CLINICAL STUDY REPORT

Pilot study for a trial to evaluate high-dose chemotherapy and autologous stem cell transplant in primary CNS lymphoma patients > 65 years

Name of test drug:	Rituximab, methotrexate, cytarabine, thiotepa, busulfan
Indication studied:	Primary central nervous system lymphoma (PCNSL)
Protocol identification/Study number:	P001032
Drug development phase:	Pilot study
Study initiation date (first patient in):	04 Dec 2015
Date of early study termination	29 Mar 2017
Study completion date (last patient out):	28 Jan 2019
Principal or Coordinating investigator:	**Dr. med. Elisabeth Schorb** Medical Center - University of Freiburg Division of Hematology, Oncology and Stem-Cell Transplantation Hugstetter Str. 55, 79106 Freiburg, Germany
Sponsor:	Medical Center - University of Freiburg - represented by the Chief Medical Officer Hugstetter Str. 49, 79106 Freiburg, Germany *moved to* Breisacher Str. 153, 79110 Freiburg, Germany
Report ID:	MARiTA_CSR
Report version:	1.0
Report date:	30 March 2020
Number of pages:	57

Quality Assurance Statement:

This trial has been performed in compliance with Good Clinical Practice (GCP), including the archiving of essential documents.

1. APPROVAL

Sponsor Representative / Coordinating Investigator

01/04/2020 (Date) | Signature

Dr. med. Elisabeth Schorb
Coordinating Investigator
Medical Center - University of Freiburg

Division of Hematology, Oncology and Stem-Cell Transplantation

Hugstetter Str. 55, 79106 Freiburg

Statistician

06/04/2020 (Date) | Signature

Dr. Gabriele Ihorst

Clinical Trials Unit, Medical Center – University of Freiburg

Elsässer Str. 2, 79110 Freiburg, Germany

2. SYNOPSIS

Name of Sponsor: Medical Center – University of Freiburg	Individual Trial Table Referring to Part <<insert part #>> of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: Not applicable, as defined by active substances		
Name of Active Ingredient: rituximab, methotrexate, cytarabine, thiotepa, busulfan		

Title of Study: Pilot study for a trial to evaluate high-dose chemotherapy and autologous stem cell transplant in primary CNS lymphoma patients >65 years

Protocol no. P001032

EudraCT no. 2015-002305-11

Investigators: Coordinating Investigator was Dr. med. Elisabeth Schorb, Deputy Principal Coordinating Investigators were Prof. Dr. Gerald Illerhaus (Klinikum Stuttgart) and Prof. Dr. Jürgen Finke (Medical center – University of Freiburg, Freiburg).

Study centres:

A total of 2 centres participated in this study in Germany and both centres enrolled patients.

Publication (reference):

none

Study period (years):	Phase of development:
First patient in: 04 Dec 2015	Phase pilot study
Last patient out: 28. Jan 2019	

Objectives:

The principal objective of the study is to investigate feasibility, tolerability, and recruitment rate of selected newly-diagnosed or relapsed PCNSL patients >65 years (patients between 65 and 70 years only if not eligible for treatment within the MATRix/IELSG43 trial). The pilot trial is projected to demonstrate a first proof-of-concept under study conditions in order to generate data for a subsequently planned multicentre phase II study.

Methodology:

This pilot trial is an open-label, bicenter trial conducted in Germany.

Number of patients (planned and analysed):

Planned:	15
Screened:	17
Enrolled/Randomized/analysed:	14

Diagnosis and main criteria for inclusion:

Primary Central Nervous System Lymphoma

Main criteria for inclusion:

1. Immunocompetent patients with newly-diagnosed or relapsed primary central nervous system B-cell lymphoma
2. Age >65 years not eligible for treatment within the MATRix/IELSG43 Trial
3. Histologically or cytologically assessed diagnosis of B-cell lymphoma by local pathologist
4. Diagnostic sample obtained by stereotactic or surgical biopsy, CSF cytology examination or vitrectomy

Name of Sponsor: Medical Center – University of Freiburg	Individual Trial Table Referring to Part <<insert part #>> of the Dossier Volume: Page:	(For National Authority Use only)
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5. Disease exclusively located in the CNS
6. At least one measurable lesion
7. Cumulative Illness Rating Scale-Geriatric (CIRS-G) <6
8. ECOG-Performance Status ≤ 2
9. Written informed consent obtained according to international guidelines and local laws by patient or authorized legal representative in case patient is temporarily legally not competent due to his or her disease

Main criteria for exclusion:

1. Congenital or acquired immunodeficiency
2. Systemic lymphoma manifestation (outside the CNS)
3. Isolated ocular lymphoma without manifestation in the brain parenchyma or spinal cord
4. Previous or concurrent malignancies with the exception of surgically cured carcinoma in-situ of the cervix, carcinoma of the skin or other kinds of cancer without evidence of disease for at least 5 years
5. Previous systemic Non-Hodgkin lymphoma at any time
6. Inadequate bone marrow (platelet count decreased ≥CTC grade 1, anaemia ≥CTC grade 1, neutrophil count decreased ≥CTC grade 1), renal (creatinine clearance <60 ml/min), cardiac (ejection fraction decreased ≥CTC grade 2), or hepatic function (blood bilirubin increased ≥CTC grade 2, alanine aminotransferase increased ≥CTC grade 2, aspartate aminotransferase increased ≥CTC grade 2 or gamma-GT increased ≥CTC grade 2)
7. HBsAg, anti-HBc or HCV positivity
8. HIV infection, previous organ transplantation or other clinical evident form of immunodeficiency
9. Concurrent treatment with other experimental drugs or participation in a clinical trial within the last thirty days before the start of this study
10. Symptomatic coronary artery disease, cardiac arrhythmias uncontrolled with medication or myocardial infarction within the last 6 months (New York Heart Association Class III or IV heart disease)
11. Severe non-compensated pulmonary disease (IVC <55%, DLCO <40%)
12. Third space fluid accumulation >500 ml
13. Hypersensitivity to study treatment or any component of the formulation
14. Taking any medications likely to cause interactions with the study medication
15. Known or persistent abuse of medication, drugs or alcohol
16. Patient without legal capacity and who is unable to understand the nature, significance and consequences of the study and without designated legal representative
17. Persons who are in a relationship of dependency/employment to the sponsor and/ or investigator
18. Any familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule

Investigational Product, dose and mode of administration, batch number:

Proprietary name:	MabThera®
Name of substance:	**Rituximab**
Manufacturer:	Roche Registration Limited; 6 Falcon Way; Shire Park/Welwyn Garden City/AL7 1TW; United Kingdom
Approved indications:	- non-Hodgkin`s lymphoma
	- chronic lymphatic leukaemia
	- rheumatoid arthritis
	- granulomatosis with polyangiitis and microscopic polyangiitis

Name of Sponsor: Medical Center – University of Freiburg	Individual Trial Table Referring to Part <<insert part #>> of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: Not applicable, as defined by active substances		
Name of Active Ingredient: rituximab, methotrexate, cytarabine, thiotepa, busulfan		

Dosage form:	Concentrate for solution for infusion
Strength:	10 mg/mL (referred to concentrate)
Dose:	1500 mg/m^2 (total), for induction treatment
Batch No.:	not applicable
Proprietary name:	Methotrexat HC 1000 mg Lösung Medac
Name of substance:	**Methotrexate**
Manufacturer:	medac; Gesellschaft fuer klinische Spezialpraeparate mbH; Fehlandtstrasse 3; D-20354 Hamburg
Approved indications:	- head and neck carcinoma - non-Hodgkin lymphoma - osteosarcoma
Dosage form:	Concentrate for solution for infusion
Strength:	109.6 mg/mL Methotrexate disodium (= 100 mg/mL Methotrexate, referred to concentrate)
Dose:	7 g/m^2 (total), for induction treatment
Batch No.:	not applicable
Proprietary name:	ARA-cell® 4000 mg Infusionslösung
Name of substance:	**Cytarabine**
Manufacturer:	cell pharm GmbH; Theodor-Heuss-Str. 52; D-61118 Bad Vilbel
Approved indications:	- refractory non-Hodgkin lymphoma - refractory acute non-lymphocytic leukaemia - refractory acute lymphoblastic leukaemia - recurrence of acute leukaemia - leukemia with special risk: secondary leukemia after previous chemotherapy and/or radiotherapy - consolidation of remission of acute non-lymphocytic leukemia in patients under 60 years
Dosage form:	Solution for infusion
Strength:	50 mg/mL
Dose:	16 g/m^2 (total), for induction treatment
Batch No.:	not applicable
Proprietary name:	TEPADINA® 100 mg
Name of substance:	**Thiotepa**
Manufacturer:	ADIENNE S.r.l.; Via Broseta 64/B; 24128 Bergamo; Italy
Approved indications:	In combination with other chemotherapeutics - with or without whole-body irradiation for conditioning before allogenic

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Name of Finished Product: Not applicable, as defined by active substances		
Name of Active Ingredient: rituximab, methotrexate, cytarabine, thiotepa, busulfan		

	or autologous hematopoietic stem cell transplantation for treatment in hematological diseases - if high-dose chemotherapy with following hematopoietic stem cell transplantation is indicated for treatment of solid tumors in adults and children
Dosage form:	Powder for concentrate for solution for infusion
Strength:	10 mg/mL (refers to concentrate)
Dose:	10 mg/kg (total), for high-dose consolidation
Batch No.:	not applicable
Proprietary name:	Busilvex®
Name of substance:	**Busulfan**
Manufacturer:	Pierre Fabre Médicament 45, Place Abel; Gance, 92654 Boulogne Billancourt Cedex; France
Approved indications:	Busilvex followed by cyclophosphamide (BuCy2) is indicated as conditioning treatment prior to conventional hematopoietic progenitor cell transplantation (HPCT) in adult patients when the combination is considered the best available option; Busilvex followed by cyclophosphamide (BuCy4) or melphalan (BuMel) is indicated as conditioning treatment prior to conventional HPCT in paediatric patients.
Dosage form:	Concentrate for solution for infusion
Strength:	6 mg/ml (refers to concentrate)
Dose:	6.4 mg/kg (total)
Batch No.:	not applicable

Duration of Treatment:

10 weeks

Criteria for evaluation:

Primary:

The primary goal of the study is to evaluate feasibility of the study procedures. The primary endpoint will be feasibility. This endpoint was chosen to be able to investigate safety of this special therapy approach in this rare disease and to generate data for the planned subsequent phase II trial.

Secondary endpoints were the following:

- Annual recruitment
- CR will be determined on day 30 after HDT-ASCT
- PFS is defined as the time from start of treatment until PD or relapse or death from any cause
- OS is defined as time from start of treatment until death from any cause
- EORTC QLQ-C30 during therapy and 1 year after EOT

- (Serious) adverse events
- Toxicity parameters graded according to CTCAE 4.0
- MMSE, EORTC QLQ-BN20, Neuro-psychological assessment

Statistical methods:

Sample size calculation:

The primary focus lays emphasis on the feasibility of the study. Because feasibility and effect size were unknown a pilot study was performed. In the context of rare disease entity it was feasible to assess 15 patients in a pilot study. It was assumed that 15 patients can be screened in the two participating centres (Medical Center - University of Freiburg and Medical Center - Klinikum Stuttgart) within a time frame of about 24 month. The samples size planning for the pilot study was based on feasibility considerations. No further power calculation is indicated at this point of time. The pilot study was designed to collect data for the planned application for the subsequent multicentre trial. The selected number of participants is sufficient to subserve this goal.

Definition of populations included in the analyses:

All patients enrolled in the study, fulfilling the inclusion criteria and for whom treatment was started will be part of the analysis set, denoted as full analysis set (FAS). Patients with major violations of inclusion criteria or for whom study treatment was not started will be listed, giving reasons.

Safety analysis will be performed for all patients for whom the treatment was started.

SUMMARY - CONCLUSIONS:

EFFICACY RESULTS:

Primary endpoint:

The primary goal of the study was to evaluate feasibility of the study procedures. Patients' recruitment and study conduct were successfully completed and served as a basis for the subsequent phase II MARTA trial.

Secondary endpoints:

- Annual recruitment

Annual recruitment/registration represents approximately 7 patients per year

- CR on day 30 after HDT-ASCT

57.1% of patients in FAS population had a complete remission on day 30 after HDT-ASCT. In total 85.7% of patients had confirmed and unconfirmed complete remission on day 30 after HDT-ASCT

- PFS

At the end of the study 92.9% of patients were progression free.

- OS

OS was 100%, as no deaths occurred during the study.

- EORTC QLQ-C30 during therapy and 1 year after EOT

Global health status measured by EORTC QLQ-C30 showed tendency towards improvement after therapy.

- MMSE

Cognitive functions measured by MMSE improved over time in 8/10 available patients with paired values before and after therapy. In 2/10 available patients, cognitive functions remained stable on

a high level.

- EORTC QLQ-BN20

There were no relevant changes regarding quality of life measured by EORTC QLQ-BN20.

- Neuro-psychological assessment

Neurocognitive tests done immediately after treatment and at the end of the study showed improvement in most assessed cognitive functions over the time.

- (Serious) adverse events, toxicity parameters graded according to CTCAE 4.0

In 7 out of 15 patients at least one AE related to at least one IMP and being CTCAE grade ≥3 was reported. The most frequently reported diagnoses were infections and gastrointestinal disorders. No deaths, no other significant AEs, no SUSARs occurred during the study.

SAFETY RESULTS:

In 7 out of 15 patients at least one AE related to at least one IMP and being CTCAE grade ≥3 was reported. The most frequently reported diagnoses were infections and gastrointestinal disorders. The most frequently documented toxicities in the study were related to bone marrow suppression. No deaths, no other significant AEs, no SUSARs occurred during the study. The evaluation of toxicities and AEs related to IMP used did not show any new safety issues.

CONCLUSIONS:

The results of this pilot trial support feasibility and effectiveness of this age-adapted approach in selected elderly patients with newly-diagnosed PCNSL. This pilot study was conducted at two canters very experienced in the management of PCNSL. Therefore, these favorable results need to be confirmed in a multicenter setting. We are currently conducting a single-arm phase II study in Germany to investigate this age-adapted protocol (15 centers, 51 patients) (MARTA trial, DRKS00011932).

Date of the Report:

30 March 2020

3. TABLE OF CONTENTS

3.1. List of In-Text Tables

3.2. List of In-Text Figures

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
ALAT=ALT	Alanine Aminotransferase=GPT
AMG	German Drug Law (Arzneimittelgesetz)
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
Anti-HBc	Total hepatitis B core antibody
AraC	Cytarabine
ASAT=AST	Aspartate Aminotransferase=GOT
ASCT	Autologous Stem-Cell Transplantation
ATC	Anatomical Therapeutic Chemical
BBB	Brain Blood Barrier
BCNU	Carmustine
BM	Bone Marrow
B-NHL	B-cell non-Hodgkin lymphoma
CA	Competent Authority
CIOMS Form I	Suspect Adverse Reaction Form
CIRS-G	Cumulative Rating Illness Scale-Geriatric
CM	Concomitant Medication
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete Remissions
CRA	Clinical Research Associate (Monitor)
CRF	Case Report Form
CRR	Complete Remission Rate
CRu	CR unconfirmed
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTU	Clinical Trials Unit (Zentrum Klinische Studien (former name: Studienzentrum) Universitätskliniken Freiburg)
d	day
DAMAST	Data Management System
DLBCL	Diffuse Large B-Cell Lymphoma
DMM	Data Management Manual
DNA	Deoxyribonucleic acid (= molecule that encodes the genetic instructions)
DSUR	Development Safety Update Report
ECOG	Eastern Cooperative Oncology Group (Performance Status)
EORTC QLQ-BN20	EORTC Quality of Life Questionnaire Brain Cancer Module - BN20
EORTC QLQ-C30	EORTC Quality of Life Questionnaire C30
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of study treatment
ESAR	Expected Serious Adverse Reaction
FAS	Full Analysis Set
FDG-PET	Fluorodeoxyglucose-Positron Emission Tomography
FFS	Failure-free survival
FPFV	First Patient First Visit
FU	Follow up
Gamma-GT	Gamma-Glutamyl Transferase
GCP-V	German Decree of 09-Aug-2004 on the Use of Good Clinical Practices
GFR	Glomerular filtration rate
GP	General Practitioner

Hb	Hemoglobin
HBsAG	Hepatitis-B-Virus s-Antigen
HCV	Hepatitis-C-Virus
HD	High Dose
HD(C)T	High Dose (Chemo)therapy
HIV	Human Immunodeficiency Virus
HPCT	Hematopoietic progenitor cell transplantation
HR	Hazard Ratio
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH-GCP	ICH Topic E6: Guideline for Good Clinical Practice (GCP)
IEC	Independent Ethics Committee
IELSG	International Extranodal Lymphoma Study Group
IMP	Investigational Medicinal Product/Study medication
IPCG	International Primary CNS Lymphoma Study Group
IPD	Important Protocol Deviation
ISF	Investigator Site file
ITT	Intention-To-Treat
i.v.	intravenous(ly)
IVC	Inspiratory Vital Capacity
LDH	Lactate dehydrogenase
LKP	Leiterin der klinischen Prüfung (Principal Coordinating Investigator, according to German Drug Law, § 4 and § 40 AMG)
LPLV	Last Patient Last Visit
MATRix	Methotrexate – AraC – Thiotepa - Rituximab
MDRD	Modification of Diet in Renal Disease
MedDRA	Medicinal Dictionary for Regulatory Activities
MMSE	Mini-Mental Status Examination
MPD	Minor Protocol Deviation
MRI	Magnetic Resonance Imaging
mRNA	Messenger RNS
MTX	Methotrexate
NCR	Non-Carbon-Required (Paper)
NCT	National Clinical Trial
NHL	Non-Hodgkin's lymphomas
NN	*Nomen nominandum* = to be named
ORR	Odds Ratio
OS	Overall Survival
PB	Peripheral blood
PCNSL	Primary CNS Lymphoma
PD	Progressive Disease
PFS	Progression-free survival
PHI	Protected Health Information
PI	Principal Investigator
PJP	Pneumocystis (carinii) Jiroveci Pneumonia
PML	progressive multifocal leukoencephalopathy
PP	Per-Protocol
PR	Partial Remission
PT	Preferred Term, MedDRA
QoL	Quality of Life
R	Rituximab
RA	Response Assessment
RNA	Ribonucleic acid
RPE	Retinal Pigment Epithelium
RSI	Reference Safety Information
RT	Radiotherapy

SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SAS	Statistical Analysis System
SD	Stable Disease
SDV	Source Data Verification
SmPC	Summary of Product Characteristics (Fachinformation)
SOC	System Organ Class, MedDRA
SOP	Standard Operating Procedure
SOS	Sinusoidal Obstruction Syndrome
SUSAR	Suspected Unexpected Serious Adverse Reaction
UAR	Unexpected Adverse Reaction
ULN	Upper Limit of Normal
VEF	Ventricular Ejection Fraction
WBC	White Blood Count
WBRT	Whole Brain Radiotherapy
WHO	World Health Organization
ZNS NHL	Non Hodgkin Central nervous system Lymphoma

5. ETHICS

5.1. Ethical Conduct of the Trial

The investigator was responsible for ensuring that the study was performed in accordance with the ethical principles of the Declaration of Helsinki as well as with national law and guidelines for the clinical testing of drugs.

5.2. Patient Information and Consent

Before enrolment in the clinical trial, the patient was informed that participation in the clinical trial is voluntary and that he/she may withdraw from the clinical trial at any time without having to give reasons and without penalty or loss of benefits to which the patient is otherwise entitled.

The treating physician provided the patient with information about the treatment methods to be compared and the possible risks involved. At the same time, the nature, significance, implications, expected benefits and potential risks of the clinical trial and alternative treatments were explained to the patient. During the informed consent discussion, the patient was also informed about the insurance cover that exists and the insured's obligations. The patient was given ample time and opportunity to obtain answers to any open questions. All questions relating to the clinical trial should be answered to the satisfaction of the patient and/or his/her legal representative. In addition, the patient was given a patient information sheet which contains all the important information in writing.

The patient's written consent must be obtained before any trial-specific tests/treatments. For this purpose, the written consent form was personally dated and signed by the trial patient and the investigator conducting the informed consent discussion.

By signing the consent form, the patient agrees to voluntarily participate in the clinical trial and declares his/her intention to comply with the requirements of the clinical trial and the investigator's instructions during the clinical trial. By signing the form, the patient also declares that he/she agrees to the recording of personal data, particularly medical data, for the trial, to their storage and codified (“pseudonymized”) transmission to the sponsor, to the ethics committee or the competent authority, and further agrees that authorized representatives of the sponsor, the Medical Center – University of Freiburg, who are bound to confidentiality, and national or foreign competent authorities may inspect his/her personal data, particularly medical data, which are held by the investigator.

After having signed the informed consent, the patient was given one copy of the signed and dated written consent form and any other written information to be provided to the patients.

In case of substantial amendments, the patient must be informed with an appropriate revised patient information/consent form. Changed trial procedures can only be carried out if they have been approved by the competent authority and the leading ethics committee, and if the patient has been appropriately informed and has given his/her written consent.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The study was supervised by the Coordinating Investigator (Leiter der klinischen Prüfung [LKP] in accordance with German Drug Law).

Table 1 Study administrative structure

Responsibility	**Institution**
Sponsor	Medical Center - University of Freiburg, represented by the Chief Medical Officer Hugstetter Str. 49, 79106 Freiburg, Germany *moved to* Breisacher Str. 153, 79110 Freiburg, Germany
Coordinating Investigator "Leiter der klinischen Prüfung /LKP" (in accordance with German Drug Law)	**Dr. med. Elisabeth Schorb** Medical Center - University of Freiburg Division of Hematology, Oncology, and Stem-Cell Transplantation Hugstetter Str. 55, 79106 Freiburg, Germany
Clinical study management, monitoring (site Freiburg) , ethics committee and authority application and correspondence, treatment randomisation, data management, pharmacovigilance and management of Trial Master File	Medical Center - University of Freiburg Clinical Trials Unit (Zentrum Klinische Studien) Elsässer Str. 2, 79110 Freiburg, Germany
Monitoring (site Stuttgart)	Medical Center - University of Freiburg Division of Hematology, Oncology, and Stem-Cell Transplantation Hugstetter Str. 55, 79106 Freiburg, Germany
Statistical planning and analysis	Medical Center - University of Freiburg Clinical Trials Unit (Zentrum Klinische Studien) Elsässer Str. 2, 79110 Freiburg, Germany
The study was financed by	Seeding grant "Programm Klinische Studien" of the Faculty of Medicine, University Medical Center Freiburg (Baden-Württemberg)

7. INTRODUCTION

7.1. Scientific background

Primary central nervous system lymphoma (PCNSL) is an aggressive Non-Hodgkin Lymphoma (NHL) mostly of B-cell origin, which exclusively invades the central nervous system compartment. It accounts for 3% to 4% of all primary brain tumours and 4% to 6% of extra-nodal lymphomas (Panageas et al., 2005). The incidence of PCNSL in immunocompetent patients has been steadily increasing over the last 30 years (Olson et al., 2002; Makino et al., 2006). High-dose methotrexate (HD-MTX) in combination with HD-cytarabine (HD-AraC) is the backbone of current treatment (Ferreri et al., 2009). A recent randomized controlled trial investigated the role of whole brain radiotherapy (WBRT) as consolidation therapy compared to no consolidation therapy, suggesting that WBRT does not prolong survival but enhances disease control (Thiel et al., 2010). However, despite treatment improvement, the prognosis of PCNSL patients is still poor compared to systemic Non-Hodgkin Lymphoma (Carrabba et al., 2010).

Patients older than 60 years account for more than 50% of all PCNSL cases. Although elderly patients are able to tolerate aggressive systemic chemotherapy, they have an inferior prognosis compared to younger patients and are more seriously affected by iatrogenic toxicity, especially neurotoxicity following WBRT (Abrey et al., 2000); therefore they represent a unique treatment subgroup (Sierra del Rio et al., 2009; Jahnke et al., 2005). An US registry study of 579 elderly patients diagnosed with PCNSL in the 1990s revealed that the median survival was only 7 months and WBRT alone was the most common treatment modality (46%) (Panageas et al., 2007).

High-dose chemotherapy with carmustine (BCNU) and thiotepa as well as with busulfan and thiotepa followed by autologous stem cell transplantation (HDT-ASCT) has been shown to be feasible and highly effective in newly-diagnosed eligible patients but also in the salvage situation (Illerhaus et al., 2006; Illerhaus et al., 2008; Kasenda et al., 2012; Soussain et al., 2012; Schorb et al., 2013). Usually, this intensive treatment approach is only offered to patients younger than 65-70 years of age. However, age alone may not be the only criterion to select patients for this effective treatment approach and probably many elderly patients are undertreated just because of advanced age.

The Cumulative Illness Rating Scale-Geriatric (CIRS-G) (Extermann et al., 1998) and the ECOG performance status are established tools to aid in defining patients who are probably fit enough to tolerate intensified treatment regimen. So far, HDT-ASCT has yet not been prospectively investigated in elderly PCNSL patients.

In the herein proposed pilot study we want to investigate feasibility, safety, and outcome of HDT-ASCT in elderly PCNSL patients (>65 years).

For further details please refer to the clinical trial protocol (CTP).

7.2. Trial purpose and rationale

The age group >60 years comprises >50% of the PCNSL patients and age >60 years at diagnosis is an important independent risk factor (Abrey et al., 2000). However, the optimal therapeutic approach for elderly patients with PCNSL still remains to be defined. Unfortunately, elderly PCNSL patients often fail to receive optimal care due to the lack of treatment standards.

In this subgroup of patients whole-brain radiotherapy (WBRT) with methotrexate-based chemotherapy causes high-rates of leukoencephalopathy with dementia, ataxia, gait disturbances, and incontinence, all significantly decreasing quality of life (Filley et al., 2001; Gavrilovic et al., 2006). During the last years, progress has been made in prolonging survival, reducing toxicity and improving quality of life for this challenging subgroup of patients. But in contrast to the younger patients we are still facing a palliative treatment approach. Thus there is an urgent medical need especially for the subgroup of physically fit patients with good ECOG Performance Status and low Cumulative Illness Rating Scale. If we could show feasibility of the high-dose treatment approach in this subgroup of patients, this would immediately impact on clinical practice since this curative treatment regimen would be the first option of treating elderly PCNSL patients with a curative treatment approach.

Usually, the curative HDT-ASCT approach is only offered to patients younger than 65 (or 70 in case of a good performance status) years of age. However, age alone may not be the only criterion to select patients for this effective treatment approach.

In many German centres, HDT-ASCT is considered standard for treating younger patients with PCNSL. There seems to be a subgroup of PCNSL patients >65 years who tolerated HDT-ASCT very well with limited toxicities (data not published). Taking into account the development of high-dose concepts in younger patients and the results of the (R-)MCP data, the next step should be to investigate the impact of a curative HDT-ASCT approach in fit patients >65 years. Thus, the rationale of this trial is to determine feasibility, recruitment rate, safety and outcome of HDT-ASCT in this special subgroup of elderly patients.

In the present study, we plan to investigate feasibility, recruitment rate, safety and outcome of HDT-ASCT in elderly PCNSL patients (>65 years, Cumulative Illness Rating Scale-Geriatric (CIRS-G) <6, ECOG-Performance Status ≤2). This pilot study should also serve for informing the planning of a multicentre phase II trial for this particular elderly patients group.

After successful recruitment of the PRIMAIN trial there is no active clinical trial for elderly PCNSL patients in Germany at the moment. Personal communication with our cooperating centres clearly shows the great need of initiating a trial for this special subgroup of PCNSL patients.

The individual patient might not only benefit from the trial by prolonged survival but also by reduced neurotoxicity and higher quality of life.

8. STUDY OBJECTIVES

The principal objective of the study was to investigate feasibility, tolerability, and recruitment rate of selected newly-diagnosed or relapsed PCNSL patients >65 years (patients between 65 and 70 years only if not eligible for treatment within the MATRix/IELSG43 trial). The pilot trial was projected to demonstrate a first proof-of-concept under study conditions in order to generate data for a subsequently planned multicentre phase II study.

9. INVESTIGATIONAL PLAN

9.1. Overall Study Design and Plan – Description

This is a bicenter, open-label, non-randomized, single-arm pilot study.

For further details see Appendix 16.1.1 CTP section 2.

9.2. Selection of Study Population

9.2.1. Inclusion Criteria

For inclusion into the trial, patients must fulfil all of the following criteria:

1. Immunocompetent patients with newly-diagnosed or relapsed primary central nervous system B-cell lymphoma
2. Age >65 years not eligible for treatment within the MATRix/IELSG43 Trial
3. Histologically or cytologically assessed diagnosis of B-cell lymphoma by local pathologist
4. Diagnostic sample obtained by stereotactic or surgical biopsy, CSF cytology examination or vitrectomy
5. Disease exclusively located in the CNS
6. At least one measurable lesion
7. Cumulative Illness Rating Scale-Geriatric (CIRS-G) <6
8. ECOG-Performance Status ≤ 2
9. Written informed consent obtained according to international guidelines and local laws by patient or authorized legal representative in case patient is temporarily legally not competent due to his or her disease

9.2.2. Exclusion Criteria

Patients were not eligible for this study if they fulfil one or more of the following exclusion criteria:

1. Congenital or acquired immunodeficiency
2. Systemic lymphoma manifestation (outside the CNS)
3. Isolated ocular lymphoma without manifestation in the brain parenchyma or spinal cord
4. Previous or concurrent malignancies with the exception of surgically cured carcinoma in-situ of the cervix, carcinoma of the skin or other kinds of cancer without evidence of disease for at least 5 years
5. Previous systemic Non-Hodgkin lymphoma at any time
6. Inadequate bone marrow (platelet count decreased ≥CTC grade 1, anaemia ≥CTC grade 1, neutrophil count decreased ≥CTC grade 1), renal (creatinine clearance <60 ml/min), cardiac (ejection fraction decreased ≥CTC grade 2), or hepatic function (blood bilirubin increased ≥CTC grade 2, alanine aminotransferase increased ≥CTC grade 2, aspartate aminotransferase increased ≥CTC grade 2 or gamma-GT increased ≥CTC grade 2)
7. HBsAg, anti-HBc or HCV positivity
8. HIV infection, previous organ transplantation or other clinical evident form of immunodeficiency
9. Concurrent treatment with other experimental drugs or participation in a clinical trial within the last thirty days before the start of this study

10. Symptomatic coronary artery disease, cardiac arrhythmias uncontrolled with medication or myocardial infarction within the last 6 months (New York Heart Association Class III or IV heart disease)
11. Severe non-compensated pulmonary disease (IVC <55%, DLCO <40%)
12. Third space fluid accumulation >500 ml
13. Hypersensitivity to study treatment or any component of the formulation
14. Taking any medications likely to cause interactions with the study medication
15. Known or persistent abuse of medication, drugs or alcohol
16. Patient without legal capacity and who is unable to understand the nature, significance and consequences of the study and without designated legal representative
17. Persons who are in a relationship of dependency/employment to the sponsor and/ or investigator
18. Any familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule

9.2.3. Removal of Patients from Therapy or Assessment

9.2.3.1. Withdrawal of patients

The patient was free to withdraw from the study for any reason and at any time without giving reason for doing so and without penalty or prejudice.

In the case of withdrawal, patients were encouraged to explain why she or he has withdrawn consent but must not to be compelled to do so.

The date of withdrawal and reasons surrounding the exit at the moment of withdrawal were documented on the CRF. All documentation concerning the patient must be as complete as possible.

For further details please refer to CTP section 9.3.1.

9.2.3.2. Early Termination of the Clinical Study

The clinical trial must be terminated prematurely if:

- the benefit-to-risk ratio for the patient changes markedly,
- the sponsor/principal coordinating investigator (German LKP) considers that the termination of the trial is necessary,
- indications arise that the trial patients' safety is no longer guaranteed,
- questions addressed in the trial can be clearly answered on the basis of results from another trial on the same subjects.

For further details on premature termination of the clinical trial please refer to Appendix 16.1.1 CTP section 9.1.

9.3. Treatments

9.3.1.1. Treatments Administered

All patients receive induction and consolidation treatment as described below.

9.3.1.2. Induction treatment

2 cycles (every 3 weeks), stem-cell harvest after first cycle:

- Rituximab 375 mg/m²/d i.v. (d 0,4)
- MTX 3.5 g/m² i.v. (d1)
- AraC 2 x 2 g/m²/d i.v. (d2-3)

9.3.1.3. Consolidation treatment

High-dose chemotherapy (HDT-ASCT):

- Busulfan 3.2 mg/kg/d i.v. (d-7and d-6)
- Thiotepa 5 mg/kg/d i.v. (d-5 and d-4)
- ASCT (d0)

9.3.1.4. Identity of Investigational Medicinal Products

In this study, the IMPs were characterized as follows:

Proprietary name:	MabThera®
Name of substance:	**Rituximab**
Manufacturer:	Roche Registration Limited 6 Falcon Way; Shire Park/Welwyn Garden City/AL7 1TW United Kingdom
Approved indications:	- Non-Hodgkin`s lymphoma - chronic lymphatic leukaemia - rheumatoid arthritis - granulomatosis with polyangiitis and microscopic polyangiitis
Dosage form:	Concentrate for solution for infusion
Strength:	10 mg/mL (referred to concentrate)
Dose:	1500 mg/m^2 (total), for induction treatment

Proprietary name:	Methotrexat HC 1000 mg Lösung Medac
Name of substance:	**Methotrexate**
Manufacturer:	medac Gesellschaft fuer klinische Spezialpraparate mbH Fehlandtstrasse 3; D-20354 Hamburg
Approved indications:	- head and neck carcinoma - non-Hodgkin lymphoma

- osteosarcoma

Dosage form:	Concentrate for solution for infusion
Strength:	109.6 mg/mL Methotrexate disodium (= 100 mg/mL Methotrexate, referred to concentrate)
Dose:	7 g/m^2 (total), for induction treatment

Proprietary name:	ARA-cell® 4000 mg Infusionslösung
Name of substance:	**Cytarabine**
Manufacturer:	cell pharm GmbH Theodor-Heuss-Str. 52; D-61118 Bad Vilbel
Approved indications:	- refractory non-Hodgkin lymphoma - refractory acute non-lymphocytic leukaemia - refractory acute lymphoblastic leukaemia - recurrence of acute leukaemia - leukemia with special risk: secondary leukemia after previous chemotherapy and/or radiotherapy - consolidation of remission of acute non-lymphocytic leukemia in patients under 60 years
Dosage form:	Solution for infusion
Strength:	50 mg/mL
Dose:	16 g/m^2 (total), for induction treatment

Proprietary name:	TEPADINA® 100 mg
Name of substance:	**Thiotepa**
Manufacturer:	ADIENNE S.r.l. Via Broseta 64/B; 24128 Bergamo; Italy
Approved indications:	In combination with other chemotherapeutics - with or without whole-body irradiation for conditioning before allogenic or autologous hematopoietic stem cell transplantation for treatment in hematological diseases - if high-dose chemotherapy with following hematopoietic stem cell transplantation is indicated for treatment of solid tumors in adults and children
Dosage form:	Powder for concentrate for solution for infusion
Strength:	10 mg/mL (refers to concentrate)
Dose:	10 mg/kg (total), for high-dose consolidation

Proprietary name:	Busilvex®
Name of substance:	**Busulfan**
Manufacturer:	Pierre Fabre Médicament 45, Place Abel Gance, 92654 Boulogne Billancourt Cedex, France
Approved indications:	Busilvex followed by cyclophosphamide (BuCy2) is indicated as conditioning treatment prior to conventional hematopoietic progenitor cell transplantation (HPCT) in adult patients when the combination is considered the best available option; Busilvex followed by cyclophosphamide (BuCy4) or melphalan (BuMel) is indicated as conditioning treatment prior to conventional HPCT in paediatric patients.
Dosage form:	Concentrate for solution for infusion
Strength:	6 mg/ml (refers to concentrate)
Dose:	6.4 mg/kg (total)

For further characteristics, see current version of the corresponding RSIs.

9.3.2. Method of Assigning Patients to Treatment Groups

Not applicable, all patients received the same treatment.

9.3.3. Selection of Doses in the Study

Study medication was administered by the investigator according to the CTP.

9.3.4. Selection and Timing of Dose for each Patient

Study medication was administered by the investigator according to the CTP.

9.3.5. Blinding

This was an unblinded trial.

9.3.6. Prior and Concomitant Therapy

For details on permitted and prohibited prior and concomitant therapy please refer to CTP section 7.

9.3.7. Treatment Compliance

IMPs had to be administrated according to the CTP. The investigator kept accurate records on the shipment and dispensing of the medication, specifying the date and amount dispensed to each patient. For further details see Appendix 16.1.1 CTP section 10.4.

9.4. Study procedures

The study procedures were to be performed according to the schedules defined in the CTP (see Appendix 16.1.1) and the schedule of events (see Table 2).

Table 2 Study Procedures

Visit schedule and assessments[1]	**Screening** **day -14 to day 0**	**Regis-tration**[2] **d 0**	**Induction treatment: Two 3-week treatment cycles**[1]		**RA I**	**Consolidation treatment**[1] **HDT-ASCT**	**RA II**	**Follow up**
			Visit 1	**Visit 2**		**Visit 3**	**EOT**	**year 1 after EOT**
			day 0 to day 4 of cycle 1**	**day 0 to day 4 of cycle 2****		**Start of HDT**	**day+30 after EOT/ASCT**	**every 3 mo**
Informed consent/ Demographic data	X							
Inclusion/exclusion criteria	X							
Registration		X						
Medical history, height	X							
Treatment administration			X	X		X		
ECOG Performance Status	X		X	X		X	X	X
MMSE, QoL (EORTC QLQ-C30, -BN20)[3]	X				X		X	X[3]
Neuropsychological battery[4]	X						X	X[3]
Weight	X		X	X		X		
Vital signs, physical + neurological examination	X*		X*	X*		X*	X*	X*
Hematology[5] / clinical chemistry[6]	X*		X*	X*		X*	X*	X*
Creatinine, estimated GFR (MDRD)			X	X		X		
LDH	X							
Hepatitis B/C serology, HIV-Test	X*							
Whole body plethysmography	X*					X*	X*	
Electrocardiography	X*					X*	X*	
Echocardiography	X*							
Testicular ultrasound	X*							
Abdominal ultrasound	X*		X*	X*				
Whole body CT scan[8]	X*							
Whole brain MRI	X				X		X	X
BM examination	X*							
Slit lamp examination	X				X[10]		X[10]	
CSF examination[9]	X				X[10]		X[10]	
Translational program	X[11]						X[12]	
Concomitant medication		X (see CTP section **Fehler! Verweisquelle konnte nicht gefunden werden.**)						

Visit schedule and assessments[1]	**Screening** **day -14 to day 0**	**Regis-tration[2]** **d 0**	**Induction treatment: Two 3-week treatment cycles[1]**		**RA I**	**Consolidation treatment[1]** **HDT-ASCT**	**RA II**	**Follow up**
			Visit 1	**Visit 2**		**Visit 3**	**EOT**	**year 1 after EOT**
			day 0 to day 4 of cycle 1**	**day 0 to day 4 of cycle 2****		**Start of HDT**	**day+30 after EOT/ASCT**	**every 3 mo**
Adverse events (CTCAE)		X (see section **Fehler! Verweisquelle konnte nicht gefunden werden.** and **Fehler! Verweisquelle konnte nicht gefunden werden.**)						

RA= response assessment; d= day; mo= months; yr= year; EOT= End of study treatment; LDH= lactate dehydrogenase; BM= bone marrow; for additional details see corresponding numbering;

* Not to be documented in the CRF

** Interval of treatment administration

1. Examinations and sample collection must be performed before treatment administration; delay up to five days. Interval between treatment cycles should be constant;
2. Informed consent must be obtained prior to any study specific (screening) examination;
3. MMSE, QoL (EORTC QLQ-C30, -BN20), neuropsychological battery only once 1 year after EOT
4. Neuropsychological battery if available at the investigation site;
5. Hematology: white blood count (WBC), neutrophils, hemoglobin, and platelets;
6. Blood chemistry: creatinine, total bilirubin, ALT, AST, LDH, and gamma-GT (only at screening);
7. Only for patients having received HDT-ASCT
8. If CT is suspicious at diagnosis: FDG-PET;
9. Only performed after excluding increased intracranial pressure by brain MRI; cytology and protein examination;
10. Only performed if positive at diagnosis, examination until results are negative;
11. Additional BM aspirate sample, CSF sample and blood sample must be taken from patients participating in the Translational Research Program before treatment administration;
12. Additional blood sample from patients participating in the translational research program at Response Assessment II or after study discontinuation.

9.5. Efficacy and Safety Variables

The endpoints described and defined in the CTP section 3 (see Appendix 16.1.1) were as described in this section.

9.5.1. Primary Efficacy Endpoint

The primary goal of the study is to evaluate feasibility of the study procedures. The primary endpoint is feasibility. This endpoint was chosen to be able to investigate safety of this special therapy approach in this rare disease and to generate data for the planned subsequent phase II trial.

9.5.2. Secondary Efficacy Endpoints

Secondary endpoints were the following:

- Annual recruitment
- CR was determined on day 30 after HDT-ASCT
- PFS is defined as the time from start of treatment until PD or relapse or death from any cause
- OS is defined as time from start of treatment until death from any cause
- EORTC QLQ-C30 during therapy and 1 year after EOT
- MMSE
- EORTC QLQ-BN20
- Neuro-psychological assessment

9.5.3. Safety Endpoints

- (Serious) adverse events
- Toxicity parameters graded according to CTCAE 4.0

9.5.4. Appropriateness of Measurements

All efficacy and safety assessments were based on accepted standard measurements.

9.5.5. Drug Concentration Measurements

Not applicable.

9.6. Data Quality Assurance

During the clinical trial, quality control and quality assurance was ensured through monitoring, auditing and supervision by the authorities.

9.6.1. Site selection and monitoring

All sites were contacted and asked for participation in this study. Before study start the investigator was informed about the investigational plan. Two sites in Germany participated in this study (both sites recruited patients) and were monitored.

Every site received a complete set of study documentation including patient information and consent forms (see Appendix 16.1.3.2), CTP (see Appendix 16.1.1), and SAE reporting

forms (see Appendix 16.1.2.□) prior to initiation. The designated CTU Clinical Research Associates (CRA) and coordinating investigator initiated the sites before enrolment of the first patient. During the study, the CRA was in regular contact with the sites and visited sites in time lags depending on site recruitment rate to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the CTP and to Good Clinical Practice/national regulatory requirement. Extent of source data verification was specified in monitoring manual.

9.6.2. Data management procedures

The study data were managed using the DAMAST Version 9.2, a proprietary data management system based on the software package SAS®, which has been developed, validated and is maintained by the Clinical Trials Unit (CTU). Details on data management (procedures, responsibilities, data corrections, for which data management staff of the CTU is responsible) were described in a data management manual (DMM) prior to the trial. The data management manual is a working document and also contains a record of all data management processes carried out during the clinical trial. Before any data is entered, the trial database was validated and specifications of the database were documented in a variables handling plan. Double data entry was performed by two different persons (with the exception of free text). The comparison of both entries and resolution of discrepancies may only be done by trained staff. An audit trail was created to provide an electronic record of which data were entered or subsequently changed by whom and when.

SAS® software was used to review the data for completeness, consistency and plausibility. The checks to be programmed were specified beforehand in a data validation plan. After running the check programs, the resulting queries were sent to the investigator for review of his/her data. Answered queries were also entered twice, verified and the updated data were then transferred to the database. All programs which can be used to influence the data or the data quality were validated (e.g. check programs, programs used for the input of external data, etc.).

Data coding

Concomitant treatments or procedures entered into the database were coded using the WHO Drug Reference List, or the Anatomical Therapeutic Chemical classification system provided by the WHO.

All AEs or SAEs were coded with MedDRA in its latest version.

9.6.3. Audits

No audits were performed in this study.

9.7. Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1. Statistical and Analytical Plans

9.7.1.1. Definition of analysis sets

All patients enrolled in the study, fulfilling the inclusion criteria and for whom treatment was started are part of the analysis set, denoted as full analysis set (FAS). Patients with major

violations of inclusion criteria or for whom study treatment was not started are listed, giving reasons.

Safety analysis is performed for all patients for whom the treatment was started.

9.7.1.2. Primary endpoint analysis

Due to the limited sample size of the pilot study since PCNSL is a rare disease, the analyses of the primary endpoint is subject to exploratory descriptive analyses with focus on 95% confidence interval estimation.

9.7.1.3. Secondary endpoint analysis

PFS is estimated by the Kaplan-Meier method.

The endpoint OS is analysed in the same way as described for PFS. Descriptive analysis of secondary endpoints is performed with two-sided 95% confidence intervals.

CR rate on day 30 after HD-ASCT is calculated based on all patients included in the FAS. Patients with missing response assessment due to death or premature study termination are evaluated as non-responders.

Quality of life (QoL) of patients is evaluated using the EORTC QLQ-C30 and EORTC QLQ-BN20 Quality of Life questionnaire. The questionnaire is answered by the patients at screening, the EOT visit and one year after EOT. For evaluating QoL, scores are calculated according to the EORTC manual (Fayers, 2001). The scores at screening are summarized and for different time points during follow-up, differences of the scores to the screening scores are calculated.

9.7.1.4. Safety analysis

Safety analysis is performed on the safety analysis set and consists of summaries of AEs and SAEs and toxicity data collected in the toxicity tables according to the CTP (see Appendix 16.1.1 CTP section 11.1.2). For further details on adverse events see CTP section 14.5.5.1.

Laboratory data documented as toxicity parameters are described by giving frequencies according to CTCAE grading. The number of patients with at least one severe toxicity (grade ≥ 3) is calculated.

Creatinine was used to calculate the GFR applying the MRDR formula and was analysed in summary tables. For lactate hydrogenase, frequencies increased/not increased are presented.

Summary tables for vital signs were produced by visit.

9.7.2. Determination of Sample Size

The primary focus lays emphasis on the feasibility of the study. Because of feasibility and effect size are unknown a pilot study was performed. In the context of rare disease entity it is feasible to assess 15 patients in a pilot study. It is assumed that 15 patients can be screened in the two participating centres (Medical Center - University of Freiburg and Medical Center - Klinikum Stuttgart) within a time frame of about 24 month. The samples size planning for the pilot study was based on feasibility considerations. No further power calculation is indicated at this point of time. The pilot study is designed to collect data for the planned application for

the subsequent multicentre trial. The selected number of participants was sufficient to subserve this goal.

9.8. Changes in the Conduct of the Study of planned Analyses

9.8.1. Changes in the Conduct of the Study

Not applicable, as the CTP was not amended during the trial.

9.8.2. Changes in the planned Analyses

Not applicable.

10. STUDY PATIENTS

10.1. Disposition of Patients

This analysis is based on the data of 17 screened* patients and includes the follow-up data up to 12 months after end of treatment. The data-cut-off date is the 29 Jan 2019. Figure 1 shows the patient recruitment of 17 patients screened* in the study from study start at 04 Dec 2015 (registration of the first patient) up to 07 Sep 2017 (registration of the last patient).

*According to the CTP screened patients had to be registered centrally.

10.2. Protocol Deviations

Six from 17 screened patients had the following protocol violations:

01/001: inclusion criterion 7 (cumulative Illness Rating Scale-Geriatric (CIRS-G) <6) (FAS/SAF, see section 10.4), study treatment administered

01/003: inclusion criterion 7 (cumulative Illness Rating Scale-Geriatric (CIRS-G) <6) (FAS/SAF, see section 10.4), study treatment administered

02/005: screening failure, inclusion criterion 7 (cumulative Illness Rating Scale-Geriatric (CIRS-G) <6) and exclusion criterion 7 (HBsAg, anti-HBc or HCV positivity); no study treatment administered;

02/006: inclusion criterion 1 (immunocompetent patients with newly-diagnosed or relapsed primary central nervous system B-cell lymphoma) and exclusion criterion 2 (systemic lymphoma manifestation (outside the CNS)); (--/SAF, see section 10.4), study treatment administered

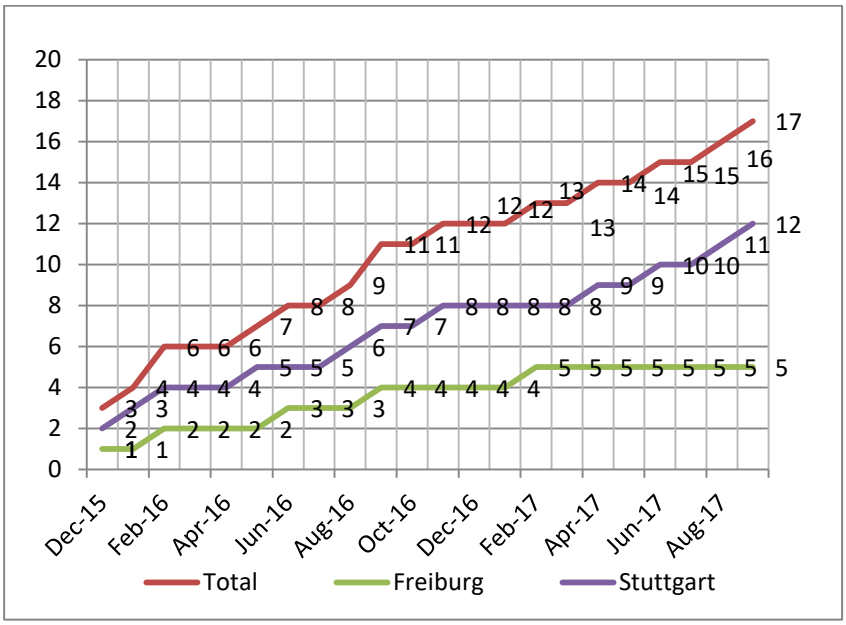
02/007: screening failure, exclusion criterion 2 (systemic lymphoma manifestation (outside the CNS)); no study treatment administered;

For details see Appendix 16.2.4.1 Table T1-1 and Appendix 16.2.6.2 Listing L5.

10.3. Patient recruitment

The study was initiated in 2 study centers in Germany. The patients were enrolled from the both centers (for details see).

Figure 1 Patient screening by site (ALL; n=17)



Recruitment in FAS population is shown in Appendix 16.2.4.1 Table T1-4.

10.4. Data Set analysed

In total 17 patients were registered in the study; three of them were excluded from the full analysis set (FAS) due to the following reasons: 02/005, 02/006, 02/007 – violation of inclusion/exclusion criteria. For details see section 10.2 and Appendix 16.2.4.1 Table T1-1. Thus, the FAS analysis is based on the data of 14 registered patients who received at least one administration of IMP.

Safety Set (SAF) includes 15 patients: all FAS patients and additionally patient 02/006 as she was administered the study medication.

10.5. Disposition of patients: premature end of study (EOS)

No patient terminated the study prematurely; see Appendix 16.2.4.1 Table T1-6.

10.6. Demographic and other Baseline Characteristics

A summary of patient characteristics and treatment outcome is shown in Table 3.

Table 3 Baseline characteristics (FAS; n=14)

Characteristics	**n (%)**
Age median (min-max) [years]	 74 (69-79)
Gender female male	 8 (57.1%) 6 (42.9%)
ECOG performance status	

Characteristics	n (%)
0	3 (21.43%)
1	8 (57.14%)
2	3 (21.43%)
Cumulative illness rating scale	
4	7 (50.0%)
5	3 (21.4%)
6	3 (21.4%)
10	1 (7.1%)
LDH at screening	
not increase	7 (53.9%)
increased	6 (41.2%)
missing	1 -
Tumour	
singular	5 (35.7%)
multiple	9 (64.3%)
Tumour characteristics	
diffuse large cell B-cell lymphoma	14 (100.0%)
CD20 positive	14 (100.0%)
Tumour localisation	
infratentorial	0 (0.0%)
supratentorial	10 (71.4%)
both	4 (28.6%)
Initial steroid therapy	
Dexamethasone	14 (100.0%)
Median dose (min-max) [mg absolute]	156 (50-348)
Median duration (min-max) [days]	11 (4-20)

Source: Appendix 16.2.4.1 Table T2-1, Appendix 16.2.4.1 Table T2-1, Appendix 16.2.4.1 Table T2-6, Appendix 16.2.4.1 Table T2-13, Appendix 16.2.4.1 Table T2-14, Appendix 16.2.4.1 Table T2-8, Appendix 16.2.4.1 Table T2-28, Appendix 16.2.4.1 Table T2-2, Appendix 16.2.4.1 Table T3-11.

ECOG = Eastern Cooperative Group

Median patients' age was 74 years (range 69-79) and median ECOG performance status was 1 (range 0-2), respectively.

All patients in FAS suffered from a CD20 positive diffuse large cell B-cell lymphoma; 9 patients had multifocal tumor and 5 patients a singular one. All patients had initial steroid therapy with a median cumulative dose of 156 mg and median therapy duration of 11 days.

10.7. Measurements of Treatment Compliance

See section 12.1 "Extent of Exposure".

11. EFFICACY EVALUATION

11.1. Efficacy Results

Results described in this section are based on the FAS, unless specified otherwise.

11.1.1. Primary endpoint analysis

The primary goal of the study was to evaluate feasibility of the study procedures. Patients' recruitment and study conduct were successfully completed and have shown that a subsequent phase II trial can be planned.

11.1.2. Secondary efficacy endpoint analyses

11.1.2.1. Annual recruitment

Annual recruitment/registration in FAS population represents approximately 7 patients per year (see Appendix 16.2.4.1 Table T1-4).

11.1.2.2. CR on day 30 after HDT-ASCT

Response assessment on day 30 after HDT-ASCT is shown in Table below.

Table 4 Response assessment on day 30 after HDT-ASCT (FAS; n=14)

Response assessment	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Complete remission (CR)	8*	57.14	8	57.14
Unconfirmed complete remission (uCR)	4	28.57	12	85.71
Partial remission (PR)	2	14.29	14	100.00

Source: Appendix 16.2.4.1 Table T4-11

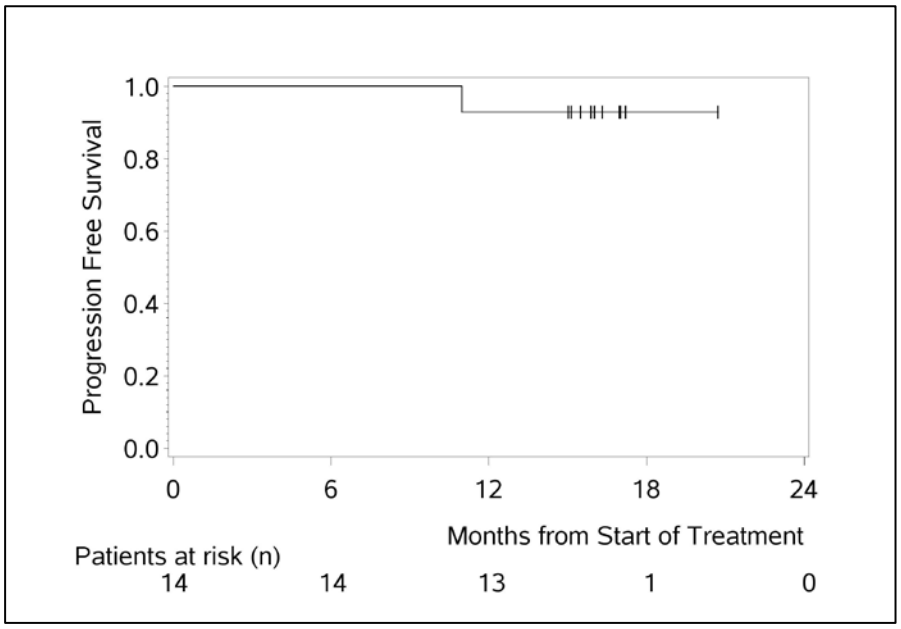
*one patient (01/001) has only received the first induction cycle as study treatment (thereafter the patient was treated with conventional chemotherapy), response assessments were done in due schedule, therefore the patient was included in the ITT analysis.

57.1% of patients in FAS population had a complete remission on day 30 after HDT-ASCT. In total 85.7% of patients had confirmed and unconfirmed complete remission on day 30 after HDT-ASCT.

11.1.2.3. PFS

PFS is defined as the time from start of treatment until PD or relapse or death from any cause. PFS over time is shown in Figure below.

Figure 1 Progression free survival over time (FAS; n=14)



Source: Appendix 16.2.4 Figure 1

One patient (02/008) who had achieved uCR after completion of therapy developed progressive disease 9 months after HCT-ASCT and died due to lymphoma progression after end of the study.

Table 5 Progression free survival rates (FAS; n=14)

PFS	PFS Distribution Function Estimate	lower 95% confidence limit	upper 95% confidence limit
6 months	100.0%	100.0%	100.0%
9 months	100.0%	100.0%	100.0%
12 months	92.9%	59.1%	99.0%
18 months	92.9%	59.1%	99.0%
24 months	-	-	-

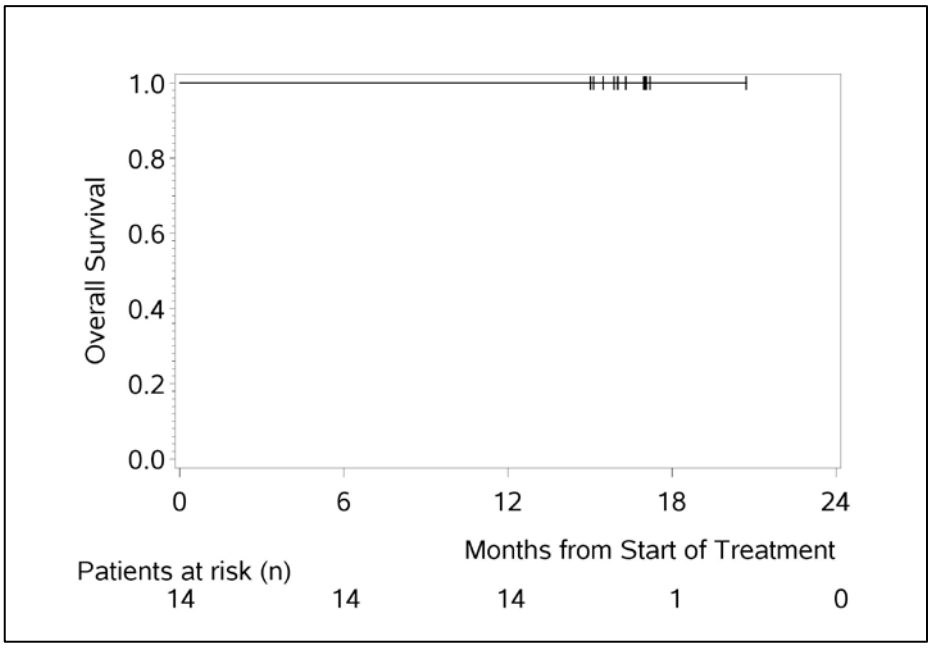
Source: Appendix 16.2.4.3 Table 2

At the end of the study 92.9% of patients were progression free.

11.1.2.4.OS

OS is defined as time from start of treatment until death from any cause and is shown on Figure below.

Figure 2 Overall survival over time (FAS; n=14)



Source: Appendix 16.2.4 Figure 2

All patients were alive at the end of the study. Overall survival rates are shown in Appendix 16.2.4.4 Table 2.

11.1.2.5.EORTC QLQ-C30

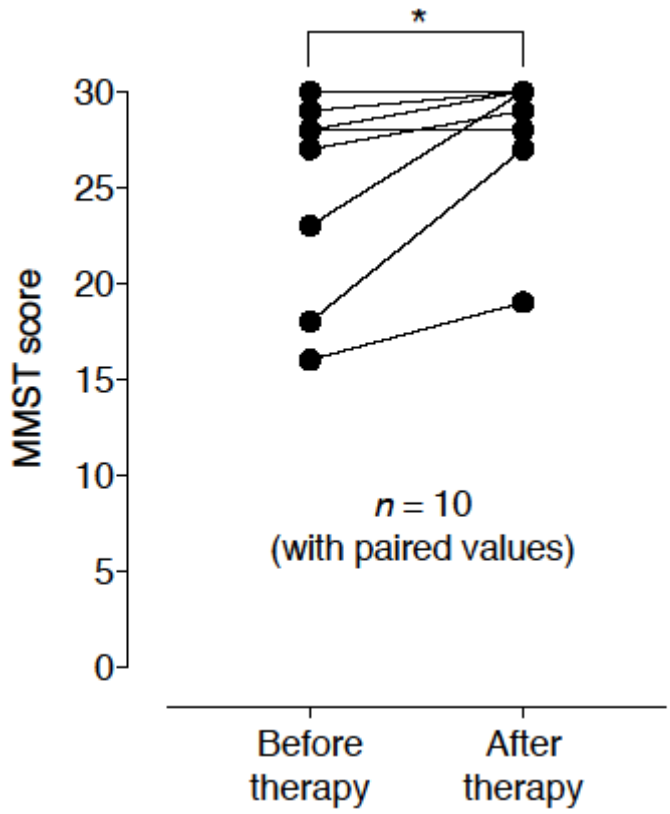
Only patients with a post baseline assessment were kept.
The QLQ-C30 includes five functional scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, nausea/vomiting and pain) and a global health status. Furthermore, it contains six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). QoL descriptive statistics tables are included in Appendix 16.2.4.2 Table T6.
Median global health status at baseline was 41.7 (range 0-83.3), at response assessment I 50 (range 33.3-100), at response assessment II 58.3 (range 16.7-83.3) and at 12 months follow-up 54.2 (range 33.3-75). Thus, global health status measured by EORTC QLQ-C30 showed tendency towards improvement after therapy.

For details regarding EORTC QLQ-C30 are shown in Appendix 16.2.4.2 Table T6 and Appendix 16.2.6.2 Listing L16.

11.1.2.6.MMSE

Paired data on MMSE/MMST (i.e. at screening and after treatment) in FAS population were available for 10 patients and are shown on Figure 4.

Figure 3 MMSE/MMST score (FAS; n=14)



*Significant difference between pretreatment and posttreatment values.

Cognitive functions measured by MMSE/MMST improved over time in 8/10 available patients with paired values before and after therapy. In 2/10 available patients, cognitive functions remained stable on a high level.

11.1.2.7.EORTC QLQ-BN20

There were no relevant changes regarding quality of life measured by QLQ-BN20.

For details regarding EORTC QLQ-BN20 are shown in Appendix 16.2.4.2 Table T6 and Appendix 16.2.6.2 Listing L16.

11.1.2.8.Neuro-psychological assessment

Neuropsychological battery test at baseline, 30 days after end of treatment and 12 months FU are presented in Table 6.

Table 6 Neuro-psychological assessment during the study

Label	Median Min-Max N valid / N missing		
	Baseline	Day 30 after end of treatment	12 Months follow-up
Digit span forward points	9.0 5.0-16.0 12/2	9.0 4.0-14.0 11/3	8.0 7.0-14.0 8/6
Digit span backward points	4.5 4.0-8.0 12/2	5.0 0-8.0 11/3	6.0 3.0-8.0 8/6
Short-term recall round 1	4.0 1.0-5.0 12/2	4.0 1.0-8.0 11/3	4.5 2.0-8.0 8/6
Short-term recall round 2	5.0 3.0-9.0 12/2	6.0 3.0-8.0 11/3	6.0 4.0-10.0 8/6
Short-term recall round 3	7.0 1.0-8.0 12/2	5.0 3.0-9.0 11/3	7.5 4.0-10.0 8/6
Short-term recall delayed	4.0 1.0-12.0 9/5	5.0 3.0-10.0 11/3	6.0 4.0-11.0 8/6
Brief test of Attention digits	5.5 1.0-9.0 8/6	5.0 0-10.0 11/3	6.5 0-9.0 8/6
Brief test of Attention letters	3.5 0-9.0 8/6	4.0 1.0-10.0 11/3	4.0 2.0-10.0 7/7
Trail Making Test trail A [min:sec]	4530.0 420.0-11940.0 10/4	4980.0 3180.0-12300.0 11/3	4110.0 2220.0-6300.0 8/6
Trail Making Test trail B [min:sec]	14400.0 600.0-18000.0 8/6	10740.0 4740.0-19800.0 9/5	11430.0 8820.0-18000.0 8/6
Grooved Pegboard right [min:sec]	8400.0 5100.0- 18000.0 8/6	8640.0 4620.0-18000.0 10/4	8250.0 4860.0-12480.0 8/6
Grooved Pegboard left [min:sec]	8760.00 5340.0- 18720.0 7/7	9000.0 6480.0-18000.0 9/5	8730.0 5640.0-13080.0 8/6
Total of correct positive answers	11.00 9.0-12.0 9/5	11.0 9.0-12.0 11/3	12.0 10.0-12.0 8/6
Semantically related false positive errors	0 0-6.0 9/5	9.0 0-6.0 11/3	0.5 0-6.0 8/6
Semantically not related false positive errors	0 0-5.0 9/5	5.0 0-4.0 11/3	0 0-6.0 8/6

Source: Appendix 16.2.4.1 Table T6-1, Appendix 16.2.4.1 Table T6-10, Appendix 16.2.4.1 Table T6-19

Neurocognitive tests done immediately after treatment and at the end of the study showed improvement in most assessed cognitive functions over the time.

11.1.2.9.Response assessment after induction

Response assessment was performed in 13 patients on day 18 – 20 of induction cycle 2 and is displayed in Table below.

Table 7 Response assessment after induction cycle 2 (FAS; n=14)

Response status	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Complete remission (CR)	2	15.38	2	15.38
Unconfirmed complete remission (uCR)	1	7.69	3	23.08
Partial remission (PR)	10	76.92	13	100.00
Not performed	1*	na	14	na

Source: Appendix 16.2.4.1 Table T4-4 and Appendix 16.2.4.1 Table T4-3
*response assessment in the patient 01/001 is missing see Appendix 16.2.6.2 listing L13

After induction 13 of 14 patients achieved a remission (2 with CR, 1 with uCR, 10 with PR).

11.1.3. Interim Analyses

Not applicable.

11.1.4. Tabulation of individual response data

See Appendix **Fehler! Verweisquelle konnte nicht gefunden werden.**

11.1.5. By-Patient Displays

See Appendix **Fehler! Verweisquelle konnte nicht gefunden werden.**

11.1.6. Efficacy Conclusions

After induction 13 of 14 patients achieved a remission (2 with complete remission (CR), 1 with unconfirmed complete remission (uCR), 10 with partial remission (PR)). Overall, 13 of 14 patients commenced HCT-ASCT; in assessment 30 days after HCT-ASCT (or after end of study treatment in one patient who did not receive HCT-ASCT) 12 patients achieved CR or uCR and 2 patients a PR, which converted to CR without any additional therapy after 3 months. One patient who had achieved uCR after completion of therapy developed progressive disease 9 months after HCT-ASCT.

One patient who had stopped trial treatment prematurely before HCT-ASCT achieved CR after additional off-study conventional chemotherapy treatment.

12. SAFETY EVALUATION

Description of safety and tolerability in this section applies to the SAF which consists of 15 patients administered study medication. The safety and tolerability analyses consist of summaries of AEs and SAEs and laboratory data described in this section. A part of safety data was collected as toxicity tables and will be shown in section 12.2.

12.1. Extent of Exposure

14 out of 15 patients (SAF) have received two induction cycles; one patient was administered only one induction cycle (Appendix 16.2.4.1 Table T3-1).

Table 8 Administered IMP doses in induction phase (SAF; n=15)

Total dose of	Induction cycle 1		Induction cycle 2	
	Mean	Standard deviation	Mean	Standard deviation
Rituximab on day 0 [mg]	666.97	48.20	669.51	43.23
Rituximab on day 4 [mg]	578.01	239.50	576.49	247.90
MTX on day 1 [g]	6.23	0.44	5.42	2.32
Ara-C on day 2 [g]	7.13	0.51	6.68	1.98
Ara-C on day 3 [g]	7.13	0.51	6.68	1.98
Total valid	15	15	14*	14*
Missing	0	0	1	1

Source: Appendix 16.2.4.1 Table T3-5 and Appendix 16.2.4.1 Table T3-9
*one patient (02/006) received in the induction cycle 2 only rituximab on day 0 (see Appendix 16.2.6.2 Listing L7).

For data on FAS population please refer Appendix 16.2.4.1 Table T3-13 and Appendix 16.2.4.1 Table T3-17.

Table 9 Administered IMP doses in consolidation phase (SAF; n=15)

Total dose of	Mean [mg]	Standard deviation [mg]
Busulfan on day -7	212.38	29.81
Busulfan on day -6	212.38	29.81
Busulfan sum dose	424.75	59.61
Thiotepa on day -5	345.46	46.47
Thiotepa on day -4	345.46	46.47
Thiotepa sum dose	690.92	92.93
Total valid	13	13

Source: Appendix 16.2.4.1 Table T3-20

13 patients in the SAF population undergone autologous stem cell transplantation (ASCT) (see Appendix 16.2.4.1 Table T3-21).

12.2. Toxicity

Status at screening and toxicities CTCAE grade ≥3 documented beginning from the start of corresponding cycle are shown in Table 10.

Details on screening are shown in Appendix 16.2.4.1 Table T5-14 until Appendix 16.2.4.1 Table T5-114.

Details on all toxicity grades are shown in Appendix 16.2.4.1 Table T5-1, Appendix 16.2.4.1 Table T5-4, Appendix 16.2.4.1 Table T5-7, Appendix 16.2.4.1 Table T5-10

Table 10 Incidence of toxicity CTCAE grade ≥3 (SAF; n=15)

MedDRA SOC [1]	Screening		Induction cycle 1		Induction cycle 2		Consolidation cycle	
	n	total %	n	total %	n	total %	n	total %
Total number of patients	15	100	15	100	15	100	15	100
Number of patients with at least one toxicity – Grade ≥3	0	0	15	100	14	93.3	13	86.7
Blood and lymphatic	0	0	15	100	14	93.3	13	86.7
Infections	0	0	3	20	4	26.7	5	33.3
Abnormal investigations	0	0	5	33.3	1	6.7	2	13.3
Gastrointestinal	0	0	1	6.7	2	13.3	5	33.3
Metabolism and nutrition	0	0	1	6.7	3	20	2	13.3
General	0	0	0	0	2	13,3	1	6,7
Vascular	0	0	2	13.3	0	0	0	0
Cardiac	0	0	1	6.7	0	0	1	6.7
Psychiatric	0	0	0	0	0	0	1	6.7
Nervous system	0	0	0	0	0	0	1	6.7
Endocrine	0	0	0	0	0	0	0	0
Musculoskeletal and connective tissue	0	0	0	0	0	0	0	0
Cardiac	0	0	0	0	0	0	0	0
Skin and subcutaneous	0	0	0	0	0	0	0	0
Respiratory / thoracic / mediastinal	0	0	0	0	0	0	0	0

Source: Appendix 16.2.4.1 Table T5-2, Appendix 16.2.4.1 Table T5-5, Appendix 16.2.4.1 Table T5-8, Appendix 16.2.4.1 Table T5-11
Ordered by total incidence during all cycles
[1]System Organ Class

There was no toxicity CTCAE grade 5 (deaths) in the study.

The most frequently reported toxicities CTCAE grade ≥3 after the first induction cycle were the following in SOC “blood and lymphatic” followed by “abnormal investigations” and “infections” and presented by the following PTs:

Blood and lymphatic

- WBC decreased (n=2 for CTCAE grade 3; n=13 for CTCAE grade 4) see Appendix 16.2.4.1 Table T5-119

- Thrombocytopenia (n=2 for CTCAE grade 3; n=13 for CTCAE grade 4) see Appendix 16.2.4.1 Table T5-121
- Neutropenia (n=5 for CTCAE grade 4) see Appendix 16.2.4.1 Table T5-120
- Anaemia (n=3; all CTCAE grade 3) see Appendix 16.2.4.1 Table T5-116
- Febrile neutropenia (n=2; both CTCAE grade 3) see Appendix 16.2.4.1 Table T5-117

Infections

- Urinary tract infection (n=3; all CTCAE grade 3) see Appendix 16.2.4.1 Table T5-167

Abnormal investigations

- ALT increase grade 3 (n=4); see Appendix 16.2.4.1 Table T5-169
- AST increase grade 3 (n=3); see Appendix 16.2.4.1 Table T5-170
- Gamma-GT increase grade 3 (n=3); see Appendix 16.2.4.1 Table T5-174

Occurrence of PTs in further cycles was similar. For details on further treatment cycles and information related to all CTCAE-grade-toxicity please refer to corresponding tables in Appendix 16.2.4.1 Table T5-217 until Appendix 16.2.4.1 Table T5-420.

12.3. Adverse Events (AEs)

12.3.1. Summary of Adverse Events

An overview of the AEs which occurred during the whole study period under analysis is provided in Table 11.

Table 11 Number of all AEs (SAF; n=15)

	All AEs	AEs CTCAE grade ≥3	SAEs	AEs related to IMPs	AEs related to IMP(s) CTCAE grade ≥3	SAEs related to IMP(s)
Total number of patients	15	15	15	15	15	15
Total number AEs*	21	14	11	13	10	8
Min number of AEs* per patient	0	0	0	0	0	0
Max number of AEs* per patient	4	4	3	3	3	2
Mean number of AEs* per patient	1.40	0.93	0.73	0.87	0.67	0.53
number of patients with at least one AE*	10	9	9	7	7	7

Source: Appendix 16.2.6.1 Table T4-1-1: Appendix 16.2.6.1 Table T4-2-1 Appendix 16.2.6.1 Table T4-3-1 Appendix 16.2.6.1 T4-4-1, Appendix 16.2.6.1 Table T4-5-1 and Appendix 16.2.6.1 Table T4-6-1
*see AE naming in column heading
AE(s)= Adverse event(s)
CTCAE= Common terminology criteria for adverse events
SAE(s)= Serious adverse event(s)
IMP(s)= Investigational medicinal product(s)

No fatal adverse events occurred in the study; see Appendix 16.2.6.1 Table T4-7-1.

12.3.1.1. All Adverse events

An overview of the incidence of AEs per SOC and per PT regardless of relationship to study medication is provided in Table 12.

Table 12 Incidence of all AEs (SAF; n=15)

		AE[1] Incidence	
System organ class	**Preferred term**	**No.**	**Total %**
Total number of patients		15	100.0
Number of patients with at least one AE[1]		10	66.7
Infections and infestations		5	33.3
	Bronchopulmonary aspergillosis	1	6.7
	Endophthalmitis	1	6.7
	Infection	1	6.7
	Pneumocystis jirovecii pneumonia	1	6.7
	Pneumonia	1	6.7
	Staphylococcal infection	1	6.7
Nervous system disorders		4	26.7
	Anosmia	1	6.7
	Aphasia	1	6.7
	Ataxia	1	6.7
	Partial seizures	1	6.7
Gastrointestinal disorders		2	13.3
	Large intestinal ulcer haemorrhage	1	6.7
	Nausea	1	6.7
Injury, poisoning and procedural complications		2	13.3
	Fall	2	13.3
Renal and urinary disorders		2	13.3
	Polyuria	1	6.7
	Renal failure	1	6.7
Blood and lymphatic system disorders		1	6.7
	Febrile neutropenia	1	6.7
Cardiac disorders		1	6.7
	Supraventricular tachycardia	1	6.7
Metabolism and nutrition disorders		1	6.7
	Hypokalaemia	1	6.7
Vascular disorders		1	6.7
	Jugular vein thrombosis	1	6.7

Source: Appendix 16.2.6.1 Table T4-1-2:
[1]AE= Adverse event

10 out of 15 patients had at least one AE. The most frequently reported AE regardless of relationship to study medication were infections and nervous system disorders.

12.3.1.2. AEs being at least severe

The incidence of AEs being at least CTCAE grade ≥3 is shown in Table 13.

Table 13 Incidence of AEs being CTCAE grade ≥3 (SAF; n=15)

		AE Incidence	
System organ class	**Preferred term**	**No.**	**Total %**
Total number of patients		15	100.0
Number of patients with at least one AE being CTCAE grade ≥3		9	60.0
Infections and infestations		5	33.3
	Bronchopulmonary aspergillosis	1	6.7
	Endophthalmitis	1	6.7
	Infection	1	6.7
	Pneumocystis jirovecii pneumonia	1	6.7
	Pneumonia	1	6.7
	Staphylococcal infection	1	6.7
Gastrointestinal disorders		2	13.3
	Large intestinal ulcer haemorrhage	1	6.7
	Nausea	1	6.7
Nervous system disorders		2	13.3
	Aphasia	1	6.7
	Partial seizures	1	6.7
Blood and lymphatic system disorders		1	6.7
	Febrile neutropenia	1	6.7
Cardiac disorders		1	6.7
	Supraventricular tachycardia	1	6.7
Renal and urinary disorders		1	6.7
	Renal failure	1	6.7

Source: Appendix 16.2.6.1 Table T4-2-2:
AE(s)= Adverse event(s)
CTCAE= Common terminology criteria for adverse events

In 9 out of 15 patients at least one AE being CTCAE grade ≥3 occurred. The most frequently reported diagnoses were infections and gastrointestinal disorders.

12.3.2. Serious Adverse Events (SAEs)

In this section the data on SAEs documented during the whole FU period under analysis are described. An overview of the incidence of SAEs per SOC and per PT regardless of relationship to study medication is provided in Table 14.

Table 14 Incidence of SAEs (SAF; n=15)

		SAE Incidence	
System organ class	**Preferred term**	**No.**	**Total %**
Total number of patients		15	100.0
Number of patients with at least one SAE		9	60.0
Infections and infestations		5	33.3
	Bronchopulmonary aspergillosis	1	6.7
	Endophthalmitis	1	6.7
	Infection	1	6.7
	Pneumocystis jirovecii pneumonia	1	6.7
	Pneumonia	1	6.7
Gastrointestinal disorders		2	13.3

		SAE Incidence	
System organ class	**Preferred term**	**No.**	**Total %**
	Large intestinal ulcer haemorrhage	1	6.7
	Nausea	1	6.7
Blood and lymphatic system disorders		1	6.7
	Febrile neutropenia	1	6.7
Cardiac disorders		1	6.7
	Supraventricular tachycardia	1	6.7
Nervous system disorders		1	6.7
	Aphasia	1	6.7
Renal and urinary disorders		1	6.7
	Renal failure	1	6.7

Source: Appendix 16.2.6.1 Table T4-3-2
SAE(s)= Serious adverse event(s)

In 9 out of 15 patients at least one SAE regardless of relationship to study medication occurred. The most frequently reported diagnoses were infections and gastrointestinal disorders.

12.3.2.1. SAEs leading to death

No fatal SAE was reported in the study. See Appendix 16.2.6.1 Table T4-7-1 and Table T4-7-2.

12.3.2.2. AEs possibly related to investigational product

An overview of the most frequently reported AE considered by the investigator to be related to at least one IMP per SOC and PT is provided Table 15.

Table 15 Incidence of AEs related to IMP(s) (SAF; n=15)

		AE Incidence	
System organ class	**Preferred term**	**No.**	**Total %**
Total number of patients		15	100.0
Number of patients with at least one AE related to IMP(s)		7	46.7
Infections and infestations		4	26.7
	Bronchopulmonary aspergillosis	1	6.7
	Infection	1	6.7
	Pneumocystis jirovecii pneumonia	1	6.7
	Pneumonia	1	6.7
	Staphylococcal infection	1	6.7
Gastrointestinal disorders		2	13.3
	Large intestinal ulcer haemorrhage	1	6.7
	Nausea	1	6.7
Nervous system disorders		2	13.3
	Anosmia	1	6.7
	Ataxia	1	6.7
Blood and lymphatic system disorders		1	6.7
	Febrile neutropenia	1	6.7
Renal and urinary disorders		1	6.7
	Renal failure	1	6.7

		AE Incidence	
System organ class	**Preferred term**	**No.**	**Total %**
Vascular disorders		1	6.7
	Jugular vein thrombosis	1	6.7

Source: Appendix 16.2.6.1 Table T4-4-2
AE(s)= Adverse event(s)
IMP(s)= Investigational medicinal product(s)

In 7 out of 15 patients at least one SAE related to at least one IMP was reported. The most frequently reported diagnoses were infections and gastrointestinal disorders.

12.3.2.3.AEs possibly related to investigational product being at least severe

Table 16 Incidence of AEs related to IMP(s) being CTCAE grade ≥3 (SAF; n=15)

		AE Incidence	
System organ class	**Preferred term**	**No.**	**Total %**
Total number of patients		15	100.0
Number of patients with at least one AE related to IMP(s) being CTCAE grade ≥3		7	46.7
Infections and infestations		4	26.7
	Bronchopulmonary aspergillosis	1	6.7
	Infection	1	6.7
	Pneumocystis jirovecii pneumonia	1	6.7
	Pneumonia	1	6.7
	Staphylococcal infection	1	6.7
Gastrointestinal disorders		2	13.3
	Large intestinal ulcer haemorrhage	1	6.7
	Nausea	1	6.7
Blood and lymphatic system disorders		1	6.7
	Febrile neutropenia	1	6.7
Renal and urinary disorders		1	6.7
	Renal failure	1	6.7

Source: Appendix 16.2.6.1 Table T4-5-2
AE(s)= Adverse event(s)
CTCAE= Common terminology criteria for adverse events
IMP(s)= Investigational medicinal product(s)

In 7 out of 15 patients at least one AE related to at least one IMP and being CTCAE grade ≥3 was reported. The most frequently reported diagnoses were infections and gastrointestinal disorders.

12.3.2.4.SAEs possibly related to investigational product

An overview of most frequently reported SAEs related to at least one IMP per SOC and PT is given in Table 17.

Table 17 Incidence of SAEs related to IMP(s) (SAF; n=15)

		SAE Incidence	
System organ class	**Preferred term**	**No.**	**Total %**
Total number of patients		15	100.0
Number of patients with at least one SAEs related to IMP(s)		7	46.7
Infections and infestations		4	26.7
	Bronchopulmonary aspergillosis	1	6.7
	Infection	1	6.7
	Pneumocystis jirovecii pneumonia	1	6.7
	Pneumonia	1	6.7
Gastrointestinal disorders		2	13.3
	Large intestinal ulcer haemorrhage	1	6.7
	Nausea	1	6.7
Blood and lymphatic system disorders		1	6.7
	Febrile neutropenia	1	6.7
Renal and urinary disorders		1	6.7
	Renal failure	1	6.7

Source: Appendix 16.2.6.1 Table T4-6-2
SAE(s)= Serious adverse events(s)
IMP(s)= Investigational medicinal product(s)

In 7 out of 15 patients at least one SAE related to at least one IMP was reported. The most frequently reported diagnoses were infections and gastrointestinal disorders.

12.3.2.5.SAEs possibly related to investigational product leading to death

No fatal SAE related to investigational product was reported in the study.

12.3.3. Analysis of Adverse Events

The most frequently documented toxicities CTCAE grade ≥3 during the therapy were the in SOC “blood and lymphatic” followed by “abnormal investigations” and “infections”.

In 9 out of 15 patients at least one AE being CTCAE grade ≥3 occurred; in 7 patients these AEs were related to at least one IMP; the most frequently reported diagnoses were infections and gastrointestinal disorders. In 7 out of 15 patients at least one SAE related to at least one IMP was reported; the most frequently reported diagnoses were infections and gastrointestinal disorders. No deaths, no other significant AEs, no SUSARs occurred during the study.

The evaluation of toxicities and AEs related to IMPs did not show any new safety issues.

12.3.4. Listing of Adverse Events by Patient

See Appendix 16.2.6.1

12.4. Deaths, other Serious Adverse Events (SAEs) and other Significant Adverse Events

Not applicable, no deaths, no other significant AEs, no SUSARs occurred during the study.

12.4.1. Other Significant Adverse Events

Not applicable.

12.4.2. Narratives of Deaths, other Serious Adverse Events and other Significant Adverse Events

Not applicable.

12.5. Clinical Laboratory Evaluation

Laboratory data documented as toxicity parameters are described by giving frequencies according to CTCAE grading (see section 12.2). The number of patients with at least one severe toxicity (grade ≥ 3) was calculated and is shown in Table 10.

For lactate hydrogenase, frequencies increased/not increased at screening for FAS population at screening are presented in Table 3. For details on SAF population are shown in Appendix 16.2.4.1 Table T2-29.

Creatinine was used to calculate the GFR applying the MRDR formula which will be analysed in summary tables.

Table 18 Laboratory data (SAF; n=15)

Parameter	Induction cycle 1		Induction cycle 2		Consolidation cycle	
	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
Creatinine [mg/dl]	0.74	0.12	0.88	0.23	0.92	0.19
GFR [ml/min]	88.9	17.5	77.56	21,00	70.9	18.33
Total valid	15	15	14	14	13	13
Missing	0	0	1	1	2	2

Source: Appendix 16.2.4.1 Table T3-2, Appendix 16.2.4.1 Table T3-6, Appendix 16.2.4.1 Table T3-18
GFR= glomerular filtration rate

There is a slight tendency towards decline of GFR during trial treatment without clinical significance.

12.6. Vital signs

Data on the patient's vital signs were taken at screening and all subsequent visits. Vital signs included body temperature, pulse rate and systolic/diastolic blood pressure, measurement of height (cm) and body weight (kg). Height is only measured at screening; weight was assessed at visit 1, 2 and 3.

Body temperature, pulse rate and blood pressure were documented at corresponding visits on toxicity table according to CTCAE grading.

In Table 19 all documented abnormal vital signs are shown independently of their etiology.

Table 19 Vital signs (SAF; n=15)

Parameter	Screening		Induction cycle 1		Induction cycle 2		Consolidation cycle	
	n/ (n valid pts)	total %	n/ (n valid pts)	total %	n/ (n valid pts)	total %	n/ (n valid pts)	total %
Fever	0	0	2/13	15.4	2/14	14.3	6/13	46.2
Pulse								
Atrial fibrillation	1/15	6.7	1/15	6.7	0	0	0	0
Palpitations	0	0	0	0	0	0	0	0
Ventricular arrhythmia	0	0	0	0	0	0	1/13	7.7
Blood pressure								
Hypertension	7/15	46.7	6/15	40.0	5/15	33.3	6/13	46.2
Hypotension	0	0	1/13	7.7	0	0	1/13	7.7

Source: Appendix 16.2.4.1 Table T5-45, Appendix 16.2.4.1 Table T5-147, Appendix 16.2.4.1 Table T5-249, Appendix 16.2.4.1 Table T5-351, Appendix 16.2.4.1 Table T5-22, Appendix 16.2.4.1 Table T5-124, Appendix 16.2.4.1 Table T5-226, Appendix 16.2.4.1 Table T5-328, Appendix 16.2.4.1 Table T5-23, Appendix 16.2.4.1 Table T5-125, Appendix 16.2.4.1 Table T5-227, Appendix 16.2.4.1 Table T5-329, Appendix 16.2.4.1 Table T5-24, Appendix 16.2.4.1 Table T5-126, Appendix 16.2.4.1 Table T5-228, Appendix 16.2.4.1 Table T5-330, Appendix 16.2.4.1 Table T5-111, Appendix 16.2.4.1 Table T5-213, Appendix 16.2.4.1 Table T5-315, Appendix 16.2.4.1 Table T5-417, Appendix 16.2.4.1 Table T5-112, Appendix 16.2.4.1 Table T5-214, Appendix 16.2.4.1 Table T5-316, Appendix 16.2.4.1 Table T5-418

Two patients in each induction cycle and 6 patients in consolidation cycle developed fever, in one patient ventricular arrhythmia occurred during consolidation treatment.

Table 20 Body weight (SAF; n=15)

Parameter	Induction cycle 1		Induction cycle 2		Consolidation cycle	
	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
Body weight [kg]	70.35	9.34	70.24	9.60	70.77	9.45
Total valid	15	15	14	14	13	13
Missing	0	0	1	1	2	2

Source: Appendix 16.2.4.1 Table T3-2, Appendix 16.2.4.1 Table T3-6, Appendix 16.2.4.1 Table T3-18

Mean body weight was stable during the study treatment.

12.7. Safety Conclusions

Overall, 13/14 patients (93%) completed the study treatment. In one patient, the treatment was stopped prematurely during the 1st cycle due to supraventricular tachycardia. Therapy was generally well tolerated, no treatment-related death occurred. In 7 out of 15 patients at least one AE related to at least one IMP and being CTCAE grade ≥3 was reported. The most frequently reported diagnoses were infections and gastrointestinal disorders.
The evaluation of toxicities and AEs related to IMPs did not reveal any new safety issues.

13. DISCUSSION AND OVERALL CONCLUSIONS

Overall, seventeen patients were screened, of which fourteen patients with newly-diagnosed PCNSL were included at two centers between December 2015 and September 2017. Median age and Eastern Cooperative Group Performance Status (ECOG PS) were 74 years (range 69-79 years) and 1 (range 0-2), respectively.

Overall, 13/14 patients (93%) completed the study treatment. In one patient, the treatment was stopped prematurely during the 1st cycle due to supraventricular tachycardia. Therapy was generally well tolerated, no treatment-related death occurred. In 7 out of 15 patients at least one AE related to at least one IMP and being CTCAE grade ≥3 was reported. The most frequently reported diagnoses were infections and gastrointestinal disorders.

After induction 13 of 14 patients achieved a remission (2 with complete remission (CR), 1 with unconfirmed complete remission (uCR), 10 with partial remission (PR)). Overall, 13 of 14 patients commenced HCT-ASCT; in assessment 30 days after HCT-ASCT (or after end of study treatment in one patient who did not receive HCT-ASCT) 12 patients achieved CR or uCR and 2 a PR, which converted to CR without any additional therapy after 3 months. One patient who had achieved uCR after completion of therapy developed progressive disease 9 months after HCT-ASCT. All other patients are in ongoing complete remission and in good mental and general condition without having received additional therapy. After 12 months, respective PFS and OS rates were 92.9% (95% CI 59.1% to 99%) and 100% (95% CI not calculated).

The results of this pilot trial support feasibility and effectiveness of this age-adapted approach in selected elderly patients with newly-diagnosed PCNSL. However, it needs to be considered that this pilot study was conducted at two tertiary referral centers both very experienced in the management of PCNSL. Therefore, these favorable results need to be confirmed in a multicenter setting. We are currently conducting a single-arm phase II study in Germany to investigate this age-adapted protocol (15 centers, 51 patients) (MARTA trial, DRKS00011932).

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

14.1. Demographic Data

See Appendix 16.2.4.1

14.2. Efficacy Data

See Appendix 16.2.4

14.3. Safety Data

14.3.1. Displays of Adverse Events

See Appendix 16.2.6.1

14.3.2. Listings of Deaths, Other Serious and Significant Adverse Events

Not applicable

14.3.3. Narratives of Deaths, Other Serious and Significant Adverse Events

Not applicable

14.3.4. Abnormal Laboratory Value Listing (each Patient)

Not applicable

15. REFERENCE LIST

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16. APPENDICES

16.1. Trial Information

16.1.1. Protocol

- CTP: Final V 01, 14.09.2015

16.1.2. Sample Case Report Forms

- CRF: Final V01, 04.11.2015
- SAE Reporting Form: Version V01, 25.09.2015

16.1.3. List of IECs and Patient Informed Consent

16.1.3.1. List of IEC

- List of IEC, V1.0

16.1.3.2. Patient Informed Consent

- MARiTA Merkblatt für Patienten: 23.07.2015
- Patient Informed Consent: V01 Final, 11.10.2015

16.1.4. List of main investigators

- List of main investigators: V1.0

16.1.5. Signatures of Principal or Coordinating Investigator(s) or Sponsor's Medical Officer

Dr. med. Elisabeth Schorb (see Body of report, Page 2)

16.1.6. Listing of Patients Receiving Test Drug(s)/Investigational Product(s) from Specific Batches

Not applicable

16.1.7. Randomization Scheme and Codes

Not applicable

16.1.8. Audit Certificates

Not applicable

16.1.9. Documentation of Statistical Methods

See Appendix CTP section 16.1.1.

16.1.10. Documentation of Inter-Laboratory Standardization Methods and Quality Assurance Procedures

Not applicable

16.1.11. Publications Based on the Trial

Not applicable

16.1.12. Important Publications Referenced in the Report

Not applicable

16.2. Patient Data Listings

16.2.1. Discontinued Patients

Not applicable

16.2.2. Protocol Deviations

See section 10.2

16.2.3. Patients Excluded from the Efficacy Analysis

See section 10.4

16.2.4. Demographic, efficacy, safety tables and figures

- 16.2.4.1 Demographics, efficacy and safety tables, 11.03.2020
- 16.2.4.2 QOL Tables, 23.03.2020
- 16.2.4.3 PFS rates, 30.03.2020
- 16.2.4.4 OS rates, 30.03.2020
- Figure 1 PFS, 11.03.2020
- Figure 2 OS, 11.03.2020

16.2.5. Compliance and/or Drug Concentration Data

See section 12.1

16.2.6. Individual Response data, Adverse Event and other Listings

- 16.2.6.1 Adverse Events, 11.03.2020
- 16.2.6.2 Listings, 11.03.2020

16.3. Case Report Forms (CRF)

16.3.1. CRFs of Deaths, Other Serious Adverse Events and Withdrawals for AE

Not applicable

16.3.2. Other CRFs Submitted

Not applicable