose of vincristine need not be postponed or reduced in the case of mild (grade 1) neurotoxicity. In the case of moderate/severe neurotoxicity related to vincristine (grade 2-3) without recovery to grade ≤ 1, the dose of **vincristine** will be reduced by 100% for all subsequent courses of therapy until the end of the combined immunochemotherapy treatment.

Neurotoxic side effects occurring on treatment with **oxaliplatin** require the response as given in table 10. A small proportion of patients (1–2%) experience a syndrome of pharyngolaryngeal dysesthesia, a special form of acute neuropathy characterized by a subjective feeling of dysphagia and dyspnea with no objective evidence of airway obstruction. This unpleasant sensation is non-life-threatening and rapidly reversible without treatment. The duration of oxaliplatin infusions should be increased to 6 hours in the following cycles. The use of calcium/magnesium infusion before and after oxaliplatin should be introduced.

**Table 10: Oxaliplatin related dose reduction of chemotherapy**

| Toxicity | Toxicity lasting between 1-7 days | Toxicity lasting >7 days | Toxicity persisting between cycles |
|---|---|---|---|
| Cold-related dysesthesia | No dose reduction | No dose reduction | Withhold oxaliplatin until recovery then restart with 25% reduction of scheduled dose, omit oxaliplatin if recurs |
| Paraesthesia without pain | No dose reduction | No dose reduction | Withhold oxaliplatin until recovery then restart with 25% reduction of scheduled dose, omit oxaliplatin if recurs |
| Paraesthesia with pain | No dose reduction | 25% reduction of scheduled dose of oxaliplatin, omit oxaliplatin if recurs | Omit oxaliplatin |
| Paraesthesia with functional impairment | No dose reduction | 25% reduction of scheduled dose of oxaliplatin, omit oxaliplatin if recurs | Omit oxaliplatin |

#### *4.6.6.3.6. Mucositis*

R-CHOP and R-DHAOx should be delayed until after recovery of mucositis to grade <1.

### *4.6.6.4. Infusion Related Reactions (IRR)*

Rituximab can be associated with IRRs, which may be related to release of cytokines and/or other chemical mediators and which might be clinically indistinguishable from hypersensitivity reactions. Severe IRR (such as bronchospasm and hypotension) may occur in about 10% of the cases. The incidence of IRR decreases substantially with subsequent infusions and is <1% of patients by the eight cycle of rituximab containing treatments. Patients with high tumor burden may be at higher risk of developing severe IRRs. Severe IRRs usually manifest within 1 to 2 hours after starting the first rituximab infusion, are characterized by pulmonary events and in some cases include features of tumor lysis syndrome in addition to fever, chills, rigors, hypotension, urticaria, angioedema and other symptoms. These symptoms are usually reversible with interruption of the infusion and should be treated with diphenhydramine and paracetamol (acetaminophen). Additional treatment with bronchodilators or IV saline may be indicated. In most cases, the infusion can be resumed at

a 50% reduction in infusion rate (*e.g.* from 100mg/h to 50mg/h) when symptoms have completely resolved. Most patients who have experienced non-life threatening IRRs have been able to complete the full course of rituximab therapy. In order to reduce the incidence and severity of IRRs, all patients should receive premedication consisting to antipyretics and antihistamines (*e.g*. paracetamol and diphenhydramine) before every infusion of rituximab.

After the subcutaneous administration, rituximab is absorbed slowly from the interstitial tissue (time to $C_{max}$ approximately 2-7 days) and the mean $C_{max}$ will be approximately 50% decreased as compared with the intravenous administration. In the SABRINA trial (Davies et al, 2014) half the patients (31 of 62) receiving rituximab SC had infusion-related reactions. Of 73 individual reactions, 69 (95%) were grade 1 or 2. Three of 62 patients (5%) had a grade 3 IRR (these were injection-site rash; dry mouth after administration; and decreased urine output with tumor lysis syndrome). There were no grade IV IRRs in the rituximab SC group.

Patients that were not able to receive the full dose of rituximab at cycle 1 as a result of IRR should also receive the second administration intravenously. Only once the patient has received a full dose of rituximab intravenously can the administration be changed to rituximab SC.

Patients with grade 3 or 4 IRR after a second intravenous application of rituximab will be withdrawn from receiving study treatment.

### 4.6.7. Description of investigational medicinal product

Trade name: MabThera SC®

INN (International Nonproprietary Name): Rituximab SC

MabThera SC® is supplied as a ready to use liquid formulation with a nominal content of 120 g/mL rituximab and must not be diluted prior to administration. The drug product contains 2,000 U/mL recombinant human hyaluronidase (rHuPH20, manufactured in CHO cell line) acting as a permeation enhancer, histidin/histidin-HCL (buffer), alpha,alpha-trehalose (bulking agent), methionine (stabilizer), and polysorbate 80 (surfactant) in water for injection at a pH of 5.5.

Presentation: The drug product is a sterile, colorless to yellowish, clear to opalescent liquid in colorless 10-mL vials (11.7 mL fill).

Dose: 1400 mg

Manufacturer: Roche

**In oncology, MabThera® SC is licenced in the EU:**

- For the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy;
- As maintenance treatment for patients with follicular lymphoma responding to induction therapy;
- For the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy;
- As monotherapy for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.

#### *4.6.7.1. Labeling of investigational medicinal product*

Study drug packaging will be overseen by the Roche clinical trials supplies department and will bear a label with the identification required by local law, the protocol number, drug identification and dosage. The packaging and labeling of the study medication will be in accordance with with Roche standards and local regulations.

In case of urgent need to start treatment before arrival of the study drug at the treating centre, commercially available Rituximab IV can be used for the first application (d1).

#### *4.6.7.2. Storage of investigational medicinal product*

The recommended storage condition for rituximab SC is 2°C-8°C, protected from light. From a microbiological point of view the product should be used immediately after first opening. If not used immediately, in-use storage times and conditions prior to use are the responsibility

of the user and would normally not be longer than 24 hours at 2°C-8°C. Batch specific details and information on shelf-life are given on the packaging label.

### 4.6.8. No deviation from clinical standards

Clinical guidelines for the treatment of adult PTLD after solid organ transplantation have been established by the German PTLD study group and the European PTLD network and have recently been summarized (Zimmermann and Trappe, 2013). The extended risk stratification introduced by this trial intends to increase the number of patients that will be treated with rituximab monotherapy. Rituximab monotherapy can be considered as a clinical standard in everyday practice (Choquet et al., 2006; Gonzalez-Barca et al., 2007; Oertel et al., 2005). Another clinical standard is sequential immunochemotherapy with 4 courses of rituximab followed by four cycles of CHOP +GCSF (PTLD-1 trial, (Trappe et al., 2012a)). The application of a more intensive treatment in patients with a considerable risk of disease progression, i.e. patients not responding to rituximab monotherapy, has not yet been defined. While chemotherapy is considered necessary in this situation, the optimal protocol still is in question. CHOP is efficient in renal and liver transplant recipients refractory to rituximab monotherapy, but heart and lung transplant recipients need a more intensive treatment (Zimmermann et al., 2013). In everyday practice treatment is guided by expert opinion in situations where clinical trial data are missing. Thus, an international expert meeting was held in San Diego in December 2012 (appendix 11.5). This expert panel advised for 6 cycles of rituximab combined with alternating cycles of CHOP and DHAOx as a reasonable treatment for heart- and lung transplant recipients refractory to upfront treatment with rituximab monotherapy.

Rituximab SC has been proven as effective as rituximab IV (Davies et al., 2014) and has been licensed as an alternative application route for rituximab oon March 28$^{th}$ 2014.

### 4.6.9. Continuation of treatment after the end of the clinical trial

Treatment of trial subjects after the end of the trial is at the discretion of the participating institution. Medical advice may be obtained from the head of the DPTLDSG. The trial

treatment does not need to be tapered off and may be discontinued without any special measures.

## 4.7. Efficacy and safety variables

### 4.7.1. Measurement of efficacy and safety variables

#### *4.7.1.1. Primary efficacy and safety outcome*

The primary efficacy and safety outcome is EFS in the low-risk group and will be analyzed in the intention to treat population. EFS is defined as time from start of treatment to documented disease progression, treatment-related grade 3 or 4 infectious toxicity (defined as any grade 3 or 4 infection during stratification to the low-risk group and final response assessment), treatment-discontinuation from any reason, or death from any reason.

Subjects will undergo physical examination, imaging, laboratory analyses and bone marrow biopsy at the schedule of assessments described in the protocol. Response to treatment will be determined according the response criteria for malignant lymphomas *(Cheson et al., 1999)*. PTLD-specific information have been added in appendix 11.10.

Adverse events will be evaluated each treatment visit. CT scans chest, abdomen and pelvis, bone marrow biopsy, blood laboratory information and disease related symptom assessment will be performed and constitute the primary source for response / progression determination.

Primary source data for all efficacy parameters and for any grade 3 and 4 infection during the treatment period will be sent to the DPTLDSG study office for central review.

The algorithms described in the following section will be used to determine the date of the event/censoring for each subject. Time to EFS in days will be calculated as the earliest day of documented progression, treatment-related infection, treatment discontinuation or death or censor date minus date of start of treatment +1. Screening tumor assessment must be performed prior to start of treatment, i.e. prior to the first application of rituximab. These will be designated as baseline. When more than one tumor assessment is performed prior to start of treatment, the last available assessment prior to start of treatment will be designated as baseline unless documented otherwise by the site.

Censoring of EFS will be performed as detailed in the table below. Note that patients need to be in CR or PR at interim staging (day 50) to be eligible for the low-risk group, while final staging is performed 4 weeks after the last application of scheduled treatment. PD can be determined prior to final staging, but PD prior to interim staging will result in stratification of a trial subject to the high-risk or very high-risk group (see table 11).

**Table 11: Algorithm to determine the date of the event/censoring for each subject**

| Situation | Date of Event or Censoring | Outcome |
|---|---|---|
| **Death following missing (scheduled) response assessments** | Date of death | Death |
| **Two sequential missed scheduled response assessments without unschedueled assessments during that period** | Date of last response assessment | Censored |
| **Documented progression at scheduled or unscheduled response assessment** | Date of response assessment | Progression |
| **Documented progression (scheduled or unscheduled) following one missing (scheduled) response assessment** | Date of missing scheduled response assessment | Progression |
| **Documented progression following two or more consecutive missing (scheduled) response assessment scans** | Date of the first missing scheduled response assessment | Progression |
| **Loss of follow-up without documented progression** | Date of last response assessment | Censored |
| **Treatment discontinuation for undocumented progression, toxicity, or other reason** | Date of discontinuation | Event (EFS only) |
| **Grade 3/4 infection during treatment** | Start date of infection | Event (EFS only) |

Note: Response assessments include the restaging procedures as scheduled. A non-missing response assessment must include all of the scheduled response determinations or a finding of unequivocal disease progression. Change in treatment includes any additional anti-lymphoma therapy, i.e. consolidative radiotherapy, other chemotherapy than that described in the protocol, but does not include changes in immunosuppression or antiviral treatment.

EFS of low-risk patients will be displayed using Kaplan-Meier methods. The EFS at two years and 95% confidence intervals will be provided and data will be compared to the data from the PTLD-1 trials.

While plans to minimize missing response data to ensure the integrity of the EFS data have been made and will be implemented, the per protocol population will also be used for

secondary analyses of the primary outcome for all EFS, PFS, TTP, duration of response and OS analyses.

#### *4.7.1.2. Secondary efficacy outcomes*

Secondary efficacy analysis will employ the intention to treat and per protocol populations. No alpha adjustment for multiplicity is to be performed unless specifically otherwise stated.

Time to disease progression (TTP), progression free survival (PFS), response and overall response (ORR) at interim staging, response and ORR after full treatment and duration of response are the key efficacy outcomes of the study. TTP is defined as time from start of treatment to documented disease progression, while PFS is defined as time from start of treatment to documented disease progression or death from any reason. TTP and PFS will be displayed using Kaplan-Meier plots. Median TTP and PFS estimates and TTP and PFS estimates at 2 and 3 years of follow-up by treatment group and 95% confidence intervals will be provided.

For the calculation of the overall response to full treatment (i.e. CR+PR) subjects non-evaluable for response (i.e. subjects that died from treatment-related toxicity before final staging and without any finding of unequivocal evidence for PD) will not be included in the denominator.

Duration of response is a subpopulation analysis on subjects demonstrating a response at final staging (i.e. CR or PR). Duration of response will be measured as time from initial response, i.e. date of documented progression minus date of first evidence of best response.

#### *4.7.1.3. Safety analysis*

The safety analysis will employ the intention to treat and per protocol populations. Overall survival (OS) is the key safety and efficacy outcome of the study. OS is defined as death due to any cause and derived as date of death/censor minus date of start of treatment +1. Non-death will be censored at the last known date alive as captured in the survival follow-up. OS will be displayed using Kaplan-Meier plots. Median OS estimates and OS estimates at 2 and 3 years of follow-up by treatment group and 95% confidence intervals will be provided.

Treatment related mortality as assessed by the treating physician has been defined as a secondary safety parameter. The denominator is the patient cohort at risk, i.e. the number of patients that started treatment and had at least one cycle of therapy. The reason of death will be categorized with a total of three categories: (1) death due PTLD progression, (2) death due to treatment toxicity, (3) death due to other or unknown reason of death. Treatment related mortality is employed in the total trial population and by treatment group.

Other exploratory safety parameters are the frequency of grade III and IV leucocytopenia and the frequency of grade III and IV infections by treatment group with adverse events recorded each treatment visit and during follow-up. The denominator is the patient cohort at risk, i.e. the number of patients that started treatment and had at least one cycle of therapy.

#### *4.7.1.4. Protocol visits and investigations during the clinical trial*

Visits will be conducted at the following times and must fall between the ‘first day possible’ and the ‘last day possible’ (measured in trial days) given in table 12.

**Table 12: Visit schedule**

| Visit | Description of visit | Scheduled for trial day | First day possible | Last day possible | Comments |
|---|---|---|---|---|---|
| 0 | Patient inclusion/baseline | 0 | -28 | 0 | |
| 1 | Cycle 1: Rituximab IV | 1 | 1 | 3 | AE assessment |
| 2 | Cycle 2: Rituximab SC | 8 | 7 | 9 | AE assessment |
| 3 | Cycle 3: Rituximab SC | 15 | 14 | 16 | AE assessment |
| 4 | Cycle 4: Rituximab SC | 22 | 21 | 23 | AE assessment |
| 5 | Interim Staging | 50 | 40 | 50 | |
| 6 a | Cycle 5a: Rituximab SC | 50 | 48 | 52 | AE assessment |
| 7 a | Cycle 6a: Rituximab SC | 71 | 69 | 73 | AE assessment |
| 8 a | Cycle 7a: Rituximab SC | 93 | 91 | 95 | AE assessment |
| 9 a | Cycle 8a: Rituximab SC | 113 | 111 | 115 | AE assessment |
| 6 b | Cycle 5b: $R^{SC}$-CHOP | 50 | 48 | 52 | AE assessment |
| 7 b | Cycle 6b: $R^{SC}$-CHOP | 71 | 69 | 73 | AE assessment |
| 8 b | Cycle 7b: $R^{SC}$-CHOP | 93 | 91 | 95 | AE assessment |
| 9 b | Cycle 8b: $R^{SC}$-CHOP | 113 | 111 | 115 | AE assessment |
| 6 c | Cycle 5c: $R^{SC}$-CHOP | 50 | 48 | 52 | AE assessment |
| 7 c | Cycle 6c: $R^{SC}$-DHAOx | 71 | 69 | 73 | AE assessment |
| 8 c | Cycle 7c: $R^{SC}$-CHOP | 93 | 91 | 95 | AE assessment |
| 9 c | Cycle 8c: $R^{SC}$-DHAOx | 113 | 111 | 115 | AE assessment |
| 10 c | Cycle 9c: $R^{SC}$-CHOP | 134 | 132 | 136 | AE assessment |
| 11 c | Cycle 10c: $R^{SC}$-DHAOx | 155 | 153 | 157 | AE assessment |
| 12* | Final staging | $143^{ab}/187^{c}$ | $136^{ab}/160^{c}$ | $150^{ab}/194^{c}$ | $^{ab}$ indicates days for patients that received cycles 6a-8a or 6b-8b, $^{c}$ indicates days for patients that received cycles 6c-11c |
| 13 | Follow-up: 3 months | $227^{ab}/271^{c}$ | $197^{ab}/241^{c}$ | $257^{ab}/301^{c}$ | |
| 14 | Follow-up: 6 months | $281^{ab}/355^{c}$ | $251^{ab}/325^{c}$ | $311^{ab}/385^{c}$ | |
| 15 | Follow-up: 9 months | $365^{ab}/439^{c}$ | $335^{ab}/409^{c}$ | $395^{ab}/469^{c}$ | |
| 16 | Follow-up: 12 months | $449^{ab}/523^{c}$ | $419^{ab}/493^{c}$ | $479^{ab}/553^{c}$ | |
| 17 | Follow-up: 18 months | $617^{ab}/691^{c}$ | $587^{ab}/661^{c}$ | $647^{ab}/721^{c}$ | |
| 18 | Follow-up: 24 months | $701^{ab}/775^{c}$ | $671^{ab}/745^{c}$ | $731^{ab}/805^{c}$ | |
| 19 | Follow-up: 36 months | $1066^{ab}/1140^{c}$ | $976^{ab}/1050^{c}$ | $1156^{ab}/1230^{c}$ | |
| 20 | Follow-up: 48 months | $1431^{ab}/1505^{c}$ | $1341^{ab}/1415^{c}$ | $1521^{ab}/1595^{c}$ | |

* There are no visits 10a, 11a, 10b, 11b.
Patients in the low risk group receive cycles 6a-9a, those in the high risk group receive cycles 6b-9b and those in the very high risk group receive cycles 6c-11c.

## Table 13: Investigations during the clinical trial

| Study Schedule Visit | Patient inclusion/ Baseline | Interim staging (at day 50, but before day 50 in case of clinical findings for disease progression) | Final staging (4 weeks after the last treatment cycle) | 3 months after therapy | 6 months after therapy | 9 months after therapy | 12 months after therapy | 18 months after therapy | 24 months after therapy | Once every six months for 3 years and yearly thereafter (for a maximum of five years) |
|---|---|---|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | | | | |
| Severe infection screening[0] | X | | | | | | | | | |
| Check in- and exclusion criteria | X | | | | | | | | | |
| Reference pathology[7] | X | | | | | | | | | |
| Medical History (see CRF) | X | | | | | | | | | |
| Physical Examination | X | X | X | X | X | X | X | X | X | X[6] |
| ECOG performance Status | X | X | | | | | | | | |
| B-Symptoms | X | X | X | X | X | X | X | X | X | X[6] |
| Ann Arbor classification | X | | | | | | | | | |
| Laboratory investigations[2] | X | X | X | X | X | X | X | X | X | X[6] |
| EBV-PCR (reference diagnostics)[1] | X | X | X | X | X | X | X | X | X | X[6] |
| Flow-cytometry (reference diagnostics)[1] | X | X | X | | X | | X | X | X | X[6] |
| Imaging: Cranial CT[3] or MRT[3] | X | | | | | | | | | |
| Imaging: Neck, Chest, Abdomen, Pelvis CT[3] or MRT[3] | X | X | X | | X | | X | | X | |
| Chest X-Ray | | | | X | | X | | X | | |
| Abdominal Ultrasound | | | | X | | X | | X | | |
| Bone marrow biopsy | X | X[4] | X[4] | X[5] | | | X[5] | | X[5] | |
| 20 ml Li-Heparin, 10ml EDTA, 10ml serum for associated research projects[1] | X | X | X | | | | X | | | |
| Adverse event assessment | | X | X | | | | | | | |

0: **obligatory:** including HIV serology, Hepatitis B Surface Antigen test, interferon-gamma release assay for Tuberculosis

1: **shipping according to appendix 11.16**

2: **hematology** (red blood cells, WBC with neutrophils, lymphocytes, monocytes, hemoglobin, platelets); **blood chemistry** (serum creatinine, ALT, LDH, albumin, total bilirubin), **quantitative immunoglobulines** (IgG, IgA, IgM)

3: including IV contrast

4: bone marrow biopsy is necessary only in case of initial bone marrow involvement or progressive disease

5: bone marrow biopsy is necessary only in case of initial bone marrow involvement and the patient did not already reached a CR

6: according to follow up standards in DLBCL, imaging is recommended only in case of clinical or laboratory findings suspicious for disease progression

### 4.7.2. Rationale for assessment procedures

Response assessment is according to international standards in the treatment of malignant lymphomas (Cheson et al., 1999).

## 4.8. Data quality assurance

### 4.8.1. Monitoring

The trial sites will be monitored to ensure the quality of the data collected. The objectives of the monitoring procedures are to ensure that the trial subject's safety and rights as a study participant are respected; that accurate, valid and complete data are collected; and that the trial is conducted in accordance with the trial protocol, the principles of GCP and local legislation.

The monitoring is done in a risk-adapted way, and is accompanied by central quality assurance measures, according to the ADAMON concept. This includes in-time reminders on missing documentation, and a comparison of trial sites on documentation quality.

All investigators agree that the monitor regularly visits the trial site and assure that the monitor will receive appropriate support in their activities at the trial site, as agreed in separate contracts with each trial site. The declaration of informed consent (see Section 5.4) includes a statement to the effect that the PCI and monitor have the right – while observing the provisions of data protection legislation – to compare the case report forms (CRFs) with the trial subject's medical records (doctor's notes, radiology reports, laboratory printouts etc.). The investigator will secure access for the monitor to all necessary documentation for trial-related monitoring. Primary source data necessary for central review will be sent to the central study office.

The aims of the monitoring visits are as follows:

- To check the declarations of informed consent
- To monitor trial subject safety (occurrence and documentation/reporting of AEs and SAEs)

- To check the completeness and accuracy of entries on the CRFs
- To check the completeness and accuracy of source documents sent to the central study office (central source data verification)
- To evaluate the progress of the trial
- To evaluate compliance with the trial protocol
- To assess whether the trial is being performed according to GCP at the trial site
- To discuss with the investigator aspects of trial conduct and any deficiencies found

A monitoring visit report is prepared for each visit describing the progress of the clinical trial and any problems (e.g. refusal to give access to documentation).

### 4.8.2. Audits/Inspections

As part of quality assurance, the sponsor (DIAKO Bremen gGmbH) and the financial supporter (ROCHE Pharma AG) have the right to audit the trial sites and any other institutions involved in the trial. The aim of an audit is to verify the validity, accuracy and completeness of data, to establish the credibility of the clinical trial, and to check whether the trial subject's rights and trial subject safety are being maintained. The sponsor and financial supporter may assign these activities to persons otherwise not involved in the trial (auditors). These persons are allowed access to all trial documentation (especially the trial protocol, case report forms, trial subjects' medical records, drug accountability documentation, and trial-related correspondence).

The sponsor and all trial sites involved undertake to support auditors and inspections by the appropriate authorities at all times and to allow the persons charged with these duties access to the necessary original documentation.

All persons conducting audits undertake to keep all trial subject data and other trial data confidential.

## 4.9. Documentation

All data relevant to the trial are documented soon after measurement by the investigator responsible in the case report form supplied and source data is sent for verification of the trial data to the central study office as indicated in the protocol and CRFs. Entering data may be delegated to members of the trial team. The CRFs are signed by the investigator.

Entries must be made in full, any corrections must leave the original entry legible and be initialed; see also ICH-GCP E6.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from the study sponsor and/or applicable regulatory authorities. Elements include:

- Subject files containing completed case report forms, informed consent forms, and subject identification list.
- Study files containing the protocol with all amendments, the summary of product characteristics, copies of pre-study documentation, and all correspondence to and from the IEC.

In addition, all original source documents supporting entries in the case report forms must be maintained and be readily available.
All study documents and source documents must be kept for at least 10 years from submission of the final study report. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify the sponsor in writing of the new responsible person and/or the new location.

### 4.9.1. Data management

The IT infrastructure and data management staff will be supplied by the Institute of Medical Statistics, Computer Sciences and Documentation at the University of Jena. The trial database will be developed and validated before data entry. The data management system will use a CDISC-SDTM structure and is based on SAS database. All changes made to the

data are documented in an audit trail. The trial software has a user and role concept that can be adjusted on a trial-specific basis. The database is integrated into a general IT infrastructure and safety concept with a firewall and backup system. The data are backed up daily. After completion and cleaning of data, the database is locked and the data subjected to statistical analysis using the validated SAS-macro-bibliography to analyse clinical trial data with CDISC-SDTM structure as developed by the TMF (Technologie- und Methodenplattform für die vernetzte medizinische Forschung e.V., Neustädtische Kirchstr. 6, 10117 Berlin). The SAS macro-bibliography is available at: http://www.tmf-ev.de/Produkte/Uebersicht/ctl/Article View/mid/807/articleId/ 286/P021011.aspx).

The arrival of CRFs at the GPTLDSG central study office is documented and the CRFs checked for completeness. Source data verification is done and discrepancies and implausible values are clarified in writing between the central study office and the trial site. The trial site has to answer these queries without unreasonable delay.

The diagnostic core units send patient data to the study site and to the central study office.

Verified trial data and integrated data from the reference diagnostic core units is sent from the central study office to the Institute of Medical Statistics, Computer Sciences and Documentation at the University of Jena. Here, independent data entry staff enters the data into the trial database using double data entry, and the data entered is compared. Plausibility checks are also conducted in the database. Discrepancies and implausible values are clarified. Further details will be specified in the data management manual.

### 4.9.2. Archiving

All CRFs, informed consent forms and other important trial materials will be archived for at least 10 years in accordance with §13 Sec. 10 of the GCP Regulations. Trial subject identification lists and trial source data at each trial site and in the central study office will be stored separately from trial documentation.

## 4.10. GPTLDSG clinical repository specimen(s)

Specimens for dynamic (non-inherited) biomarker discovery and validation will be collected from consenting subjects.

These specimens will be used for research purposes to identify dynamic biomarkers that predict response to treatment (in terms of dose, safety and tolerability) and will help to better understand the pathogenesis, course and outcome of PTLD. Specimens for dynamic biomarker discovery will be identified by single codes like any other clinical sample (labeled and tracked using the subject`s study identification number).

Specimens for genetic biomarker (inherited) discovery and validation will also be collected from consenting subjects.

The pharmacogenetic information gathered through the analysis of specimens from the GPTLDSG clinical repository is hoped to improve subject outcome by predicting which subjects are more likely to respond to specific drug therapies, predicting which subjects are susceptible to developing adverse side effects and/or predicting which subjects are likely to progress to more severe disease states.

The result of specimen analysis from the GPTLDSG clinical repository will facilitate the rational design of new trials and the development of diagnostic tests, which may allow for individualized drug therapy for subjects in the future.

All GPTLDSG clinical repository specimens will be destroyed no later than 20 years after the final freeze of the respective clinical database unless regulatory authorities require that specimens be maintained for a longer period. The specimens in the GPTLDSG clinical repository will be made available for future biomarker research towards further understanding of treatment of PTLD, related disease and adverse events and for the development of potential associated diagnostic assays. The implementation and use of the GPTLDSG clinical repository specimens is governed by the GPTLDSG board to ensure appropriate use of the GPTLDSG clinical repository specimens.

### 4.10.1. PMBC and Serum repository

Blood (two approximately 10ml sample with Li-Heparin, one approximately 10ml sample with EDTA, one approximately 10ml serum sample) for PBMC isolation and and serum isolation will be obtained before the first administration for induction treatment, at interim staging, at final staging and one year after treatment as indicated in Table 13. These samples will be used for biomarker assays.

### 4.10.2. Tumor repository and tumorcytogenetics

**Remaining formalin fixed tumor tissues embedded in paraffin blocks form consenting subjects will automatically be collected at the reference pathology units and unequivocally labeled as a GPTLDSG clinical repository specimen.** Tumor tissue blocks will be potentially used to create a tissue microarray (TMA) for extended IHC analysis and for extraction of tumor RNA and DNA.

Tumor blocks that will be used to set up a tissue microarray (TMA): tissue cores from tumor will be taken out using a puncher and then rearranged as an array into a block of wax. A single array may include tissues core from different patients. Markers of angiogenesis, tumor biology, tumor necrosis, vascularity, cell turnover, and their signaling pathway molecules and others may be assessed.

Tumor blocks that will be used for tumor RNA and DNA extraction: 10 to 30µm slices from the tumor block will be prepared and subjected to RNA and DNA extraction. MicroRNA expression, gene expression, DNA mutation and modification may be assessed.

# 5. Ethical and regulatory aspects

## 5.1. Independent ethics committee

The clinical trial will not be started before approval of the appropriate ethics committee.

In each trial site, the clinical study will not be started before approval of the appropriate local ethics committee concerning the suitability of the trial site and the qualifications of the investigators.

## 5.2. Ethical basis for the clinical trial

The present trial protocol and any amendments were and will be prepared in accordance with the Declaration of Helsinki in the version of October 1996 (48th General Assembly of the World Medical Association, Somerset West, Republic of South Africa).

### 5.2.1. Legislation and guidelines used for preparation

The present clinical trial will be conducted in accordance with the published principles of the guidelines for Good Clinical Practice (ICH-GCP) and applicable legislation (especially the Federal Drug Law [AMG] and the GCP-V). These principles cover, amongst other aspects, ethics committee procedures, the obtaining of informed consent from trial subjects, adherence to the trial protocol, administrative documentation, documentation regarding the IMP, data collection, trial subjects' medical records (source documents), documentation and reporting of adverse events (AEs), preparation for inspections and audits, and the archiving of trial documentation. All investigators and other staff directly concerned with the study will be informed that domestic and foreign supervisory bodies, the appropriate federal authorities and authorized representatives of the sponsor have the right to review trial documentation and the trial subjects' medical records at any time.

## 5.3. Notification of the authorities, approval and registration

Before the start of the clinical trial, all necessary documentation will be submitted to the appropriate supreme federal authority for approval (Paul Ehrlich Institut, Langen). The state authorities in each federal state in which the trial will be conducted will also be notified.

Before the trial is started, it will be registered with Deutsches Register klinischer Studien (DRKS) (http://www.drks.de) and ClinicalTrial.gov (http://clinicaltrial.gov).

## 5.4. Obtaining informed consent from trial subjects

Trial subjects may not be enrolled into the present trial unless they have consented to take part in the trial after having been informed verbally and in writing in comprehensible language of the nature, scope and possible consequences by a trial investigator. Together with the consent to take part in the trial, the trial subject must also agree to representatives of the sponsor (e.g. monitors or auditors) or the appropriate supervisory or federal authorities having access to the data recorded within the framework of the clinical trial. The trial subject will be informed of the potential benefit and possible side effects of the IMP, and of the need and reasons to conduct clinical trials. It must be clear to trial subjects that he or she can withdraw his or her consent at any time without giving reasons and without jeopardizing his / her further course of treatment.

The original signed consent form is archived in the investigator site file. Trial subjects receive copies of the written information sheet, confirmation of insurance with conditions, and the signed informed consent form. A copy of the written information sheet and the signed informed consent form will be filed in the patient’s record.

The patient information sheet, informed consent form, all other documents handed out to the trial subject and any recruitment advertisements must be submitted to the ethics committee for approval before use. Part of the monitoring activities are to check that the most recent informed consent form was used before the trial subject was enrolled and that it was dated and signed by the trial subject himself or herself.

## 5.5. Insurance of trial subjects

All trial subjects enrolled are insured in accordance with § 40 AMG under the insurance contract of DIAKO – Ev. Diakonie-Krankenhaus Bremen gGmbH with Zurich insurance plc. The headquarters, policy number and telephone and fax number will be included in the patient information sheet.

## 5.6. Data protection

The provisions of data protection legislation will be observed. It is assured by the sponsor that all investigational materials and data will be pseudonymised in accordance with data protection legislation before scientific processing.

Trial subjects will be informed that their pseudonymised data will be passed on in accordance with provisions for documentation and notification pursuant to § 12 and § 13 of the GCP Regulations to the recipients described there. Subjects who do not agree that the information may be passed on in this way will not be enrolled into the trial.

# 6. Statistical methods and sample size calculation

## 6.1. Statistical and analytical plan

### 6.1.1. Trial populations

All analyses will be conducted on three trial populations:

The primary dataset for analysis is derived from the intention-to-treat (ITT) population. This dataset includes all trial subjects enrolled into the trial.

The secondary dataset for analysis is derived from the per-protocol (PP) population. This dataset includes all trial subjects who were treated according to protocol and reached a defined endpoint as detailed in table 14.

The tertiary dataset for analysis is the safety population. This population includes all trial subjects who received any trial treatment.

**Table 14: Parameters for the inclusion of patients in the dataset for the per-protocol analysis**

| Situation | Patients included | Comment |
|---|---|---|
| **Calculation of response rates at interim staging** | All patients from the ITT population without major eligibility violations (all inclusion criteria) and without CNS-involvement that had at least two treatment cycles with all information available, necessary to determine the remission status at interim staging | |
| **Calculation of response rates at final staging** | All patients from the ITT population without major eligibility violations (all inclusion criteria) and without CNS-involvement that had at least 5 treatment cycles with all information available, necessary to determine the remission status | Patients that died from TRM without restaging information generally are excluded from this dataset |

| | | |
|---|---|---|
| **EFS, PFS, TTP, duration of response, OS** | All patients from the ITT population without major eligibility violations (all inclusion criteria) and without CNS-involvement that received the study treatment without major treatment violation as outlined in the protocol | Patients that prematurely stopped study treatment for any reason and patients that had additional lymphoma treatment (i.e. additional radiotherapy) are censored with the time of protocol violation |
| **Subject was treated in a different treatment-group as stratified** | The patient is not eligible for the inclusion in the per-protocol dataset | |
| **Subject had dose reductions of more than 50% divergent from the reduction scheme given in the protocol** | The patient is not eligible for the inclusion in the per-protocol dataset | Unjustified dose reductions less than 50% of total therapy are acceptable for inclusion in the PP dataset, patients will not be censored |
| **Critical protocol violation not falling in the categories detailed above** | Inclusion of the subject and potential censoring is on the discretion of the Steering committee | The Steering committee will review the case, using blinded data if possible and decide how this should be handled |

### 6.1.2. Description of trial subject groups

(1) Total trial cohort: All patients that started treatment.

(2) Rituximab monotherapy / low-risk group:

- patients that reached a complete remission with the first 4 applications of rituximab monotherapy
- patients that reached a partial remission with the first 4 applications of rituximab monotherapy with a baseline IPI of 0, 1 or 2

(3) $R^{SC}$-CHOP / high-risk group:

- patients that reached a partial remission with the first 4 applications of rituximab monotherapy with a baseline IPI of 3, 4 or 5
- patients that were diagnosed with stable disease 4 weeks after the $4^{th}$ application of rituximab monotherapy
- non-heart and non-lung transplant recipients and patients without a combination of organs transplanted including a heart or lung transplant that showed disease

progression during rituximab monotherapy, the 4 weeks interval without treatment or at staging 4 weeks after the 4th application of rituximab monotherapy

(4) $R^{SC}$-CHOP/DHAOx / very high-risk group:

- heart and lung transplant recipients and patients with a combination of organs transplanted including a heart or lung transplant that showed disease progression during rituximab monotherapy, the 4 weeks interval without treatment or at staging 4 weeks after the 4th application of rituximab monotherapy

### 6.1.3. Primary target variable

Event free survival in the rituximab monotherapy (low-risk) group using Kaplan-Meier statistics.

Following situations will be considered an event:

- any grade III/IV infections between day 50 and day 143
- treatment discontinuation from any reason
- disease progression
- death from any reason

### 6.1.4. Secondary target variables

Response and overall response at interim staging, response and overall response to full treatment, duration of response, time to progression, progression free survival, overall survival, treatment related mortality, frequency of grade III and IV leucocytopenia, grade III and IV infections and of local reactions after subcutaneous injection of rituximab in the total patient cohort and by treatment group will be analyzed as secondary target variables. Statistics are descriptive using Fishers exact test for categorical variables and Kaplan-Meier statistics for time to event outcomes. Data will be compared to the corresponding treatment groups from the PTLD-1 ST (Trappe et al., 2012) and PTLD-1 RSST (Trappe et al., 2017) trials using Log-rank statistics and Cox regression analyses.

### 6.1.5. Subgroup analyses

Subgroup analyses are planned according to EBV-association and gender. EBV-association is an important prognostic factor in PTLD, influencing the pattern of involvement, treatment-related toxicity and response to treatment (Trappe et al., 2012a). Rituximab IV serum concentrations during immunochemotherapy are known to correlate with patient gender and clinical response (Jäger et al., 2012). While the difference in clinical response is suggested to be dose-dependent, 1400 mg rituximab SC might overcome the less favorable outcome of males with 375 mg/m$^2$ rituximab IV (Cartron et al., 2011).

While the expected gender distribution in the trial will be a reflection of the gender distribution after solid organ transplantation with a predominance of males over females, and gender-specific differences in response to rituximab SC might be small, an inter-trial comparison with combined data from the PTLD-1 ST and PTLD-1 RSST trial will be performed to detect gender-specific differences in the response to rituximab SC compared to rituximab IV.

### 6.1.6. Interim analysis

The planned interim analyses do not analyze the primary target variable. Thus, no adaptive design is necessary. Statistic is descriptive.

## 6.2. Sample size calculation

This phase II study is a one-arm survival study using a historical control group. For sample size estimation exponential survival is assumed. For the historical control group from the PTLD-1 trial the event free survival probability at 24 months is known to be 0.51. For a similar risk group the event free survival probability at 24 months in the PTLD-2 trial is assumed to be 0.82.

The accrual period will be set to 72 months and the minimum follow-up time will be 12 months, that is total study duration will be 84 months.

The following calculations are based on the assumptions of uniform accrual over time, no loss to follow-up, exponentially distributed death times and use of the exponential MLE test.

The important normal approximation used in the sample size and power calculations is equation 3.2.7 (page 108) of (Lawless, 1982).

A 0.050 two-sided significance level will be used and 90% power will be required to test the null hypothesis that the exponential parameter $\lambda_0 = -\ln(0.51)/24 = 0.028$ vs. the alternative $\lambda_1 = -\ln(0.82)/24 = 0.008$.

Based on these assumptions a total of 15 patients within the low-risk group in the ITT population is needed. This calculation was performed using the web site https://stattools.crab.org/Calculators/oneArmSurvivalColored.html. This site follows the ideas from (Lawless, 1982).

Data from the PTLD-1 RSST trial suggest that 38% of all patients can be expected to be stratified to the low-risk group. This corresponds to a minimum of 40 patients needed.

With a calculated drop-out rate and a safety margin of 33%, the total number of patients to perform the trial is 60.

The planned recruitment thus is 60 patients with ≥17 evaluable patients in the low-risk rituximab monotherapy arm.

# 7. Safety

## 7.1. Definitions of adverse events and adverse drug reactions

### 7.1.1. Adverse event

An adverse event (AE) is any untoward medical occurrence in a trial subject administered an IMP. There does not necessarily have to be a causal relationship with this treatment.

**All** AEs have to be documented.

Concomitant diseases

The deterioration of a preexisting illness is also an AE in the context of a clinical trial. The following, however, is not regarded as an AE: a preexisting disease that led to a planned treatment measure before the start of the clinical trial, e.g. admission to hospital as an inpatient. This should be made clear in the trial subject's medical records and should also be documented in the CRF (see Section 7.1.3).

Pregnancy

For reasons of drug safety, the occurrence of a pregnancy during the conduct of this trial is to be regarded as an AE. For details of special reporting requirements for pregnancy, see Section 7.3.

### 7.1.2. Adverse drug reaction

An adverse drug reaction (ADR) is any noxious and unintended response to an investigational medicinal product (IMP) related to any dose with at least a reasonably possible causal relationship with the IMP.

### 7.1.3. Serious adverse events and serious adverse reactions

A serious AE (SAE) or serious ADR (SADR) is any untoward medical occurrence that at any dose

1. results in death,
2. is life-threatening at the time of the event,
3. requires inpatient hospitalization or prolongation of existing hospitalization,
4. results in persistent or significant disability/incapacity,
5. is a congenital anomaly or birth defect (1.-4.: § 3(8) GCP Regulations),
6. that in the opinion of the investigator, fulfills any other criteria similar to 1.–4.

Inpatient hospitalization is defined as any stay in hospital on the part of a trial subject that includes at least one night (midnight to 06:00). Admission to hospital as an inpatient planned before the first admission of the IMP are not SAEs, but must be documented in the proper manner in the trial subject's medical records and CRF (see Section 7.1.1).

If an AE is classified as an SAE, this is documented on a separate SAE sheet in addition to the standard AE documentation. The authorities must be notified of SAEs by law (for procedure, see 7.3)

### 7.1.4. Unexpected adverse drug reaction

An unexpected ADR is an ADR which, the nature or severity of which is not consistent with the applicable product information available for the IMP. Expected ADRs are listed in the appropriate reference documents, e.g. Investigator's Brochure; Summary of Product Characteristics [Fachinformation].

### 7.1.5. Suspected unexpected serious adverse reactions

A suspected unexpected serious adverse reaction (SUSAR) is an adverse event the nature or severity of which is not consistent with the product information available for the IMP, is regarded as serious, and has at least a possible causal relationship with the IMP.

#### 7.1.6. Adverse events of special interest (AESIs)

The following adverse events have been defined to be of special interest:

- Local skin reactions at injection site (Rituximab sc)
- Infusion related reactions (rituximab)
- Infections
- Progressive multifocal Leukencephalopathy
- Pneumocystis jirovecei pneumonia
- Skin reactions such as Toxic Epidermal Necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome

### 7.2. Documentation and follow-up of adverse events

The sponsor ensures that all persons involved in the treatment of trial subjects are adequately informed of the responsibilities and actions required when AEs occur. Trial subjects will be asked at each visit whether they have experienced AEs or SAEs. AEs will be documented in the trial subject's medical records and in the CRF.

For the procedure of SAE-reporting see section 7.3.

#### 7.2.1. Documentation of adverse events, AESIs and adverse drug reactions

All AEs will be documented in the CRF including all information listed below. AESIs will be listed separately on the CRF for each visit.

AEs as well as AESIs are documented in the CRF including the following information:

- Date and time of onset and resolution
- Severity

Regardless of whether a causal relationship between the AE and the IMP is suspected, trial subjects who develop adverse events must be monitored until all symptoms have been

subsided, pathological laboratory values have returned to pre-event levels, a plausible explanation is found for the AE, the trial subject has died, or the study has been terminated for the trial subject concerned.

The maximal follow-up observation period is 30 days after the study is completed in the subject.

Preexisting diseases (before administration of the IMP) are not documented as adverse events but as concomitant diseases. New diseases and preexisting diseases that worsen during the trial are documented as AEs.

#### 7.2.2. Severity of the adverse event

The investigator will classify the severity of AEs according to the National Cancer Institute Common Toxicity Criteria, version 4.0 that is included in the investigator's site file.

#### 7.2.3. Causal relationship between adverse event and investigational medicinal product

The investigator will assess for every AE whether a causal relationship with the IMP can be assumed or not. The assessment includes consideration of the nature and type of reaction, the temporal relationship with the IMP, the clinical status of the trial subject, concomitant medication and other relevant clinical factors. If the event is considered due to lack of efficacy or as a symptom or sign of the underlying disorder, no causal relationship will be assumed. This assessment will be documented in the appropriate report form.

### 7.3. Reporting of serious adverse events, pregnancy and changes in risk-benefit assessment

Regardless of the assumed causal relationship, every SAE that occurs during a trial must be documented in the appropriate part of the CRF and on an SAE sheet sent to the sponsor. Pregnancies must also be documented on separate pregnancy forms and reported to the sponsor within the defined periods (see Section 7.3.1.).

### 7.3.1. Serious adverse events reporting

The investigator must **unhesitatingly** (within 24 hours) report all serious adverse events on a separate SAE report form to the Principal Coordinating Investigator [PCI]. SAEs will be collected and recorded throughout the study period, beginning after informed consent has been obtained until 28 days after the last administration of treatment. Additionally all serious adverse events related to study medication (= adverse drug reactions) must be recorded through the follow-up visit which occurs 18 months after last study drug administration.

### 7.3.2. Reports from the investigator to the sponsor

The investigator will inform the sponsor of the occurrence or receipt of knowledge of the occurrence of an SAE without delay, at the latest within 24 hours of being made aware of the SAE by sending a FAX or email to:

**DIAKO Ev. Diakonie-Krankenhaus Bremen gGmbH**

**Studienzentrale der Deutschen PTLD Studiengruppe**
**Gröpelinger Heerstrasse 406-408**
**28239 Bremen**
**Fax: 0421-61021471**
**Email: safetyptld2@gwdg.de**

Not subject to this are the following events:

- Hospitalization for the administration of chemotherapy or pre-planned diagnostics
- Hospitalization for safety reasons during chemotherapy-associated neutropenia

The investigator will also inform the sponsor without delay about any pregnancy that occurs during the trial, i.e. within 24 hours of being made aware of such. This will be documented on a separate pregnancy form. The pregnant trial subject will be asked to give separate informed consent for pregnancy follow-up.

### 7.3.3. Assessment of event by sponsor

All cases of suspected SAEs are assessed by the PCI and/or steering committee with regard to seriousness (see Section 7.1.3), causality (see Section 7.2.3) and expectedness (see Section 7.1.4), regardless of the investigator's assessments according to the GPTLDSGs SOP.

### 7.3.4. Notification of ethics committee and appropriate supreme federal authority

Every SUSAR that becomes known in a clinical trial will be reported by the sponsor or PCI to the appropriate supreme federal authority and the ethics committee.

Fatal and life-threatening SUSARs

The appropriate supreme federal authority and the ethics committee responsible must be informed by the sponsor or PCI of all fatal or life-threatening SUSARs. This must be done without delay, at the latest 7 calendar days after becoming aware of the minimum criteria for reporting. In all cases, attempts must be made to obtain further relevant information which must be supplied to the appropriate supreme federal authority and the ethics committee within a further 8 days. Furthermore, if a trial subject dies, this information must be passed on to the ethics committee responsible for the region in which the death occurred.

SUSARs that are not fatal or life-threatening

The appropriate supreme federal authority and the ethics committee responsible will be informed without delay by the sponsor or PCI of all SUSARs, at the latest within 15 calendar days of becoming aware of the minimum criteria for reporting. Further relevant details will be passed on as soon as possible.

If the information at the time of reporting is incomplete, further information to enable adequate assessment of the case will be requested from the reporter or other available sources.

### 7.3.5. Review and reporting of changes in the risk-benefit ratio

Without delay, and at the latest within 15 days of the decision for the need to do so, the sponsor or PCI will inform the appropriate supreme federal authority, the ethics committee responsible and the appropriate authorities of all other member states of the EU or EEA where the trial is being conducted, of any events or factors that mean that the risk-benefit ratio of the IMP has to be reviewed. These consist of especially:

- Individual reports of expected serious ADRs with an unexpected outcome
- A clinically relevant increase in the rate of occurrence of expected SADRs
- SUSARs in trial subjects who have already completed the follow-up period of the clinical trial (”end-of-trial visit”)
- Factors emerging in connection with trial conduct or the development of the IMP that may affect the safety of persons concerned.

### 7.3.6. Informing the Data Monitoring Committee

The DMC will be informed of all safety-relevant events by the sponsor or PCI. SAEs and SUSARS will be supplied.

### 7.3.7. Informing the investigators

The sponsor or PCI will inform investigators of all SUSARs including all relevant further information within the periods set by the supreme federal authority.

If new information becomes known that is different from the scientific information given to the investigator, all investigators will be informed of this by the sponsor or PCI.

### 7.3.8. Informing the marketing authorization holder

The sponsor or PCI will send all SAEs and SUSARs to Roche for internal tracking of product safety including information reported to the appropriate supreme authority and ethics committee in accordance with contractual agreements.

## 7.4. Annual safety report of trial subjects

Once per year, the sponsor or PCI will supply a report on the safety of trial subjects with all available relevant information concerning patient safety during the reference period to the appropriate supreme federal authority and the appropriate authorities of all other member states of the EU or EEA where the trial is being conducted. This report will also be supplied to the responsible ethics committee.

The annual safety report will be compiled according to the corresponding ICH guideline E2F „Development Safety Update Report – DSUR“

The data lock point for the patient data to be included and analyzed is the day of the approval of the clinical trial.

The sponsor or PCI will supply the report within 60 days of one year after the reference date (data-lock point).

# 8. Use of trial findings and publication

## 8.1. Reports

### 8.1.1. Interim reports

Section 7.4 describes the requirements for annual reports on the safety of trial subjects. Progress of recruitment is reported at least once every six months to all investigators and to Roche.

### 8.1.2. Final report

The appropriate authority and ethics committee will be informed within 90 days that the trial has officially ended.

Within one year of the completion of the trial, the appropriate federal authority and the ethics committee will be supplied with a summary of the final report on the clinical trial containing the principle results.

## 8.2. Publication

It is planned to publish the trial results, in mutual agreement with the PCI, in a scientific journal and at German or international congresses. Publication of the results of the trial as a whole is intended. Any publication will take account of the 'Uniform requirements for manuscripts submitted to biomedical journals (International Committee of Medical Journal Editors' (ICMJE) [JAMA 1997;277:927-34]).

First author of the final publication will be the PCI. All participating sites recruiting at least 10% of the patients and all national coordinating PIs will become a co-author of the final publication if possible according to the publication policy of the journal. Persons involved in planning, conducting and evaluation of the trial will be offered co-authorship according to their input and the publication policy of the journal. All co-authors will get the option to comment on the manuscript before publication.

The trial will be registered in a public register in accordance with the recommendations of the ICMJE (see also Section 5.3).

Any published data will observe data protection legislation covering the trial subject and investigators. Success rates or individual findings at individual trial sites are known only to the sponsor.

Roche will receive data from this trial and will be informed of the results of the trial.

Publications or lectures on the findings of the present clinical trial either as a whole or at individual investigation sites must be approved by the sponsor in advance, and the sponsor reserves the right to review and comment on such documentation before publication.

By signing the contract to participate in this trial, the investigator declares that he or she agrees to submission of the results of this trial to national and international authorities for approval and surveillance purposes, and to the Federal Physicians Association, the Association of Statutory Health Fund Physicians and to statutory health fund organizations, if required. At the same time, the investigator agrees that his or her name, address, qualifications and details of his or her involvement in the clinical trial may be made known to these bodies.

## 9. Amendments to the trial protocol and compensation of trial subjects

To ensure that comparable conditions are achieved as far as possible at individual trial sites and in the interests of a consistent and valid data analysis, changes to the provisions of this trial protocol are not planned. In exceptional cases, however, changes may be made to the trial protocol. Such changes can only be made if agreed by the sponsor's representative, the PCI and biometrician, and all authors of this trial protocol. Any changes to the trial procedures must be made in writing and must be documented with reasons and signed by all authors of the original trial protocol.

Amendments made in accordance with § 10 Secs. 1 and 4 GCP Regulations that require approval are submitted to the ethics committee and the supreme federal authority and will not be implemented until approved. Exceptions to this are amendments made to avoid immediate dangers.

The appendices, attached to this protocol and referred to in the protocol, form an integral part of the protocol.

Subjects will not be paid for participation in this clinical trial.

# 10. References

## 10.1. References related to PTLD

Caillard, S., Lamy, F.X., Quelen, C., Dantal, J., Lebranchu, Y., Lang, P., Velten, M., and Moulin, B. (2012). Epidemiology of posttransplant lymphoproliferative disorders in adult kidney and kidney pancreas recipients: report of the French registry and analysis of subgroups of lymphomas. Am. J. Transplant. *12*, 682–693.

Cartron, G., Trappe, R.U., Solal-Celigny, P., and Hallek, M. (2011). Interindividual variability of response to rituximab: from biological origins to individualized therapies. Clin Cancer Res *17*, 19–30.

Cheson, B.D., Horning, S.J., Coiffier, B., Shipp, M.A., Fisher, R.I., Connors, J.M., Lister, T.A., Vose, J., Grillo-Lopez, A., Hagenbeek, A., et al. (1999). Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol *17*, 1244.

Choquet, S., Leblond, V., Herbrecht, R., Socié, G., Stoppa, A.-M., Vandenberghe, P., Fischer, A., Morschhauser, F., Salles, G., Feremans, W., et al. (2006). Efficacy and safety of rituximab in B-cell post-transplantation lymphoproliferative disorders: results of a prospective multicenter phase 2 study. Blood *107*, 3053–3057.

Choquet, S., Oertel, S., LeBlond, V., Riess, H., Varoqueaux, N., Dörken, B., and Trappe, R. (2007a). Rituximab in the management of post-transplantation lymphoproliferative disorder after solid organ transplantation: proceed with caution. Ann. Hematol. *86*, 599–607.

Choquet, S., Trappe, R., Leblond, V., Jager, U., Davi, F., and Oertel, S. (2007b). CHOP-21 for the treatment of post-transplant lymphoproliferative disorders (PTLD) following solid organ transplantation. Haematologica *92*, 273–274.

Davies, A., Merli, F., Mihaljevic, B., Siritanaratkul, N., Solal-Céligny, P., Barrett, M., Berge, C., Bittner, B., Boehnke, A., McIntyre, C., et al. (2014). Pharmacokinetics and safety of subcutaneous rituximab in follicular lymphoma (SABRINA): stage 1 analysis of a randomised phase 3 study. Lancet Oncol. *15*, 343–352.

Dierickx, D., Tousseyn, T., Sagaert, X., Fieuws, S., Wlodarska, I., Morscio, J., Brepoels, L., Kuypers, D., Vanhaecke, J., Nevens, F., et al. (2013). Single-center analysis of biopsy-confirmed posttransplant lymphoproliferative disorder: incidence, clinico-pathological characteristics and prognostic factors. Leuk. Lymphoma. 54, 2433-2440.

Engels, E.A., Pfeiffer, R.M., Fraumeni, J.F., Kasiske, B.L., Israni, A.K., Snyder, J.J., Wolfe, R.A., Goodrich, N.P., Bayakly, A.R., Clarke, C.A., et al. (2011). Spectrum of Cancer Risk among U.S. Solid Organ Transplant Recipients: The Transplant Cancer Match Study. J. Am. Med. Assoc. *306*, 1891–1901.

Evens, A.M., David, K.A., Helenowski, I., Nelson, B., Kaufman, D., Kircher, S.M., Gimelfarb, A., Hattersley, E., Mauro, L.A., Jovanovic, B., et al. (2010). Multicenter analysis of 80 solid organ transplantation recipients with post-transplantation lymphoproliferative disease: outcomes and prognostic factors in the modern era. J. Clin. Oncol. *28*, 1038–1046.

Evens, A.M., Choquet, S., Kroll-Desrosiers, A.R., Jagadeesh, D., Smith, S.M., Morschhauser, F., Leblond, V., Roy, R., Barton, B., Gordon, L.I., et al. (2013). Primary CNS Posttransplant Lymphoproliferative Disease (PTLD): An International Report of 84 Cases in the Modern Era. Am. J. Transplant. *13*, 1512–1522.

Fisher, S.G., and Fisher, R.I. (2006). The emerging concept of antigen-driven lymphomas: epidemiology and treatment implications. Curr. Opin. Oncol. *18*, 417–424.

Ghobrial, I.M., Habermann, T.M., Maurer, M.J., Geyer, S.M., Ristow, K.M., Larson, T.S., Walker, R.C., Ansell, S.M., Macon, W.R., Gores, G.G., et al. (2005). Prognostic analysis for survival in adult solid organ transplant recipients with post-transplantation lymphoproliferative disorders. J. Clin. Oncol. *23*, 7574–7582.

Gisselbrecht, C., Glass, B., Mounier, N., Singh Gill, D., Linch, D.C., Trneny, M., Bosly, A., Ketterer, N., Shpilberg, O., Hagberg, H., et al. (2010). Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol *28*, 4184–4190.

Gonzalez-Barca, E., Domingo-Domenech, E., Capote, F.J., Gomez-Codina, J., Salar, A., Bailen, A., Ribera, J.M., Lopez, A., Briones, J., Munoz, A., et al. (2007). Prospective phase II

trial of extended treatment with rituximab in patients with B-cell post-transplant lymphoproliferative disease. Haematologica *92*, 1489–1494.

Hanada, K., Suda, M., Kanai, N., and Ogata, H. (2010). Pharmacokinetics and toxicodynamics of oxaliplatin in rats: application of a toxicity factor to explain differences in the nephrotoxicity and myelosuppression induced by oxaliplatin and the other platinum antitumor derivatives. Pharm. Res. *27*, 1893–1899.

Hourigan, M.J., Doecke, J., Mollee, P.N., Gill, D.S., Norris, D., Johnson, D.W., and Gandhi, M.K. (2008). A new prognosticator for post-transplant lymphoproliferative disorders after renal transplantation. Br. J. Haematol. *141*, 904–907.

Jäger, U., Fridrik, M., Zeitlinger, M., Heintel, D., Hopfinger, G., Burgstaller, S., Mannhalter, C., Oberaigner, W., Porpaczy, E., Skrabs, C., et al. (2012). Rituximab serum concentrations during immuno-chemotherapy of follicular lymphoma correlate with patient gender, bone marrow infiltration and clinical response. Haematologica *97*, 1431–1438.

Klapper, W., Kreuz, M., Kohler, C.W., Burkhardt, B., Szczepanowski, M., Salaverria, I., Hummel, M., Loeffler, M., Pellissery, S., Woessmann, W., et al. (2012). Patient age at diagnosis is associated with the molecular characteristics of diffuse large B-cell lymphoma. Blood *119*, 1882–1887.

Lawless, J.F. (1982). Statistical Models and Methods for Lifetime Data (New York: John Wiley and Sons).

Leblond, V., Dhedin, N., Mamzer Bruneel, M.F., Choquet, S., Hermine, O., Porcher, R., Nguyen Quoc, S., Davi, F., Charlotte, F., Dorent, R., et al. (2001). Identification of prognostic factors in 61 patients with posttransplantation lymphoproliferative disorders. J. Clin. Oncol. *19*, 772–778.

Lignon, J., Sibon, D., Madelaine, I., Brice, P., Franchi, P., Briere, J., Mounier, N., Gisselbrecht, C., Faure, P., and Thieblemont, C. (2010). Rituximab, dexamethasone, cytarabine, and oxaliplatin (R-DHAX) is an effective and safe salvage regimen in relapsed/refractory B-cell non-Hodgkin lymphoma. Clin. Lymphoma Myeloma Leuk. *10*, 262–269.

Lindner, L.H., Ostermann, H., Hiddemann, W., Kiani, A., Würfel, M., Illmer, T., Karsch, C., Platzbecker, U., Ehninger, G., and Schleyer, E. (2008). AraU accumulation in patients with renal insufficiency as a potential mechanism for cytarabine neurotoxicity. Int. J. Hematol. *88*, 381–386.

Martin-Subero, J.I., Ammerpohl, O., Bibikova, M., Wickham-Garcia, E., Agirre, X., Alvarez, S., Brüggemann, M., Bug, S., Calasanz, M.J., Deckert, M., et al. (2009). A comprehensive microarray-based DNA methylation study of 367 hematological neoplasms. PloS One *4*, e6986.

Muchtar, E., Kramer, M.R., Vidal, L., Ram, R., Gurion, R., Rosenblat, Y., Bakal, I., and Shpilberg, O. (2013). Posttransplantation Lymphoproliferative Disorder in Lung Transplant Recipients: A 15-Year Single Institution Experience. Transplantation. 96, 657-663.

Nourse, J.P., Crooks, P., Keane, C., Nguyen-Van, D., Mujaj, S., Ross, N., Jones, K., Vari, F., Han, E., Trappe, R., et al. (2012). Expression profiling of Epstein-Barr virus-encoded microRNAs from paraffin-embedded formalin-fixed primary Epstein-Barr virus-positive B-cell lymphoma samples. J. Virol. Methods. 184, 46-54.

Oertel, S.H., Papp-Vary, M., Anagnostopoulos, I., Hummel, M.W., Jonas, S., and Riess, H.B. (2003). Salvage chemotherapy for refractory or relapsed post-transplant lymphoproliferative disorder in patients after solid organ transplantation with a combination of carboplatin and etoposide. Br J Haematol *123*, 830–835.

Oertel, S.H., Verschuuren, E., Reinke, P., Zeidler, K., Papp-Vary, M., Babel, N., Trappe, R.U., Jonas, S., Hummel, M., Anagnostopoulos, I., et al. (2005). Effect of Anti-CD 20 Antibody Rituximab in Patients with Post-Transplant Lymphoproliferative Disorder (PTLD). Am. J. Transplant. *5*, 2901–2906.

Penn, I., Hammond, W., Brettschneider, L., and Starzl, T.E. (1969). Malignant lymphomas in transplantation patients. Transplant. Proc. *1*, 106–112.

Quinlan, S.C., Morton, L.M., Pfeiffer, R.M., Anderson, L.A., Landgren, O., Warren, J.L., and Engels, E.A. (2010). Increased risk for lymphoid and myeloid neoplasms in elderly solid-organ transplant recipients. Cancer Epidemiol Biomark. Prev *19*, 1229–1237.

Quinlan, S.C., Pfeiffer, R.M., Morton, L.M., and Engels, E.A. (2011). Risk factors for early-onset and late-onset post-transplant lymphoproliferative disorder in kidney recipients in the United States. Am. J. Hematol. *86*, 206–209.

Radeski, D., Cull, G.M., Cain, M., Hackett, L.P., and Ilett, K.F. (2011). Effective clearance of Ara-U the major metabolite of cytosine arabinoside (Ara-C) by hemodialysis in a patient with lymphoma and end-stage renal failure. Cancer Chemother. Pharmacol. *67*, 765–768.

Reshef, R., Vardhanabhuti, S., Luskin, M.R., Heitjan, D.F., Hadjiliadis, D., Goral, S., Krok, K.L., Goldberg, L.R., Porter, D.L., Stadtmauer, E.A., et al. (2011). Reduction of immunosuppression as initial therapy for posttransplantation lymphoproliferative disorder. Am J Transpl. *11*, 336–347.

Richter, J., Schlesner, M., Hoffmann, S., Kreuz, M., Leich, E., Burkhardt, B., Rosolowski, M., Ammerpohl, O., Wagener, R., Bernhart, S.H., et al. (2012). Recurrent mutation of the ID3 gene in Burkitt lymphoma identified by integrated genome, exome and transcriptome sequencing. Nat. Genet. *44*, 1316–1320.

Sebastián, E., Alcoceba, M., Balanzategui, A., Marín, L., Montes-Moreno, S., Flores, T., González, D., Sarasquete, M.E., Chillón, M.C., Puig, N., et al. (2012). Molecular Characterization of Immunoglobulin Gene Rearrangements in Diffuse Large B-Cell Lymphoma: Antigen-Driven Origin and IGHV4-34 as a Particular Subgroup of the Non-GCB Subtype. Am. J. Pathol. 181, 1879-1888.

Shpilberg, O., and Jackisch, C. (2013). Subcutaneous administration of rituximab (MabThera) and trastuzumab (Herceptin) using hyaluronidase. Br. J. Cancer *109*, 1556–1561.

Smets, F., Latinne, D., Bazin, H., Reding, R., Otte, J.B., Buts, J.P., and Sokal, E.M. (2002). Ratio between Epstein-Barr viral load and anti-Epstein-Barr virus specific T-cell response as a predictive marker of posttransplant lymphoproliferative disease. Transplantation *73*, 1603–1610.

Stamatopoulos, K., Belessi, C., Moreno, C., Boudjograh, M., Guida, G., Smilevska, T., Belhoul, L., Stella, S., Stavroyianni, N., Crespo, M., et al. (2007). Over 20% of patients with

chronic lymphocytic leukemia carry stereotyped receptors: Pathogenetic implications and clinical correlations. Blood *109*, 259–270.

Swerdlow, S.H., Webber, S.A., Chadburn, A., and Ferry, J.A. (2008). Post-transplant lymphoproliferative disorders. In WHO Classification of Tumours of Haematopoetic and Lymphoid Tissues, S.H. Swerdlow, E. Campo, N.L. Harris, E.S. Jaffe, S.A. Pileri, H. Stein, J. Thiele, and J.W. Vardiman, eds. (Lyon: International Agency for Research on Cancer), pp. 343–350.

Swinnen, L.J., LeBlanc, M., Grogan, T.M., Gordon, L.I., Stiff, P.J., Miller, A.M., Kasamon, Y., Miller, T.P., and Fisher, R.I. (2008). Prospective study of sequential reduction in immunosuppression, interferon alpha-2B, and chemotherapy for posttransplantation lymphoproliferative disorder. Transplantation *86*, 215–222.

Takimoto, C.H., Remick, S.C., Sharma, S., Mani, S., Ramanathan, R.K., Doroshow, J., Hamilton, A., Mulkerin, D., Graham, M., Lockwood, G.F., et al. (2003). Dose-escalating and pharmacological study of oxaliplatin in adult cancer patients with impaired renal function: a National Cancer Institute Organ Dysfunction Working Group Study. J. Clin. Oncol. *21*, 2664–2672.

Takimoto, C.H., Graham, M.A., Lockwood, G., Ng, C.M., Goetz, A., Greenslade, D., Remick, S.C., Sharma, S., Mani, S., Ramanathan, R.K., et al. (2007). Oxaliplatin pharmacokinetics and pharmacodynamics in adult cancer patients with impaired renal function. Clin. Cancer Res. *13*, 4832–4839.

The International Non-Hodgkin's Lymphoma Prognostic Factors Project (1993). A predictive model for aggressive non-Hodgkin's lymphoma. N. Engl. J. Med. *329*, 987–994.

Thieblemont, C., Briere, J., Mounier, N., Voelker, H.-U., Cuccuini, W., Hirchaud, E., Rosenwald, A., Jack, A., Sundstrom, C., Cogliatti, S., et al. (2011). The Germinal Center/Activated B-Cell Subclassification Has a Prognostic Impact for Response to Salvage Therapy in Relapsed/Refractory Diffuse Large B-Cell Lymphoma: A Bio-CORAL Study. J. Clin. Oncol. *29*, 4079–4087.

Trappe, R., Zimmermann, H., Fink, S., Reinke, P., Dreyling, M., Pascher, A., Lehmkuhl, H., Gärtner, B., Anagnostopoulos, I., and Riess, H. (2011). Plasmacytoma-like post-transplant

lymphoproliferative disorder, a rare subtype of monomorphic B-cell post-transplant lymphoproliferation, is associated with a favorable outcome in localized as well as in advanced disease - a prospective analysis of 8 cases. Haematologica *96*, 1067–1071.

Trappe, R., Oertel, S., Leblond, V., Mollee, P., Sender, M., Reinke, P., Neuhaus, R., Lehmkuhl, H., Horst, H.A., Salles, G., et al. (2012a). Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicentre phase 2 PTLD-1 trial. Lancet Oncol. *13*, 196–206.

Trappe, R.U., Choquet, S., Dierickx, D., Mollee, P., Zaucha, J.M., Dreyling, M.H., Dührsen, U., Tarella, C., Shpilberg, O., Sender, M., et al. (2015). International Prognostic Index, Type of Transplant and Response to Rituximab Are Key Parameters to Tailor Treatment in Adults with CD20-Positive B Cell PTLD: Clues From the PTLD-1 Trial. Am. J. Transplant. 15, 1091–1100.

Trappe, R.U., Dierickx, D., Zimmermann, H., Morschhauser, F., Mollee, P., Zaucha, J.M., Dreyling, M.H., Dührsen, U., Reinke, P., Verhoef, G., et al. (2017). Response to Rituximab Induction Is a Predictive Marker in B-Cell Post-Transplant Lymphoproliferative Disorder and Allows Successful Stratification Into Rituximab or R-CHOP Consolidation in an International, Prospective, Multicenter Phase II Trial. J Clin Oncol 35, 536–543.

Waldmann, T., Strober, W., and Blaese, R. (1972). Immunodeficiency disease and malignancy. Various immunologic deficiencies of man and the role of immune processes in the control of malignant disease. Ann. Intern. Med. *77*, 605–628.

Witzens-Harig, M., Hess, G., Atta, J., Zaiss, M., Lenz, G., Scholz, C., Repp, R., Reiser, M., Pott, C., Pelz, H., et al. (2012). Current treatment of mantle cell lymphoma: results of a national survey and consensus meeting. Ann. Hematol. *91*, 1765–1772.

Zimmermann, H., and Trappe, R.U. (2013). EBV and posttransplantation lymphoproliferative disease: what to do? Hematol. Am. Soc. Hematol. Educ. Program *2013*, 95–102.

Zimmermann, H., Reinke, P., Neuhaus, R., Lehmkuhl, H., Oertel, S., Atta, J., Planker, M., Gärtner, B., Lenze, D., Anagnostopoulos, I., et al. (2012a). Burkitt post-transplantation lymphoma in adult solid organ transplant recipients: Sequential immunochemotherapy with

rituximab (R) followed by cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or R-CHOP is safe and effective in an analysis of 8 patients. Cancer. 118, 4715-4724.

Zimmermann, H., Oschlies, I., Fink, S., Pott, C., Neumayer, H.H., Lehmkuhl, H., Hauser, I.A., Dreyling, M., Kneba, M., Gärtner, B., et al. (2012b). Plasmablastic Posttransplant Lymphoma: Cytogenetic Aberrations and Lack of Epstein-Barr Virus Association Linked With Poor Outcome in the Prospective German Posttransplant Lymphoproliferative Disorder Registry. Transplantation *93*, 543–550.

Zimmermann, H., Choquet, S., Dierickx, D., Dreyling, M.H., Moore, J., Valentin, A., Striefler, J.K., Riess, H., Leblond, V., and Trappe, R.U. (2013). Early and Late Posttransplant Lymphoproliferative Disorder After Lung Transplantation—34 Cases From the European PTLD Network: Transplant. J. *96*, e18–e19.

### 10.2. References related to the conduct of the trial

The European Agency for the Evaluation of Medicinal Product. Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95).

The European Agency for the Evaluation of Medicinal Product. Note for Guidance Structure and Content of Clinical Study Reports (CPMP/ICH/137/95).

National Cancer Institute. Protocol Templates, Applications and Guidelines http://ctep.cancer.gov/guidelines/templates.html.

EMEA-Guideline On Data Monitoring Committees: EMEA/CHMP/EWP/5872/03 Corr

The DAMOCLES Study Group. A proposed charter for clinical trial 2005 data monitoring committees: helping them do their job well. Lancet 2005; 365: 711-22

Clinical trial registration: a statement from the International Committee of Medical Journal Editors. Accessed at http://www.icmje.org/clin_trial.pdf on 22 May 2007.

WHO. Causality Assessment of Suspected Adverse Reactions. http://www.who-umc.org/DynPage.aspx?id=22682

# 11. Appendices

## 11.1. Trial sites and principle investigators

1. PD. Dr. med. Bastian von Treschkow
   Department I of Internal Medicine
   University Hospital of Cologne
   Kerpener Str. 62
   50937 Cologne
   Germany

2. Dr. med. J. Schleicher
   Department of Hematology and Oncology
   Hospital Stuttgart
   Kriegsberg Str. 60
   70174 Stuttgart
   Germany

3. PD Dr. med. N. Meidenbauer
   Medical Department V: Hematology and Oncology
   University Hospital Erlangen
   Ulmenweg 18
   91054 Erlangen
   Germany

4. Prof. Dr. med. M. Dreyling
   Medical Department III
   University of Munich - Campus Grosshadern
   Marchionistr. 15
   81377 München
   Germany

5. Prof. Dr. med. T. Südhoff
Medical Department II
Hospital Passau
Innstr. 76
94032 Passau
Germany

6. Prof. Dr. med. K. Budde (in cooperation with trial site 7)
Department of Nephrology
Charite - Universitätsmedizin Berlin, Campus Mitte
Charitéplatz 1
10115 Berlin
Germany

7. Prof. Dr. med. Dr. H. Riess
Department of Oncology, Hematology and Tumorimmunology, Campus Virchow-Klinikum
Department of Oncology and Hematology, Campus Mitte
Charite - Universitätsmedizin Berlin
Charitéplatz 1
10115 Berlin
Germany

8. Prof. Dr. med. Ralf Ulrich Trappe
Department of Hematology and Oncology
DIAKO Ev. Diakonie-Krankenhaus Bremen gemeinnützige GmbH
Gröpelinger Heerstrasse 406-408
28239 Bremen
Germany

9. Prof. Dr. med. I. Hauser (in cooperation with trial site 8)

Medical Department III, Nephrology
University of Frankfurt
Theodor-Stern-Kai 7
60569 Frankfurt am Main
Germany

10. Prof. Dr. med. M. Rummel
Medical Department, Division of Hematology, Oncology
University of Gießen/Marburg, Campus Gießen
Klinikstr. 33
35392 Gießen
Germany

11. Priv.-Doz. Dr. med. S. Boettcher
Division of Hematology, Oncology
University of Rostock
E. Heydemann Str. 6
18057 Rostock
Germany

13. Dr. med. C. Könecke
Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation
Hannover Medical School
Carl-Neuberg-Str. 1
30625 Hannover
Germany

14. Dr. med. Metzner
Hospital Oldenburg
Medical Department II
Rahel-Straus-Str. 10
26133 Oldenburg

Germany

15. Dr. med. M. Tometten
Department of Oncology, Hematology und Stemcell transplantation (Med. Dep. IV)
University Clinic Aachen
Pauwelsstr. 30
52074 Aachen
Germany

16. Prof. Dr. med. Dominik Wolf
Division of Hematology, Oncology
University of Bonn
Sigmund-Freud-Str. 25
53127 Bonn
Germany

17. PD Dr. med. Hüttmann
Department of Hematologyl
University of Duisburg-Essen
Hufellandstr. 55
45122 Essen
Germany

18. PD Dr. G. Hess
Department of Internal Medicine III
Mainz University Medical Center
Langenbeckstr. 1
55101 Mainz
Germany

19. Prof. Dr. med. C. Pott
Department of Hematology and Oncology

University Medical Center Schleswig-Holstein, Campus Kiel
Arnold Heller Strasse 3
24105 Kiel
Germany

20. Dr. med. J. Benk
Medical Department I
Malteser Hospital Flensburg, St. Franziskus Hospital
Waldstr. 17
24939 Flensburg
Germany

21. Prof. Dr. med. Georg Lenz
Department of Internal Medicine A
University hospital Münster
Albert-Schweitzer-Campus 1
Gebäude D3
Domagkstr. 3
48149 Münster
Germany

22. Dr. med. Matthias Grube
University hospital Regensburg
Department of Internal Medicine III
Franz-Josef-Strauß-Allee 11
93053 Regensburg
Germany

23. Dr. med. J.T. Bittenbring
Saarland University hospital
Department of Internal Medicine I
Kirrberger Str. 100, Gebäude 41

66421 Homburg/Saar

Germany

## 11.2. Protocol Agreement Form

**Investigator's Agreement**

I have read the attached protocol entiteld

"**RISK-STRATIFIED SEQUENTIAL TREATMENT OF POST-TRANSPLANT LYMPHOPROLIFERATIVE DISEASE WITH 4 COURSES OF RITUXIMAB SC FOLLOWED BY 4 COURSES OF RITUXIMAB SC, 4 COURSES OF RITUXIMAB SC COMBINED WITH CHOP-21 OR 6 COURSES OF RITUXIMAB SC COMBINED WITH ALTERNATING CHOP-21 AND DHAOX: THE PTLD-2 TRIAL**"

version 3-0 of 30 September 2017 and agree to abide by all provisions set forth therein. I agree to comply with the International Conference of Harmonisation Tripartite Guideline on Good Clinical Practice.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the study sponsor.

_____

Signature

_____ _____

Name of Principal Investigator Date (DD Month YYY)

_____

Investigator's Institution

### 11.3. Steering Committee

Dr. med. Heiner Zimmermann
DIAKO Ev. Diakonie-Krankenhaus Bremen gemeinnützige GmbH
Gröpelinger Heerstrasse 406-408
28239 Bremen
Germany

Dr. med. Matthias Gabriel Berthold von Papp-Vary
DIAKO Ev. Diakonie-Krankenhaus Bremen gemeinnützige GmbH
Gröpelinger Heerstrasse 406-408
28239 Bremen
Germany

Dr. Zimmermann and Dr. Papp-Vary have major experience in the field of post-transplant lymphoma proven by a significant publication record. They have worked together with the PCI for several years and are employed at the PCI´s institution as clinicians and scientists. They will continuously monitor the progress of the trial and will be responsible for central source data verification in the GPTLDSG study office together with the PCI.

The steering committee and the PCI take consensus decisions on all questions.

## 11.4. Data Monitoring Committee

Prof. Dr. med. Dr. rer. nat. Michael Kneba
Department of Hematology and Oncology
University Medical Center Schleswig-Holstein, Campus Kiel
Arnold Heller Strasse 3
24105 Kiel
Germany

Prof. Kneba is Head of the Department of Hematology and Oncology at the Medical University Center of Schleswig-Holstein, Campus Kiel. He has conducted numerous clinical trials in the field of lymphoma and is personally not involved in the conduct of this trial.

Prof. Dr. Ulrich Jäger
Department of Internal Medicine I, Division of Hematology
Medical University of Vienna
Waehringer Guertel 18-20
1090 Vienna
Austria

Prof. Jäger is Head of the Department of Hematology at Vienna University Hospitals. The focus of his clinical and scientific work is the study of lymphoproliferative disorders (leukemia and lymphoma). He has profound expertise in the conduct of clinical trials in the lymphoma field. He was the President of the European Haematology Association (EHA) from 2011 to 2013. Prof. Jäger is personally not involved in the conduct of this trial.

## 11.5. Advisory Committee

Dr. Sylvain Choquet
Department of Hematology
Hopital Pitie-Salpêtriere
Université Pierre et Marie Curie
75013 Paris
France

Dr. Daan Dierickx
Department of Haematology
University Hospital Gasthuisberg Leuven
3000 Leuven
Belgium

Dr. Peter Mollee
Department of Haematology, Pathology Queensland
Princess Alexandra Hospital
4001 Brisbane
Australia

Prof. Dr. med. C. Schmitt
Department of Hematology and Oncology and Tumorimmunology
Charite - Universitätsmedizin Berlin, Campus Virchow-Klinikum
Augustenburger Platz 1
13353 Berlin
Germany

Prof. Ofer Shpilberg
Institute of Haematology

Rabin Medical Centre, Petach Tikva and Sackler Faculty of Medicine
Tel Aviv University
49100 Tel Aviv
Israel

Prof. Corrado Tarella
Department of Haematology, A.O. Mauriziano
University of Torino
10128 Torino
Italy

Dr. Jan M. Zaucha
Department of Haematology
Medical University of Gdansk
81-519 Gdansk
Poland

The advisory committee has been involved in the planning of the trial and will be involved the evaluation.

## 11.6. Study laboratories and other technical resources

**Reference Pathology:**

(1) Prof. Ioannis Anagnostopoulos
Institute of Pathology
Charité – Universitätsmedizin Berlin, Campus Mitte
Charitéplatz 1
10115 Berlin
Germany

(2) Prof. Wolfram Klapper
Institute of Pathology
University Medical Center Schleswig-Holstein, Campus Kiel
Arnold Heller Strasse 3
24105 Kiel
Germany

**Reference Cytogenetics:**

For reference tumor-cytogenetics the reference pathologists will send representative patient tissue samples to:

Prof. Reiner Siebert
Department of Human Genetics
Ulm University Hospital
Albert-Einstein-Allee 11
89081 Ulm
Germany

**Reference Flow-cytometry:**

Dr. Matthias Ritgen
Department of Hematology and Oncology
University Medical Center Schleswig-Holstein, Campus Kiel
Arnold Heller Strasse 3
24105 Kiel
Germany

**Reference EBV-load measurement in peripheral blood samples:**

Prof. Schulze
Institute of Virology
University Medical Center Hannover
OE 5230
Carl-Neuberg-Strasse 1
30625 Hannover
Germany

## 11.7. ECOG performance status and IPI score

### ECOG performance status:

| Grade | Description |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, *e.g.*, light housework of office work |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours |
| 3 | Capable of only limited self-care, confined to a bed or chair >50% of waking hours |
| 4 | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair |
| 5 | Dead |

### IPI-score:

**Five adverse prognostic factors were selected**

1. Age >60 (*vs*. ≤60)
2. Ann Arbor Stage III-IV (*vs*. I-II)
3. More than one extranodal manifestation (vs ≤ 1)
4. ECOG ≥2 (*vs*. 0,1)
5. Serum LDH level > normal (*vs*. ≤ normal)

## 11.8. Ann-Arbor Classification System

**Stage I:**

- I = Involvement of a single lymph node region.
- IE = Localized involvement of a single extralymphatic organ or site.

**Stage II:**

- II = Involvement of 2 or more lymph node regions on the same side of the diaphragm.
- IIE = Localized involvement of a single associated extralymphatic organ or site and its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm.

**Stage III:**

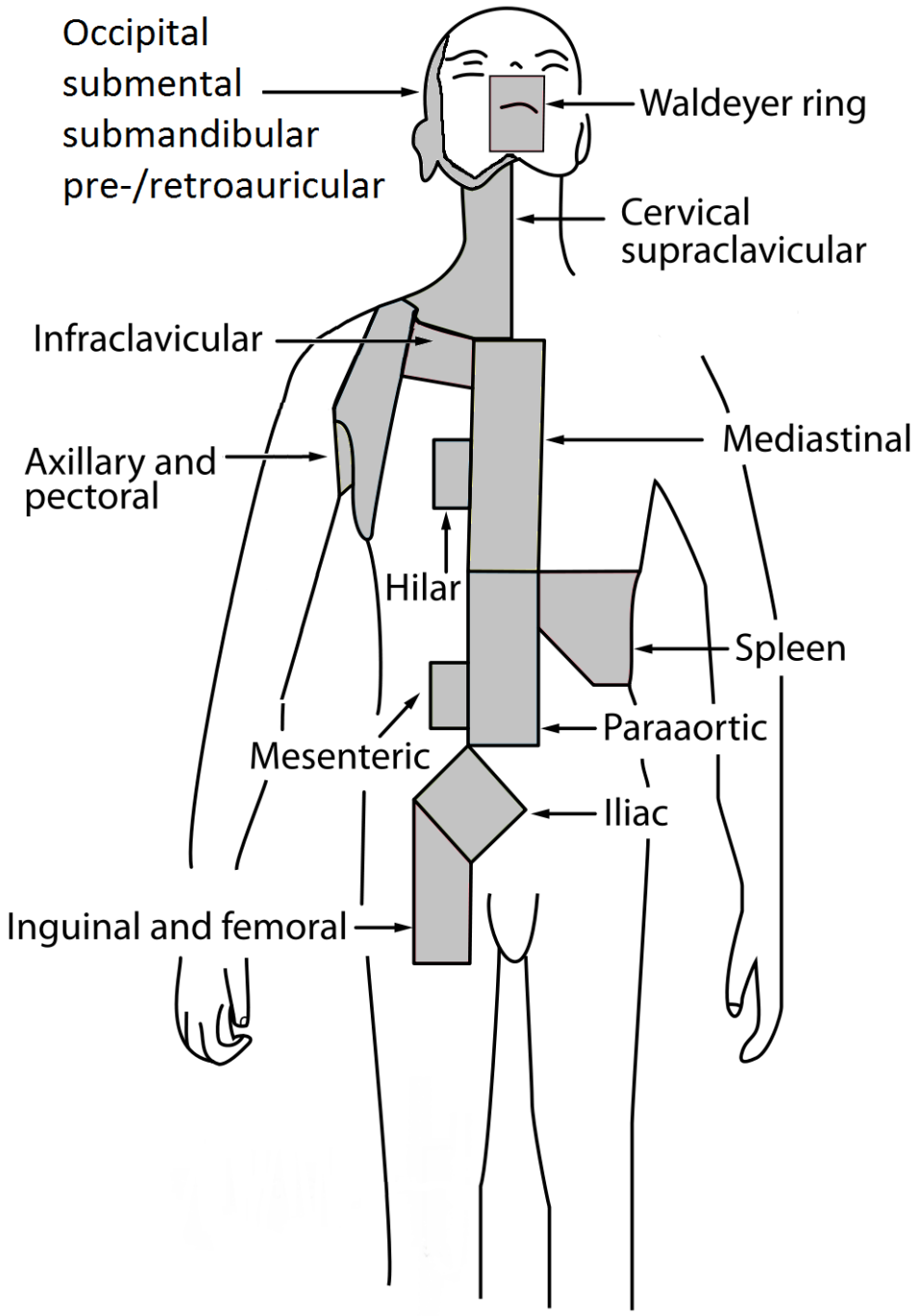
- III = Involvement of lymph node regions on both sides of the diaphragm.
- IIIE = Involvement of lymph node regions on the both sides of the diaphragm accompanied by localized involvement of an extralymphatic organ or site.
- IIIS = Involvement of lymph node regions on both sides of the diaphragm accompanied by involvement of the spleen*.
- IIIS+E = Both IIIS+IIIE*.

* of note, in PTLD post liver transplantation, spleen size is often increased by the underlying disease, and spleen involvement should only be considered in case of infiltration by imaging techniques or because of a size increase as compared to pre-baseline parameters

**Stage IV:**

- IV = Disseminated (multifocal) involvement of 1 or more extralymphatic sites with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (non regional) nodal involvement.
- IVE = Extranodal lymphoid malignancies arise in tissue separate from, but near, the major lymphatic aggregates.

## 11.9. Nodal Areas



## 11.10. PTLD adapted International Working Group response criteria for NHL

Assessment of response will be performed based on the response criteria for malignant lymphoma (Cheson et al., 1999).

**For response assessment measurable extranodal disease should be assessed in a manner similar to that for nodal disease**. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

### Complete response (CR)

A complete response requires the following:

1. Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalization of those biochemical abnormalities (e.g., lactate dehydrogenase [LDH]) definitely assignable to PTLD.

2. All lymph nodes and nodal masses must have regressed to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to ≤ 1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).

3. The spleen, if considered to be enlarged due to lymphoma before therapy on the basis of a CT scan, must have regressed in size and must not be palpable on physical examination. **This excludes the commonly longstanding splenomegaly in patients after liver transplantation.** Any macroscopic nodules in any organs detectable on imaging techniques should no longer be present. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.

4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

5a. Residual masses should not be assigned CRu status, but should be considered partial responses.

**Partial response (PR)**

A partial response requires the following:

1. At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

2. No increase should be observed in the size of other nodes, liver, or spleen.

3. Splenic and hepatic nodules must regress by ≥50% in their SPD or, for single nodules, in the greatest transverse diameter.

4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and not measurable disease.

5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B-cells). **Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.**

6. No new sites of disease.

**Stable disease (SD)**

Stable disease (SD) is defined as the following:

1. A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]).

**Progressive disease (PD)**

Progressive disease is defined as follows:

***Relapsed Disease (after CR) / Progressive Disease (after PR, SD)***

Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0 cm. Lymph nodes ≤ 1.0 x ≤ 1.0 cm will not be considered as abnormal for relapse or progressive disease.

1. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size.

2. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥50% and to a size of 1.5x1.5 cm or more than 1.5 cm in the long axis.

3. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.

## 11.11. ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for expedited reporting, Topic E2

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that at any dose fulfills at least one of the following criteria:

- is fatal; (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 immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- requires in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the sponsor is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

An unexpected AE is one, the nature or severity of which is not consistent with information in the applicable product information.

Causality is initially assessed by the investigator. For Serious Adverse Events, possible causes of the event are indicated by selecting one or more options.

- Pre-existing/Underlying disease - specify
- Study-treatment - specify the drug(s) related to the event
- Other treatment (concomitant or previous) - specify
- Protocol-related procedure
- Other (e.g. accident, new or intercurrent illness) - specify

The term severe is a measure of intensity, thus a severe AE is not necessarily serious. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious. A serious adverse event occurring during the study or which comes to the attention of the investigator within 15 days after stopping the treatment or during the protocol-defined follow-up period, if this is longer, whether considered treatment-related or not, must be reported. In addition, a serious adverse event that occurs after this treatment, if considered related to test "drug", should be reported.

## 11.12. Patient information sheet and informed consent form

Patient information sheet and informed consent form are available in the investigator's site file:

Patienteninformation und -Einwilligung zur klinischen Prüfung

Anhang zur AMG-Patienten-Information

Patienteninformation und -Einwilligung zur Teilnahme am wissenschaftlichen Begleitprogramm PTLD-Tumorbank

Patienteninformation und -Einwilligung zur Teilnahme am wissenschaftlichen Begleitprogramm PTLD-Blutprobenbank

## 11.13. Prescribing information

Summaries of product characteristics [Fachinformationen] are available in the investigator's site file for the following substances:

- Mabthera IV
- Mabthera SC
- Cyclophosphamide
- Vincristine
- Adriamycin/Doxorubicin
- Prednisolone
- Cytarabine
- Dexamethasone
- Oxaliplatin

## 11.14. Confirmation of insurance

ZURICH

### Versicherungsbestätigung

Hiermit wird bestätigt, dass die Firma

DIAKO Ev. Diakonie-Krankenhaus gGmbH, Postfach 21 01 05, 28221 Bremen

unter der Vertragsnummer 800.520.029.997 bei unserer Gesellschaft seit dem 01.03.2014 zu den nachfolgenden Konditionen versichert ist:

**Bedingungen und Umfang des Vertrages**
Der Versicherungsschutz umfasst nur die klinische Prüfung:
**DPTLDSG-IIT-PTLD-2, EudraCT-Nr. 2013-004479-11, DRKS00005380**
**RISKO-STRATIFIZIERTE SEQUENTIELLE BEHANDLUNG DER POST-TRANSPLANTIONS LYMPHOPROLIFERATIVEN ERKRANKUNG MIT 4 KURSEN RITUXIMAB SC GEFOLGT VON 4 ZYKLEN RITUXIMAB SC ODER 4 ZYKLEN RITUXIMAB SC KOMBINIERT MIT CHOP-21 ODER 6 ZYKLEN RITUXIMAB SC KOMBINIERT MIT ALTERNIEREND CHOP-21 UND DHAOX: Die PTLD-2-Studie**

Die Probandenversicherung bezieht sich auf die Allgemeinen Versicherungsbedingungen für eine versicherungspflichtige klinische Prüfung von Arzneimitteln (AVB-Prob/AMG-Objekt )

die ab dem 01.03.2014 mit voraussichtlich 90 **Probanden** in Deutschland durchgeführt wird.
Die Studie wird voraussichtlich am 31.03.2018 beendet sein.

**Versicherungssummen**
Die Höchstleistung beträgt für alle Versicherungsfälle aus der klinischen Prüfung dieser Studie 5.000.000,-- EUR.
Die Versicherungsleistungen für die einzelnen versicherten Personen ermäßigen sich im entsprechenden Verhältnis, wenn die Summe der einzelnen Versicherungsleistungen diesen Höchstbetrag überschreiten würde. Je versicherte Person bilden 500.000,- EUR die Höchstgrenze für die Leistungen des Versicherers.

**Vertragsdauer**
Der Vertrag ist abgeschlossen bis zum Ende der klinischen Prüfung, längstens jedoch bis zum 31.03.2018.

Köln. den 27.01.2014

Zurich Insurance plc NfD

**Zurich Insurance plc**
**Niederlassung für Deutschland**
**Zurich Kunden Service**

**Richten Sie ihre Post an**
Zurich Insurance plc NfD
53287 Bonn
Telefon: 01802 02505050*)
Telefax: 01802 02505059*)

**Bankverbindung**
Commerzbank AG, Frankfurt am Main
BLZ 500 400 00
Kto.-Nr. 580 650 002

**Bei Zahlungen aus dem Ausland:**
IBAN DE11 5004 0000 0580 6500 02
SWIFT(BIC) COBADEFFXXX

**Angaben zur Umsatzsteuer:**
Steuernummer: DE815195011
Versicherungsprämien sind umsatzsteuerfrei

**Rechtsform der Gesellschaft**
Public company limited by shares
(Aktiengesellschaft nach irischem Recht)
**Hauptsitz** Dublin (Irland)
**Vertretung der Gesellschaft**
Patrick Manley (Chief Executive Officer)
**Verwaltungsratsvorsitzender**
Dr. Axel Lehmann
**Companies Registry Office** (entspricht dem dt. Registergericht) Registernr. 13460

**Hauptbevollmächtigter der Niederlassung**
Ralph Brand
**Sitz der Niederlassung**
Frankfurt/Main
Registernr. HRB 88353
Solmsstraße 27-37, 60486 Frankfurt am Main

*) 6 ct/Anruf dt. Festnetz; max. 42 ct/Min. Mobilfunk

Diese Versicherungsbestätigung dient lediglich Informationszwecken. Maßgebend für den Umfang des Versicherungsschutzes bleiben ausschließlich die vertraglichen Vereinbarungen des Vertrages Nummer 800.520.029.997 .

## 11.15. Conditions of insurance (Zurich insurance plc.)

# Allgemeine Versicherungsbedingungen für eine versicherungspflichtige klinische Prüfung von Arzneimitteln (AVB-Prob/AMG-Objekt)

**Stand: 01/2008**



## 1 Versichertes Risiko

### 1.1 Gegenstand der Versicherung, Versicherungsfall

Der Versicherer gewährt Versicherungsschutz für den Fall, dass bei der im Versicherungsschein dokumentierten, vom Versicherungsnehmer durchgeführten oder veranlassten oder als Sponsor i. S. v. § 4 Abs. 24 AMG verantworteten versicherungspflichtigen klinischen Prüfung eines Arzneimittels in Deutschland eine Person, bei der die klinische Prüfung durchgeführt wurde (versicherte Person), getötet oder ihr Körper oder ihre Gesundheit verletzt wird (Gesundheitsschädigung).

Als versicherte Person gilt auch die bei der Durchführung der klinischen Prüfung bereits gezeugte Leibesfrucht der versicherten Person.

### 1.2 Ethikkommission und Genehmigungsbehörde

Voraussetzung für den Versicherungsschutz ist, dass gemäß § 40 Abs. 1 Satz 2 AMG für die Durchführung der klinischen Prüfung vor deren Beginn eine zustimmende Bewertung der zuständigen Ethikkommission erteilt wird und die zuständige Bundesoberbehörde die Durchführung der klinischen Prüfung genehmigt.

Der Versicherungsschutz erlischt in dem Zeitpunkt, in dem die Genehmigung durch die zuständige Bundesoberbehörde zurückgenommen, widerrufen oder ruhend gestellt wird. Jedoch besteht für alle Maßnahmen, die im Zusammenhang mit der klinischen Prüfung bis zum Zeitpunkt der Rücknahme, des Widerrufs oder der Ruhendstellung der zuständigen Bundesoberbehörde durchgeführt wurden, weiterhin Versicherungsschutz im Rahmen und Umfang des Vertrages. Versicherungsschutz im Rahmen und Umfang des Vertrages besteht ebenfalls für nach der Rücknahme, dem Widerruf oder der Ruhendstellung notwendige Abschlussmaßnahmen (sogenannter Follow-up) bei bereits in die klinische Prüfung einbezogenen versicherten Personen, längstens jedoch für sechs Monate ab Wirksamkeit der Rücknahme, des Widerrufs oder der Ruhendstellung. Eine Verlängerung dieser Frist bedarf besonderer Vereinbarung.

### 1.3 Versicherungsumfang

**1.3.1** Versicherungsschutz besteht für Gesundheitsschädigungen, die Folge von den bei der klinischen Prüfung angewandten Arzneimitteln und/oder Stoffen sind.

**1.3.2** Unter den Versicherungsschutz fallen auch Gesundheitsschädigungen durch Maßnahmen, die an dem Körper der versicherten Person im Zusammenhang mit der klinischen Prüfung des Arzneimittels durchgeführt werden.

**1.3.3** Soweit unabhängig von der klinischen Prüfung bestehende Krankheiten oder andere Ursachen bei der Gesundheitsschädigung mitgewirkt haben, besteht Versicherungsschutz nur für den entsprechenden ursächlichen Anteil der klinischen Prüfung an der Gesundheitsschädigung.

### 1.4 Ausschlüsse

Ausgeschlossen von der Versicherung sind:

**1.4.1** Gesundheitsschädigungen einer versicherten Person, wenn sie an einer Krankheit leidet, zu deren Behebung das zu prüfende Arzneimittel angewendet werden soll, und soweit diese Gesundheitsschädigungen

(1) durch mit Sicherheit eintretende und der versicherten Person bekannt gemachte Wirkungen/Ereignisse verursacht worden sind und

(2) über ein nach den Erkenntnissen der medizinischen Wissenschaft vertretbares Maß nicht hinausgehen.

**1.4.2** Gesundheitsschädigungen und Verschlimmerungen bereits bestehender Gesundheitsschädigungen, die auch dann eingetreten wären oder fortbestünden, wenn die versicherte Person nicht an der klinischen Prüfung teilgenommen hätte;

**1.4.3** genetische Schädigungen (Veränderung am Erbgut [Genom], an den Chromosomen, an den Genen oder an einzelnen Nukleotiden). Versicherungsschutz besteht jedoch, soweit die Veränderung bei der versicherten Person organische Gesundheitsschädigungen mit Auswirkungen auf das klinische Erscheinungsbild (Phänotyp) zur Folge haben;

**1.4.4** Gesundheitsschädigungen, soweit sie eingetreten sind, weil die versicherte Person vorsätzlich den ausdrücklichen Anweisungen der Personen, die mit der Durchführung der klinischen Prüfung beauftragt sind, zuwidergehandelt hat.

### 1.5 Zeitliche Geltung

**1.5.1** Die klinische Prüfung umfasst, sofern der Prüfplan keine anderweitige Regelung vorsieht, den Zeitraum von der Screening-/Rekrutierungsphase bis hin zu eventuell vorgesehenen Nachbehandlungen/-beobachtungen.

**1.5.2** Versicherungsschutz besteht für Gesundheitsschädigungen, die spätestens fünf Jahre nach Abschluss der bei der versicherten Person durchgeführten klinischen Prüfung eingetreten sind und nicht später als zehn Jahre nach Beendigung der klinischen Prüfung dem Versicherer gemeldet werden.

Die Gesundheitsschädigung gilt im Zweifel als in dem Zeitpunkt eingetreten, in dem der Geschädigte erstmals einen Arzt wegen Symptomen konsultiert hat, die sich bei diesem Anlass oder später als Symptome der betreffenden Gesundheitsschädigung erweisen.

## 2 Beginn des Versicherungsschutzes, Dauer des Vertrages

**2.1** Der Versicherungsschutz beginnt zu dem im Versicherungsschein angegebenen Zeitpunkt, wenn der Versicherungsnehmer den einmaligen oder ersten Beitrag rechtzeitig im Sinne von Ziffer 6.1 zahlt.

**2.2** Der Vertrag ist für die im Versicherungsschein angegebene Zeit abgeschlossen. Eine Verlängerung des Vertrages bedarf besonderer Vereinbarung.

## 3 Leistungen des Versicherers

### 3.1 Versicherungsleistung, Versicherungssummen

#### 3.1.1 Versicherungsleistung

(1) Der Versicherer leistet im Rahmen der vereinbarten Versicherungssummen nach Maßgabe von Ziffer 3.1.2 den Geldbetrag, der zum Ausgleich des durch die Gesundheitsschädigung der versicherten Person oder durch deren Tod eingetretenen materiellen Schadens im Sinne der Absätze (2) bis (4) erforderlich ist. Immaterielle Schäden (z. B. Schmerzensgeld) bleiben vom Versicherungsschutz ausgeschlossen.

(2) Materieller Schaden ist der Unterschiedsbetrag zwischen der tatsächlichen Vermögenslage der versicherten Person und der Vermögenslage, die bestehen würde, wenn die Gesundheitsschädigung nicht eingetreten wäre. Folgende von Dritten zu gewährende Leistungen sind beim Vergleich der Vermögenslagen mindernd zu berücksichtigen: Ansprüche der versicherten Person oder ihrer Hinterbliebenen auf Leistung aus einer Sozialversicherung, gegen einen Krankenversicherer oder ein gesetzlicher Anspruch auf Lohn- und Gehaltsfortzahlung, auf Fortzahlung von Dienst- oder Amtsbezügen oder auf Gewährung von Versorgungsbezügen. Bei Streit über die Entstehung solcher Ansprüche wird der Versicherer gegen Abtretung der strittigen Ansprüche die Leistung vorab gewähren.

Im Übrigen finden bei der Berechnung des Schadens die Grundsätze der §§ 249, 843 BGB entsprechende Anwendung. Das heißt, die versicherte Person wird so gestellt, wie sie stehen würde, wenn ein Schädiger ihr gegenüber nach deutschem Recht haftpflichtig wäre.

(3) Im Falle der Verletzung des Körpers oder der Gesundheit leistet der Versicherer im Rahmen des Angemessenen

a) Heilbehandlungskosten;

b) eine Geldrente, wenn infolge der Gesundheitsschädigung die Erwerbsfähigkeit der versicherten Person aufgehoben oder gemindert wird, oder eine Vermehrung seiner Bedürfnisse eintritt. Im Einvernehmen von Versicherer und versicherter Person kann anstelle einer Rentenleistung eine Kapitalabfindung gewährt werden;

c) sonstige vermehrte Aufwendungen.

(4) Im Falle des Todes der versicherten Person ersetzt der Versicherer demjenigen die Kosten der Beerdigung, welchem die Verpflichtung obliegt, die Kosten zu tragen. Stand die versicherte Person zu diesem Zeitpunkt zu einem Dritten in einem Verhältnis, aufgrund dessen sie diesem gegenüber kraft Gesetzes unterhaltspflichtig war oder unterhaltspflichtig werden konnte, und ist dem Dritten infolge der Tötung das Recht auf den Unterhalt entzogen, so erbringt der Versicherer Unterhaltsleistungen insoweit, als die versicherte Person während der mutmaßlichen Dauer ihres Lebens zur Gewährung des Unterhalts verpflichtet gewesen sein würde. Der Versicherer erbringt die Leistungen auch dann, wenn der Dritte zur Zeit des Todes der versicherten Person gezeugt, aber noch nicht geboren war.

(5) Mögliche Ansprüche auf Grundlage ausländischen Rechts bleiben vom Versicherungsschutz ausgeschlossen.

(6) Hat der Versicherungsnehmer an den Geschädigten Rentenzahlungen zu leisten und übersteigt der Kapitalwert der Rente die Versicherungssumme oder den nach Abzug etwaiger sonstiger Leistungen aus dem Versicherungsfall noch verbleibenden Restbetrag der Versicherungssumme, so wird die zu leistende Rente nur im Verhältnis der Versicherungssumme bzw. ihres Restbetrages zum Kapitalwert der Rente vom Versicherer erstattet.

Für die Berechnung des Rentenwertes gilt die entsprechende Vorschrift der Verordnung über den Versicherungsschutz in der Kraftfahrzeug-Haftpflichtversicherung in der jeweils gültigen Fassung zum Zeitpunkt des Versicherungsfalles.

**3.1.2** Versicherungssummen

(1) Es gelten die im Versicherungsschein genannten Versicherungssummen

- für die einzelne versicherte Person und
- für alle Versicherungsfälle einer klinischen Prüfung.

(2) Die Versicherungsleistungen für die einzelnen versicherten Personen ermäßigen sich - soweit nicht etwas anderes vereinbart wurde - im entsprechenden Verhältnis, wenn die Summe der einzelnen Versicherungsleistungen die Versicherungssumme für alle Versicherungsfälle einer klinischen Prüfung überschreiten würde.

### 3.2 Kosten

**3.2.1** Der Versicherer übernimmt auch die auf seine Anweisung oder mit seinem Einverständnis erwachsenden notwendigen Kosten einer medizinischen Begutachtung.

**3.2.2** Vom Versicherungsschutz ausgeschlossen bleiben Kosten, die dem Versicherungsnehmer durch die Zuziehung eines rechtlichen Beistandes entstehen.

**3.2.3** Ziffer 3.4.2 (3) bleibt unberührt.

### 3.3 Erklärung über die Leistungspflicht

Der Versicherer ist verpflichtet, sich innerhalb von einem Monat darüber zu erklären, ob und inwieweit eine Entschädigungspflicht anerkannt wird. Die Frist beginnt mit dem Eingang der notwendigen Unterlagen, die zur Feststellung des Schadens dem Grunde und der Höhe nach beizubringen sind.

### 3.4 Verfahren bei Meinungsverschiedenheiten

**3.4.1** Entscheidung des Ärzteausschusses

(1) Im Falle von Meinungsverschiedenheiten über Art und Umfang der Gesundheitsschädigung oder darüber, ob und in welchem Umfang die Gesundheitsschädigung auf die klinische Prüfung im Sinne der Ziffer 1.3 zurückzuführen ist, entscheidet ein Ärzteausschuss, für alle sonstigen Streitpunkte sind die ordentlichen Gerichte zuständig.

(2) Die Entscheidung des Ärzteausschusses ist von der versicherten Person bis zum Ablauf von sechs Monaten, nachdem ihr die Erklärung des Versicherers nach Ziffer 3.3 zugegangen ist, zu beantragen. Versicherer und versicherte Person können jedoch bis zum Ablauf dieser Frist verlangen, dass anstelle des Ärzteausschusses die ordentlichen Gerichte entscheiden. Wird dieses Verlangen gestellt, so kann die versicherte Person nur Klage erheben.

(3) Lässt der Anspruchserhebende die unter Abs. (2) genannte Frist verstreichen, ohne dass er entweder die Entscheidung des Ärzteausschusses verlangt oder Klage erhebt, so sind weitergehende Ansprüche, als sie vom Versicherer anerkannt sind, ausgeschlossen. Auf diese Rechtsfolge hat der Versicherer in seiner Erklärung hinzuweisen.

**3.4.2** Für den Ärzteausschuss gelten folgende Bestimmungen:

(1) Zusammensetzung:

a) Der Ärzteausschuss setzt sich zusammen aus zwei Ärzten, von denen jede Partei einen benennt, und einem Obmann. Dieser wird von den beiden von den Parteien benannten Ärzten gewählt und muss ein auf dem medizinischen Fachgebiet, in das die klinische Prüfung fällt, erfahrener Arzt sein, der nicht in einem Abhängigkeitsverhältnis zu einer der Parteien steht. Einigen sich die von den Parteien gewählten Ärzte nicht binnen eines Monats über den Obmann, so wird dieser auf Antrag einer Partei von dem Vorsitzenden der für den letzten inländischen Wohnsitz der versicherten Person zuständigen Ärztekammer benannt. Hat die versicherte Person keinen inländischen Wohnsitz, so ist die für den Sitz des Versicherers zuständige Ärztekammer maßgebend. Der Obmann kann einen auf dem betroffenen Fachgebiet besonders erfahrenen medizinischen oder pharmakologischen Sachverständigen als Gutachter zuziehen.

b) Benennt eine Partei ihr Ausschussmitglied nicht binnen eines Monats, nachdem sie von der anderen Partei hierzu aufgefordert ist, so wird dieses Ausschussmitglied gleichfalls durch den Vorsitzenden der Ärztekammer ernannt.

(2) Verfahren:

a) Sobald der Ausschuss zusammengesetzt ist, hat der Versicherer unter Einsendung der erforderlichen Unterlagen den Obmann um die Durchführung des Verfahrens zu ersuchen.

b) Der Obmann bestimmt im Benehmen mit den beiden Ausschussmitgliedern Ort und Zeit des Zusammentritts und gibt hiervon den Parteien mindestens eine Woche vor dem Termin Nachricht. Es bleibt ihm unbenommen, sich wegen weiterer Aufklärung des Sachverhalts an die Parteien zu wenden.

Im Rahmen der Sitzung ist die versicherte Person, soweit möglich, zu hören und erforderlichenfalls zu untersuchen. Erscheint die versicherte Person unentschuldigt nicht, so kann der Ausschuss aufgrund der Unterlagen entscheiden.

c) Die Entscheidung ist schriftlich zu begründen und vom Obmann zu unterzeichnen.

(3) Kosten:

Ist die Entscheidung des Ärzteausschusses für die versicherte Person günstiger als das ursprüngliche Angebot des Versicherers, so sind die Kosten vom Versicherer zu tragen. Anderenfalls werden sie zu 10% der geforderten Entschädigung, höchstens bis zu 5.000 EUR der versicherten Person auferlegt.

## 4 Obliegenheiten

### 4.1 Vorvertragliche Anzeigepflichten des Versicherungsnehmers

#### 4.1.1 Vollständigkeit und Richtigkeit von Angaben über gefahrerhebliche Umstände

Der Versicherungsnehmer hat bis zur Abgabe seiner Vertragserklärung dem Versicherer alle ihm bekannten Gefahrumstände anzuzeigen, nach denen der Versicherer in Textform gefragt hat und die für den Entschluss des Versicherers erheblich sind, den Vertrag mit dem vereinbarten Inhalt zu schließen. Der Versicherungsnehmer ist auch insoweit zur Anzeige verpflichtet, als nach seiner Vertragserklärung, aber vor Vertragsannahme der Versicherer in Textform Fragen im Sinne des Satzes 1 stellt. Gefahrerheblich sind die Umstände, die geeignet sind, auf den Entschluss des Versicherers Einfluss auszuüben, den Vertrag überhaupt oder mit dem vereinbarten Inhalt abzuschließen.

Wird der Vertrag von einem Vertreter des Versicherungsnehmers geschlossen und kennt dieser den gefahrerheblichen Umstand, muss sich der Versicherungsnehmer so behandeln lassen, als habe er selbst davon Kenntnis gehabt oder dies arglistig verschwiegen.

#### 4.1.2 Rücktritt

(1) Unvollständige und unrichtige Angaben zu den gefahrerheblichen Umständen berechtigen den Versicherer, vom Versicherungsvertrag zurückzutreten.

(2) Der Versicherer hat kein Rücktrittsrecht, wenn der Versicherungsnehmer nachweist, dass er oder sein Vertreter die unrichtigen oder unvollständigen Angaben weder vorsätzlich noch grob fahrlässig gemacht hat.

Das Rücktrittsrecht des Versicherers wegen grob fahrlässiger Verletzung der Anzeigepflicht besteht nicht, wenn der Versicherungsnehmer nachweist, dass der Versicherer den Vertrag auch bei Kenntnis der nicht angezeigten Umstände, wenn auch zu anderen Bedingungen, geschlossen hätte.

(3) Im Fall des Rücktritts besteht kein Versicherungsschutz.

Tritt der Versicherer nach Eintritt des Versicherungsfalls zurück, bleibt er zur Leistung verpflichtet, wenn der Versicherungsnehmer nachweist, dass der unvollständig oder unrichtig angezeigte Umstand weder für den Eintritt des Versicherungsfalls noch für die Feststellung oder den Umfang der Leistung ursächlich war. Auch in diesem Fall ist er aber von der Verpflichtung zur Leistung frei, wenn der Versicherungsnehmer die Anzeigepflicht arglistig verletzt hat.

Dem Versicherer steht der Teil des Beitrages zu, der der bis zum Wirksamwerden der Rücktrittserklärung abgelaufenen Vertragszeit entspricht.

#### 4.1.3 Beitragsänderung oder Kündigungsrecht

Ist das Rücktrittsrecht des Versicherers ausgeschlossen, weil die Verletzung einer Anzeigepflicht weder auf Vorsatz noch auf grober Fahrlässigkeit beruhte, kann der Versicherer den Vertrag unter Einhaltung einer Frist von einem Monat in Schriftform kündigen.

Das Kündigungsrecht ist ausgeschlossen, wenn der Versicherungsnehmer nachweist, dass der Versicherer den Vertrag auch bei Kenntnis der nicht angezeigten Umstände, wenn auch zu anderen Bedingungen, geschlossen hätte.

Kann der Versicherer nicht zurücktreten oder kündigen, weil er den Vertrag auch bei Kenntnis der nicht angezeigten Umstände, aber zu anderen Bedingungen, geschlossen hätte, werden die anderen Bedingungen auf Verlangen des Versicherers rückwirkend Vertragsbestandteil. Hat der Versicherungsnehmer die Pflichtverletzung nicht zu vertreten, werden die anderen

Bedingungen ab Kenntnis des Versicherungsnehmers von den gefahrerheblichen Umständen Vertragsbestandteil.

Erhöht sich durch die Vertragsanpassung der Beitrag um mehr als 10% oder schließt der Versicherer die Gefahrabsicherung für den nicht angezeigten Umstand aus, kann der Versicherungsnehmer den Vertrag innerhalb eines Monats nach Zugang der Mitteilung des Versicherers fristlos in Schriftform kündigen.

Der Versicherer muss die ihm nach Ziffer 4.1.2 und 4.1.3 zustehenden Rechte innerhalb eines Monats schriftlich geltend machen. Die Frist beginnt mit dem Zeitpunkt, zu dem er von der Verletzung der Anzeigepflicht, die das von ihm geltend gemachte Recht begründet, Kenntnis erlangt. Er hat die Umstände anzugeben, auf die er seine Erklärung stützt, er darf nachträglich weitere Umstände zur Begründung seiner Erklärung abgeben, wenn für diese die Monatsfrist nicht verstrichen ist.

Dem Versicherer stehen die Rechte nach den Ziffern 4.1.2 und 4.1.3 nur zu, wenn er den Versicherungsnehmer durch gesonderte Mitteilung in Textform auf die Folgen einer Anzeigepflichtverletzung hingewiesen hat.

Der Versicherer kann sich auf die in den Ziffern 4.1.2. und 4.1.3 genannten Rechte nicht berufen, wenn er den nicht angezeigten Gefahrumstand oder die Unrichtigkeit der Anzeige kannte.

**4.1.4 Anfechtung**

Das Recht des Versicherers, den Vertrag wegen arglistiger Täuschung anzufechten, bleibt unberührt. Im Fall der Anfechtung steht dem Versicherer der Teil des Beitrages zu, der der bis zum Wirksamwerden der Anfechtungserklärung abgelaufenen Vertragszeit entspricht.

**4.1.5 Anspruch der versicherten Person**

Im Falle der Leistungsfreiheit bleibt der Versicherer der versicherten Person nicht aber dem Versicherungsnehmer zur Leistung verpflichtet. Dem Versicherer steht insoweit ein Rückgriffsrecht gegen den Versicherungsnehmer zu.

**4.2 Obliegenheiten des Versicherungsnehmers vor Eintritt des Versicherungsfalles**

**4.2.1** Soweit der Versicherungsnehmer die klinische Prüfung selbst durchführt, ist er verpflichtet,

(1) die Vorschriften der §§ 40 bis 42 a des Arzneimittelgesetzes (AMG) einzuhalten und die Arzneimittelprüfrichtlinien (§ 26 AMG) in ihrer jeweils gültigen Fassung zu beachten,

(2) die versicherten Personen bzw. in den Fällen des § 40 Abs. 4 AMG und § 41 Abs. 2 und 3 AMG den gesetzlichen Vertreter oder Bevollmächtigten über das Bestehen des Vertrages zu unterrichten und

(3) die versicherten Personen bzw. in den Fällen des § 40 Abs. 4 AMG und § 41 Abs. 2 und 3 AMG den gesetzlichen Vertreter oder Bevollmächtigten ausdrücklich anzuweisen,

a) dass sich die versicherte Person während der Dauer der klinischen Prüfung nur nach Rücksprache mit dem klinischen Prüfer einer anderen medizinischen Behandlung unterziehen darf, es sei denn, es handelt sich um einen medizinischen Notfall,

b) den klinischen Prüfer von einer Notfallbehandlung unverzüglich zu unterrichten.

**4.2.2** Soweit der Versicherungsnehmer die klinische Prüfung durch von ihm beauftragte Dritte durchführen lässt, hat er diese zur Wahrung der Pflichten gem. 4.2.1 vertraglich anzuhalten.

**4.3 Obliegenheiten des Versicherungsnehmers und der versicherten Person nach Eintritt des Versicherungsfalles**

**4.3.1** Eine Gesundheitsschädigung, die als Folge der klinischen Prüfung eingetreten sein könnte, ist dem Versicherer unverzüglich anzuzeigen.

**4.3.2** Der Versicherungsnehmer und die versicherte Person müssen nach ihren Möglichkeiten jeweils für die Abwendung und Minderung des Schadens sorgen. Sie haben dem Versicherer ausführliche und wahrheitsgemäße Schadenberichte zu erstatten und ihn bei der Schadenermittlung und -regulierung zu unterstützen. Weisungen des Versicherers sind dabei zu befolgen, soweit es für sie zumutbar ist. Alle Umstände, die nach Ansicht des Versicherers für die Bearbeitung des Schadens wichtig sind, müssen mitgeteilt sowie alle dafür angeforderten Schriftstücke übersandt werden.

**4.3.3** Hat der Versicherungsfall den Tod zur Folge, so ist dies unverzüglich anzuzeigen (Ziff. 9.1), und zwar auch dann, wenn eine Meldung nach Ziffer 4.3.1 bereits erfolgt ist. Dem Versicherer ist das Recht zu verschaffen, eine Obduktion durch einen von ihm beauftragten Arzt vornehmen zu lassen.

**4.3.4** Die Obliegenheiten der versicherten Person gelten in den Fällen des § 40 Abs. 4 AMG und § 41 Abs. 2 und 3 AMG für deren gesetzlichen Vertreter oder Bevollmächtigten entsprechend.

**4.4 Rechtsfolgen von Obliegenheitsverletzungen**

**Rechtsfolgen**

**4.4.1 des Versicherungsnehmers**

(1) Verletzt der Versicherungsnehmer oder dessen mit der Leitung der klinischen Prüfung verantwortlich Beauftragte eine Obliegenheit aus diesem Vertrag, die er vor Eintritt des Versicherungsfalles zu erfüllen hat, kann der Versicherer den Vertrag innerhalb eines Monats ab Kenntnis von der Obliegenheitsverletzung fristlos kündigen. Der Versicherer hat kein Kündigungsrecht, wenn der Versicherungsnehmer nachweist, dass die Obliegenheitsverletzung weder auf Vorsatz noch auf grober Fahrlässigkeit beruhte.

(2) Verletzt der Versicherungsnehmer oder dessen mit der Leitung der klinischen Prüfung verantwortlich Beauftragte eine Obliegenheit aus diesem Vertrag vorsätzlich, so bleibt der Versicherer der versicherten Person nicht aber dem Versicherungsnehmer zur Leistung verpflichtet. In diesem Fall steht dem Versicherer ein Rückgriffsrecht gegen den Versicherungsnehmer zu.

Bei grob fahrlässiger Verletzung einer Obliegenheit ist der Versicherer berechtigt, sein Rückgriffsrecht in einem der Schwere des Verschuldens des Versicherungsnehmers entsprechenden Verhältnis auszuüben.

Der vollständige oder teilweise Wegfall der Leistungspflicht gegenüber dem Versicherungsnehmer hat bei Verletzung einer nach Eintritt des Versicherungsfalls bestehenden Auskunfts- oder Aufklärungsobliegenheit zur Voraussetzung, dass der Versicherer den Versicherungsnehmer durch gesonderte Mitteilung in Textform auf diese Rechtsfolge hingewiesen hat.

Weist der Versicherungsnehmer nach, dass er die Obliegenheit nicht grob fahrlässig verletzt hat, entfällt das Rückgriffsrecht.

Das Rückgriffsrecht entfällt auch dann, wenn der Versicherungsnehmer nachweist, dass die Verletzung der Obliegenheit weder für den Eintritt oder die Feststellung des Versicherungsfalls noch für die Feststellung oder den Umfang der dem Versicherer obliegenden Leistung ursächlich war. Das gilt nicht, wenn der Versicherungsnehmer die Obliegenheit arglistig verletzt hat.

Die vorstehenden Bestimmungen dieses Absatzes (2) gelten unabhängig davon, ob der Versicherer ein ihm nach Abs. (1) zustehendes Kündigungsrecht ausübt.

**4.4.2 der versicherten Person**

Verletzt die versicherte Person eine Obliegenheit vorsätzlich, so ist der Versicherer nicht zur Leistung verpflichtet.

Bei grob fahrlässiger Verletzung einer Obliegenheit ist der Versicherer berechtigt, seine Leistung in einem der Schwere des Verschuldens entsprechenden Verhältnis zu kürzen.

Der vollständige oder teilweise Wegfall der Leistungspflicht gegenüber der versicherten Person hat bei Verletzung einer nach Eintritt des Versicherungsfalls bestehenden Auskunfts- oder Aufklärungsobliegenheit zur Voraussetzung, dass der Versicherer die versicherte Person durch gesonderte Mitteilung in Textform auf diese Rechtsfolge hingewiesen hat.

Weist die versicherte Person nach, dass sie die Obliegenheit nicht grob fahrlässig verletzt hat, bleibt die Leistungspflicht bestehen.

Die Leistungspflicht bleibt auch bestehen, wenn die versicherte Person nachweist, dass die Verletzung der Obliegenheit weder für die Feststellung des Versicherungsfalls noch für die Feststellung oder den Umfang der dem Versicherer obliegenden Leistung ursächlich war. Das gilt nicht, wenn die versicherte Person die Obliegenheit arglistig verletzt hat.

Die Regelungen dieser Ziffer 4.4.2 gelten in den Fällen von Obliegenheitsverletzungen durch den gesetzlichen Vertreter oder Bevollmächtigten gemäß § 40 Abs. 4 AMG und § 41 Abs. 2 und 3 AMG entsprechend.

## 5 Gefahrerhöhung

### 5.1 Begriff der Gefahrerhöhung

Eine Gefahrerhöhung liegt vor, wenn nach Abgabe der Vertragserklärung des Versicherungsnehmers die tatsächlich vorhandenen Umstände so verändert werden, dass der Eintritt des Versicherungsfalls oder eine Vergrößerung des Schadens oder die ungerechtfertigte Inanspruchnahme des Versicherers wahrscheinlicher wären. Dies ist der Fall, wenn eine nachträgliche Änderung der klinischen Prüfung im Sinne des § 10 Abs. 1 Nr. 1 der Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung bei Menschen (GCP-V) erfolgt, die geeignet ist, sich auf die Sicherheit der versicherten Personen auszuwirken und die von der zuständigen Ethikkommission zustimmend bewertet sowie von der zuständigen Bundesoberbehörde genehmigt wurde.

### 5.2 Pflichten des Versicherungsnehmers

**5.2.1** Der Versicherungsnehmer darf nach Abgabe seiner Vertragserklärung ohne vorherige Zustimmung des Versicherers keine Gefahrerhöhung vornehmen oder deren Vornahme durch einen Dritten gestatten.

**5.2.2** Erkennt der Versicherungsnehmer nachträglich, dass er ohne vorherige Zustimmung des Versicherers eine Gefahrerhöhung vorgenommen oder gestattet hat, so muss er diese dem Versicherer unverzüglich anzeigen.

**5.2.3** Tritt nach Abgabe der Vertragserklärung des Versicherungsnehmers eine Gefahrerhöhung unabhängig von seinem Willen ein, muss er sie dem Versicherer unverzüglich anzeigen, nachdem er von der Gefahrerhöhung Kenntnis erlangt.

### 5.3 Rechtsfolgen von Pflichtverletzungen

**5.3.1 Kündigung**

Verletzt der Versicherungsnehmer seine Verpflichtung nach Ziffer 5.2.1, kann der Versicherer den Vertrag fristlos kündigen, wenn der Versicherungsnehmer seine Verpflichtung vorsätzlich oder grob fahrlässig verletzt hat. Beruht die Verletzung auf einfacher Fahrlässigkeit, kann der Versicherer den Vertrag unter Einhaltung einer Frist von einem Monat kündigen. Der Versicherer kann nicht kündigen, wenn der Versicherungsnehmer nachweist, dass er die Pflichtverletzung nicht zu vertreten hat.

Wird dem Versicherer eine Gefahrerhöhung in den Fällen nach Ziffer 5.2.2 und 5.2.3 bekannt, kann er den Vertrag unter Einhaltung einer Frist von einem Monat kündigen.

**5.3.2 Vertragsanpassung**

Statt der Kündigung kann der Versicherer ab dem Zeitpunkt der Gefahrerhöhung einen seinen Geschäftsgrundsätzen für diese höhere Gefahr entsprechenden höheren Beitrag verlangen oder die Absicherung der höheren Gefahr ausschließen.

Erhöht sich in diesem Fall der Beitrag um mehr als 10% oder schließt der Versicherer die Absicherung der höheren Gefahr aus, kann der Versicherungsnehmer den Vertrag innerhalb eines Monats nach Zugang der Mitteilung des Versicherers ohne Einhaltung einer Frist kündigen. In der Mitteilung hat der Versicherer den Versicherungsnehmer auf dieses Kündigungsrecht hinzuweisen.

**5.3.3 Erlöschen**

Die Rechte des Versicherers zur Kündigung oder Vertragsanpassung erlöschen, wenn diese nicht innerhalb eines Monats ab Kenntnis des Versicherers von der Gefahrerhöhung ausgeübt werden oder wenn der Zustand wiederhergestellt ist, der vor der Gefahrerhöhung bestanden hat.

### 5.4 Umfang des Versicherungsschutzes bei Gefahrerhöhung

**5.4.1** Tritt nach einer Gefahrerhöhung der Versicherungsfall ein, ist der Versicherer nicht zur Leistung verpflichtet, wenn der Versicherungsnehmer seine Pflichten nach Ziffer 5.2.1 vorsätzlich verletzt hat. Verletzt der Versicherungsnehmer diese Pflichten grob fahrlässig, so ist der Versicherer berechtigt, seine Leistung in dem Verhältnis zu kürzen, das der Schwere des Verschuldens des Versicherungsnehmers entspricht. Das Nichtvorliegen einer groben Fahrlässigkeit hat der Versicherungsnehmer zu beweisen.

**5.4.2** Bei einer Gefahrerhöhung nach Ziffer 5.2.2 und 5.2.3 ist der Versicherer bei vorsätzlicher Verletzung der Pflichten von der Leistung frei, wenn der Versicherungsfall später als einen Monat nach dem Zeitpunkt eintritt, zu dem die Anzeige dem Versicherer hätte zugegangen sein müssen. Verletzt der Versicherungsnehmer seine Pflichten grob fahrlässig, so gelten Ziffer 5.4.1 Satz 2 und 3 entsprechend. Der Versicherer ist in diesen Fällen gleichwohl zur Leistung verpflichtet, wenn dem Versicherer die Gefahrerhöhung zu dem in Satz 1 genannten Zeitpunkt bekannt war.

**5.4.3** Der Versicherer bleibt ferner zur Leistung verpflichtet,

a) soweit der Versicherungsnehmer nachweist, dass die Gefahrerhöhung nicht ursächlich für den Eintritt des Versicherungsfalles oder den Umfang der Leistungspflicht war oder

b) wenn zur Zeit des Eintrittes des Versicherungsfalles die Frist für die Kündigung des Versicherers abgelaufen und eine Kündigung nicht erfolgt war.

### 5.5 Mitversicherte Gefahrerhöhung

Die vorstehenden Regelungen der Ziffern 5.2. bis 5.4 finden keine Anwendung, wenn sich die Gefahr nur unerheblich erhöht hat oder nach den Umständen als vereinbart anzusehen ist, dass die Gefahrerhöhung mitversichert sein soll.

**5.6 Anspruch der versicherten Person**

Im Falle der Leistungsfreiheit bleibt der Versicherer der versicherten Person nicht aber dem Versicherungsnehmer zur Leistung verpflichtet. Dem Versicherer steht insoweit ein Rückgriffsrecht gegen den Versicherungsnehmer zu.

## 6 Beitragszahlung

**6.1 Zahlung und Folgen verspäteter Zahlung/einmaliger oder erster Beitrag**

**6.1.1** Der einmalige oder erste Beitrag wird unverzüglich nach Ablauf von zwei Wochen nach Zugang des Versicherungsscheines fällig.

Ist die Zahlung des Beitrages in Raten vereinbart, gilt als erster Beitrag nur die erste Rate des ersten Beitrages.

**6.1.2** Zahlt der Versicherungsnehmer den einmaligen oder ersten Beitrag nicht rechtzeitig, kann der Versicherer vom Vertrag zurücktreten, solange der Beitrag nicht gezahlt ist. Der Versicherer kann nicht zurücktreten, wenn der Versicherungsnehmer nachweist, dass er die Nichtzahlung nicht zu vertreten hat.

**6.1.3** Zahlt der Versicherungsnehmer den einmaligen oder ersten Beitrag nicht rechtzeitig, sondern zu einem späteren Zeitpunkt, beginnt der Versicherungsschutz erst ab diesem Zeitpunkt. Für Versicherungsfälle, die in der Zwischenzeit eintreten, bleibt der Versicherer der versicherten Person nicht aber dem Versicherungsnehmer zur Leistung verpflichtet. In diesem Fall steht dem Versicherer ein Rückgriffsrecht gegen den Versicherungsnehmer zu.

Das gilt nicht, wenn der Versicherungsnehmer nachweist, dass er die Nichtzahlung nicht zu vertreten hat.

Für Versicherungsfälle, die bis zur Zahlung des Beitrages eintreten, ist der Versicherer dem Versicherungsnehmer gegenüber nur dann nicht zur Leistung verpflichtet, wenn er den Versicherungsnehmer durch gesonderte Mitteilung in Textform oder durch einen auffälligen Hinweis im Versicherungsschein auf diese Rechtsfolge der Nichtzahlung des Beitrages aufmerksam gemacht hat.

**6.2 Zahlung und Folgen verspäteter Zahlung/Folgebeitrag**

**6.2.1** Die Folgebeiträge sind, soweit nicht etwas anderes bestimmt ist, am Monatsersten des vereinbarten Beitragszeitraumes fällig.

Die Zahlung gilt als rechtzeitig, wenn sie zu dem im Versicherungsschein oder in der Beitragsrechnung angegebenen Zeitpunkt erfolgt.

**6.2.2** Wird ein Folgebeitrag nicht rechtzeitig gezahlt, gerät der Versicherungsnehmer ohne Mahnung in Verzug, es sei denn, dass er die verspätete Zahlung nicht zu vertreten hat.

Der Versicherer ist berechtigt, Ersatz des ihm durch den Verzug entstandenen Schadens zu verlangen.

Wird ein Folgebeitrag nicht rechtzeitig gezahlt, kann der Versicherer dem Versicherungsnehmer auf dessen Kosten in Textform eine Zahlungsfrist bestimmen, die mindestens zwei Wochen betragen muss. Die Bestimmung ist nur wirksam, wenn sie die rückständigen Beträge des Beitrages, Zinsen und Kosten im Einzelnen beziffert und die Rechtsfolgen angibt, die nach den Ziffern 6.2.3 und 6.2.4 mit dem Fristablauf verbunden sind.

**6.2.3** Ist der Versicherungsnehmer nach Ablauf dieser Zahlungsfrist noch mit der Zahlung in Verzug, ist der Versicherer ab diesem Zeitpunkt bis zur Zahlung der versicherten Person nicht aber dem Versicherungsnehmer zur Leistung verpflichtet. In diesem Fall steht dem Versicherer ein Rückgriffsrecht gegen den Versicherungsnehmer zu, wenn dieser mit der Zahlungsaufforderung nach Ziffer 6.2.2 Satz 3 und 4 darauf hingewiesen wurde.

**6.2.4** Ist der Versicherungsnehmer nach Ablauf dieser Zahlungsfrist noch mit der Zahlung in Verzug, kann der Versicherer den Vertrag ohne Einhaltung einer Frist kündigen, wenn er den Versicherungsnehmer mit der Zahlungsaufforderung nach Ziffer 6.2.2 Satz 3 und 4 darauf hingewiesen hat.

Hat der Versicherer gekündigt, und zahlt der Versicherungsnehmer danach innerhalb eines Monats den angemahnten Betrag, besteht der Vertrag fort. Für Versicherungsfälle, die zwischen dem Zugang der Kündigung und der Zahlung eingetreten sind, ist der Versicherer der versicherten Person nicht aber dem Versicherungsnehmer zur Leistung verpflichtet. In diesem Fall steht dem Versicherer ein Rückgriffsrecht gegen den Versicherungsnehmer zu.

**6.3 Rechtzeitigkeit der Zahlung bei Lastschriftermächtigung**

Ist die Einziehung des Beitrages von einem Konto vereinbart, gilt die Zahlung als rechtzeitig, wenn der Beitrag zum Fälligkeitstag eingezogen werden kann und der Versicherungsnehmer einer berechtigten Einziehung nicht widerspricht.

Konnte der fällige Beitrag ohne Verschulden des Versicherungsnehmers vom Versicherer nicht eingezogen werden, ist die Zahlung auch dann noch rechtzeitig, wenn sie unverzüglich nach einer in Textform abgegebenen Zahlungsaufforderung des Versicherers erfolgt.

Kann der fällige Beitrag nicht eingezogen werden, weil der Versicherungsnehmer die Einzugsermächtigung widerrufen hat, oder hat der Versicherungsnehmer aus anderen Gründen zu vertreten, dass der Beitrag nicht eingezogen werden kann, ist der Versicherer berechtigt, künftig Zahlung außerhalb des Lastschriftverfahrens zu verlangen. Der Versicherungsnehmer ist zur Übermittlung des Beitrages erst verpflichtet, wenn er vom Versicherer hierzu in Textform aufgefordert worden ist.

**6.4 Teilzahlung und Folgen bei verspäteter Zahlung**

Ist die Zahlung des Beitrages in Raten vereinbart, sind die noch ausstehenden Raten sofort fällig, wenn der Versicherungsnehmer mit der Zahlung einer Rate im Verzug ist.

## 7 Ergänzende Bestimmungen zur Beitragsberechnung

**7.1** Der Beitrag richtet sich, soweit nichts anderes vereinbart ist, nach der Anzahl der an der klinischen Prüfung teilnehmenden Probanden/Patienten (versicherte Personen).

Der in Rechnung gestellte Beitrag enthält die Versicherungsteuer, die der Versicherungsnehmer in der jeweils vom Gesetz bestimmten Höhe zu entrichten hat.

**7.2** Die Berechnung des Beitrages erfolgt für den vereinbarten Versicherungszeitraum als vorläufiger Beitrag und wird im Voraus erhoben.

Nach Abschluss der klinischen Prüfung wird eine endgültige Beitragsberechnung vorgenommen. Zu diesem Zweck hat der Versicherungsnehmer nach Aufforderung nachfolgende Angaben zu machen. Die Angaben sind innerhalb eines Monats nach Zugang der Aufforderung zu machen:

- tatsächliche Anzahl der in die klinische Prüfung einbezogenen Probanden/Patienten (versicherte Personen),
- das tatsächliche Beginn- und Endedatum der klinischen Prüfung.

**7.3** Soweit nichts anderes vereinbart ist, ist der Versicherer berechtigt, einen angemessenen Beitrag zu verlangen, wenn die klinische Prüfung nicht begonnen wurde.

## 8 Rechtsverhältnis Dritter

**8.1** Die Ausübung der Rechte aus dem Versicherungsvertrag steht dem Versicherungsnehmer zu. Den Anspruch auf die Versicherungsleistung kann auch die versicherte Person unmittelbar geltend machen.

**8.2** Alle für den Versicherungsnehmer bzw. die versicherte Person geltenden Vorschriften finden auf deren Rechtsnachfolger Anwendung.

**8.3** Die Versicherungsansprüche können vor ihrer endgültigen Feststellung ohne ausdrückliche Zustimmung des Versicherers weder übertragen noch verpfändet werden.

## 9 Sonstige Bestimmungen

### 9.1 Anzeigen und Willenserklärungen

**9.1.1** Alle für den Versicherer bestimmten Anzeigen und Erklärungen sollen an die Hauptverwaltung des Versicherers oder an die im Versicherungsschein oder in dessen Nachträgen als zuständig bezeichnete Geschäftsstelle gerichtet werden.

**9.1.2** Hat der Versicherungsnehmer eine Änderung seiner Anschrift dem Versicherer nicht mitgeteilt, genügt für eine Willenserklärung, die dem Versicherungsnehmer gegenüber abzugeben ist, die Absendung eines eingeschriebenen Briefes an die letzte dem Versicherer bekannte Anschrift. Die Erklärung gilt drei Tage nach der Absendung des Briefes als zugegangen. Dies gilt entsprechend für den Fall einer Namensänderung des Versicherungsnehmers.

**9.1.3** Hat der Versicherungsnehmer die Versicherung für seinen Gewerbebetrieb abgeschlossen, finden bei einer Verlegung der gewerblichen Niederlassung die Bestimmungen der Ziffer 9.1.2 entsprechende Anwendung.

### 9.2 Zuständiges Gericht

**9.2.1** Für Klagen aus dem Versicherungsvertrag gegen den Versicherer bestimmt sich die gerichtliche Zuständigkeit nach dem Sitz des Versicherers oder seiner für den Versicherungsvertrag zuständigen Niederlassung. Ist der Versicherungsnehmer eine natürliche Person, ist auch das Gericht örtlich zuständig, in dessen Bezirk der Versicherungsnehmer zur Zeit der Klageerhebung seinen Wohnsitz oder, in Ermangelung eines solchen, seinen gewöhnlichen Aufenthalt hat.

**9.2.2** Ist der Versicherungsnehmer eine natürliche Person, müssen Klagen aus dem Versicherungsvertrag gegen ihn bei dem Gericht erhoben werden, das für seinen Wohnsitz oder, in Ermangelung eines solchen, den Ort seines gewöhnlichen Aufenthalts zuständig ist. Ist der Versicherungsnehmer eine juristische Person, bestimmt sich das zuständige Gericht auch nach dem Sitz oder der Niederlassung des Versicherungsnehmers. Das Gleiche gilt, wenn der Versicherungsnehmer eine Offene Handelsgesellschaft, Kommanditgesellschaft, Gesellschaft bürgerlichen Rechts oder eine eingetragene Partnerschaftsgesellschaft ist.

**9.2.3** Sind der Wohnsitz oder der gewöhnliche Aufenthalt des Versicherungsnehmers im Zeitpunkt der Klageerhebung nicht bekannt, bestimmt sich die gerichtliche Zuständigkeit für Klagen aus dem Versicherungsvertrag gegen den Versicherungsnehmer nach dem Sitz des Versicherers oder seiner für den Versicherungsvertrag zuständigen Niederlassung.

### 9.3 Anzuwendendes Recht

Für diesen Vertrag gilt deutsches Recht.

### 9.4 Gesetzliche Verjährung

**9.4.1** Die Ansprüche aus dem Versicherungsvertrag verjähren in drei Jahren. Die Fristberechnung richtet sich nach den allgemeinen Vorschriften des Bürgerlichen Gesetzbuches.

**9.4.2** Ist ein Anspruch aus dem Versicherungsvertrag bei dem Versicherer angemeldet worden, ist die Verjährung von der Anmeldung bis zu dem Zeitpunkt gehemmt, zu dem die Entscheidung des Versicherers dem Anspruchsteller in Textform zugeht.