Gefördert vom:

Bundesministerium für Bildung und Forschung

High-dose chemotherapy and autologous stem cell transplant or consolidating conventional chemotherapy in primary CNS lymphoma - randomized phase III trial

Amended Clinical Trial Protocol

MATRix / IELSG43

(**M**ethotrexate, **A**ra-C, **T**hiotepa, **Ri**tu**x**imab)

EudraCT-No.	2012-000620-17
DRKS-No.	DRKS00005503
ClinicalTrials.gov Identifier:	NCT02531841

Protocol History

Version	V 01 Final 13.05.2014
Version	V 02 Final 09.12.2015 non substantial amendment
Version	V 04 Final 14.06.2018 substantial amendment
Amended Protocol Version	**V 04 Final 14.06.2018**
Development Phase	Phase III

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Approval of the amended Clinical Trial Protocol

High-dose chemotherapy and autologous stem cell transplant or consolidating conventional chemotherapy in primary CNS lymphoma - randomized phase III trial

	MATRix / IELSG43
EudraCT No.:	2012-000620-17
Protocol Version No:	**V 04 14.06.2018**

Coordinating Investigator:
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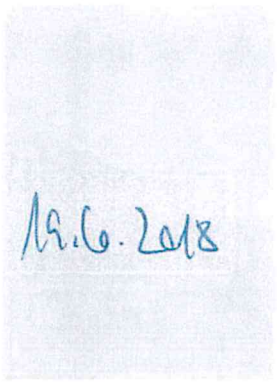

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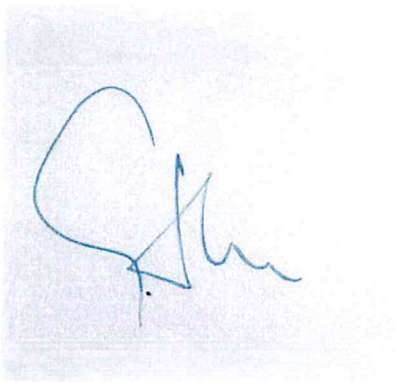

Signature

Biostatstician:
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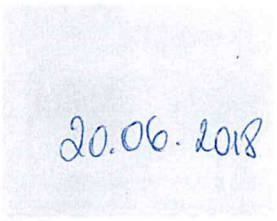

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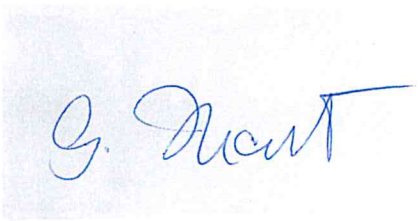

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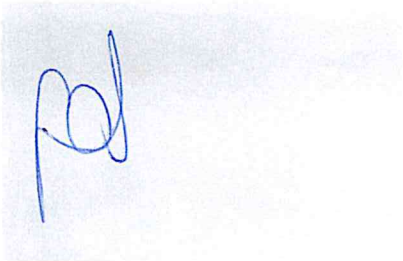

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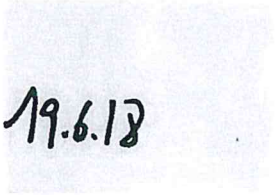
Sponsor:
Stuttgart, represented by the Executive Medical Director
Medical Center Stuttgart



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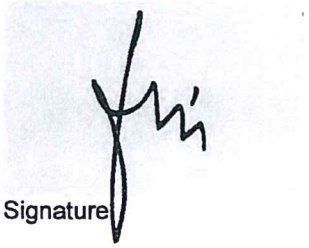

Signature

High-dose chemotherapy and autologous stem cell transplant or consolidating conventional chemotherapy in primary CNS lymphoma - randomized phase III trial

	MATRix / IELSG43
EudraCT No.:	2012-000620-17
Protocol Version No:	**V 04 14.06.2018**

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Outside of Germany
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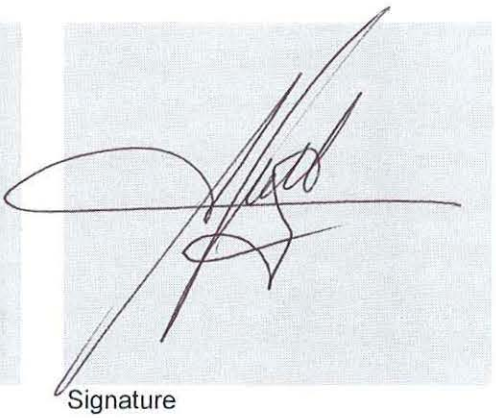


Signature

Protocol Short Title:	MATRix / IELSG43
EudraCT No.:	2012-000620-17
Amended Protocol Version No:	V 04 14.06.2018
Trial Center:	<Center No. and Name of Trial Center>
Investigator:	<Name of Investigator>

I confirm that I have read the Clinical Trial Protocol and hereby commit myself to adhere to all actions and terms as specified in the relevant sections of the clinical, ethical and general paragraphs.

I confirm that I and my colleagues will abide by the local legislation (in Germany, the German Pharmaceutical Law with the appropriate amendments). I further confirm that the Clinical Trial will be carried out in compliance with the Declaration of Helsinki and ICH-GCP guidelines.

I acknowledge that all confidential information in this document, apart from the evaluation of the Clinical Trial will not be used or circulated without the prior written consent of the Sponsor.

Under my supervision I put copies of this Clinical Trial Protocol and possible updates as well as access to all information regarding the carrying out of this Clinical Trial at the disposal of my colleagues; in particular I will promptly forward all information from the Sponsor in relation to Pharmaceutical Safety (SUSAR) to my colleagues.

I confirm that I and my colleagues were informed by a responsible scientist about the results and expected risks of the pharmacological and toxicological examination associated with the clinical trial.

I will discuss this Clinical Trial Protocol in detail with my colleagues and ensure that they are comprehensively informed about the trial compound/preparation and the execution of the trial.

Furthermore I commit myself not to commence patient enrolment before obtaining approval by the authorities and acceptance by the relevant/responsible Ethics Committee.

Date	Name of Investigator	Signature of Investigator
Date	Name of Investigator	Signature of Deputy Investigator

Table of Contents

List of Tables

List of Abbreviations

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
BMBF/DLR	Bundesministerium für Bildung und Forschung/Deutsches Zentrum für Luft- und Raumfahrtforschung (Federal Department of Education and Research Germany)
B-NHL	B-cell non-Hodgkin lymphoma
CA	Competent Authority
CIOMS Form I	Suspect Adverse Reaction Form
CM	Concomitant Medication
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete Remissions
CRR	Complete Remission Rate
CRA	Clinical Research Associate (Monitor)
CRF	Case Report Form
CRu	CR unconfirmed
CSF	Cerebrospinal Fluid
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTU	Clinical Trials Unit (Studienzentrum Universitaetsklinikum Freiburg)
DAMAST	**Da**ta **Ma**nagement **S**yst**e**m
DLBCL	Diffuse Large B-Cell Lymphoma
DMM	Data Management Manual
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid (= molecule that encodes the genetic instructions)
DSUR	Development Safety Update Report

ECOG	Eastern Cooperative Oncology Group (Performance Status)
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-BN20	EORTC Quality of Life Questionnaire Brain Cancer Module - BN20
EORTC QLQ-C30	EORTC Quality of Life Questionnaire C30
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
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
HBc	(anti-HBc) Antikörper
HBsAG	Hepatitis-B-Virus s-Antigen
HCV	Hepatitis-C-Virus
HD	High Dose
HD(C)T	High Dose (Chemo)therapy
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
ICF	Informed Consent Form
ICH-GCP	ICH Topic E6: Guideline for Good Clinical Practice (GCP)
IEC	Independent Ethics Committee
IELSG	**I**nternational **E**xtranodal **L**ymphoma **S**tudy **G**roup
IP	Investigational Product/Study medication
IPCG	International Primary CNS Lymphoma Study Group
IPD	Important Protocol Deviation
ISF	Investigator Site file
ITT	Intention-To-Treat
IVC	Inspiratory Vital Capacity
LDH	Lactatdehydrogenase
LKP	Leiter der klinischen Prüfung (Principal Coordinating Investigator, according to German Drug Law, § 4 [25] and § 40 AMG)
LPLV	Last Patient Last Visit
MATRix	**M**ethotrexate – **A**raC – **T**hiotepa - **Ri**tu**x**imab
MDRD	Modification of Diet in Renal Disease
MedDRA	Medicinal Dictionary for Regulatory Activities

MESNA	Uromitexan
MMSE	Mini-Mental Status Examination
MPD	Minor Protocol Deviation
MRI	Magnetic Resonance Imaging
mRNA	Messenger RNS
MTX	Methotrexat
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
plt	Patent Law Treaty
PJP	Pneumocystis (carinii) Jiroveci Pneumonia
PML	progressive multifocal leukoencephalopathy
PP	Per-Protocol
PR	Partial Remission
PT	Preferred Term
QoL	Quality of Life
R	Rituximab
R-DeVIC	Rituximab, Dexamethasone, VP-16 (Etoposide), Ifosfamide, Carboplatin
RA	Response Assessment
RNA	Ribonucleic acid
RPE	Retinal Pigment Epithelium
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
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
VP-16	Etoposide
WBC	White Blood Count
WBRT	Whole Brain Radiotherapy
WHO	World Health Organization
ZNS NHL	Non Hodgkin Lymphom des zentralen Nervensystems

Synopsis

TITLE OF TRIAL	High-dose chemotherapy and autologous stem cell transplant or consolidating conventional chemotherapy in primary CNS lymphoma – randomized phase III trial
SHORT TITLE	MATRix / IELSG43
EudraCT NO	2012-000620-17
MAIN DIAGNOSIS	Primary central nervous system lymphoma (PCNSL)
PHASE	Phase III
OBJECTIVES	Primary: To demonstrate the efficacy measured as progression-free survival (PFS) of intensive chemotherapy followed by autologous stem-cell transplantation compared to conventional chemotherapy Secondary: To compare high-dose chemotherapy followed by autologous stem cell transplantation with optimized conventional chemotherapy regarding OS, treatment response and treatment related morbidities (neurotoxicity and adverse advents) in patients with primary CNS lymphoma.
INTERVENTIONS **INDUCTION**	Induction treatment: 4 cycles MATRix (every 3 weeks), stem-cell harvest after 2nd cycle: - Rituximab 375 mg/m²/d i.v. (d0,5) - MTX 3.5 g/m² i.v. (d1) - Ara-C 2 x 2 g/m²/d i.v. (d2-3) - Thiotepa 30 mg/m² i.v. (d4)
ARM A: **R-DeVIC**	Consolidation 2 cycles of R-DeVIC (every 3 weeks): - Rituximab 375 mg/m²/d i.v. (d0) - Dexamethasone 40 mg/d i.v. (d1-3) - Etoposide 100 mg/m²/d i.v. (d1-3) - Ifosfamide 1500 mg/m²/d i.v. (d1-3) - Carboplatin 300 mg/m² i.v. (d1)
ARM B: **HDT-ASCT**	Consolidation: High-dose chemotherapy (HDT): - BCNU* 400 mg/m² i.v. (d-6) - Thiotepa 2 x 5 mg/kg/d i.v. (d-5-(-4)) - ASCT (d0) *if not available at study site, Busulfan can be administered instead: - Busulfan 3,2 mg/kg/d i.v. (d-8-(-7)) - Thiotepa 2 x 5 mg/kg/d i.v. (d-5-(-4)) - ASCT (d0)
INCLUSION CRITERIA	1. Immunocompetent patients with newly-diagnosed primary central nervous system B-cell lymphoma 2. Age 18-65 years irrespective of ECOG or 66-70 years (with ECOG Performance Status ≤2) 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. Previously untreated patients (previous or ongoing steroid treatment admitted) 8. Sexually active patients of childbearing potential who agree to take adequate contraceptive measures during study participation 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

ADDITIONAL RANDOMIZATION CRITERIA	1. Sufficient stem cell harvest (≥ 3 x 10^6 CD34+ cells/kg of body weight) 2. Complete remission, unconfirmed complete remission or partial remission 3. Central pathology results confirming local results 4. Exclusion criterion **no. 6** not applicable for re-check for randomization
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 Non-Hodgkin lymphoma at any time 6. Only applicable for patient inclusion (registration) not applicable for re-check for randomization. Inadequate bone marrow (platelet count decreased ≥CTC grade 1, anemia >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 19. Concurrent (or planned) pregnancy or lactation 20. Fertile patients refusing to use safe contraceptive methods during the study (for details see clinical trial protocol section 4.4)
ENDPOINTS	<u>Primary efficacy endpoint:</u> Progression-free survival (PFS) time from randomization until progression, relapse, or death from any cause <u>Secondary endpoints:</u> Efficacy: • Complete response (CR) • Response duration • Overall survival (OS) • Quality of life (QOL): EORTC QLQ-C30 Safety: • (Serious) adverse events • Toxicity • Neurotoxicity (MMSE, EORTC QLQ-BN20, neuropsychological test battery)

TRIAL DESIGN	Randomized, controlled, open-label, multicenter, with 2 parallel arms	
STATISTICAL ANALYSIS EFFICACY	Primary endpoint: The primary efficacy endpoint PFS will be analyzed with a Cox proportional hazards regression model. The primary analysis will be conducted according to the intention-to-treat principle. Secondary efficacy endpoints: CR will be analyzed applying logistic regression, remission duration and OS will be investigated with Cox proportional hazards regression, QOL will be analyzed descriptively according to the EORTC manual	
STATISTICAL ANALYSIS SAFETY	Secondary safety endpoint: Rates of adverse events and of serious adverse events. Toxicity and neurotoxicity will be analyzed descriptively.	
SAMPLE SIZE CALCULATION	Sample size calculation is based on the primary endpoint PFS. We assume that the PFS rate for patients treated according to the conventional intervention (arm A) will be approximately 50% after 3 years. For comparison of the two treatment groups, a hazard ratio of 1.8 of the conventional intervention compared to the high-dose treatment (arm B) is considered to be clinically relevant. This corresponds to a PFS rate after 3 years of 68% in the high-dose intervention group, which is considered realistic. To detect a difference between arm A and arm B with a power of 80% at a two-sided significance level of 5% under this assumption, a total number of 92 events is required. Assuming an exponential model for PFS, an accrual period of 62 months and an additional follow up time of 2 years, 200 patients will have to be randomized. As follow up may be incomplete for a small number of patients, 220 patients will have to be randomized. Furthermore, some patients (about 15%) will fail to attain complete or partial remission during the first 4 chemotherapy cycles or will not be eligible for randomization due to toxicity of the induction therapy or other reasons (about 20%) and will therefore not be randomized. We assume that approximately 330 patients will need to be included in the study (start induction treatment).	
SAMPLE SIZE	To be assessed for eligibility:	n = 360
	To be included in study:	n = 330
	To be randomized:	n = 220
	To be analyzed:	n = 220
TRIAL DURATION FOR EVALUATION OF PRIMARY ENDPOINT	Recruitment period (months):	62
	First patient in to last patient out (months):	90
	Duration of the entire trial (months):	113
	Treatment duration per patient (months):	approx. 4
	Follow up per patient (months):	24
TIMETABLE FOR EVALUATION OF PRIMARY ENDPOINT	Enrolment of first patient (FPFV)	July 2014
	Enrolment of last patient (registration)	August 31, 2019
	End of trial for last patient (LPLV)	4th quarter 2021
	Final statistical analysis	4th quarter 2022
PARTICIPATING CENTERS	The study is conducted in 6 countries: Germany, Italy, Denmark, Norway, Czech Republic and Switzerland. In particular, 36 sites are involved in Germany, 41 in Italy, 4 in Denmark, 2 in Norway, 3 in Czech Republic and 6 in Switzerland.	
KEY WORDS	Primary central nervous system lymphoma (PCNSL), high-dose chemotherapy (HDT), autologous stem cell transplantation (ASCT), conventional chemotherapy	

Flow Chart

Visit schedule and assessments[1]	Screen period d -16 until d -2	Regis-tration d -1	Induction treatment: four 3-week cycles[1] (d0 to d20)						Re-Check[2]/ Randomization	Consolidation treatment[1]			EOT Visit	Follow up	FU[16]
										Arm A: R-DeVIC two 3-week cycles		Arm B: HDT-ASCT (day -8 to day 0)			
			Visit 1	Visit 2	RA I	Visit 3	Visit 4	RA II		Visit 5	Visit 6	Visit 5	RA III	Yr 1-2	Yr *** 3-5 every 6 mo
			day 0 to day 5 of cycle 1**	day 0 to day 5 of cycle 2**	d 18 to day 20 of cycle 2	day 0 to day 5 of cycle 3**	day 0 to day 5 of cycle 4**	d 18 to day 20 of cycle 4		day 0 of cycle 1	day 0 of cycle 2	Start of HDT	day 60 after[15] randomi-zation	every 3mo	Yr >5 every1 2 mo
Informed consent/ Demographic data[3]	X														
Inclusion/ Exclusion criteria	X								X						
Registration/ Randomization		X							X						
Medical history, height	X														
Pregnancy test (serum beta-hCG)	X							X					X	X****	
Treatment administration			X	X		X	X			X	X	X			
ECOG	X		X	X		X	X			X	X	X	X	X	X
MMSE, QOL (EORTC QLQ-C30, -BN20)	X							X					X	X[5]	X[5]
Neuropsychological battery[4]	X												X	X[5]	X[5]
Weight	X		X	X		X	X			X	X	X			
Vital signs*, physical and neurological examination	X		X*	X*		X*	X*			X*	X*	X*	X*	X*	X*
Hematology[6]* / clinical chemistry[7]*	X		X	X		X	X			X	X	X	X	X	X
Creatinine, estimated GFR (MDRD)	X		X	X		X	X			X	X	X			
LDH	X														
Hepatitis B/C serology, HIV test*	X														
Whole body plethysmography*	X											X	X[8]		
Electrocardiography*	X									X		X	X		
Echocardiography*	X														
Testicular ultrasound*	X														
Abdominal ultrasound*			X	X		X	X								
Whole body CT scan[9]*	X														
Whole brain MRI and response statement according to IPCG criteria	X				X			X					X	X	X
Central pathology	X								X[14]						
BM examination *	X														
Slit lamp examination	X				X[11]			X[11]					X[11]		
CSF examination[10]	X				X[11]			X[11]					X[11]		
Translational program	X[12]												X[13]		

Visit schedule and assessments[1]	**Screen period**	**Regis-tration**	**Induction treatment: four 3-week cycles**[1] **(d0 to d20)**						**Re-Check**[2]**/ Randomization**	**Consolidation treatment**[1]			**EOT Visit**	**Follow up**	**FU**[16]
										Arm A: R-DeVIC two 3-week cycles		**Arm B: HDT-ASCT (day -8 to day 0)**			
	d -16 until d -2	**d -1**	**Visit 1**	**Visit 2**	**RA I**	**Visit 3**	**Visit 4**	**RA II**		**Visit 5**	**Visit 6**	**Visit 5**	**RA III**	**Yr 1-2**	**Yr *** 3-5 every 6 mo**
			day 0 to day 5 of cycle 1**	**day 0 to day 5 of cycle 2****	**d 18 to day 20 of cycle 2**	**day 0 to day 5 of cycle 3****	**day 0 to day 5 of cycle 4****	**d 18 to day 20 of cycle 4**		**day 0 of cycle 1**	**day 0 of cycle 2**	**Start of HDT**	**day 60 after**[15] **randomi-zation**	**every 3mo**	**Yr >5 every1 2 mo**
Concomitant medication	X (see section 6.6)														
Adverse events/toxicity CTCAE			X (see section 10.1 and 10.1.2)												

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
*** Thereafter annual control examinations are recommended
**** Pregnancy test (serum beta-hCG) only once at the end of 1st year after EOT

1. Examinations and sample collection must be performed before treatment administration; delay up to five days. Interval between treatment cycles should be constant;
2. Re-evaluation of eligibility criteria;
3. Informed consent must be obtained prior to any study specific (screening) examination;
4. Neuropsychological battery;(see investigator site file division 10.2)
5. MMSE, QOL (EORTC QLQ-C30, -BN20), Neuropsychological battery after the end of therapy every 12 months;
6. Hematology: white blood count (WBC), neutrophils, hemoglobin, and platelets;
7. Blood chemistry: creatinine, total bilirubin, ALT, AST, LDH, and gamma-GT (only at screening);
8. Only for patients having received HDT-ASCT (Arm B);
9. If CT is suspicious at diagnosis: FDG-PET;
10. Only performed after excluding increased intracranial pressure by brain MRI; cytology and protein examination;
11. Only performed if positive at diagnosis, examination until results are negative;
12. Additional BM aspirate sample, CSF sample and blood sample must be taken from patients participating in the Translational Research Program before treatment administration;
13. Additional blood sample from patients participating in the translational research program at Response Assessment III or after study discontinuation;
14. Confirmation of diagnosis by central pathology must be available before randomization.
15. If start of consolidation therapy has to be postponed, RA III should be done 60 days after actual start of consolidation therapy.
16. Follow up every 6 months is recommended for **yr3-yr5**; annual follow up is recommended **> yr5** for evaluation of overall survival and late toxicities

Documentation in the CRF:

Physical and neurological examinations are recommended to be done according to the flow chart; detailed findings concerning neurological examinations must be documented in the CRF at screening.

Hematological tests and blood chemistry should be done twice a week during therapy.

Data on physical examination, vital signs and neurological evaluation will be collected by means of toxicity tables before initiating each chemotherapy cycle and at the EOT visit.

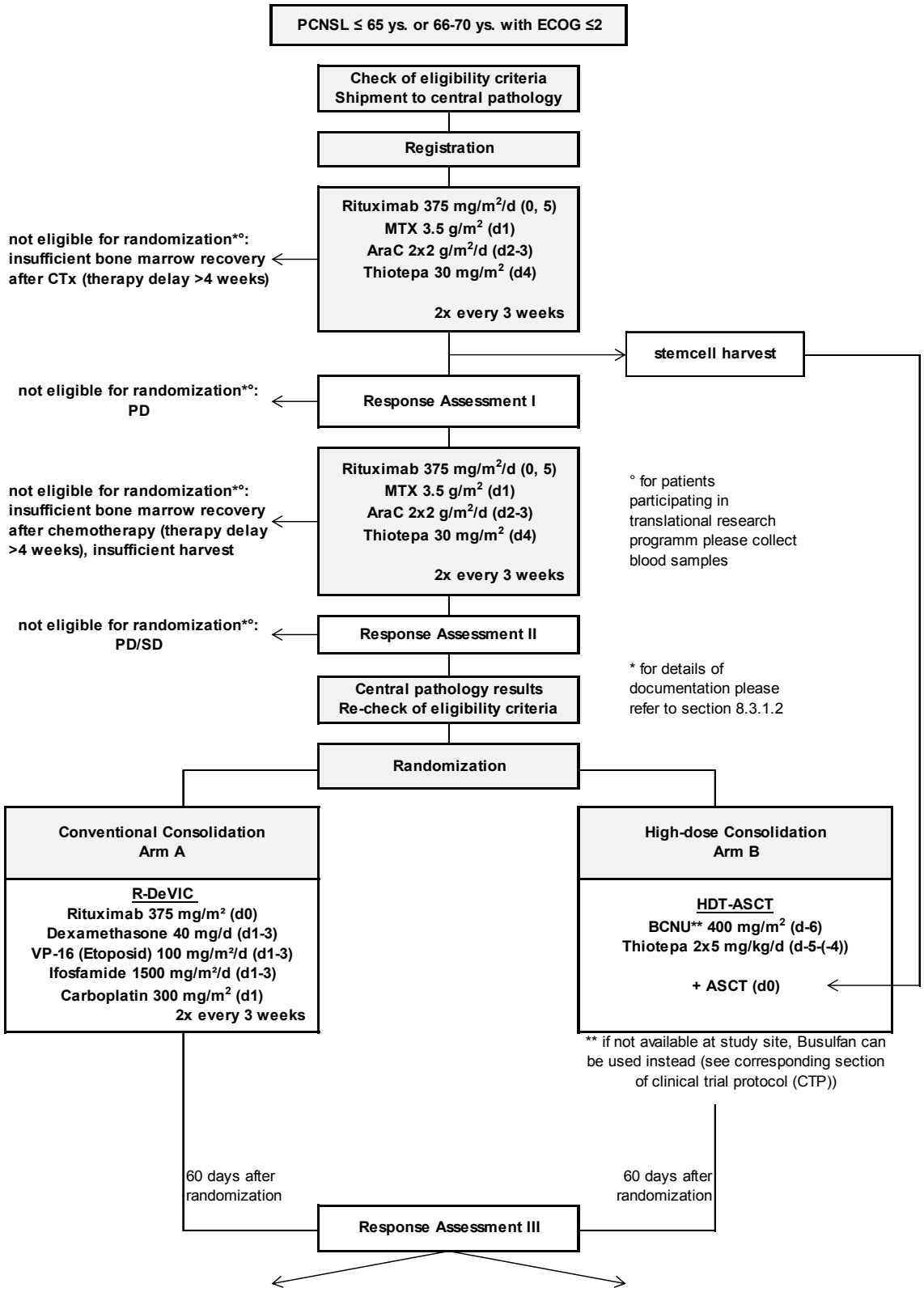
Laboratory data will be documented at screening, during therapy, at the EOT visit and during follow-up as toxicity parameters and graded according to CTCAE 4.0. Hematology includes

assessments of white blood count (WBC), neutrophils, hemoglobin, and platelets. Blood chemistry comprises creatinine, total bilirubin, ALT, AST, and gamma-GT (only at screening).

During therapy creatinine must be documented in the CRF in the measured unit to allow approximation of the kidney glomerular filtration rate (GFR) using the MDRD (Modification of Diet in Renal Disease) formula. Lactate dehydrogenase will be documented at screening by indicating "not increased" or "increased".

If a symptom/diagnosis/laboratory parameter is not available on the toxicity table an AE must be documented on the CRF AE page. If any serious criterion is fulfilled, an SAE must be reported. For details please refer to section 10.

Intervention Scheme



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1 Background and rationale

1.1 Scientific background

Primary CNS lymphoma (PCNSL) accounts for 1 to 2% of all Non-Hodgkin's lymphomas (NHL) and for 2 to 7% of all primary CNS tumors. Its incidence has increased over the past 30 years, particularly in immunocompetent individuals. Over 90% of PCNSL are lymphomas of B-cell origin, accounting to the subtype diffuse large B-cell lymphoma (DLBCL).

Prognosis without treatment resembles that of systemic high-grade NHL, and the median survival of untreated patients with PCNSL is approximately 3 months. Even though therapy has improved the outcome of PCNSL patients remains unsatisfactory when compared to patients with extra-CNS-NHL. Many questions about what constitutes the optimal therapeutic approach remain unanswered, and these must be addressed in future trials.

Historically, radiotherapy (RT) has been the standard treatment for PCNSL with response rates of 60 to 97%, a median survival of 14 months, and a 5-year survival of 3 to 26% [1]. Despite the high CR rates, almost all patients treated only with RT relapse after a few months [2]. Initial improvements were achieved with the combination of HD-MTX-based chemotherapy and WBRT leading to median survival times of 36 to 60 months [3-5]. Therefore, the addition of chemotherapy to RT has been recommended to improve the survival of PCNSL patients [6, 7]. The superiority of a combined strategy is also reinforced by three large retrospective multicenter surveys reporting therapeutic results in over 1000 patients treated in Europe and Japan [6, 8]. These studies uniformly showed that HD-MTX is the most efficient known cytostatic agent, while any regimen including all other standard regimens for treating extra-CNS malignant lymphoma without HD-MTX are associated with outcomes no better than with RT alone. Several attempts were made to optimize chemotherapy in PCNSL. As the most active drugs and regimens such as anthracycline- and cyclophosphamide-based therapies yielded unsatisfactory results due to their incapacity to cross the blood brain barrier (BBB) several attempts were made to combine the most active agent (HD-MTX) with other drugs penetrating the BBB. A first randomized phase II trial with completed recruitment on primary chemotherapy in PCNSL documented the clear superiority of combining high-dose cytarabine (HD-Ara-C) and HD-MTX compared to HD-MTX alone.[9] Complete and partial remission rates in the MTX/Ara-C arm were 46% and 23%, compared to 18% and 23% in the HD-MTX arm, respectively. Failure-free survival and OS were higher in the combined treatment group. At a median follow-up of 30 months (range 12 to 55), the HD-MTX group's 3-year FFS was 21% and 38% in the MTX/Ara-C group (p=0.01), with 3-year overall survival of 32% and 46%, respectively, (p=0.07). In a follow-up analysis OS was significantly higher with extended 46-month follow-up (45% vs. 24%; p=0.05) [personal communication with A. Ferreri, IELSG-Group]. Other agents such as lomustine, procarbacine, vincalkaloids, temozolomide and thiotepa have also been added to HD-MTX showing promising remission rates and acceptable toxicity profiles; however randomized trials to prove the superiority of these combinations over HD-MTX alone are lacking and should be initiated in the future. Rituximab is a standard agent for treating systemic B-cell lymphomas.[10] However, in PCNSL, although already in wide use, the value of rituximab

rests mainly on evidence from systemic lymphoma trials, but is now under investigation in two large ongoing randomized PCNSL studies (NCT01011920, NTR2427).

The role of high-dose chemotherapy followed by autologous stem-cell transplant (HDT-ASCT) has been investigated in several phase II trials for primary, relapsed, or refractory PCNSL and revealing promising results concerning response and survival rates.[11-15] However, randomized trials demonstrating a benefit of this concept over conventional optimized combination chemotherapy have not yet been carried out and are therefore needed. Thus the MATRix trial described herein is designed to determine whether HDT-ASCT is superior to conventional therapy as consolidation after intensified immunochemotherapy in newly diagnosed PCNSL.

The efficacy of WBRT (the current standard for consolidation after HD-MTX-based systemic treatment) is being compared to HDT-ASCT in the ongoing IELSG-32 trial. A similar question has been addressed in the current “Freiburger ZNS-NHL-Studie” focused on efficacy of the upfront transplantation, which recently finished recruitment.

1.2 Evidence: clinical trials

High-dose chemotherapy and ASCT are known to be a highly efficient treatment strategy for NHL. In the pre-rituximab-era it was the therapeutic backbone for the treatment of relapsed and refractory DLBCL as well as first-line treatment for high-risk DLBCL. Treatment of PCNSL differs from that in other DLBCL-locations due to the fact that most of the active drugs in NHL-treatment cannot pass the BBB. This problem can be overcome by using drugs penetrating the CNS and/or by increasing the doses in order to reach higher drug-levels in the CNS.

The most active chemotherapeutic drug in the treatment of PCNSL is HD-MTX. Beside protocols applying HD-MTX as a single agent, various treatment regimens containing additional chemotherapeutics have been proposed, but the only agent yet tested in a randomized trial is cytarabine, which - in addition to HD-MTX - leads to improved response and survival rates.[9] Other combinations have been investigated, of which thiotepa-containing schedules have revealed promising response and survival rates. A single-arm phase II trial assessing the chemotherapy combination named “MATILDE” included thiotepa.[16] This combination was associated with an overall response rate of 72% and a CR rate of 46% with a 5-yr OS of 42% and a persisting plateau in the survival curve. The use of thiotepa seems justified by its great bioavailability in the CNS, its high efficacy in aggressive lymphoma and in recently reported trials on PCNSL.[11, 12, 16]

Based on experience with other hematological malignancies and the need for effective consolidation treatment, HDT-ASCT was also evaluated in PCNSL. The rationale for the impact of HDT-ASCT in PCNSL is its delivery into the CNS of blood-brain-barrier (BBB) penetrating agents at several-fold higher concentrations than conventional therapy, which cannot provide such penetration. [17, 18] In recent trials we demonstrated a high rate of continuous remissions after treatment with HDT-ASCT with or without WBRT. In a first pilot and phase-II study, we treated 30 patients with PCNSL ≤ 65 years with sequential induction chemotherapy including three cycles of HD-MTX, HD-AraC, and thiotepa followed by stem-

cell harvest. The conditioning regimen consisted of carmustine and thiotepa followed by ASCT; WBRT was given as consolidation.[11] Twenty-three of the 30 patients proceeded to HDT-ASCT resulting in CR and PR in 15 and 8 patients, respectively. Twenty-one patients subsequently underwent WBRT and all achieved CR. With a median follow-up of 63 months, the 5-year OS was 69% for all patients and 87% for those completing HDT and ASCT, respectively. Five-year relapse-related mortality was 21% for all patients (n=30) and 8.7% for those 23 treated with HDT and ASCT, respectively. In a follow-up pilot study, induction chemotherapy was intensified, the thiotepa dose was doubled, and only those patients not achieving CR after induction therapy underwent WBRT.[12] Seven of eleven patients were in CR following ASCT, and 3 in PR upon ASCT received radiotherapy as consolidative treatment. After a median follow-up of 25 months, 3-year OS was 77%. None of the patients suffered from severe neurotoxicity during the follow-up period. Both trials suggest a curative effect of HDT-ASCT in young PCNSL patients. This concept, supplemented by rituximab immunotherapy, was evaluated in a phase II trial ("Freiburg ZNS-NHL Trial", ClinicalTrials.gov Identifier: NCT00647049).

Preliminary results showed an overall remission rate (ORR) for the intention-to-treat population of 91% (77% CR and 14% PR), for patients treated with HDT and ASCT (n=73) ORR was 91%.[19] After a median follow-up of 35 months, 3-year overall survival was 77.6% for all patients and 87.1% for patients after HDT.

In light of these positive findings, we initiated an ongoing international randomized phase-II trial (2 randomizations, 1st 3 arms, 2nd 2 arms) in collaboration with the International Extranodal Lymphoma Study Group (IELSG) on primary chemotherapy with HD-MTX and HD-Ara-C with or without thiotepa, and with or without rituximab (1st randomization), followed by whole brain radiotherapy vs. high-dose chemotherapy supported by autologous stem-cell transplantation (2nd randomization) for immunocompetent patients with newly-diagnosed primary CNS lymphoma (ClinicalTrials.gov Identifier: NCT01011920). In this trial, we anticipate being able to determine what constitutes the best induction treatment, as well as the superiority of HDT-ASCT or WBRT as consolidation treatment. Pilot patients have shown, apart from expected hematotoxicity, good tolerability of the combination of rituximab, MTX, Ara-C and thiotepa. This multicenter trial is being conducted in Italy, Germany, Switzerland, Denmark, Norway and the Czech Republic, and is being co-chaired equally by Andres Ferreri and Gerald Illerhaus. Gerald Illerhaus is the coordinating principal investigator of the German centers.

The "Freiburg Protocol" for HDT-ASCT as well as the "IELSG-32 Trial" are both being conducted by the "Cooperative Primary CNS-Lymphoma Study Group Freiburg" with more than 20 medical centers in Germany.

Several trials have demonstrated that consolidating strategies with non-cross-resistant cytostatic agents in first-line treatment yielded promising results in the treatment of PCNSL. In a recently published trial, etoposide in combination with cytarabine as consolidation after an induction therapy with HD-MTX, rituximab and temozolamide showed encouraging results with a 2-year time to progression of 77% in patients who completed consolidation.[20] Another regimen with dexamethasone, etoposide, ifosfamide and carboplatin (DeVIC) revealed high response rates in patients with PCNSL.[21]

1.3 Overview of products

The current standard recommendation for previously untreated PCNSL is the combination of HD-MTX and HD-Ara-C followed by WBRT.[9] In order to improve the response, the combination of HD-MTX/HD-Ara-C with thiotepa and rituximab was investigated in consecutive trials demonstrating feasibility and high efficacy [19] ClinicalTrials.gov Identifier: NCT01011920. Therefore we chose the combination of rituximab, HD-MTX, HD-Ara-C and thiotepa (4 cycles), which is assumed to be the most effective arm of the IELSG-32-trial as induction treatment.

In view of the high efficacy of the Freiburg Protocol high-dose chemotherapy with BCNU and thiotepa and autologous stem-cell transplantation was chosen as high-dose consolidation (arm B).

For the conventional consolidation (arm A) we chose a treatment of 2 cycles of R-DeVIC. The DeVIC combination chemotherapy regimen has been applied in recurrent and refractory as well as in newly diagnosed PCNSL. A retrospective analysis of 21 patients with newly-diagnosed PCNSL who received DeVIC chemotherapy followed by WBRT showed high efficacy and a good safety profile.[21] Overall response rate was 95.2% in newly diagnosed PCNSL and 83% in refractory and recurrent PCNSL. Median progression-free survival (PFS) time in newly-diagnosed PCNSL was 37.4 months, median OS time 47.8 months. The most frequent grade 3-4 adverse events related to DeVIC chemotherapy are bone marrow suppression, appetite loss, stomatitis, gastrointestinal side effects, hypokalemia and hyponetremia and about 9% grade 4 febrile neutropenias. The most common non-hematologic toxicity related to DeVIC chemotherapy was pretibial edema. All side effects were manageable, and no treatment-related deaths have been reported so far. In patients receiving WBRT after DeVIC chemotherapy important neurotoxic effects were observed in 31.6%.[21, 22]

For further characteristics of investigational products, including their side effects, see the section below and current version of corresponding SmPCs or/and Investigator's Brochure (IB), if applicable.

1.3.1 Rituximab

1.3.1.1 Background information

Rituximab is a chimeric monoclonal antibody directed against the B-lymphocyte antigen CD20. This antibody has been largely used in the treatment of B-cell lymphomas with excellent results. In particular, the addition of rituximab to CHOP chemotherapy regimen has been associated with a significant improvement in outcome in patients with diffuse large B-cell lymphoma.[23] This is a relevant aspect considering that this lymphoma category constitutes the most common histological form of PCNSL.[6] Nevertheless, rituximab has been used in PCNSL infrequently as there are many doubts about its capability to cross the blood-brain barrier (BBB). The feasibility of a combination of HD-MTX and rituximab has been demonstrated in various investigations, [19, 24] (ClinicalTrials.gov Identifier: NCT01011920), but its real contribution in the management of PCNSL remains to be defined.

1.3.1.2 Side effects

Rituximab is usually a well-tolerated agent, with some forms of infusion-related reactions (rush, bronchospasm, allergic reactions, fever, hypotension). Severe events are rare and may be related to a high tumor burden, and, with the single exception of intravascular large B-cell lymphoma,[25] they have not been reported in lymphoma patients with CNS involvement.

For further details please refer to current version of corresponding SmPCs and/or the Investigator's Brochure.

1.3.2 Methotrexate

1.3.2.1 Background information

Methotrexate functions as an antimetabolite by reversibly inhibiting dihydrofolate reductase, the enzyme that reduces folic acid to tetrahydrofolic acid. The most favorable administration schedule for MTX in PCNSL remains to be defined, due to the wide range of different doses (1-8.4 g/m^2) used in prospective trials and to its frequent association with different drugs and/or RT. The timing of HD-MTX administration has been analyzed in a single small series and no significant difference in terms of survival or toxicity was observed between the administration of 3.5 g/m^2 every 3 weeks or every 10 days.[26]

Methotrexate enters the cells in part via an active transport mechanism and is bound as polyglutamate conjugates. During longer periods of drug exposure, a higher polyglutamate formation rate is observed and more cells enter phase S, resulting in increased cytotoxicity. In a study comparing 3- vs. 6-hour infusions of MTX, the former was significantly associated with a higher response rate and increased CSF levels, although no difference in survival was observed.[27] The optimal HD-MTX schedule seems to be an initial rapid administration to overcome the distribution phase of clearance followed by a 3-hour infusion for doses up to 5 g/m^2.

In order to counter the toxic effect of HD-MTX multiple leucovorin doses should be administered ("leucovorin rescue", see Appendix 9). Before every single MTX administration, third space compart fluid must be excluded by abdominal ultrasound.

Patients with renal or hepatic insufficiency require a lower MTX dose. Peak serum levels occur within 30 to 60 min with parenteral doses; maximum myelosuppression occurs within 7 to 10 days; the duration of tumor response and hematopoietic effects is 7 to 14 days; protein binding is 50%; cerebrospinal fluid concentrations are 1% of the simultaneous serum concentration; volume of distribution is 0.4 to 0.9 L/kg; elimination half-life is 8 to 15 h; minimal hepatic metabolism is followed with 48% to 100% excreted unchanged in the urine and 9% in the feces.

Methotrexate is an effective antineoplastic agent against a variety of cancers, such as breast cancer, acute lymphoblastic leukemia, osteogenic sarcoma, head and neck cancer, ovarian cancer, NHL, colorectal carcinoma, and Hodgkin's lymphoma. In addition, the drug is used extensively for severe cases of recalcitrant psoriasis, severe rheumatoid arthritis, systemic

lupus erythematosus, and inflammatory bowel disease; however, due to potential toxicity, it should be used with caution in these patients.

1.3.2.2 Side effects

Adverse effects include leukopenia, thrombocytopenia, anemia, pancytopenia, vasculitis, neurotoxicity, headache, fever, paraplegia, cerebellar dysfunction, cranial nerve palsies, seizures, dementia, ataxia, drowsiness, paresis, colitis, toxic megacolon, gingivitis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal bleeding, stomatitis, pseudomembranous colitis, nephrotoxicity, cystitis, menstrual dysfunction, oligospermia, infertility, hepatotoxicity, conjunctivitis, blurred vision, interstitial pneumonitis, alopecia, rash, toxic epidermal necrolysis, phototoxicity, systemic lupus erythematosus, and hypersensitivity with anaphylaxis. In addition, MTX has been associated with tumor lysis syndrome and potentially life-threatening or fatal opportunistic infections.

For further details please refer to the current version of corresponding SmPCs and/or the Investigator's Brochure.

1.3.3 Cytarabine

1.3.3.1 Background information

Cytarabine is a synthetic antimetabolite that is cell-cycle specific. Ara-C is cytotoxic primarily to cells in the S-phase. High-dose therapy consists of 1-3 gr/m^2 every 12 hours. Following intravenous administration, Ara-C is widely distributed to areas including the CNS and tears. Ara-C is metabolized in the liver to an inactive metabolite; both Ara-C and its metabolite are excreted in the urine. The elimination half-life is between 1 and 3 hours.

Ara-C is useful in various neoplastic disorders including chronic myelocytic leukemia, lymphoblastic leukemia, acute lymphocytic leukemia, acute non-lymphocytic leukemia, meningeal leukemia, and NHL. Other disease states in which Ara-C has been used include herpes virus infections and psoriasis.

Ara-C has been used in different combinations with HD-MTX in the treatment of PCNSL, with encouraging results. The clinical benefit of adding HD-Ara-C to HD-MTX has been suggested by a large retrospective series [28] and a meta-analysis of 19 prospective trials [29], and was confirmed by the first worldwide randomized trial with complete accrual in PCNSL.[9] As the main conclusion from that trial, the combination of HD-MTX and HD-Ara-C could be used as control arm for future randomized trials assessing new chemotherapy combinations for newly-diagnosed PCNSL.

1.3.3.2 Side effects

The major toxic effect of Ara-C is myelosuppression resulting in megaloblastic changes in erythropoiesis and reticulocytopenia. Other adverse effects include neuropathies, gastrointestinal distress, hepatic toxicity, and hypersensitivity.

For further details please refer to current version of corresponding SmPCs and/or the Investigator's Brochure.

1.3.4 Thiotepa

1.3.4.1 Background information

Thiotepa is a cytotoxic agent of the polyfunctional alkylating type (more than one reactive ethylenimine group), related chemically and pharmacologically to nitrogen mustard. Its radiomimetic action is believed to occur through the release of ethylenimine radicals which, like irradiation, disrupt DNA bonds. One of the principal bond disruptions is initiated by alkylation of guanine at the N-7 position, which severs the linkage between the purine base and the sugar and liberates alkylated guanines. Thiotepa has been tried with varying results in the palliation of a wide variety of neoplastic diseases. However, the most consistent results have been noted in the following tumors: adenocarcinoma of the breast and ovary; for controlling intracavitary effusions secondary to neoplastic diseases of various serosal cavities; for the treatment of superficial papillary carcinoma of the urinary bladder. Some efficacy has been proven for Hodgkin's disease and other lymphomas.

Thiotepa is capable of cross-linking the DNA within a cell and changing its nature. The replication of the cell is, therefore, altered, and thiotepa may be described as mutagenic. Effective contraception should be used during thiotepa therapy if either the patient or the partner is of childbearing potential. In patients treated with thiotepa, cases of myelodysplastic syndromes and acute nonlymphocytic leukemia have been reported. There is no known antidote for overdosage with thiotepa.

A single-arm phase II trial assessing the chemotherapy combination named "MATILDE" included thiotepa.[16] This combination was associated with an ORR of 72% and a CRR of 46%, with a 5-yr OS of 42% and a persistent plateau in the survival curve. Thiotepa has been used in combination with other alkylating agents as conditioning regimens for ASCT in patients with PCNSL, both at diagnosis or relapse.[11, 12]

1.3.4.2 Side effects

Thiotepa is highly toxic to the hematopoietic system, and bone-marrow depression must be expected. Other adverse effects include: fatigue, weakness, allergic reactions, nausea, vomiting, abdominal pain, anorexia, dysuria, urinary retention, dizziness, headache, blurred vision, dermatitis, alopecia, amenorrhea, interference with spermatogenesis.

For further details please refer to current version of corresponding SmPCs and/or the Investigator's Brochure.

1.3.5 Carmustine (BCNU)

1.3.5.1 Background information

Carmustine is an alkylating agent belonging to the nitrosoureas group. These agents act by the alkylation process to inhibit DNA repair. Nitrosoureas can cross the blood-brain barrier

and are therefore used to treat brain tumors. BCNU is also effective as a single agent against lymphomas and Hodgkin's disease.

This drug has been largely used in primary brain tumors, and, importantly, in PCNSL, both at conventional doses [30] and as part of conditioning regimens before ASCT.[11, 12]

1.3.5.2 Side effects

Bone marrow suppression, notably thrombocytopenia and leukopenia, is the most common and severe toxic effect of BCNU. Myelosuppression appears later (14-28 days) and lasts longer (up to 6-8 weeks) than with most other cytotoxic drugs. Other less frequent adverse side-effects are nausea, vomiting, diarrhea, pulmonary fibrosis, skin flashing, amenorrhea and interference with spermatogenesis. Secondary carcinogenesis has occasionally been reported, as well as secondary acute myeloid leukemias.

For further details please refer to current version of corresponding SmPCs and/or the Investigator's Brochure.

1.3.6 Busulfan

Busulfan can be used if carmustine is not available at the study site.

1.3.6.1 Background information

Busulfan is an alkylating agent which reacts with the N-7 position of guanosine and interferes with DNA replication and RNA transcription. Busulfan has a more marked effect on myeloid cells than on lymphoid cells and is also very toxic to hematopoietic stem cells. Busulfan exhibits little immunosuppressive activity, and interferes with the normal function of DNA by alkylation and cross-linking the strands of DNA.

This drug has been successfully used as part of conditioning regimen before ASCT in the salvage situation.[14]

1.3.6.2 Side effects

Most frequent side effects (>10%) are bone marrow suppression, notably neutropenia (onset: 4 days; median recovery: 13 days), thrombocytopenia, lymphopenia and anemia. Furthermore tachycardia, hypertension, edema, thrombosis, chest pain, vasodilation, hypotension, insomnia, fever, anxiety, headache, chills, pain, dizziness, depression, confusion, rash, pruritus, alopecia, hypomagnesemia, hyperglycemia, hypokalemia, hypocalcemia, hypophosphatemia, vomiting, nausea, mucositis/stomatitis, anorexia, diarrhea, abdominal pain, dyspepsia, constipation, xerostomia, rectal disorder, abdominal fullness, hyperbilirubinemia, increased ALT, hepatic sinusoidal obstruction syndrome (SOS; veno-occlusive disease), alkaline phosphatase increased, jaundice, weakness, myalgia, arthralgia, rhinitis, lung disorder, cough, epistaxis, dyspnea, infections and allergic reactions.

For further details please refer to current version of corresponding SmPCs and/or the Investigator's Brochure.

1.3.7 Dexamethasone

1.3.7.1 Background information

Dexamethasone possesses verifiable high cytotoxic effectiveness for the treatment of NHL. In some PCNSL patients treated with dexamethasone monotherapy the tumor disappeared completely for several months or even years. Dexamethasone is an integral component of the pediatric multi-center-protocol for the therapy of child Burkitt-lymphoma with initial CNS-manifestation.[31] Many of the steroid-induced side effects are even more severe in patients with PCNSL, because they have often been on dexamethasone medication for several weeks before having begun the specific chemotherapy to reduce cerebral edema. Regarding possible complications under high-dose-polychemotherapy, the immunosuppression caused by the primary disease is extremely unfavorable and it is even increased in case of long-term steroid medication. However, discontinuation of steroid treatment is desirable but often not realizable. For this reason, dexamethasone should be reduced gradually and have ceased as soon as possible after initiating the specific therapy.

Because of its cytotoxic potency, dexamethasone treatment should only be included in the protocol provided the taking of steroids was discontinued several weeks prior to administration of the specific therapy.

1.3.7.2 Side effects

Most frequent side effects are adrenal suppression, immunosuppression, Kaposi's sarcoma, myopathy, psychiatric disturbances, arrhythmia, edema, hypertension, syncope, thromboembolism, vasculitis, headache, vertigo, acne, allergic dermatitis, alopecia, angioedema, hirsutism, hyper-/hypopigmentation, hypertrichosis, petechiae, rash, skin atrophy, striae, Cushing's syndrome, diabetes mellitus, hyperglycemia, menstrual irregularities, abdominal distention, increased appetite, gastrointestinal hemorrhage, gastrointestinal perforation, nausea, pancreatitis, peptic ulcer, ulcerative esophagitis, altered (increased or decreased) spermatogenesis, hepatomegaly, arthropathy, aseptic necrosis (femoral and humoral heads), fractures, muscle mass loss, neuropathy, osteoporosis, parasthesia, tendon rupture, vertebral compression fractures, weakness, cataracts, exophthalmus, glaucoma, increased intraocular pressure, pulmonary edema, anaphylaxis, moon face and secondary malignancy.

For further details please refer to current version of corresponding SmPCs and/or the Investigator’s Brochure.

1.3.8 VP-16 (Etoposide)

1.3.8.1 Background information

VP-16 (Etoposide) belongs to the drug type topoisomerase inhibitor causing errors in DNA synthesis and by doing so promoting apoptosis of the cancer cells. The most frequent indications for the use of etoposide in oncologic treatments are sarcoma, lymphoma, glioblastoma and lung and testicular cancer. Etoposide can be given orally or intravenously

and often in combination with other cytotoxic drugs. It can cross the BBB and is thus effective in the treatment of intrecerebral malignancies.

1.3.8.2 Side effects

Most frequent side effects (>10%) are myelosuppression (leukopenia, thrombocytopenia, anemia) alopecia, nausea/vomiting, anorexia and diarrhea. Other less frequent side effects are hypotension, stomatitis, abdominal pain, hepatic toxicity, peripheral neuropathy, anaphylactic-like reaction and secondary AML.

For further details please refer to current version of corresponding SmPCs and/or the Investigator's Brochure.

1.3.9 Ifosfamide

1.3.9.1 Background information

Ifosfamid is an alkylating agent. Its effective metabolites are activated in the liver. It connects covalently to proteins as well as to DNA. It anastomoses with DNA-strangs, can also cause cut offs, and furthermore block DNA-synthesis. Hemorrhagic cystitis can be prevented when treating the patient with uromitexan (MESNA). The MESNA prophylaxis is applied 0, 4, and 8h after the end of the ifosamidinfusion.

1.3.9.2 Side effects

Most frequent side effects (>10%) are myelosuppression (leukopenia, anemia, thrombopenia), CNS toxicity or encephalopathy, alopecia, metabolic acidosis, nausea/vomiting, hematuria. Less frequent side effects are fever, anorexia, neutropenic fever, bilirubin increased, liver dysfunction, transaminases increased, phlebitis, renal impairment and infection.

For further details please refer to current version of corresponding SmPCs and/or the Investigator's Brochure.

1.3.10 Carboplatin

1.3.10.1 Background information

Carboplatin is an alkylating cytotoxic drug that binds covalently to DNA bases and disrupts DNA function. It is administered intraveneously as monotherapy or in most indications, in combination with other cytotoxic drugs. Carboplatin is widely used to treat different malignant tumors such as lung cancer, gynecologic malignancies, bladder cancer, head and neck tumors. The dosage must be calculated according to the patient's pre-existing renal function as those with impaired renal function are at high risk of severe bone marrow suppression.

Carboplatin crosses the blood-brain-barrier and is thus effective in the treatment of CNS lymphoma and other brain malignancies.

1.3.10.2 Side effects

The most important toxicities observed under carboplatin treatment are alopecia, skin rash, gastrointestinal side effects such as nausea, vomiting and diarrhea, hepatic toxicities, bone marrow suppression, peripheral neuropathies, nephrotoxicity, bronchospasm, and seldom reported, anaphylactic reactions.

For further details please refer to current version of corresponding SmPCs and/or the Investigator's Brochure.

1.4 Trial purpose and rationale

Primary central nervous system lymphoma (PCNSL) is a highly aggressive disease with rising incidence over the past 30 years. Similar to other hematological diseases, the rationale for consolidation in PCNSL is the elimination of minimal residual disease. The efficacy of WBRT, which is the current standard for consolidation after HD-MTX-based systemic treatment, is being compared to HDT-ASCT in the ongoing IELSG-32 trial.

High-dose chemotherapy with carmustine or busulfan and thiotepa followed by autologous stem cell transplantation has been shown to be feasible and highly effective in newly diagnosed eligible patients, but also in the salvage situation.[11, 12, 14]

The question we aim to answer is whether HDT-ASCT is superior to conventional therapy as consolidation after intensified immunochemotherapy in newly diagnosed PCNSL.

1.4.1 Rationale for this study

Based on previously-obtained good results from the treatment of recurrent or refractory PCNSL the DeVIC protocol was chosen for conventional consolidation treatment. This protocol, originally designed as a salvage protocol for agressive NHL, crosses the blood-brain barrier and consists of multidrug resistant-unrelated agents.[21, 22]

As described above, the investigators presented encouraging remission- and survival rates with the introduction of high-dose carmustine/thiotepa and ASCT in first-line treatment for newly-diagnosed PCNSL.[11, 12] Because of these data, the high-dose protocol the investigators established is now considered the standard for treating younger patients with PCNSL in Germany. However, these findings are from non-randomized phase-II trials including well-selected patients. Furthermore, this aggressive HDT-ASCT approach is accompanied with a potentially higher risk for treatment-associated morbidities, as well as higher health costs. Whether PFS and OS benefits outweigh these potential limitations is still unclear. This is why a randomized phase-III trial to compare HDT-ASCT with optimized conventional chemotherapy is urgently needed to answer these important clinical questions.

1.4.2 Translational research program

For details please refer to Appendix 7.

1.4.3 Rationale for dose regimen

All induction-therapy drugs and arm B of the consolidating regimen will be administered according to our ongoing IELSG 32 trial and prior trials of our study group. For Drug administration see Appendix 8.

1.4.3.1 Rituximab

Rituximab will be given intravenously at 375 mg/m^2. The first dose of Rituximab of each cycle will be administered on day 0. The second dose of Rituximab of each cycle will be administered on day 5. The chosen dose is the current standard in NHL treatment protocols. The day 0 and +5 schedule was chosen as the bioavailability in the CNS is compromised due to the blood-brain-barrier. By applying 2 doses before and after chemotherapy, we are assuming that the intracerebral dose is superior to one dose every 2 weeks.

1.4.3.2 Methotrexate

High-dose MTX has been established as the most effective drug in PCNSL. The most favorable administration schedule for MTX in PCNSL still needs to be defined due to its wide range of doses (1-8.4 g/m^2) used in prospective trials and to its frequent association with different drugs. The timing of MTX administration was analyzed in a single small series of patients, and no significant difference in terms of survival or toxicity was observed between the administration of 3.5 g/m^2 every 3 weeks or every 10 days.[32] MTX will be administered at day 1 of each induction treatment cycle and will be given intravenously at 0.5 g/m^2 in 15 minutes and then 3 g/m^2 as a 3-hour infusion. High-dose MTX administration requires a urinary pH ≥8 and a diuresis >100 ml/h.

1.4.3.3 Cytarabine (Ara-C)

High-dose cytarabine has been used in different combinations with HD-MTX in the treatment of PCNSL, mostly yielding encouraging results. High-dose therapy consists of 1-3 g/m^2 every 12 hours. Cytarabine will be given intravenously at 2 g/m^2 over 1 hour, twice a day (every 12 hours) on two consecutive days (days 2 and 3).

1.4.3.4 Thiotepa

Thiotepa has been used in combination with other alkylating agents as conditioning regimens for ASCT in patients with PCNSL, both at diagnosis or relapse [11, 12, 14]. A single-arm phase II trial assessing the chemotherapy combination named "MATILDE" included thiotepa [16]. This combination has been associated with a persistent plateau on the survival curve. Thiotepa will be given intravenously at 30 mg/m^2 over 30 minutes on day 4 during induction chemotherapy.

1.4.3.5 Rituximab, Dexamethasone, VP-16 (Etoposide), Ifosfamide, Carboplatin

The doses of this medication within the R-DeVIC-regimen are standard doses within common lymphoma protocols.

1.4.3.6 Carmustine (BCNU) and Thiotepa in high-dose consolidation

We investigators have investigated extensively the combination of high-dose carmustine and thiotepa in previous trials. Escalation of the thiotepa dose did not result in higher toxicities. The dose-limiting toxicity of the combination of BCNU and thiotepa is hematotoxicity, compensated by stem-cell rescue. BCNU will be given intravenously at 400 mg/m² over 1 hour on day -6. Thiotepa will be given intravenously at 5 mg/kg over 2 hours twice a day (every 12 hours) on two consecutive days (days -5 and -4).

1.4.3.7 Busulfan and Thiotepa in high-dose consolidation

The combination of busulfan and thiotepa has been investigated as a conditioning regimen in the salvage situation [14, 33], showing promising results; it can therefore be administered if carmustine is not available at the investigation site. Analogous to the carmustine/thiotepa regimen, the dose-limiting hematoxicity of the combination busulfan and thiotepa is compensated by stem-cell rescue. Busulfan will be given intravenously at 3,2 mg/kg over 2 hours on two consecutive days (days -8 and -7). Thiotepa will be given intravenously at 5 mg/kg over 2 hours twice a day (every 12 hours) on two consecutive days (days -5 and -4).

1.5 Risk-benefit assessment

Untreated PCNSL has a dismal prognosis with a median survival time of approximately 3 months. Current treatment strategies have genuinely improved survival and shown a curative potential in a considerable number of patients. The combination of rituximab, HD-MTX, Ara-C and thiotepa as well as conditioning regimens including HD-chemotherapy (BCNU/ thiotepa) and DeVIC have demonstrated feasibility and high efficacy in former and ongoing trials (IELSG-Trial). Thus the treatment regimens are considered active and safe, having improved the outcome of patients suffering from PCNSL. We therefore expect that our trial's results will provide evidence of the benefit of this treatment, overcoming the potential risks.

2 Objectives and endpoints

Comparison of high-dose chemotherapy followed by autologous stem cell transplantation with optimized conventional chemotherapy regarding PFS, OS, treatment response (rate of complete responses) and treatment related morbidities (neurotoxicity and adverse advents) in patients with primary CNS lymphoma.

Table 1 Objectives and related endpoints

	Objectives	Endpoints
Primary	To demonstrate the efficacy measured as progression-free survival (PFS) of intensive chemotherapy followed by autologous stem-cell transplantation compared to conventional chemo-therapy	PFS is defined as the time from randomization until PD or relapse or death from any cause
Secondary Efficacy	To compare HDT-ASCT with optimized conventional chemotherapy regarding CR	CR will be determined on day 60 after randomization

	Objectives	Endpoints
	To compare HDT-ASCT with optimized conventional chemotherapy regarding response duration	Response duration is defined as time from CR, CRu or PR until relapse or PD
	To compare HDT-ASCT with optimized conventional chemotherapy regarding OS over time	OS is defined as time from randomization until death of any cause
	To compare HDT-ASCT with optimized conventional chemotherapy regarding quality of life (QOL) over time	EORTC QLQ-C30
Secondary Safety	To compare HDT-ASCT with optimized conventional chemotherapy regarding safety	(Serious) adverse events
	To compare HDT-ASCT with optimized conventional chemotherapy regarding toxicity	toxicity tables
	To compare HDT-ASCT with optimized conventional chemotherapy regarding neurotoxicity	MMSE, EORTC QLQ-BN20, Neuro-psychological battery

2.1 Primary objective and endpoint

The primary endpoint of this study is progression-free survival (PFS), defined as time from randomization to disease progression (PD), disease relapse after achieving CR, or death from any cause.

2.2 Secondary objectives and endpoints

For definitions of IPCG response criteria please refer to Appendix 2.

Response evaluation during this trial will be determined by an independent radiological review committee, not involved in the conception of the study

CR will be determined on day 60 after randomization.

For PFS, OS, and response duration observation times for patients in whom the event of interest was not observed will be censored at the time last seen alive without the respective event.

3 Clinical trial plan

3.1 Trial design

This is a randomized, controlled, open-label, multicenter phase III trial with two parallel arms.

3.2 Treatment arms

All enrolled patients will receive induction chemotherapy with rituximab, HD-MTX, HD-Ara-C and thiotepa (MATRix regimen). The maximum number of induction chemotherapy courses will be four. Chemotherapy will be administered every three weeks. Patients in complete

remission (CR), unconfirmed complete remission (CRu), partial remission (PR) or stable disease (SD) after 2 courses will receive additional two courses of the primary chemotherapy regimen. Stem-cell harvest will be performed after the second course for all patients.

Response assessment by brain MRI will be done after the second and the fourth course. Patients not achieving CR, CRu, PR or SD after the second course, and patients not achieving CR, CRu or PR after the fourth course, as well as those who experience progressive disease (PD) at any time will be assigned to off-study salvage therapy. Patients whose stem-cell harvest is insufficient after three cycles of induction treatment will be treated off-study as well.

For the documentation of survival data after premature study termination please refer to section 8.3.2.3.

After 4 cycles of induction chemotherapy, the inclusion and exclusion criteria will be re-evaluated (for details see section 4.5). Only those patients achieving PR or CR after 4 cycles of induction chemotherapy are eligible for randomization. The enrolled patients will be randomized to undergo conventional consolidation with R-DeVIC (arm A) or consolidating high-dose chemotherapy with BCNU (or busulfan if BCNU is not available) and thiotepa followed by ASCT (arm B).

After the end of treatment visit, patients will remain in follow-up for at least 24 months. Further annual control examinations are recommended afterwards as described in the study flow chart. Patients who achieve a CR, unconfirmed CR or PR (in comparison to baseline MRI) will proceed to regular follow-up. In case of CRu and PR (in comparison to baseline MRI), close monitoring of the patient by MRI is recommended to confirm the response status. Patients with PD (in comparison to baseline / best response) or relapse after randomization will undergo WBRT or salvage high dose chemotherapy according to the investigators choice.

For details on treatment arms, refer to the section 6.1.

3.3 Treatment duration

Patients will continue on therapy until the completion of induction and consolidation treatment, discontinuation due to intolerable toxicity, withdrawal of consent, death or termination of the trial.

3.4 Trial timetable (for trial duration is valid for evaluation of primary endpoint)

Enrolment of first patient (FPFV)	July 2014
Enrolment of last patient (registration)	August 31, 2019
End of trial for last patient (LPLV)	4th quarter 2021
Final statistical analysis	4th quarter 2022
Treatment duration per patient	approx. 4 months

3.5 Participating sites

We plan to recruit patients from 36 sites in Germany. Furthermore, the International Extranodal Lymphoma Study Group (IELSG) participates in the trial with the following countries : Italy, Denmark, Norway, Czech Republic and Switzerland. In particular, 36 sites are involved in Germany, 41 in Italy, 4 in Denmark, 2 in Norway, 3 in Czech Republic and 6 in Switzerland.

3.6 Number of patients

250 patients will be enrolled in the study
To be assessed for eligibility (n = 360)
To be included in study (n = 330)
To be randomized (n = 220)
To be analyzed (n = 220)

4 Trial population and selection criteria

4.1 Target population / main diagnosis

4.1.1 Target population

Immunocompetent patients (age 18-65 years irrespective of ECOG or 66-70 years (with ECOG Performance Status ≤ 2) with newly-diagnosed, histologically proven PCNSL considered eligible for the study treatment at the time of diagnosis will be included in the study. Due to the median age of 60 years at the diagnosis of PCNSL, we will have a large majority of patients potentially qualified for this trial.

4.2 Inclusion criteria

Patients eligible for inclusion in this trial must meet all of the following criteria:

1. Immunocompetent patients with newly-diagnosed primary central nervous system B-cell lymphoma
2. Age 18-65 years irrespective of ECOG or 66-70 years
   (with ECOG Performance Status ≤ 2)
3. Histologically or cytologically assessed diagnosis of B-cell lymphoma by local pathologist. Diagnostic sample obtained by stereotactic or surgical biopsy, CSF cytology examination or vitrectomy
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. Previously untreated patients (previous or ongoing steroid treatment admitted)

8. Sexually active patients of childbearing potential who agree to take adequate contraceptive measures during study participation
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

4.3 Additional randomization criteria:

1. Sufficient stem cell harvest (≥3x 10^6 CD34+ cells/kg of body weight)
2. Complete remission, unconfirmed complete remission or partial remission
3. Central pathology results confirming local results.
4. Exclusion criterion **no. 6** not applicable for re-check for randomization

4.4 Exclusion criteria

Patients eligible for this trial must not present any of the following 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 Non-Hodgkin lymphoma at any time
6. Only applicable for patient inclusion (registration) not applicable for re-check for randomization. Inadequate bone marrow (platelet count decreased ≥CTC grade 1, anemia ≥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 study inclusion
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
19. Concurrent (or planned) pregnancy or lactation
20. Fertile patients refusing to use safe contraceptive methods during the study

Female patients:

Women can only take part in this study if the risk of becoming pregnant is absolutely minimized. Therefore, only the following conditions are suitable:

- Women, who use safe contraception throughout the duration of the study (i.e. from the time of written consent until 12 month after study treatment discontinuation)
  The following safe methods of contraception for women must be used: female condoms, diaphragm or coil, each used in combination with spermicides; intrauterine device; hormonal contraception in combination with a mechanical method of contraception.
- Women, who can present a negative pregnancy test 2 weeks before registration
- Surgically-sterilized women (tubal ligation, hysterectomy) with a written certificate issued by the treating physician
- Postmenopausal women who have not had a menstrual period for at least 2 years

According to the SmPC (summary of product characteristics) of methotrexate women of childbearing potential should not be started on methotrexate until pregnancy is excluded. Women undergoing treatment with methotrexate should use effective contraceptive methods during therapy and until 6 months after discontinuation of therapy. Women should be fully counselled on the serious risk to the foetus should they become pregnant while undergoing treatment. Methotrexate can cause genetic damage.

Men and women undergoing treatment with methotrexate should use effective contraceptive methods during and after discontinuation of therapy.

According to the SmPC of rituximab women of childbearing potential must be informed during the informed consent procedure that they must not become pregnant during the study. Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during and for 12 months following treatment with rituximab.

According to the SmPC of thiotepa women of childbearing potential have to use effective contraception during treatment and a pregnancy test should be performed before treatment

is started. In pre-clinical studies thiotepa, as most alkylating agents,has been shown to cause embryofoetal lethality and teratogenicity. Therefore, thiotepa is contraindicated during pregnancy.

Patients must agree to abstain from donating blood during study participation until 12 months after study treatment discontinuation.

Male patients:

Men must agree to use a latex condom during sexual contact with females of childbearing potential while participating in this study and until 12 month after study treatment discontinuation even if he has undergone a successful vasectomy.

According to the SmPC of **methotrexate** it can induce chromosomal damage in human spermatozoa. Men undergoing treatment with methotrexate should use effective contraceptive methods during and until 6 months after treatment. Men should seek advice on sperm preservation due to the possibility of irreversible infertility caused by therapy.

According to the SmPC of **rituximab** patients must be informed, that due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during and for 12 months following treatment with Rituximab.

According to the SmPC of **thiotepa** male patients must be informed during the informed consent procedure that they should seek for sperm cryopreservation before therapy is started and should not father a child while treated and during the year after cessation of treatment.

Men will be warned that sharing the study drug is prohibited and will be counseled about pregnancy precautions and the potential risk of fetal exposure.

Patients must agree to abstain from donating blood or sperm during study participation until 12 months after study treatment discontinuation.

If pregnancy or a positive pregnancy test does occur in a study patient or the partner of a male study patient during study participation, the study drug must be discontinued immediately.

4.5 Re-evaluation of eligibility

Patients eligible for randomization in this trial must meet all of the above mentioned inclusion and exclusion criteria. As randomization takes place after 4 courses of chemotherapy, a re-evaluation of eligibility criteria will be conducted, adding the following inclusion and exclusion criteria:

<u>Additional randomization criteria:</u>

- Sufficient stem cell harvest (≥ 3 x 10^6 CD34+ cells/kg of body weight)
- Complete remission, unconfirmed complete remission or partial remission

- Central pathology results confirming local results.
- Exclusion criterion **no. 6** not applicable for re-check for randomization

5 Enrolment and patient registration

5.1 Patient eligibility

If a patient appears to be eligible for the trial, the investigator will inform the patient about the trial and ask the patient for his/her written consent. It is imperative that written consent is obtained prior to any trial-specific procedures. The investigator will then record the details of these trial patients on the following trial-specific lists:

- **Patient screening log**: for trial documentation: patients whose eligibility was checked before initiating the clinical trial. The following will be entered: the identification code*, the dates of written consent, screening and mode of enrolment (e.g. registration/randomization), as well as details of whether the patient was enrolled in the trial and, if not, the reason for not enrolling the patient.

- **Patient identification log**: A confidential log of the names of all trial patients with the identification code* assigned to each patient at the time of enrollment in the clinical trial. With this list, each patient's identity can be revealed. The list must be kept confidential and must not leave the institution. It must remain at the trial center and must not be copied or otherwise passed on! Sponsor representatives, auditors and representatives of authorities must be allowed to inspect the list on request.

* Patient identification code: A unique trial-specific identification number will be assigned to each patient. The first 2 digits correspond to the number of the site, the next 3 digits stand for the consecutively screened patients at the particular site, for example: 01001 (Site 1, Patient 1), so that each patient has a unique number across the entire database.

5.2 Patient registration and randomization for all German sites and all IELSG sites

Patients fulfilling the eligibility criteria will be centrally registered at the randomization and data management office at the Clinical Trials Unit (CTU) of the Medical Center – University of Freiburg. Treatment should start as soon as possible after registration. After 4 cycles of induction therapy and re-checking the eligibility criteria, i.e. immediately before starting consolidation treatment, the patient will be centrally randomized at the CTU to the treatment arms. The entire procedure is described in the section below.

5.2.1 Patient registration

The patient identification code assigned for the trial will be entered on the registration form and the questions on inclusion/exclusion criteria, presence of informed consent, sex and patient's agreement to participate in the Translational Research Program on the form will be answered. The biopsy sample should be shipped to central pathology. A shipment form for the shipping of samples will be made available to the sites together with the ISF (Investigator

site file) when the site is initiated. A shipment form (ISF) must be filled out. The fully completed registration form should then be faxed to the CTU for registration:

Clinical Trials Unit
Medical Center - University of Freiburg
Fax: +49 761 270-74390

Registration times:
Monday to Friday from 9:00 to 16:30

The CTU will review the patient's details on the registration fax. It will then confirm the patient's enrollment in the trial by fax.

The shipping of the biopsy samples must be confirmed on the registration form.

5.2.2 Central randomization by fax

The patient identification code - the same number as in the registration - will be entered on the randomization form and the questions on re-checking the inclusion/exclusion criteria on the form will be answered. The fully completed form will then be faxed to the CTU for randomization (the same contact data as for registration see above).

The CTU will review the patient's details on the randomization fax and randomize the patient. The treatment can be initiated according to the randomized treatment arm.

If the details on the randomization fax appear incomplete or implausible, the CTU will send the investigator a query fax for clarification.

5.2.3 Randomization methodology

A randomized design (block randomization with randomly-varying block sizes with an allocation ratio of 1:1) is applied in order to ensure comparability of the treatment groups. Central randomization by fax will be performed to guarantee concealment of the treatment allocation. Stratification according to response status (CR or PR) after 4 courses of induction chemotherapy will be performed. Patients with SD or PD after induction treatment will be treated off-study. No stratification by study centers will take place, because many centers having small numbers of patients will be included in the trial. Study site-initiated stratification could create problems with the statistical analysis (unstable treatment effect estimation). See EMA Points to Consider on Adjustment for Baseline Covariates, section II.3, CPMP/EWP/2863/99. Randomization will take place after 4 cycles of induction therapy, i.e. immediately before starting treatment with either HDT-ASCT or R-DeVIC in order to enable an analysis according to the intention-to-treat (ITT) principle with as few protocol violators or drop-outs as possible.

The block lengths will be documented separately and will not be disclosed to the centers. The randomization code will be produced by validated programs based on the Statistical Analysis System (SAS®).

6 Treatment plan and procedure

6.1 Interventions

for details please see Appendix 8

6.1.1 Induction treatment

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

- Rituximab 375 mg/m²/d i.v. (d 0,5)
- MTX 3,5 g/m² i.v. (d1)
- Ara-C 2 x 2 g/m²/d i.v. (d2-3)
- Thiotepa 30 mg/m² i.v. (d4)

Patients with PD after two cycles, SD/PD after four cycles of induction therapy or insufficient stem-cell harvest after three cycles are ineligible for randomization.

6.1.2 Consolidation Arm A

2 cycles of R-DeVIC (every 3 weeks):

- Rituximab 375 mg/m²/d i.v. (d0)
- Dexamethasone 40 mg/d i.v. (d1-3)
- Etoposide 100 mg/m²/d i.v. (d1-3)
- Ifosfamide 1500 mg/m²/d i.v. (d1-3)
- Carboplatin 300 mg/m² i.v. (d1)

6.1.3 Consolidation Arm B

High-dose chemotherapy (HDT-ASCT):

- BCNU* 400 mg/m² i.v. (d-6)
- Thiotepa 2 x 5 mg/kg/d i.v. (d-5-(-4))
- ASCT (d0)

* if BCNU is not available at the investigation site, busulfan can be administered instead:
- Busufan 3,2 mg/kg/d (d-8-(-7))
- Thiotepa 2 x 5 mg/kg/d i.v. (d-5-(-4))
- ASCT (d0)

6.2 Dose modification and dose delay in case of hematologic toxicity

Investigators should follow the guidelines below for dose modification of treatment with investigational product; any deviation must be discussed previously with the sponsor unless it concerns a patient's safety. All dose changes or interruptions must be recorded on the appropriate CRF page.

In case of inadequate bone marrow recovery, that is ANC <1.500/µl (<1.200/µl in arm "A") and platelets <90.000/µl, on the intended day of re-treatment, the start of the next cycle can

be delayed for a maximum of 4 weeks. Thereafter, chemotherapy must be discontinued, and patients will be treated according to the investigator's decision. For documentation details in the CRF please refer to section 8.3.1.2 .

The dose of cytostatics during the following courses will be determined according to the nadir neutrophil or platelet counts of the previous course as follows:

Table 2 Dose reduction procedure in case of hematologic toxicity: neutrophils

Nadir neutrophils/µl	Induction treatment	R-DeVIC Arm A	HDT-ASCT Arm B
Complicated neutropenia	25% decrease of Ara-C dose*	30% decrease of carboplatin, ifosfamide, etoposide	Unchanged

*Ara-C dose reduction consists of the omission of the 4th dose of the drug (2nd dose of the day 3)

Table 3 Dose reduction procedure in case of hematologic toxicity: platelets

Nadir platelets/µl	Induction treatment	R-DeVIC Arm A	HDT-ASCT Arm B
Complicated grade 4 thrombopenia	25% decrease of Ara-C* and thiotepa dose	30% decrease of carboplatin, ifosfamide, etoposide	Unchanged

*Ara-C dose reduction consists of the omission of the 4th dose of the drug (2nd dose of the day 3)

6.3 Dose modification and dose delay in case of non-hematologic toxicity

Dose modification should be managed according to the investigator`s judgement and as recommended in the drug information. Rituximab infusion reactions will be managed according to international guidelines.

6.4 Permitted prior/concomitant treatment/medication

6.4.1 Permitted prior treatment/medication

Patients with newly-diagnosed PCNSL often receive corticosteroids to reduce perifocal brain edema. However, whenever possible, steroids should be tapered out as early as possible before biopsy or at the very latest, once chemotherapy has started. If patients suffer from epilepsy due to lymphoma manifestations, anti-epileptic drugs are allowed and can be continued as clinically indicated (see 6.4.2).

The patient must notify the investigational site about any new medications he or she is taking after starting the trial medication.

6.4.2 Permitted concomitant treatment/medication

The following drugs can be applied in our trial: antiemetics, analgesics, antibiotics, anticonvulsants, sedatives, antihyperuricemic agents as well as other therapies to control metabolic and malnutrition disturbances.

Corticosteroids during treatment and their definitive interruption will depend on clinical requirements. If possible, corticosteroids should be tapered out once chemotherapy has started. It is important that the type and doses of corticosteroids be accurately recorded. Oral antiviral, antifungal and antipneumocystic prophylaxis is strongly suggested. Antimicrobial drugs should be interrupted during chemotherapy administration to avoid potentially negative pharmacological interactions.

Rituximab infusion reactions will be managed according to international guidelines.

Folinic-acid rescue starts 24 hours after the start of MTX infusion and is recommended to be scheduled and documented according to the attached leucovorin rescue sheet (see Appendix 9). The post-MTX hydration should attain a total volume of 2000 ml.

All further medications during the trial must be documented in the patient file, as well as the indication, dosage and period of administration. All medications not triggering known interactions can be given during the trial if necessary and clinically indicated.

Note: Avoid the use of other hepatotoxic (azathioprine, retinoids, sulfasalazin) and renal toxic (NSAIDs, cotrimoxazole, allopurinole, aciclovir) agents during MTX exposure. Within two days prior/after MTX administration proton pump inhibitors should be stopped and contrast agents should not be administered.

Patients who achieve a CR, unconfirmed CR or PR after randomized study treatment in comparison to baseline will be preceded to regular follow-up. In case of CRu and PR in comparison to baseline, a close monitoring of the patient by MRI is recommended to confirm response status.

Patients who do not respond to the induction therapy or experience radiologically or cyto-histologically proven relapse or progression during or after the randomized study treatment in arm A or B will be submitted to a salvage treatment according to the investigator´s choice. Salvage therapy can start anytime during or after primary chemotherapy if progressive disease has been documented, provided recovery from hematological toxicity from the last chemotherapy has been verified.

6.4.3 Treatment in an emergency

Patients should receive treatment/medication appropriate to their clinical condition in an emergency.

6.5 Prohibited concomitant therapy

Additional cytotoxic therapy, biological responsive modifiers and drugs possibly interfering in the action or pharmacokinetics of rituximab, MTX, Ara-C, thiotepa, dexamethasone, etoposide, ifosfamide, carboplatin or BCNU (busulfan where necessary) must be avoided.

6.6 Documentation of concomitant medication in the CRF

The following CM must be documented in the CRF: corticosteroids and PJP prophylaxis. Documentation of the stated above CM starts beginning from the registration date and ends with the date of PD confirmation or end of the study (whichever occurs first).

6.7 Treatment and health care after end of the study

After two years of follow-up, control examinations should take place every six months within years 3 to 5 and annually thereafter (for details see study flow chart).

7 Visit schedule and assessments

7.1 Flow and visit schedule

A detailed Flow Chart (Visit schedule and assessments) is provided in the synopsis (see page 17). The schedule of assessment lists all of the assessments and indicates with an “X” the visits when they are be made. All data obtained from these assessments must be verifiable in the patient’s source documentation and are to be documented in the CRF (except those marked with “*”).

7.2 Visit and assessment windows

Screening evaluations must be performed within 14 days prior to registration between days -16 and -2.

During the course of the trial visits and test procedures should be conducted on schedule whenever possible; visits that occur ±5 days from the scheduled date will not be considered a protocol deviation.

7.3 Screening and registration

The investigator is obliged to give the patient or his/her legal representative thorough information about the trial and the trial-related assessments. The patient or his/her legal representative should be given ample time to consider his or her participation. The investigator must not start any trial-specific procedure before the Informed Consent Form (ICF) has been signed and dated by both the patient or legal representative (and impartial witness, if applicable) and the investigator.

7.3.1 Screening

After having been informed about the trial and after having given their written Informed Consent, patients must undergo the examinations listed in section 5 prior to registration. Results of examinations routinely performed due to a medical condition are acceptable if they were done within two weeks prior to registration.

Patients must meet all inclusion criteria and none of the exclusion criteria to be considered eligible. Patients considered eligible by the investigator should be registered in the trial (for registration details see section 5.2.1).

7.3.2 Data to be collected on screening failures

Screening failures are defined as patients who signed an ICF but failed to be registered in the study for any reason. These patients are to be documented on the subject screening log (see section 5.1). For these patients, the screening CRFs and CRF pages with inclusion/exclusion criteria must be completed and "screening failure" stated on the registration fax naming at least one inclusion criteria not fulfilled or one exclusion criteria present.

7.3.3 Assessments at screening (day -16 until day -2)

The data to be collected at screening include the following. Please refer to section 5 for a precise definition of assessments:

- Informed consent
- Demographic data
- Verification of inclusion / exclusion criteria
- Medical history, height
- Pregnancy test (serum beta-hCG)
- ECOG Performance Status
- Mini-Mental Status Examination (MMSE)
- Quality of Life (EORTC QLQ-C30, -BN20)
- Neuropsychological battery
- Weight
- Vital signs*
- Physical and neurological examination
- Creatinine, estimated GFR (MDRD)
- Hematology/clinical chemistry**
- LDH
- Virology (Hepatitis B, C serology, HIV test)*
- Whole body plethysmography*
- Shipment of biopsy sample to central pathology
- Electrocardiography*
- Echocardiography*
- Testicular ultrasound*
- Whole body CT scan* (If CT is suspicious at diagnosis: FDG-PET)
- Whole brain MRI
- Bone marrow examination*
- Slit lamp examination
- CSF examination
- Translational program: additional BM, blood and CSF samples*
- Concomitant medication/s

* not to be documented in the CRF
** to be documented according to CTCAE

7.3.4 Registration (day -1)

Patients considered eligible by the investigator once all screening procedures are complete will be registered in the trial (see section 5.2.1).

7.4 Induction treatment phase

Following trial inclusion, the patient should visit the trial site as stated below.

Patients should be hospitalized during cytopenia (at least during the first induction cycle and in case of additional risk factors thereafter) and if possible, corticosteroids should be tapered out once chemotherapy has started. It is important, that the type and doses of corticosteroids are accurately recorded. Oral antiviral, antifungal, antipneumocystic and antibiotic prophylaxis (e.g. with ciprofloxacin) should be administered according to the chemotherapy protocol (Appendix 8).

7.4.1 Assessments at Visit 1 (cycle 1 day 0 until day 5)

The following assessments must be carried out:

- Treatment administration
- ECOG Performance Status
- Weight
- Vital signs*
- Physical and neurological examination*
- Hematology/clinical chemistry**
- Creatinine, estimated GFR (MDRD)
- Abdominal ultrasound*
- Adverse events/CTCAE
- Concomitant medication/s

* not to be documented in the CRF
** to be documented according to CTCAE

7.4.2 Assessments at Visit 2 (cycle 2 day 0 until day 5) (+/- 5 days)

The following assessments must be carried out:

- Treatment administration
- ECOG Performance Status
- Weight
- Vital signs*
- Physical and neurological examination*
- Hematology/clinical chemistry**
- Creatinine, estimated GFR (MDRD)
- Abdominal ultrasound*
- Adverse events/CTCAE
- Concomitant medication/s

* not to be documented in the CRF
** to be documented according to CTCAE

7.4.3 Response Assessment I (cycle 2 day 18-20) (+/- 5 days)

The first response assessment must be done between days 18 and 20 of induction cycle 2. The following assessments are to be conducted:

- Whole brain MRI

- Slit lamp examination (if positive at diagnosis)
- CSF examination (if positive at diagnosis)
- Response statement according to IPCG criteria (see Appendix 2)

7.4.4 Assessments at Visit 3 (cycle 3 day 0 until day 5) (+/- 5 days)

The following assessments must be carried out:

- Treatment administration
- ECOG Performance Status
- Weight
- Vital signs*
- Physical and neurological examination*
- Hematology/clinical chemistry**
- Creatinine, estimated GFR (MDRD)
- Abdominal ultrasound*
- Adverse events/CTCAE
- Concomitant medication/s

* not to be documented in the CRF
** to be documented according to CTCAE

7.4.5 Assessments at Visit 4 (cycle 4 day 0 until day 5) (+/- 5 days)

The following assessments must be carried out:

- Treatment administration
- ECOG Performance Status
- Weight
- Vital signs*
- Physical and neurological examination*
- Hematology/clinical chemistry**
- Creatinine, estimated GFR (MDRD)
- Abdominal ultrasound*
- Adverse events/CTCAE
- Concomitant medication/s

* not to be documented in the CRF
** to be documented according to CTCAE

7.4.6 Response Assessment II (cycle 4 day 18-20) (+/- 5 days)

The second response assessment is to be done between days 18 and 20 of induction cycle 4:

- Whole brain MRI
- Slit lamp examination (if positive at Response Assessment I)
- CSF examination (if positive at Response Assessment I)
- Pregnancy test (serum beta-hCG)
- Response statement according to IPCG criteria (see Appendix 2)
- MMSE

- QOL (EORTC QLQ-C30, -BN20)

7.5 Randomization

Randomization will take place after 4 cycles of induction therapy after re-checking inclusion/exclusion criteria and checking the randomization criteria (see 4.3). Exclusion criterion **no. 6** ist not applicable for re-check for randomization

Central pathology results confirming primary central nervous system B-NHL must be obtained before randomization. For CRF documentation related to patients ineligible for randomization please refer to section 8.3.1.2 .

7.6 Consolidation treatment phase

7.6.1 Arm A: Assessments at Visit 5 (consolidation cycle 1 day 0) (+/- 5 days)

The following assessments must be carried out:

- Treatment administration
- ECOG Performance Status
- Weight
- Vital signs*
- Physical and neurological examination*
- Hematology/clinical chemistry**
- Creatinine, estimated GFR (MDRD)
- Electrocardiography*
- Adverse events/CTCAE
- Concomitant medication/s

* not to be documented in the CRF
** to be documented according to CTCAE

7.6.2 Arm A: Assessments at Visit 6 (consolidation cycle 2 day 0) (+/- 5 days)

The following assessments must be carried out:

- Treatment administration
- ECOG Performance Status
- Weight
- Vital signs*
- Physical and neurological examination*
- Hematology/clinical chemistry**
- Creatinine, estimated GFR (MDRD)
- Adverse events/CTCAE
- Concomitant medication/s

* not to be documented in the CRF
** to be documented according to CTCAE

7.6.3 Arm B: Assessments at Visit 5 (day before start of HDT-ASCT) (+/- 5 days)

This visit is to be carried out before starting HDT-ASCT.

- Treatment administration
- ECOG Performance Status
- Weight
- Vital signs*
- Physical and neurological examination*
- Hematology/clinical chemistry**
- Creatinine, estimated GFR (MDRD)
- Whole body plethysmography*
- Electrocardiography*
- Adverse events/CTCAE
- Concomitant medication/s

* not to be documented in the CRF
** to be documented according to CTCAE

7.6.4 EOT Visit / Response Assessment III (day 60 after randomization) (+/- 5 days)

This response assessment is to be done on day 60 after randomization. If start of consolidation therapy has to be postponed, RA III should be done 60 days after actual start of consolidation therapy

- ECOG Performance Status
- MMSE
- QOL (EORTC QLQ-C30, -BN20)
- Neuropsychological battery
- Vital signs*
- Pregnancy test (serum beta-hCG)
- Physical and neurological examination*
- Hematology/clinical chemistry**
- Whole body plethysmography (only Arm B)*
- Electrocardiography*
- Whole brain MRI
- Slit lamp examination (only if positive at Response Assessment II)
- CSF examination (only if positive at Response Assessment II)
- Response statement according to IPCG criteria (see Appendix 2)
- Translational program: additional blood and CSF sample*
- Adverse events/CTCAE
- Concomitant medication/s

* not to be documented in the CRF
** to be documented according to CTCAE

7.6.5 Follow up visits

The following assessments are to be done at follow-up visits (for details on assessments see section 7.7):

Year 1-2: Every 3 months

- ECOG Performance Status
- MMSE annually
- QOL (EORTC QLQ-C30, -BN20) annually
- Neuropsychological battery annually
- Vital signs*
- Pregnancy test (serum beta-hCG, at the end of year 1)
- Physical and neurological examination*
- Hematology/clinical chemistry**
- Whole brain MRI
- Response statement according to IPCG criteria (Appendix 2)

* not to be documented in the CRF
** to be documented according to CTCAE

Year 3-5: Every 6 months

Between years 3 and 5 we recommend, that the following examinations should be conducted every 6 months:

- ECOG Performance Status
- MMSE annually
- Quality of Life (EORTC QLQ-C30, -BN20) annually
- Neuropsychological battery annually
- Vital signs*
- Physical and neurological examination*
- Hematology/clinical chemistry**
- Whole brain MRI
- Response statement according to IPCG criteria (Appendix 2)

* not to be documented in the CRF
** to be documented according to CTCAE

Year > 5: Every 12 months

We recommend the following examinations to be done annually after 5 years:

- ECOG Performance Status
- MMSE annually
- Quality of Life (EORTC QLQ-C30, -BN20)
- Neuropsychological battery
- Vital signs*
- Physical and neurological examination*
- Hematology/clinical chemistry**

- Whole brain MRI
- Response statement according to IPCG criteria (Appendix 2)

* not to be documented in the CRF
** to be documented according to CTCAE

7.7 Description of examinations during the trial

7.7.1 Patient demographics

Demographic data to be collected on patient characteristics at screening including year of birth, sex and childbearing potential.

7.7.2 Medical history

At screening relevant past medical history including date of diagnosis and assessments of any current medical conditions must be documented in the CRF.

7.7.3 Pregnancy test

All women of childbearing potential must undergo a serum beta-hCG test at screening, at response assessment II and at response assessment III to confirm trial eligibility.

In case of pregnancy the patient must be immediately withdrawn from the trial and the pregnancy must be reported to the sponsor on the pregnancy form.

7.7.4 Physical and neurological examination

Thorough physical examination includes cardiovascular, gastrointestinal, hepatobiliary, respiratory, musculoskeletal, genitourinary/renal and integumentary systems. A neurological examination should also be performed at screening and all subsequent visits.

7.7.5 Vital signs, height and weight

Data on the patient's vital signs must be taken at screening and all subsequent visits. Results must appear on the patient’s chart. Vital signs include body temperature, pulse rate and systolic/diastolic blood pressure, measurement of height (cm) and body weight (kg). Height is only measured at screening; weight is to be assessed at all visits.

7.7.6 Performance status

Performance status will be recorded in the CRF as defined by the ECOG, see Appendix 3. Alternatively, the Karnofsky Performance Status can be recorded.

7.7.7 Neuropsychological Assessment/Quality of Life

All of the following tests must be carried out at screening, at day 60 after randomization and annually thereafter.

7.7.8 Mini-Mental Status Examination (MMSE)

Screening for cognitive impairment will be recorded as defined by the MMSE, see Appendix 4.

7.7.8.1 Quality of Life

Quality of Life Questionnaire is to be filled out by the patient him/herself. It is important that the investigator not influence the patient in any way. The European Organization for Research and Treatment of Cancer QOL Questionnaire-30 (EORTC QLQ-C30) and Brain Cancer Module-20 (EORTC QLQ-BN20) are used. The EORTC QLQ-C30 measures five functional scales and global QOL. The EORTC QLQ-BN20 assesses items such as visual disorders, communication deficit, and future uncertainty (see Appendix 5, Appendix 6)

7.7.9 Brief repeatable battery of neuropsychological tests

A standardized test battery designed to evaluate neurotoxicity in multi-national PCNSL trials [34] is to be used if available at the investigation site. Neuropsychological evaluation is done in about 30-60 minutes. The tests measure attention and executive function as well as motor skills and are performed at screening, the EOT visit, and annually thereafter with documentation in the CRF.

7.7.10 Laboratory tests

Hematological tests and blood chemistry are recommended to be done twice a week during the therapy. Laboratory data must be checked by the investigator.

The following laboratory data are to be documented as toxicity parameters and graded according to CTCAE 4.0: Hematology includes assessment of white blood count (WBC), neutrophils, hemoglobin, and platelets. Blood chemistry comprises creatinine, total bilirubin, ALT, AST, and gamma-GT (only at screening).

During therapy, creatinine must be documented in the CRF in the measured unit to permit approximation of the kidney glomerular filtration rate (GFR) using the MDRD (Modification of Diet in Renal Disease) formula. Lactate dehydrogenase will be documented at screening by indicating "not increased" or "increased".

If an abnormal laboratory parameter is not listed in the toxicity table, an AE must be documented on the CRF AE page. If any of the seriousness criteria are fulfilled, a SAE must be reported. For details please refer to section 10.

7.7.11 Testicular ultrasound

Testicular ultrasound is necessary at screening to exclude testicular lymphoma.

7.7.12 Abdominal ultrasound

Abdominal sonography is necessary before each methotrexate administration to exclude third space fluid accumulation.

7.7.13 Imaging

Response assessment according to the IPCG Response criteria (see Appendix 2) is strongly recommended before the starting each chemotherapy course beyond the imaging evaluations specified in response assessments.

Whole brain MRI must be done at screening. During induction treatment, whole-brain MRI must be conducted at the end of the 2nd and the 4th courses. Whole-brain MRI after consolidation therapy is carried out on day 60 after randomization.

After the conclusion of treatment, the disease is to be assessed every three months during the first two years, every six months during the following three years, and annually thereafter.

Tumor size, location(s) (only at screening and in case of PD) and manifestation (singular/multiple; only at screening) must be documented in the CRF at the mentioned time points. In case of multiple tumors, one reference tumor is measured. The response is evaluated by comparison to the screening MRI.

Response evaluation during the trial is to be determined by an independent radiological review committee not involved in the study's conception.

7.7.14 Slit lamp examination

A slit lamp examination must take place at screening. This examination need only be carried out at response assessments when positive ocular involvement was detected at diagnosis. Slit lamp exams should continue to be done until the findings are negative and documented accordingly.

7.7.15 CSF examination

CSF examination must be performed after increased intracranial pressure has been excluded via MRI. Cytology and protein examination are necessary at screening. CSF protein levels should only be assessed on lumbar puncture samples because ventricular CSF has a lower normal value. CSF should be sampled before or 1 week after surgical biopsy to avoid falsepositive results; a minimum of 3 ml and ideally 10 ml should be sent for cytologic evaluation [35]. In case of positive findings at diagnosis, this examination must take place at the time of response assessments by MRI until the findings are negative and documented accordingly.

7.7.16 Harvest

Leukapheresis and cryopreservation: Starting at day 10 during the second chemotherapy course, absolute CD34+ cell count per µl of blood should be determined daily. The objective is to harvest a minimum of $5x10^6$ CD34+ cells/kg of body weight with as few as possible leukapheresis sessions on consecutive days. CD34+ cells are to be collected, processed and stored according to conventional guidelines. Leukapheresis and cryopreservation is a standard procedure in hematology.

Any patient with an insufficient stem cell harvest after three cycles of induction treatment will be excluded from randomization. They will undergo conventional chemotherapy or RT and be considered evaluable for the first randomization endpoints.

Stem cells of patients who had a sufficient stem cell harvest but do not undergo HDT-ASCT within the trial (due to premature end of treatment or randomization to conventional

consolidation therapy (arm A)) will be stored according to local standard of care and can be used in case of relapsed or refractory disease.

7.7.17 ASCT

Autologous stem cell transplantation is to be performed according to standard procedures.

7.8 Translational program

Additional blood samples will be taken from patients participating in the translational research program at screening and at Response Assessment III. Furthermore, additional bone marrow aspirate and a CSF sample will be taken at screening. In case of study discontinuation translational samples also have to be collected.

8 Discontinuation criteria

8.1 Premature termination of one of the treatment arms or the entire trial

The sponsor/coordinating investigator is under obligation to monitor the progress of the clinical trial with regard to safety-relevant developments and, if necessary, initiate the premature termination of a treatment arm or the entire clinical trial. The sponsor/coordinating investigator will be supported in this responsibility by the DMC, if necessary.

A treatment arm or the entire clinical trial must be terminated prematurely if:

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

If the clinical trial is prematurely terminated or suspended for any reason, the investigator should promptly inform the trial patients and ensure their appropriate therapy and follow-up. Where required by the applicable regulatory requirements, the competent authority(ies) and the ethic committee(s) will also be informed. This is done by the sponsor.

8.2 Premature termination of the trial at one of the trial centers

Both the investigator and sponsor have the right to terminate the trial at one of the centers.

The clinical trial can be terminated prematurely at his center by the investigator if, for instance, unforeseeable circumstances have arisen at the trial center which preclude the continuation of the clinical trial, if the investigator considers that the resources for continuation are no longer available, or if the investigator believes that the trial's continuation is no longer ethically or medically justifiable.

The Sponsor can initiate a center's exclusion from further participation if, for instance, patient recruitment is inadequate or serious problems arise with regard to the quality of the collected data which cannot be resolved.

Premature termination at one of the trial centers does not automatically mean termination of the trial for trial patients already enrolled. A separate decision on further treatment must be made for each patient, depending on the overall situation. Adequate further treatment and follow-up of enrolled trial patients must be ensured. The documentation of enrolled trial patients will be reviewed for completeness and plausibility. Queries may be raised for further clarification before the center is closed. These queries must be answered properly by the center. The competent authority(ies) and ethics committee(s) must be duly notified of the center's closure including reasons within the specified period. The trial center in question will be closed in stages by the CRA when a decision has been made on the further treatment of the patients concerned.

8.3 Discontinuation criteria for individual trial patients

A distinction must be made between a patient whose trial treatment was stopped prematurely and one whose trial participation was discontinued prematurely.

In case a patient's trial treatment was stopped prematurely, further follow-up visits and assessment of the trial endpoints are essential to enable an analysis of the full analysis set according to the intention-to-treat principle. Further visits, follow-up and documentation should always be ensured in this case.

These include:

- the follow-up of AEs
- the time of termination
- the results available at that time and, if known, documentation of the termination of treatment on the CRF and in the medical record, giving reasons, a final examination and documentation according to the protocol (if possible).

If a patient's trial participation ceased prematurely, the conduct of further follow-up visits is no longer possible.

Under these circumstances the documentation should be completed as thoroughly as possible, meaning that a final examination and documentation according to the protocol should be done if feasible. Reasons for premature trial termination should be listed and documented on the CRF and in the medical record. Appropriate further treatment and follow-up outside the trial should be ensured. The patient’s GP should be informed about the termination if necessary, provided the patient agrees. In trials that assess survival status, an attempt should be made at least to assess the patient's survival status by telephone follow-up unless informed consent for documentation has been withdrawn.

8.3.1 Premature discontinuation of trial treatment

The trial patient can have his/her trial treatment terminated prematurely at any time, without having to give reasons.

The investigator responsible for the trial has the right to terminate a patient's treatment according to the following conditions:

- adverse events (including intercurrent illnesses) which preclude further treatment with the investigational medicinal product or make further participation in the clinical trial inadvisable because the informational value of the trial results is impaired,
- premature termination of the trial treatment is considered to be medically indicated, e.g. because it is subsequently found that inclusion/exclusion criteria were violated,
- continuation of the trial treatment is unacceptable when the risks outweigh the benefits,
- pregnancy
- significant violations of the trial protocol or lack of compliance on the part of the patient (e.g. taking prohibited medication) and
- logistical reasons (patient changes his/her doctor or hospital, or moves to another location).

8.3.1.1 Study-specific termination of trial treatment

In case of PD at any time before randomization, SD after four cycles of induction chemotherapy, insufficient stem-cell harvest, inadequate bone marrow recovery (discontinuation of chemotherapy in case of delay of more than four weeks) before randomization or toxicity before randomization, trial treatment is terminated prematurely.

8.3.1.2 Data to be collected

In case a patient's trial treatment has been stopped prematurely **before randomization**, all CRF pages until the time of termination must be completed including the premature end of treatment" page and "re-check of inclusion and exclusion criteria". To document a patient's survival and remission status, the follow-up pages for non-randomized patients indicating patient "dead" or "alive" and "remission status" must also be completed.

In case a patient's trial treatment has been stopped prematurely **after randomization**, all CRF pages must be completed including the "premature end of treatment" page and regular follow-up pages.

8.3.2 Premature termination of trial participation

8.3.2.1 General

The trial patient can withdraw his/her consent at any time, without having to give reasons, and terminate his/her entire trial participation prematurely. However, the prerequisite for this is that the patient actively terminates trial participation by withdrawing his/her consent for the study’s follow-up and documentation.

The responsible investigator may only withdraw a patient from trial participation for the following reasons:

- loss of contact
- when extreme circumstances arise which make any trial-relevant follow-up impossible

8.3.2.2 Study-specific termination of trial participation

In case of a patient's death, study participation is terminated prematurely.

8.3.2.3 Data to be collected

In case a patient's trial participation has been stopped prematurely, the CRF pages must be completed until the date of termination (including the "premature termination of study" page).

9 Investigational medicinal products

9.1 Investigational medicinal products

The investigational products used in this trial are characterized as follows with reference to German sites:

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:	3000 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 Fehlandtstrase 3 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:	14 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 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:	32 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:	30mg/m^2 (total), for induction treatment 20mg/kg (total), for high-dose consolidation

Proprietary name:	CARMUBRIS®
Name of substance:	**Carmustine / BCNU**
Manufacturer:	Bristol-Myers Squibb GmbH & Co. KGaA

	Arnulfstraße 29 80636 München
Approved indications:	indicated as adjuvant treatment for surgical operations and radiotherapy or in established combination therapy with other approved chemotherapeutic agents in the following: - brain tumors: glioblastoma, brainstem glioma, medulloblastoma, astrocytoma, ependymoma, and metastatic brain tumors. - multiple myeloma: in combination with other chemotherapeutic agents und adrenocorticosteroids like prednisone. - malignant tumors of lymphatic system: Hodgkin's disease, lymphatic sarcoma, dendritic reticular cell sarcoma, in combination with other substance and after failure of primary therapies. - malignant tumors of the gastrointestinal tract: only for patients who relapse undergoing primary therapy, or who fail to respond to primary therapy.
Dosage form:	Powder and solvent for solution for infusion
Strength:	3,3 mg/mL (refers to concentrate)
Dose:	400 mg/m^2 (total), for consolidation in experimental intervention

Proprietary name:	Busilvex(R)
Name of substance:	**Busulfan**
Manufacturer:	Pierre Fabre Médicament 45, Place Abel Gance, 92654 Boulogne Billancourt Cedex
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:	6,4mg/kg (total)

Proprietary name:	Fortecortin® Inject 40 mg
Name of substance:	**Dexamethasone**
Manufacturer:	Merck Serono GmbH Alsfelder Straße 17 64289 Darmstadt
Approved indications:	- cerebral edema by brain tumor - polytraumatic shock/prophylaxis of posttraumatic shock lung - anaphylactic shock (after primary epinephrine injection)

Dosage form:	Solution for injection
Strength:	8,744 mg/ml Dexamethason-21-dihydrogen phosphate disodium (= 8 mg/ml dexamethasone)
Dose:	240 mg (total), for consolidation Arm A

Proprietary name:	ETOPOPHOS® 1000 mg
Name of substance:	**Etoposide / VP-16**
Manufacturer:	Pharmaceutical entrepreneur: Bristol-Myers Squibb GmbH & Co. KGaA Arnulfstraße 29 80636 München Manufacturer: Corden Pharma Latina Via del Murillo km 2,800 04013 Sermoneta (LT) Italien
Approved indications:	- small cell carcinoma of the lung. - accute monocytic and myelomonocytic leukaemia. - Hodgkin's disease. - Non-Hodgkin's lymphoma. - testicular tumors.
Dosage form:	Powder for solution for infusion
Strength:	11,4 mg/mL Etoposide phosphate (= 10 mg/mL Etoposide, referred to concentrate)
Dose:	600 mg/m^2 (total), for consolidation Arm A

Proprietary name:	IFO-cell® 5 g
Name of substance:	**Ifosfamide**
Manufacturer:	cell pharm GmbH Theodor-Heuss-Str. 52 61118 Bad Vilbel
Approved indications:	- testicular tumor - cervical carcinoma - breast carcinoma - non-small-cell bronchogenic carcinoma - small-cell bronchogenic carcinoma - soft tissue sarcoma (including osteogenic sarcoma and rhabdomyosarcoma) - Ewing`s sarcoma - non-Hodgkin`s lymphoma - Hodgkin's lymphoma
Dosage form:	Concentrate for solution for infusion

Strength:	200 mg/mL
Dose:	9000 mg/m^2 (total), for consolidation Arm A

Proprietary name:	CARBO-cell® 10 mg/ml Infusionslösung
Name of substance:	**Carboplatin**
Manufacturer:	cell pharm GmbH Theodor-Heuss-Str. 52 61118 Bad Vilbel
Approved indications:	Is indicated as single agent or in combination with other antineoplastic agents to treat the following malignant tumors: - ovarian carcinoma of epithelial origin - small-cell bronchogenic carcinoma - squamous cell carcinoma of the head-neck region - cervical carcinoma, in local recurrence or distant metastasis
Dosage form:	Concentrate for solution for infusion
Strength:	10 mg/mL
Dose:	600 mg/m^2 (total), for consolidation Arm A

For further characteristics, details on indication, side effects and further features see corresponding current version of corresponding SmPC.

9.2 Packaging, labeling, supply and storage

All drugs used in the study are commercially available worldwide and will be provided by each participating institute in their commercially available forms and stored according to their SmPC.

9.3 Preparation and dispensing

Drugs will be prepared according to SmPC. Medications will be administered to the patient at the study site after their pharmacies have prepared and dispensed them.

9.4 Drug compliance and accountability

Information about drugs given to the patient must be entered in the source documents and in the CRFs to accurately determine the patient's drug exposure throughout the trial.

Drug accountability will be performed according to the routine pharmacy practice without study specific documentation in the Investigator Site/Pharmacy File.

10 Safety monitoring and reporting

10.1 Adverse events (AEs)

10.1.1 Definition of AEs

An adverse event (AE) is any untoward medical occurrence in a patient administered any dose of a pharmaceutical product and which does not necessarily have to have a causal relationship with the product's use. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the product.

- Irrespective of any causal relationship, all AEs spontaneously reported by the patient or observed by the investigator will be continuously documented in the medical record and on the designated case report form (AE CRF page).

- All AEs must be described by diagnosis or, if an underlying diagnosis is not known, by symptoms or medically significant laboratory or instrumental abnormalities. The AEs will be documented as shown in the section below.

- Symptoms or medically-significant laboratory or instrumental (e.g. electro-cardiographic) abnormalities concerning a pre-existing disease should not be considered an AE. However, occurrences of new symptoms or laboratory or instrumental abnormalities as well as worsening of pre-existing symptoms are considered AEs.

- In order to monitor the conditions of the patients from the point in time when they receive the first dose of the investigational product, the investigator is requested to report any untoward clinical event on an AE-page of the CRF. Any untoward medical occurrence that occurs after the patient's follow-up period as defined in the protocol is not considered an AE.

- All AEs, no matter how intense, are to be followed up by the investigator in accordance with good clinical practice until resolved or judged no longer clinically relevant, or in case of a chronic condition, until it is fully characterized.

10.1.2 Documentation of AEs

Adverse events must be documented in the CRF starting from the first administration of the study medication until day 60 after randomization. If patient could not be randomized, AE documentation and reporting should be made until day 60 after last administration of study medication. After this time period until the end of the study only serious AEs judged by the investigator to be related to at least one of investigational products (see section 1.3) have to be documented on the AE-page in the CRF and reported to the sponsor accordingly (see section 10.1.3.2 and 10.1.4). During induction and consolidation treatment and before beginning each chemotherapy cycle, the CRF-toxicity table must be thoroughly completed by the investigator. The investigator has to state the presence of a toxicity grade (CTCAE) in terms of several laboratory parameters and symptoms or diagnoses. If the symptom,

diagnosis, or laboratory parameter is not stated on the toxicity table, an AE must be documented on the CRF AE page. If any of the seriousness criteria are fulfilled, an SAE must be reported. For details please refer to section 10.1.4.

Characterization of the event:

- onset
- end
- severity according to the current version of CTCAE
- relationship to the investigational medicinal product
  Note:According to the CIOMS VI Working group the causal relationship between the investigational product and the adverse event should be characterized as "related" or "not related" (the various gradients of relatedness offer little or no advantages in data analysis or regulatory reporting).
- serious or non-serious
- action taken with investigational medicinal product
- outcome

10.1.3 Definition and documentation of serious adverse events (SAEs)

10.1.3.1 Definitions of SAE

A Serious Adverse Event (SAE) is any untoward medical occurrence that:

- results in the patient's death (except death from the underlying disease),
- is life-threatening,
- requires the trial patient's inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect,
- other medically important conditions.

A hospitalization fulfilling the regulatory requirement as a "serious" criterion is any inpatient hospital admission that includes a minimum of an overnight stay in a healthcare facility, unless hospitalization is for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under trial and that has not worsened since signing the informed consent.
- social reasons and respite care in the absence of any deterioration in the patient's general condition.
- elective hospitalizations for administering the investigational product or any other trial assessment.

Patients may be hospitalized throughout the treatment phase of this trial according to the institution's policy. Hospitalizations will therefore be treated as SAEs only if serious or unexpected events caused either their prolongation or a re-admission as an inpatient after the patient's discharge.

Other conditions which, in the investigator's opinion, may not be immediately life-threatening or result in hospitalization, but may jeopardize the patient's safety or may require intervention to prevent one of the other outcomes listed in the definition above, may also be considered serious. Examples of such conditions include: allergic bronchospasm requiring treatment in an emergency room or at home; unexpected convulsions (i.e. convulsions which cannot be explained by the underlying illness) that do not result in hospitalization; development of investigational product dependency or drug abuse; suspected transmission of infectious agents by the medicinal product, etc.

10.1.3.2 Documentation of SAEs

All SAEs that occur starting from the first administration of the study medication until day 60 after randomization will be documented in the CRF and on the provided SAE reporting form. This applies to events:

- that are only documented on the toxicity table,
- that are **related and not related** to the study medications, and
- events of any CTCAE grade.

If patient could not be randomized, SAE documentation and reporting should be made until day 60 after last administration of study medication.

After this time period SAEs need only be reported to the sponsor and documented on the CRF if judged by the investigator to be related to at least one of investigational products (see section 1.3).

The SAE reporting form will be processed as described in the section below.

10.1.4 Reporting requirements for SAEs

10.1.4.1 Investigator requirements for SAE Reporting

All SAEs must be reported by fax to the following address within **24 hours** after knowledge by the investigator:

SAE Management Center
Clinical Trials Unit
Medical Center - University of Freiburg
Elsaesser Str. 2
79110 Freiburg

SAE Fax No.

+49 (0)761 270 74390

According to section 12, subsection 6 GCP-V, in the event of the death of a patient, the investigator must submit all information to the competent ethics committee, the other ethics committee involved, and the competent authority and sponsor that is required for the fulfilment of his or her duties (note that personal data must be transmitted using the trial-specific patient identification number, i.e. in anonymized form).

An exception to this principal rule is:
As this trial involves patients suffering from malignancies associated with significant mortality/morbidity, and because relapse/progression are trial endpoints (i.e. anticipated clinical outcomes) collected on the specific CRF pages and taking into consideration recommendations of the CIOMS working group VI concerning management of safety information from clinical trials, the investigator need not inform the sponsor about the events below, as they are not considered SAEs in this disease context:

- relapse
- progression

A study patient's relapse or progression will be documented on specific CRFs pages and should not be communicated to the Sponsor as SAEs. Nevertheless, the investigator must fax the CRF page designated for relapse documentation to the SAE Management Center CTU within 3 working days after knowledge.

Patient's death

Please note that "death" is usually an SAE outcome and not an SAE per se. Only in cases where the clinical circumstances before the death are unknown (i.e. patient died without a determinable cause of death), then the diagnosis "death" itself should be reported as an SAE. In case of fatal outcome of an already-registered SAE, a follow-up notification must be done.

If a patient dies, the CRF page "premature termination of study" must be faxed to the SAE Management Center within 3 working days after knowledge.

10.1.4.2 Sponsor requirements for SAE reporting

SUSARs:

The sponsor's expedited reporting requirements are particularly relevant to suspected unexpected serious adverse reactions (SUSARs). The definition is a combination of the definitions of serious adverse reaction (for seriousness criteria see section 10.1.3) and unexpected adverse reaction (an adverse reaction, the nature or severity of which is inconsistent with the applicable product information for the investigational medicinal product).

Causal relationship:

According to guideline CPMP/ICH/377/95 (ICHE2A), all events suspected by either the investigator or the sponsor as having a reasonable causal relationship to the administration of the investigational medicinal product qualify as suspected adverse reactions (SARs). The expression causal relationship means that there is evidence or argument to suggest a causal relationship between the event and the administration of the investigational medicinal product. According to guideline ENTR/CT 3, all cases of suspected unexpected serious adverse reactions for which a causal relationship with a investigational medicinal product (test or reference drug) is suspected by an investigator or the sponsor are patient to the expedited reporting requirements.

Reporting Requirements:

The sponsor's reporting requirements are divided into **expedited** reporting and reporting that must be done annually or on request. The sponsor's expedited reporting requirements comprise the following:

- all SUSARs must be reported within 15 days after knowledge (section 13, subsection 2 GCP-V),

- all SUSARs that are life-threatening or result in death must be reported within 7 days after knowledge (section 13, subsection 3 GCP-V),

- all circumstances requiring a review of the benefit/risk evaluation of the investigational medicinal product must be reported within 15 days after knowledge (e.g. expected serious adverse reaction with unexpected outcome, increased incidence of expected serious adverse reactions, SUSARs after the end of the patient's participation in the clinical trial, events in connection with the trial conduct or the development of the investigational medicinal product which may affect the safety of the trial patients) (section 13, subsection 4 GCP-V).

Development Safety Update Report (DSUR):

In addition to the expedited reporting, the sponsor shall submit an annual report **once a year** or on request throughout the clinical trial period, according to section 13, subsection 6 GCP-V. According to ICH guideline E2F, this annual report should include the following points:

- a report on the safety of the trial patients in the clinical trial concerned,
- a list of all suspected serious adverse reactions (including all SUSARs) that occurred in the clinical trials concerned,
- a summary list of suspected serious adverse reactions (specified by organ system, treatment arm and type of adverse reaction) that occurred in the clinical trial concerned.

To fulfill these requirements the investigator must fax the CRF page designated for premature treatment/study discontinuation to the SAE Management Center CTU within 3 working days after knowledge.

10.1.4.3 Pregnancies

Any pregnancy that occurs during trial participation must be reported to the Sponsor on the SAE-reporting form within 24 hours of learning of its occurrence. The pregnancy should be followed up by the sponsor to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications.

11 Data handling and data management

11.1 Data confidentiality

Information about trial patients will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed patient authorization informing the patient of the following:

- what protected health information (PHI) will be collected from patients in this trial;
- who will have access to that information and why;
- who will use or disclose that information;
- right of trial patients to revoke their authorization for use of their PHI.

In the event that a patient revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients who have revoked authorization to collect or use their PHI, attempts should be made to obtain permission to collect data with reference to their vital status (i.e. that the patient is alive) at the end of their scheduled trial phase.

The histological material encrypted, used for the diagnosis, will be revised on a national basis. Once the revision will be completed the material will be sent back to the site.

For paper-based trials (using DAMAST, SAS®-based data management system):

The data collection system for this trial uses built-in security features to prevent unauthorized access to confidential participant information. Access to the system will be controlled by individually-assigned user identification codes and passwords made available only to authorized personnel who have completed prerequisite training.

11.2 Documentation of trial data

11.2.1 Documentation in medical records

The investigator will record participation in the trial, the frequency of trial visits, relevant medical data, concomitant treatment/s and the occurrence of adverse events in each trial patient's medical record.

11.2.2 Documentation in CRF

The investigator or anyone designated by the investigator shall document the trial data on a trial-specific case report form (CRF) as promptly as possible.

Hard-copy CRFs will be used in this trial. The hard copy CRFs consist of 3-layer Non-Carbon-Required paper (NCR paper). For further details please refer to the CRF completion Instructions. All data collected during the trial will be entered on the trial-specific CRF pages by the responsible investigator, or a person designated by the investigator.

Corrections and subsequent changes to CRF pages must be made according to the ICH-GCP guidelines provided in the CRF Completion instructions at the beginning of each CRF-folder.

11.3 Data management

The study data will be 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, which may be made by Data Management staff themselves) will be 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 and deviations of version 01 of the DMM. Before any data is entered, the trial database will be validated and specifications of the database documented in a variables handling plan. Double data entry will be 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 will be created to provide an electronic record of which data were entered or subsequently changed by whom and when.

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

11.4 Data coding

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

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

12 Quality assurance

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

12.1 Monitoring procedure

Monitoring is done by CRAs from the Clinical Trial Unit, Medical Center - University of Freiburg and the CRA from the Department of Hematology and Oncology, Medical Center – University of Freiburg for all German participating sites. Adapted monitoring will be done according to ICH-GCP E6 and standard operating procedures (SOP) to verify that patients' rights and well-being have been protected, reported trial data are accurate, complete and verifiable from source documents and that the trial is being conducted in compliance with the currently-approved protocol/amendment, with GCP and with the applicable regulatory requirements to ensure the safety and integrity of clinical trial data.

The investigator will accept monitoring visits before, during and after the clinical trial. Under the prerequisite that all necessary site documents such as the signed contract and authority approvals are available and finalized, a site initiation visit will be conducted to start the trial and to train and introduce the investigators and their staff to the trial protocol, essential documents, handling of routinely-prescribed medicinal products and related trial-specific procedures, ICH-GCP and national or local regulatory requirements.

In the course of the trial, the monitor will visit the site regularly depending on the recruitment rate in order to assess the data and ensure its quality. During these on-site visits, the monitor has to verify, that the trial is being conducted according to the trial protocol. He must ensure75 that trial specific procedures and ICH-GCP and national/local regulatory requirements are met. The monitor must verify the existence of signed informed consents, patients' eligibility, primary endpoint, dosing of chemotherapy, the trial conduct according to the protocol and documentation/reporting of safety data (e.g. AE/SAE). The monitor also verifies source data to ensure that clinical trial data have been collected and documented accurately and completely in the CRF. The extent of source data verification and frequency of monitor visits at the sites depends on the site's data quality or number of protocol violations. All trial-specific monitoring procedures, monitoring visit frequency and the extent of SDV will be predefined in a trial-specific monitoring manual. The investigator must provide source documents for each patient in the trial consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information

recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries.

12.2 Source data verification (SDV)

Source data as defined by ICH-GCP include original documents, data, and records such as hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial.

Source data verification is done to verify the accuracy and completeness of the entries on the case report form (CRF) by comparing them with the source data, and to ensure and improve data quality. All data subject to SDV must have been entered in the medical record or, in the case of source documents, enclosed with the medical record. The investigators will guarantee the CRA access to the medical records to conduct SDV.

The extent of Source Data verification will be specified in the in the Monitoring Manual (see section 12.1).

12.3 Auditing procedures and inspections

According to the ICH-GCP guidelines, audits will be performed within a quality assurance system. Audits and/or inspections may be conducted by the sponsor, authority(ies) or an independent external party.

The purpose of a sponsor’s audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements. All persons who conduct an audit undertake in writing to treat all data related to medical secrecy or which could reveal the patient's identity in absolute confidence, and to restrict the use of such data to the purposes agreed by the patient in writing.

Proposed dates for sponsor’s audit, characteristics of the selected patients and further information will be transmitted to the investigator by the CRA in a timely manner.

The investigator will inform the CTU immediately of an inspection requested by a regulatory authority. The investigator is responsible for making source data/documents during audits or inspections available.

13 Biostatistical planning and analysis

Before initiating the final analysis, a detailed statistical analysis plan (SAP) will be prepared. This will be completed during the 'blind review' of the data, at the latest. This blind review, i.e. data checking and assessment, will be undertaken after the end of the recruitment period and the planned follow-up period without observing the randomized treatment for each patient. If the SAP contains any changes to the analyses outlined in the trial protocol, they will be marked as such, and reasons for amendments will be given.

All statistical programming for analysis will be performed with the Statistical Analysis System (SAS).

13.1 Trial design

For details on trial design, see section 3.1 of the protocol.

13.2 Objectives and endpoints

For details on endpoints, see section 2 of the protocol.

13.3 Sample size calculation

Sample size calculation is based on the primary endpoint PFS. We are assuming that the PFS rate for patients treated with the conventional intervention (arm A) is approximately 50% after 3 years. To compare the two treatment groups, a hazard ratio of 1.8 of the conventional intervention vs. the high-dose treatment (arm B) is considered to be clinically relevant. This corresponds to a PFS rate after 3 years of 68% in the high-dose group, which is considered as realistic. In order to detect a difference between arm A and arm B with a power of 80% at a two-sided significance level of 5% under this assumption, a total number of 92 events is required. Assuming an exponential model for survival, an accrual period of 62 months and an additional follow-up time of 2 years, 330 patients should be included.

As follow-up may be incomplete for a few patients, 220 patients will be randomized. Furthermore, we anticipate that some patients (about 15%) will fail to attain complete or partial remission during the first 4 chemotherapy cycles (start induction treatment) or will not be eligible for randomization due to toxicity of the induction therapy or other reasons (about 20%) and will therefore not be randomized. We therefore assume that approximately 330 patients will need to be included in the study (start induction treatment).

13.4 Definition of populations included in the analyses

The primary analysis will be conducted according to the intention-to-treat principle and will therefore be based on the full analysis set (FAS). The FAS includes all randomized patients in whom therapy after randomization was started, and patients are analyzed as belonging to their randomized arm, regardless of whether they refused or discontinued therapy, or whether other protocol deviations are known. Patients will be censored at the time of last follow-up provided no event of interest has occurred so that as many patients as possible can be included in the analysis.

The per-protocol (PP) population is a subset of the FAS and is defined as the group of patients who had no major protocol violations, received a predefined minimum dose of the treatment and underwent the examinations required for assessment of the endpoints at relevant, predefined times. The PP group will be assessed in the context of a sensitivity analysis.

Safety analyses will be based on the safety set (SAF), which contains all randomized patients in whom therapy was initiated. Patients will be analyzed according to the therapy they underwent.

13.5 Methods of analysis

13.5.1 Patient demographics/other baseline characteristics

Demographic and other baseline data (including disease characteristics) will be summarized descriptively by treatment arm using the FAS.

Continuous data will be summarized by arithmetic mean, standard deviation, minimum, 25% quantile, median, 75% quantile, maximum, and the number of complete and missing observations. If appropriate, continuous variables can also be presented in categories.

Categorical data will be summarized by the total number of patients in each category and the number of missing values. Relative frequencies are displayed as valid % (number of patients divided by the number of patients with non-missing values).

13.5.2 Treatments (trial treatment and compliance, concomitant medication)

13.5.2.1 Trial medication

Duration of trial treatment exposure, cumulative dose and dose intensity will be summarized by treatment arm. The number of patients with dose changes/interruptions will be presented by treatment arm.

13.5.2.2 Concomitant medication

The concomitant medications will be summarized by ATC level 1/3/5. In each table, patients will be counted once, if they took at least one medication from the respective ATC level. The number of patients and percentage of the total number of patients in the respective population will be given.

13.5.3 Primary endpoint

The primary endpoint PFS will be analyzed with a Cox proportional hazards model, containing the randomized treatment as hypothesis variable and the stratification variable response status as a covariate. The test of the primary hypothesis (null hypothesis: equality of PFS rates) will be conducted within this model. The treatment effect will be described by the estimated hazard ratio from this model and will be presented with a two-sided 95% confidence interval. The null hypothesis will be rejected if the value 1 is not contained in the

two-sided 95% confidence interval for the hazard ratio describing the relation between treatment groups. Additionally, the PFS rates will be estimated by the Kaplan-Meier method.

13.5.4 Secondary endpoints for efficacy

The endpoint OS will be analyzed in the same way as described for PFS. The endpoint CR rate will be analyzed as the dependent variable of a logistic regression model with treatment assignment as independent variable. The endpoint response duration will be estimated with a Cox-regression model. Death without former progression will be analyzed as competing event. The regression models allow the inclusion of further potentially important prognostic factors. Details will be determined in a Statistical Analysis Plan (SAP) to be finalized before the analysis starts.

For the evaluation of CR on day 60 after randomization, patients not completing therapy will be counted as non-responders.

With respect to the endpoint QOL, the treatment groups will be compared descriptively according to the EORTC manual.

All p-values from analyses of secondary endpoints will be interpreted in a descriptive sense.

Further descriptive analyses will consider all patients included in the trial, i.e. data from start of induction therapy with Rituximab, MTX, Ara-C, Thiotepa will be analyzed. We will analyze PFS and OS starting at registration for all patients, and we will consider three groups (two treatment arms, not randomized).

13.5.4.1 Subgroup Analyses

Subgroup analyses will be conducted based on response status (CR versus PR) as evaluated by contrast enhanced MRI at the time of randomization. Of note, response status is a stratification factor, thus the number of patients with either CR or PR between the two arms will very likely be balanced.

We hypothesize that particularly those patients with PR will benefit more from the more aggressive approach HDT-ASCT than patients with CR, because patients who do not respond completely after 4 cycles of conventional chemotherapy might be suffering from a lymphoma that is more resistant to conventional chemotherapy than the lymphomas in those patients who had already achieved a complete response. Therefore, the response status can be considered as a surrogate for a certain lymphoma biology that tends to be more aggressive, something not yet well understood.

We will estimate these subgroup effects for PFS and OS using Cox regression analyses including the following variables in the models: treatment allocation and response status at randomization. An appropriate interaction term (treatment allocation*response status) will be added to the model. We will illustrate subgroup effects using forest plots and provide the P value for the interaction test. Whether the number of events (around 7 per variable) suffices to designate OS will have to be seen. If not, we will conduct the subgroup analyses only for PFS.

13.5.4.2 Prognostic analyses

Based on the IELSG risk score, [36] we will evaluate the prognostic impact (PFS and OS) of the following baseline variables at the time of study inclusion before starting any chemotherapy: age (as continuous variable), performance score (ECOG 0-1 versus ECOG >1), liquor-protein elevation (yes versus no), involvement of deep-brain structures (yes versus no), and elevated serum LDH (yes versus no). We will use Cox regression analyses without variable selection procedures to explore these risk factors.

13.5.5 Safety parameters

13.5.5.1 Toxicity parameters

Toxicity parameters will be graded according to CTCAE 4.0 and analyzed descriptively by cycle and follow-up period. The maximum grade per patient will be compared between treatment arms for all parameters.

13.5.5.2 Neurotoxicity

Neurotoxicity parameters will be analyzed descriptively.

13.5.5.3 Adverse events

All safety parameters ((serious) adverse reactions, toxicity assessments) will be listed by center and patient and displayed in summary tables. The adverse events (AEs) are displayed in summary tables by treatment as follows:

The incidence of AEs defined by preferred term (PT) according to MedDRA will be calculated as the number of patients who experienced at least one AE with the respective PT in percentage of the total number of patients in the safety population. In the incidence tables the PTs will be grouped by system organ class (SOC) according to MedDRA. Additionally, the incidence of AEs defined by SOC will be calculated as the number of patients who experienced at least one AE in the respective SOC as a percentage of the total number of patients in the safety population.

Each table will be produced for the following AE-sets:

- AEs being at least severe (grade 3-4)
- Serious Adverse Events (SAEs) being at least severe (grade 3-4)

13.5.5.4 Laboratory data

The following laboratory data will be documented as toxicity parameters and graded according to CTCAE 4.0: Hematology includes assessment of white blood count (WBC), neutrophils, hemoglobin, and platelets. Blood chemistry comprises creatinine, total bilirubin, ALT, AST, and gamma-GT (only at screening).

If an abnormal laboratory parameter is not provided in the toxicity table, an AE must be documented on the CRF AE page. If any of the seriousness criteria are fulfilled, an SAE is to be reported. For details please refer to section 10.

13.5.5.5 Interim Analysis

Not applicable for this study

14 Data monitoring committee (DMC)

An independent Data Monitoring Committee (DMC) will be established. The DMC will consist of two medical scientists and one statistician with longstanding experience in clinical trials (see section Responsibility page 22). The DMC's function is to monitor the study's course and if necessary make recommendations to the steering committee for study discontinuation, modification or continuation the underlying principles for the DMC are the patients' ethical and safety aspects. It is the task of the DMC to examine whether the study's conduct is still ethically justifiable, whether security of the patients is ensured and whether the study's conduct is acceptable. The DMC will be informed about adherence to the protocol, patient recruitment, observed serious adverse events and deaths. The DMC will receive the corresponding reports (DSURs) at regular intervals. Recommendations on further continuation or modification of the study will be given to the steering committee. The composition and responsibilities of the DMC, the structure and procedures of its meetings, and its relationship to other key study team members (steering committee), will be laid down in a separate DMC charter.

15 Ethical and legal principles

15.1 Regulatory and ethical compliance

This clinical trial was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

15.2 Responsibilities of the investigator and IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Independent Ethics Committee (IEC) before trial start. A signed and dated statement that the protocol and informed consent have been approved by the IEC must be given to sponsor before initiation of the trial. Prior to the start of the trial, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the trial in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to sponsor monitors, auditors, sponsor Clinical Quality Assurance representatives, designated agents of sponsor, IECs and regulatory authorities as required.

15.3 Informed consent procedures

Before enrollment in the clinical trial, the patient will be 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 will provide 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 will be explained to the patient. During the informed consent discussion, the patient will also be informed about the insurance cover that exists and the insured's obligations. The patient will be 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 will be 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 will be 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 competent authority or the competent authority, and further agrees that authorized representatives of the sponsor University Medical Center 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 signing, the patient will be given one copy of the signed and dated written consent form and any other written information to be provided to the patients.

In the 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.

** ICH-GCP 4.8.9: If a patient is unable to read or if a legal representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to patients is read and explained to the patient or the patient's legal representative, and after the patient or the patient's legal representative has orally consented to the patient's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally*

date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the patient or the patient's legal representative, and that informed consent was freely given by the patient or the patient's legal representative.

Fertile men and women of child-bearing potential should be informed that taking the investigational product may involve unknown risks to the fetus if pregnancy were to occur during the trial and agree that in order to participate in the trial, they must adhere to the contraception requirement for the trial's duration. If there is any doubt that the patient may not reliably comply, they should not be entered in the trial.

15.4 Patient insurance

Subject insurance (minimum: € 500,000 per subject) according to § 40, section 1, subsection 8 and section 3 AMG has been taken out with the following insurance for all subjects participating in the clinical trial in all German sites:

Zurich Insurance plc NfD
- Policy No 800-520.020.990 –

Zurich Insurance plc 53287 Bonn Tel. 0228 268-650	Ecclesia Vers.dienst GmbH (Policy broker) Klingenbergtrasse 4 32758 Detmold Tel. 05231 – 6030 Fax 05231 - 603197

The investigator or an individual, who is designated by the investigator, will inform the subject of the existence of the insurance, including the obligations arising from it. The trial subjects must be afforded access to insurance documents and provided with a copy of the general conditions of insurance on request.

15.5 Confidentiality of trial documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to the sponsor. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

15.6 Financial disclosure

Financial disclosures should be provided by trial personnel directly involved in the treatment or evaluation of patients at the site - prior to trial start.

16 Trial documents and archiving

16.1 Trial documents/investigator site file

The investigator will be given an investigator site file containing all the necessary essential trial documents for initiation of the trial at his/her site. The essential documents include a list on which the investigator will enter all appropriately qualified persons to whom he/she has delegated important trial-related tasks.

The investigator or an individual designated by the investigator will be responsible for the maintenance and completeness of the trial documents during the clinical trial. At the request of the CRA, auditor, ethics committee or competent authority(ies), the investigator shall make available all the requested trial-related records for direct access. Essential documents must not be removed permanently.

16.2 Archiving

After completion of the clinical trial, the essential trial documents - as defined by ICH-GCP E6 section 8 - from clinical trials will be retained at the trial site for a sufficient period so that they are available for future audits and inspections by the authorities.

The investigator is responsible for document storage. The following retention periods will apply after the completion/termination of the clinical trial:

- The above-mentioned essential documents must be retained for at least 10 years (section 13, subsection 10 GCP-V); the identification codes of studies submitted for investigational product approval must be retained for at least 15 years (2001/83/EC).

- The medical records and other source documents must be retained for the longest possible period allowed by the hospital, institution or private practice.

The investigator/the institution should take measures to prevent accidental or premature destruction of these documents. The sponsor will notify the investigator in writing when the trial-related essential documents are no longer required.

17 Protocol adherence and amendments

17.1 Protocol adherence

Investigators commit themselves to “I apply due diligence to avoid protocol deviations”. If the investigator is convinced a protocol deviation would improve the conduct of the trial significantly this must be considered a protocol amendment. Unless such an amendment is agreed upon by sponsor and approved by the IEC and the CA it cannot be implemented.

17.2 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by sponsor, CA where required, and the IEC.

Only changes to the protocol that are required for patient safety may be implemented prior to IEC approval. Despite the need for approval for formal protocol amendments, the investigator is expected to take any immediate action required to ensure the safety of any patient enrolled in this trial, even if such action represents a protocol deviation. In such cases, the sponsor should be notified as soon as possible of this action; the IEC should be informed correspondingly.

17.3 Protocol deviations

Minor and important protocol deviations will be documented and processed according to procedure described in the corresponding SOP of the CTU.

A minor protocol deviation (MPD) is a deviation of the clinical trial protocol that does not significantly affect the subject's safety, his/her physical or mental integrity and/or the scientific value of the trial, for example: missing laboratory values that are not related to the patient's safety. Minor protocol deviations must be documented on a minor protocol deviation log and signed by the respective clinical research associate (CRA).

An important protocol deviation (IPD) is a protocol deviation that significantly affects the subject's safety, the physical or mental integrity of the subject and/or the scientific value of the trial, such as an unsigned informed consent form or use of an invalid version of the informed consent. An IPD must be documented on an important protocol deviation log and signed by the principal investigator and the respective clinical research associate.

18 Administrative Agreements

18.1 Financing of the trial

The clinical trial will be financed by public funds via the Federal Department of Education and Research (BMBF/DLR).

18.1.1 Trial agreement/investigator compensation

According to ICH-GCP 4.9.6, a trial agreement on the conduct of the clinical trial and on compensation for conducting the trial will be signed between the clinical trial's sponsor and its investigators including their heads of administration.

18.1.2 Reimbursement of trial patients

There is no payment planned for patients.

18.2 Trial language

English

18.3 Trial reports

After completion of the analysis by the responsible biostatistician, the coordinating investigator will prepare and sign the final integrated medical and statistical report jointly with the biostatistician.

Except when required by law, no one will disclose a result of the clinical trial to third parties unless all parties involved have first agreed on the results of the analysis and their interpretation.

The final trial report will be written and signed in cooperation between the coordinating investigator and the CTU of the Medical Center – University of Freiburg.

18.4 Clinical trials registry

The sponsor assures that the key design elements of this protocol will be posted in a publicly accessible clinical trials registry such as DRKS (German registry for clinical trials)/ clinicaltrials.gov.

18.5 Publication of trial protocol and results

Upon trial completion, the results of this trial will be submitted for publication and/or posted in a publicly-accessible database of clinical trial results. Reporting guidelines will be taken into account (see www.equator-network.org), e.g. the CONSORT statement should be adhered to when drafting papers on the results of randomized studies.

Each publication of trial results will occur in mutual agreement between the principal investigator, any other investigators involved, and the CTU. All data collected in connection with the clinical trial will be treated in confidence by the coordinating investigator and all others involved in the trial until publication. Interim data and final results may only be published (orally or in writing) with agreement from the coordinating investigator and the CTU. This is essential for a thorough exchange of information between the afore mentioned parties and will ensure that the opinions of all parties involved have been heard before publication. This agreement, which does not include any veto right or right of censorship for any of the parties involved, may not be refused without good reason.

Appendices

Appendix 1 Relevant Guidelines and Laws

Declaration of Helsinki	http://www.wma.net/en/30publications/10policies/b3/
ICH-GCP Guidelines	http://www.ich.org
EMA Guidelines	http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/landing/human_medicines_regulatory.jsp&mid=WC0b01ac058001ff89
AMG/GCP-V	http://www.gesetze-im-internet.de
Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0	http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Appendix 2 IPCG Response criteria*

Response Criteria for Primary Central Nervous System (CNS) Lymphoma

Response	Brain Imaging	Corticosteroid Dose	Eye Examination	CSF Cytology
CR	No contrast enhancement	None	Normal	Negative
CRu	No contrast enhancement	Any	Normal	Negative
	Minimal abnormality	Any	Minor RPE abnormality	Negative
PR	50% decrease in enhancing tumor compared to baseline	Irrelevant	Minor RPE abnormality or normal	Negative
	No contrast enhancement	Irrelevant	Decrease in vitreous cells or retinal infiltrate	Persistent or suspicious
PD	25% increase in lesion compared to baseline or to best response (smallest in case of multiple)	Irrelevant	Recurrent or new ocular disease	Recurrent or positive
	Any new site of disease: CNS or systemic			
SD	Stable disease is defined as less than a PR but is not progressive disease.			
Relapsed disease	(only applicable to patients with a prior CR, CRu) requires the following: (1) Appearance of any new lesion.			

** derived from "Report of an International Workshop to Standardize Baseline Evaluation and Response Criteria for Primary CNS Lymphoma." [35]*

Abbreviations:

CR Complete Remission
CRu unconfirmed Complete Remission
CSF Cerebrospinal Fluid
PD Progressive Disease
PR Partial Remission
RPE Retinal Pigment Epithelium
SD Stable Disease

Appendix 3 ECOG Performance Status

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
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 house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

** Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.*

Appendix 4 Mini-Mental Status Examination (MMSE)

Neuropsycholgische Test battery

Mini **Mental Status Test (MMST)** **Appendix 4**

Pat.-Nr: |_____|	**Initialen** |__|__|	**Zentrum:** |____|	**Datum** |____|___|_____|	**Score gesamt**	**/30**

A. Orientierung

Score

Zeit *(z. B. Welchen Tag haben wir heute?)*	1.	Jahr	①
	2.	Jahreszeit	①
	3.	Datum	①
	4.	Wochentag	①
	5.	Monat	①
Ort *(z. B. Wo sind wir?)*	6.	Land/Staat	①
	7.	Bundesland	①
	8.	Stadt/Ortschaft	①
	9.	Klinik/Praxis/Altersheim	①
	10.	Stockwerk	①
		Summe (max. 10)	|__|

B. Merkfähigkeit

Der Untersucher nennt folgende drei Gegenstände und fordert den Patienten auf, die Begriffe zu wiederholen (1 Punkt für jede richtige Antwort) Der Untersucher wiederholt die Wörter so lange, bis der Patient alle drei gelernt hat (höchstens 6 Wiederholungen).	1.	"Auto"	①
	2.	"Blume"	①
	3.	"Kerze"	①
		Summe (max. 3)	|__|

C. Aufmerksamkeit und Rechenfähigkeit

Von 100 an sind jeweils 7 abzuziehen. Falls ein Rechenfehler gemacht wird und die darauf folgenden Ergebnisse "verschoben" sind, so wird nur ein Fehler gegeben.	1.	93	O	①
	2.	86	I	①
ODER	3.	79	D	①
	4.	72	A	①
Falls der Patient die Aufgabe nicht durchführen kann oder will, "RADIO" rückwärts buchstabieren lassen: O-I-D-A-R	5.	65	R	①
			Summe (max. 5)	|__|

D. Erinnerungsfähigkeit

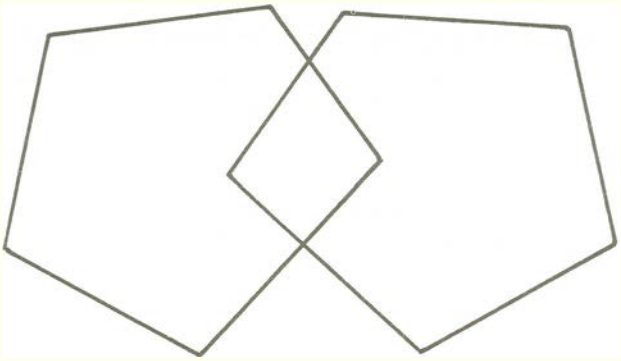
Der Untersucher fragt nach den drei zuvor genannten Wörtern.	1.	"Auto"	①
	2.	"Blume"	①
	3.	"Kerze"	①
		Summe (max. 3)	|__|

E. Sprache

Der Untersucher zeigt zwei Gegenstände und fordert den Patienten auf, sie zu benennen.	1.	Armbanduhr	①
	2.	Bleistift	①
Der Untersucher fordert den Patienten auf, nachzusprechen	3.	"Sie leiht ihm kein Geld mehr"	①
Der Untersucher läßt den Patienten folgende Kommandos befolgen	4.	"Nehmen sie dieses Blatt in die rechte Hand."	①
	5.	"Falten sie es in der Mitte."	①
	6.	"Legen sie es auf den Boden"	①
Der Untersucher dreht das Blatt um und fordert den Patienten auf,	7.	die Anweisung auf der nächsten Seite zu befolgen	①
	8.	einen vollständigen Satz zu schreiben (nächste Seite)	①
Der Patient soll die auf der Rückseite vorgegebene Figur nachzeichnen (alle Seiten und Winkel sollen stimmen und die sich überschneidenden Linien sollen ein Viereck bilden)	9.	Nachzeichnen (nächste Seite)	①
		Summe (max. 9)	|__|

Gesamtsumme bitte oben eintragen!

Bitte schließen Sie die Augen!



Neuropsychologische IPCG Testbatterie

Stammblatt: Soziodemographische Variablen

Zentrum: |__| |__|

Patienten-Initialien: |__| |__|

Patienten-Nr.: |__| |__| |__|

laufende Nummer: |__| |__| |__| |__|

Untersuchungsdatum: |__| |__| .|__| |__| .|__| |__| |__| |__|
Tag Monat Jahr

Alter: |__||__||__|Geb.-Datum: |__| |__| .|__| |__| .|__| |__| |__| |__|
Tag Monat Jahr

Geschlecht: □ männlich □ weiblich

Händigkeit: □ rechts □ links

Größe des Wohnortes: □ < 2500 Einwohner
□ > 2500 Einwohner

Beruf: _____

Schulbildung: _____Absolvierte Schuljahre: |__| |__|

Testbehindernde Faktoren:

_____

_____

Datum: …… Unterschrift des Untersuchers: ……

1) Zahlenspanne

Beispiel vorwärts: 7-1-9

Zahlen vorwärts	Punkte (0, 1)	Punkte (0, 1, 2)
1-7		
6-3		
5-8-2		
6-9-4		
6-4-3-9		
7-2-8-6		
4-2-7-3-1		
7-5-8-3-6		
6-1-9-4-7-3		
3-9-2-4-8-7		
5-9-1-7-4-2-8		
4-1-7-9-3-8-6		
5-8-1-9-2-6-4-7		
3-8-2-9-5-1-7-4		
2-7-5-8-6-2-5-8-4		
7-1-3-9-4-2-5-6-8		
Zahlen vorwärts Gesamt-Punkte (max=16)		

Beispiel rückwärts: 3-4-8

Zahlen rückwärts	Punkte (0, 1)	Punkte (0, 1, 2)
2-4		
5-7		
6-2-9		
4-1-5		
3-2-7-9		
4-9-6-8		
1-5-2-8-6		
6-1-8-4-3		
5-3-9-4-1-8		
7-2-4-8-5-6		
8-1-2-9-3-6-5		
4-7-3-9-1-2-8		
9-4-3-7-6-2-5-8		
7-2-8-1-9-6-5-3		
Zahlen rückwärts Gesamt-Punkte (max=14)		

vorwärts	+	rückwärts	=	Gesamt (max=30)

2) Wortliste, Lerndurchgänge 1-3

Wortliste
Tasse
Rum
Sieb
Dolch
Schwert
Schüssel
Cognac
Schnaps
Teller
Bombe
Revolver
Gin

Punkteverteilung:
- 1 Punkt pro korrekt erinnertem Wort

	Punkte	max
Durchgang 1		12
Durchgang 2		12
Durchgang 3		12
Gesamt Durchgang 1-3		36
Verzögerter Abruf		12
Wiedererkennung		12

Lerndurchgänge						verzögerter Abruf (nach 20-25 min)	
Durchgang 1	✓	Durchgang 2	✓	Durchgang 3	✓	Durchgang 4	✓
Punkte (max=12)							

Testende Durchgang 3: _____ Testbeginn Durchgang 4: _____

3) Kurzer Aufmerksamkeitstest

Zahlen	Lösung	Antwort	Punkte (0, 1)
Beispiel 1: 7-B-X	1		-
Beispiel 2: F-3-6	2		-
5-K-7-H	2		
T-6-1-A-6-T	3		
L-1-3-Q-J-2-N-F-8	4		
9-X-9-7-Y-F-8-X-5	5		
1-Q-2-U-2-Q-3-4-5-Q-6-U	7		
K-3-G-3-X-B-C-3-B-1-3-Z	5		
K-4-2-K-A-8-K-H-8-A-J-8-K-2-U	6		
7-U-2-5-3-C-2-3-V-B-G-6-3-6-G	9		
9-M-1-N-9-1-N-1-9-A-8-8-8-N-8-N-3-1	12		
C-Z-3-T-B-4-C-3-T-D-P-3-T-Z-3-T-4-B	6		
Gesamt-Punkte Zahlen (max=10)			

Buchstaben	Lösung	Antwort	Punkte (0,1)
Beispiel 1: 7-B-X	2		-
Beispiel 2: F-3-6	1		-
5-K-7-H	2		
T-6-1-A-6-T	3		
L-1-3-Q-J-2-N-F-8	5		
9-X-9-7-Y-F-8-X-5	4		
1-Q-2-U-2-Q-3-4-5-Q-6-U	5		
K-3-G-3-X-B-C-3-B-1-3-Z	7		
K-4-2-K-A-8-K-H-8-A-J-8-K-2-U	9		
7-U-2-5-3-C-2-3-V-B-G-6-3-6-G	6		
9-M-1-N-9-1-N-1-9-A-8-8-8-N-8-N-3-1	6		
C-Z-3-T-B-4-C-3-T-D-P-3-T-Z-3-T-4-B	12		
Gesamt-Punkte Buchstaben (max=10)			

Zahlen	+	Buchstaben	=	Gesamt (max=20)

4) Zahlen- bzw. Buchstabenverbindungstest

	Zeit (Minuten:Sekunden)	
Trail A		max. 3 Min
Trail B		max. 5 Min

5) Stifte Stecken (grooved Pegboard)

	Zeit (Minuten:Sekunden)
rechts	
links	

6) Wortliste, langfristiger Abruf

Achtung: Wortliste nicht nochmal vorlesen!
nach 20-25 min: Verzögerter Abruf, s. Tabelle, Durchgang 4
danach: Wiedererkennung

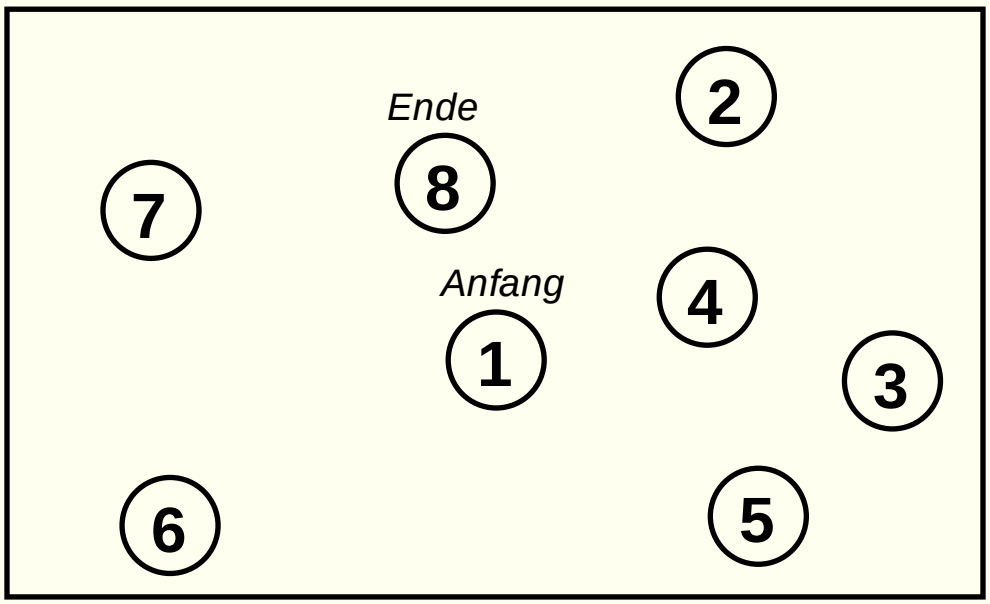
Wiedererkennung								
Cognac	J	N	Schüssel	J	N	Füller	J	N
Löffel	J	N	Wein	J	N	Messer	J	N
Bombe	J	N	Gin	J	N	Tasse	J	N
Sieb	J	N	Teller	J	N	Zitrone	J	N
Gold	J	N	Schwert	J	N	Revolver	J	N
Topf	J	N	Gewehr	J	N	Bier	J	N
Harmonika	J	N	Forelle	J	N	Puppe	J	N
Schnaps	J	N	Rum	J	N	Dolch	J	N

	Punkte	max
Gesamtzahl der richtig-positiven Antworten (keine Schattierung)		12
semantisch-verwandte falsch-positive Fehler (helle Schattierung)		6
semantisch-nicht-verwandte falsch-positive Fehler (dunkle Schattierung)		6
Gesamtzahl falsch-positiver		12

TRAIL MAKING

Part A

Beispiel

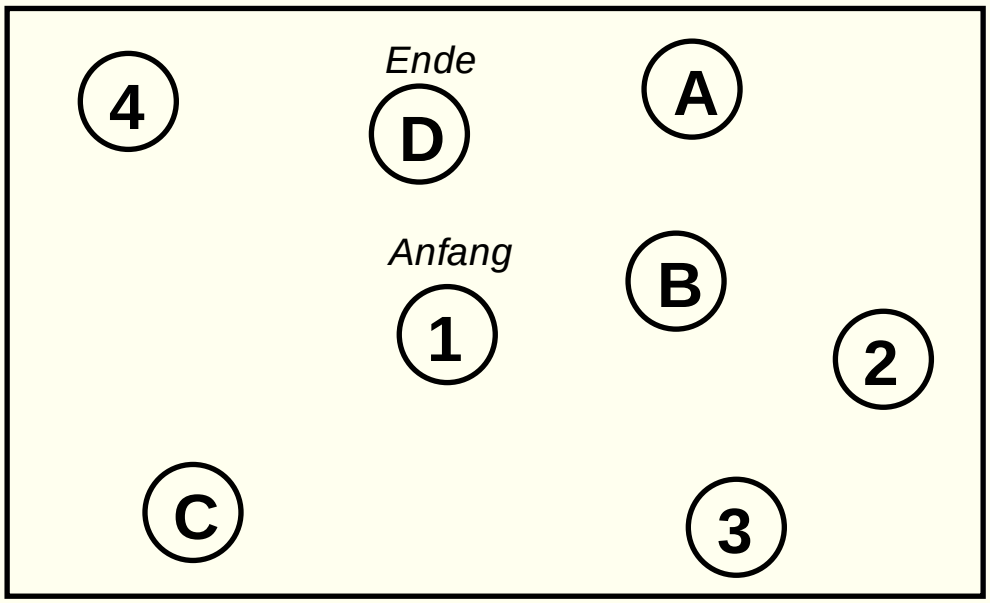


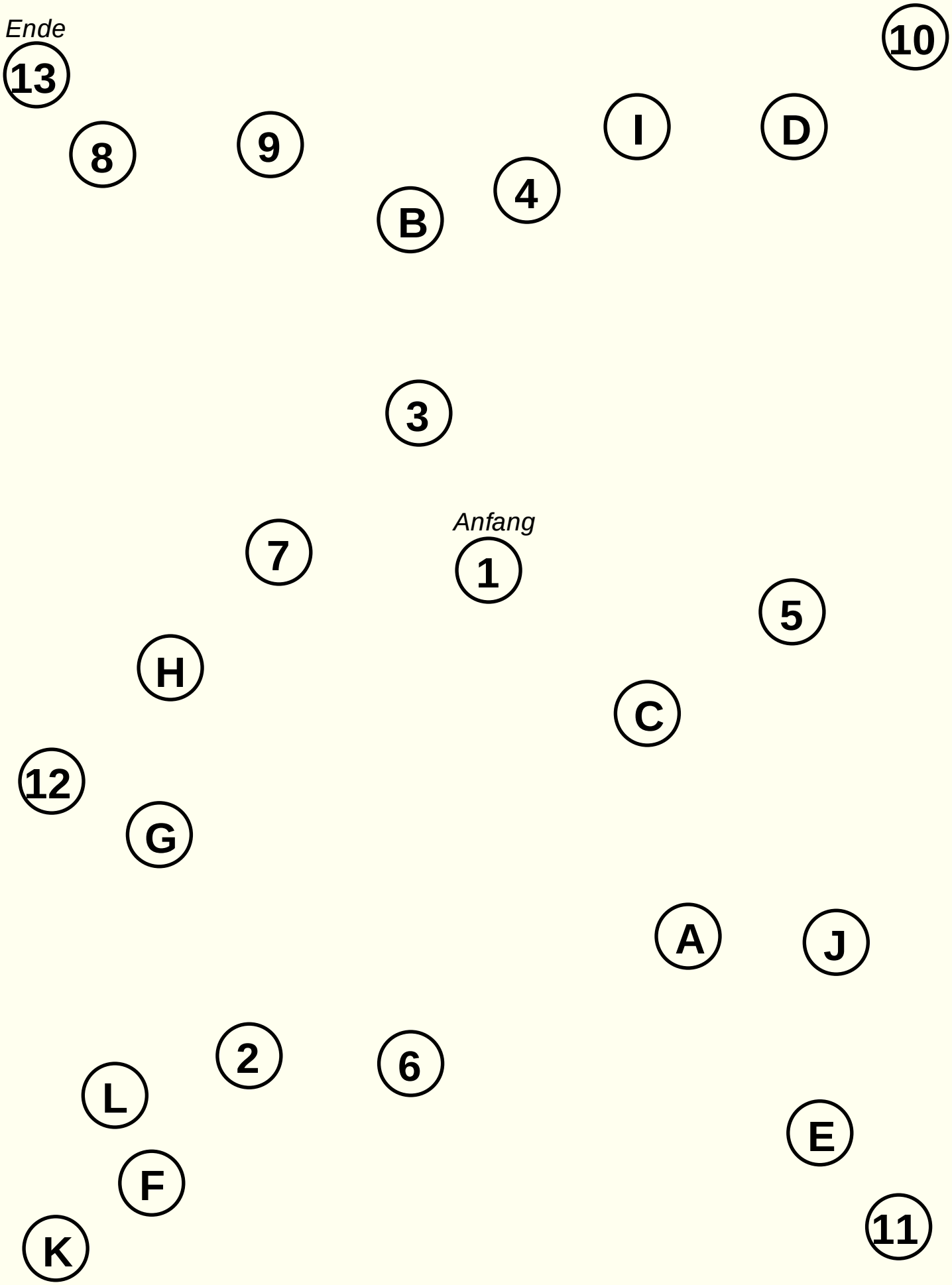

15
17
21
20
19
16
18
4
22
5
13
6
Anfang
24
1
7
14
2
10
8
3
Ende
9
11
25
12
23

TRAIL MAKING

Part B

Beispiel




Ende
13
10
8
9
I
D
4
B
3
Anfang
7
1
5
H
C
12
G
A
J
2
6
L
E
F
11
K

Appendix 5 EORTC QLQ-C30

Appendix 5

1.1 EORTC QLQ-C30 (Version 3.0)

Wir sind an einigen Angaben interessiert, die Sie und Ihre Gesundheit betreffen. Bitte beantworten Sie die folgenden Fragen selbst, indem Sie die Zahl ankreuzen, die am besten auf Sie zutrifft. Es gibt keine “richtigen” oder “falschen” Antworten. Ihre Angaben werden streng vertraulich behandelt.

Bitte tragen Sie Ihre Initialen ein (Vorname | Nachname) ___ | ___

Ihr Geburtstag (Tag, Monat, Jahr): ___ | ___ | ___

Das heutige Datum (Tag, Monat, Jahr): ___ | ___ | ___

		nicht	wenig	mäßig	sehr
1.	Bereitet es Ihnen Schwierigkeiten sich körperlich anzustrengen (z.B. eine schwere Einkaufstasche oder einen Koffer zu tragen?)	1	2	3	4
2.	Bereitet es Ihnen Schwierigkeiten, einen längeren Spaziergang zu machen?	1	2	3	4
3.	Bereitet es Ihnen Schwierigkeiten, eine kurze Strecke außer Haus zu gehen?	1	2	3	4
4.	Müssen Sie tagsüber im Bett liegen oder in einem Sessel sitzen?	1	2	3	4
5.	Brauchen Sie Hilfe beim Essen, Anziehen, Waschen oder Benutzen der Toilette?	1	2	3	4

Während der letzten Woche:

		nicht	wenig	mäßig	sehr
6.	Waren Sie bei Ihrer Arbeit oder bei anderen tagtäglichen Beschäftigungen eingeschränkt?	1	2	3	4
7.	Waren Sie bei Ihren Hobbys oder anderen Freizeitbeschäftigungen eingeschränkt?	1	2	3	4
8.	Waren Sie kurzatmig?	1	2	3	4
9.	Hatten Sie Schmerzen?	1	2	3	4
10.	Mussten Sie sich ausruhen?	1	2	3	4
11.	Hatten Sie Schlafstörungen?	1	2	3	4
12.	Fühlten Sie sich schwach?	1	2	3	4
13.	Hatten Sie Appetitmangel?	1	2	3	4
14.	War Ihnen übel?	1	2	3	4
15.	Haben Sie erbrochen?	1	2	3	4

Bitte wenden

Während der letzten Woche:

		nicht	wenig	mäßig	sehr
16.	Hatten Sie Verstopfung?	1	2	3	4
17.	Hatten Sie Durchfall?	1	2	3	4
18.	Waren Sie müde?	1	2	3	4
19.	Fühlten Sie sich durch Schmerzen in Ihrem alltäglichen Leben beeinträchtigt?	1	2	3	4
20.	Hatten Sie Schwierigkeiten sich auf etwas zu konzentrieren, z.B. auf das Zeitungslesen oder das Fernsehen?	1	2	3	4
21.	Fühlten Sie sich angespannt?	1	2	3	4
22.	Haben Sie sich Sorgen gemacht?	1	2	3	4
23.	Waren Sie reizbar?	1	2	3	4
24.	Fühlten Sie sich niedergeschlagen?	1	2	3	4
25.	Hatten Sie Schwierigkeiten, sich an Dinge zu erinnern?	1	2	3	4
26.	Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Familienleben beeinträchtigt?	1	2	3	4
27.	Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Zusammensein oder Ihre gemeinsamen Unternehmungen mit anderen Menschen beeinträchtigt?	1	2	3	4
28.	Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung für Sie finanzielle Schwierigkeiten mit sich gebracht?	1	2	3	4

Bitte kreuzen Sie bei den folgenden Fragen die Zahl zwischen 1 und 7 an, die am besten auf Sie zutrifft

29. Wie würden Sie insgesamt Ihren Gesundheitszustand während der letzten Woche einschätzen?

1 2 3 4 5 6 7

sehr schlecht ausgezeichnet

30. Wie würden Sie insgesamt Ihre Lebensqualität während der letzten Woche einschätzen?

1 2 3 4 5 6 7

sehr schlecht ausgezeichnet

Appendix 6 EORTC QLQ-BN20

Appendix 6

1.1 EORTC QLQ - BN20

Patienten berichten manchmal die nachfolgend beschriebenen Symptome oder Probleme. Bitte beschreiben Sie, wie stark Sie diese Symptome oder Probleme während der letzten Woche empfunden haben.

Während der letzten Woche:

	nicht	wenig	mäßig	sehr
Fühlten Sie sich unsicher in Bezug auf die Zukunft?	1	2	3	4
Hatten Sie das Gefühl, gesundheitliche Rückschläge erlitten zu haben?	1	2	3	4
Waren Sie besorgt, dass Ihr Familienleben gestört werden könnte?	1	2	3	4
Hatten Sie Kopfschmerzen?	1	2	3	4
Hat sich Ihre Einstellung zur Zukunft verschlechtert?	1	2	3	4
Haben Sie doppelt gesehen?	1	2	3	4
Haben Sie verschwommen gesehen?	1	2	3	4
Hatten Sie Schwierigkeiten beim Lesen?	1	2	3	4
Hatten Sie Anfälle?	1	2	3	4
Hatten Sie ein Schwächegefühl auf einer Körperseite?	1	2	3	4
Bereitete es Ihnen Mühe, die richtigen Worte zu finden, um sich auszudrücken?	1	2	3	4
Hatten Sie Schwierigkeiten beim Sprechen?	1	2	3	4
Bereitete es Ihnen Mühe, anderen Ihre Gedanken mitzuteilen?	1	2	3	4
Fühlten Sie sich tagsüber schläfrig?	1	2	3	4
Hatten Sie Koordinationsprobleme?	1	2	3	4
Machte Ihnen Haarverlust zu schaffen?	1	2	3	4
Machte Ihnen Hautjucken zu schaffen?	1	2	3	4
Hatten Sie Schwächegefühle in beiden Beinen?	1	2	3	4
Fühlten Sie sich unsicher auf den Beinen?	1	2	3	4
Hatten Sie Mühe, Ihre Blase zu kontrollieren?	1	2	3	4

Appendix 7 Translational research program

Processing the primary tumor samples available in the study biobank we are planning to analyse the genomic profile, mRNA and miRNA expression. A multivariate analysis investigating the correlation of the molecular findings with data regarding the response to therapy, the clinical course and the overall survival of the patients should be conducted.

Processing the blood and bloodserum samples available in the study biobank, established prognostic factors (e.g. lactate dehydrogenase levels) should be verified and unknown factors should be identified.

Processing the CSF samples available in the study biobank the observation that certain miRNAs can be used for diagnosis and molecular monitoring of PCNSL should be verified in a prospective manner.

Appendix 8 Chemotherapy protocols, Freiburg

Rituximab/MTX/Cytarabin/Thiotepa

Chemotherapie

Tag	zeitl. Ablauf	Substanz	Dosierung	Trägerlösung (ml)	Appl.	Inf.-dauer	Bemerkungen
0	0	Rituximab	375 mg/m²	500 ml NaCl 0,9%	i.v.	initial 50mg/h	
1	0	Methotrexat	500 mg/m²	250 ml NaCl 0,9%	i.v.	15min	*0,5g/m² in 15min., dann 3g/m² in 3h
1	+15min	Methotrexat	3000 mg/m²	500 ml NaCl 0,9%	i.v.	3h	
2-3	0	Cytarabin	2000 mg/m²	250 ml NaCl 0,9%	i.v.	1h	im Abstand von 12h
2-3	+12h	Cytarabin	2000 mg/m²	250 ml NaCl 0,9%	i.v.	1h	im Abstand von 12h
4	0	Thiotepa	30 mg/m²	Glucose 5%	i.v.	30min	
5	0	Rituximab	375 mg/m²	500 ml NaCl 0,9%	i.v.	initial 50mg/h	

Diese Zytostatikatherapie birgt letale Risiken. Die Anwendung darf nur durch erfahrene Onkologen/Hämatologen und entsprechend ausgebildetes Pflegepersonal erfolgen. Die Dosisberechnung und Anforderung obliegt der Verantwortung des bestellenden Arztes und muss in jedem Fall sorgfältig überprüft werden. Die Herausgeber übernehmen keine Verantwortung für die Chemoanforderung.

Stammzellharvest
nach 2. Induktions-Zyklus:
mind. 5x10⁶ CD34⁺ Zellen/kgKG in mögl. wenigen Leukapherese-sitzungen an aufeinander-folgenden Tagen

CAVE MTX-Interaktionen:
keine nephro- u. hepatotoxischen Medikamente
keine gleichzeitige Einnahme von Protonenpumpen-Inhibitoren
CAVE bei gleichzeitiger Einnahme von NSAI und Antibiotika

Therapieablauf:

Induktion:
2 Zyklen MATRix → Stammzell-Harvest → 2 Zyklen MATRix
(= 4 Zyklen MATRix insgesamt)

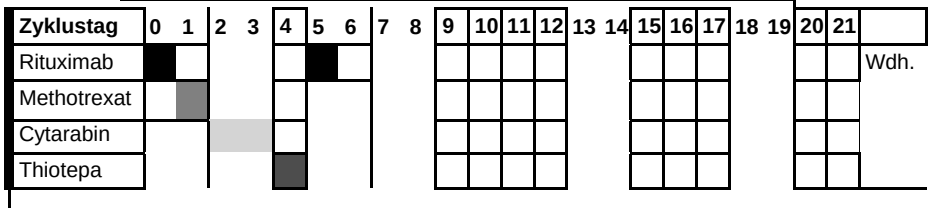
Konsolidierung:

2 Zyklen R-DeVIC
Arm A

Hochdosistherapie
mit BCNU/Thiotepa
+ PBSCT
ArmB

FN-Risiko >20 %:
entweder **24h nach CTx** Primärprophylaxe mit Pegfilgrastim/Neulasta® 6mg s.c. einmalig **(nicht im Zyklus 2, da SZ-Harvest)**
oder **ab d6** Filgrastim/Neupogen® 5µg/kg/d s.c. tägl. bis Durchschreiten des Nadir

Bei Stammzellmobilisierung:
Filgrastim-Gabe vor geplanter Leukapherese ab d9: 5µg/kgKG/d s.c. morgens (>70kg: 480µg,<70kg:300µg) bis Ende der Apherese.



Memo: Thiotepa wird im Schweiß abgesondert. Zur Vermeidung einer toxisch bedingten Erythrodermie (besonders axillär und inguinal) häufig mit nassem Waschlappen abwaschen (keine Seife bis einschl. am Tag nach der Thiotepa-Gabe)

Achtung: Betrifft NaHCO3/Alkalisierung + Kontrolle
- Strikte Urinalkalisierung,
- bei Beginn der Urinalkalisierung erste 12h 4-6 stündlich venöse BGAs
- **Zielbereich Urin pH vor** Therapiestart **bis Ende** Leucovorinrescue**: 7,4 - 8,5**
- unter Therapie pH-Kontrolle bei jeder Miktion (mindestens alle 8h)
- bei Urin-pH < 7,4 -> zusätzliche NaHCO3 Gabe, pH-Kontrolle siehe oben
- auf Urinausscheidung achten Ziel > 100ml/h, Bedarfsmedikation Furosemid/ Hydrierung
- Elektrolytkontrolle (Natrium, Kalium), Serumkreatinin, Harnstoff 24h und 48h nach Start MTX
- auf Bewässerung / Alkalisierung und entsprechendes Monitorisieren an Folgetagen achten.

Achtung: Betrifft Leukovorin-Rescue
Leukovorin alle 6h Dosierung nach Schema, erster Tag i.v.; Start 24h nach Beginn MTX-Infusion. Weiterführung des Leukovorin-Rescues **bis 6. Tag nach MTX.**
Bei **verzögerter MTX-Ausscheidung Verlängerung und Erhöhung** des Leukovorin-Rescues gemäß LV Rescue Bogen für ZNS-NHL
MTX-Spiegel: +3h15min (unmittelbar nach MTX-Ende), +24h (vor erster Rescue), dann tgl. morgens und abends

Obligate Prä- und Begleitmedikation

Tag	zeitl. Ablauf	Substanz	Dosierung	Trägerlösung (ml)	Appl.	Inf.-dauer	Bemerkungen
0	-1h	Paracetamol/Paracetamol ratio®	1000 mg		p.o.		

0	-30min	NaCl 0,9 %		500 ml	i.v.		während der Rituximab-Gabe
0	-30min	Clemastin/Tavegil® 2mg (bzw. Dimetinden/Fenistil® 1ml/10kg KG)	2 mg		i.v.	B	
0	-30min	Dexamethason	8 mg		i.v.	B	vor Rituximab-Erstgabe obligat; bei Folgegaben in Abhängigkeit von Verträglichkeit
1	-24h vor Start Methotrexat	NaCl 0,9% + Glucose 5% (+20ml KCl 7,45%+100ml $NaHCO_3$ 8,4%)		3000 ml	i.v.	21h	im Wechsel; Ziel Urin pH 7,4-8,5
1	-3h	NaCl 0,9% (+20ml KCl 7,45% + $NaHCO_3$ 8,4%)		500 ml	i.v.	2h	Ziel Urin pH 7,4-8,5 ; 2-4ml/kg $NaHCO_3$ 8,4%
1	-1h	NaCl 0,9 %		500 ml	i.v.	5h	
2-4	-30min	NaCl 0,9 %		2000 ml	i.v.	24h	kontinuierlich
1-4	-30min	Granisetron/Kevatril®	1 mg		i.v.	B	
1-3	-30min	Dexamethason	8 mg		i.v.	B	
1	+4h	NaCl 0,9% (+20ml KCl 7,45% + $NaHCO_3$ 8,4%)		2000 ml	i.v.	20h	Ziel Urin pH 7,4-8,5 ; 2-4ml/kg $NaHCO_3$ 8,4%
1	+6h	Furosemid/Lasix®	40 mg		i.v.	B	slow Bolus
2-3	+11h30min	Granisetron/Kevatril®	1 mg		i.v.	B	
2-3	+11h30min	Dexamethason	8 mg		i.v.	B	
2-4	1-1-1-1	Dexa-Sine SE® Augentropfen	2 Trpf.		i.o.		alle 6 Stunden
5-9	1-1-1-1	Corneregel® Augentropfen	1 Trpf.		i.o.		alle 6 Stunden
5	-1h	Paracetamol/Paracetamol ratio®	1000 mg		p.o.		
5	-30min	NaCl 0,9%		500 ml	i.v.		während der Rituximab-Gabe
5	-30min	Clemastin/Tavegil® 2mg (bzw. Dimetinden/Fenistil® 1ml/10kg KG)	2 mg		i.v.	B	
5	-30min	Dexamethason	8 mg		i.v.	B	vor Rituximab-Erstgabe obligat; bei Folgegaben in Abhängigkeit von Verträglichkeit
0-21	1-1-1-1	Aciclovir/Zovirax®	200 mg		p.o.		kontinuierlich, bei Auftreten von Mukositis ≥ Grad 2
0-21	0-1-0-0	Cotrimoxazol/Cotrim®forte	960 mg		p.o.		Mo, Mi, Fr; Pause d1 bis Ende Leukovorin-Rescue
6-21	1-0-1-0	Ciprofloxacin*	500 mg		p.o.		Antibiotische Prophylaxe gemäß lokaler Standardbehandlung (z.B. **Ciprofloxacin**) ab **d6** täglich bis nach dem Leukocyten Nadir

Erstellt: 25.10.2013

Bedarfsmedikation: Kalium/Kalinor®, $NaHCO_3$ 50 ml/2h Infusion, Metoclopramid/Paspertin®, Famotidin/Pepdul®, Analgesie, Antibiose, Allopurinol, Antikonvulsiva, Sedativa, Solu-Decortin 50mg i.v. vor und während Rituximab

FN-Risiko: > 20% --> Primärprophylaxe mit Filgrastim/Neupogen® oder Pegfilgrastim/Neulasta®, siehe Kurzfassung Leitlinien G-CSF

Kontrollen: siehe Studienprotokoll: ECOG, Gewicht, Vitalzeichen, körperliche und neurologische Untersuchung, Blutbild, Serumelektrolyte, eGFR, Ultraschall (Abdomen), Begleitmedikation, Nebenwirkungen

Dosisreduktion: siehe Studienprotokoll: **hämatologische Toxizitäten:** schwerwiegende Neutropenie: DR Cytarabin im Folgezyklus um 25% d.h. 4. Dosis (2. Gabe an d3 weglassen), schwerwiegende Thrombopenie Grad 4: DR Cytarabin im Folgezyklus um 25% d.h. 4. Dosis (2. Gabe an d3 weglassen), DR Thiotepa um 25%; **nicht hämatologische Toxizitäten:** Dosisreduktion laut Fachinformation

Cave: keine gleichzeitige Anwendung von Thiotepa und CYP3A4-Inhibitoren (z.B. Itraconazol, Voriconazol und Posaconazol, Makrolid-Antibiotika) Therapievoraussetzung: ANC > 1 500/mm^3 und Thrombozyten > 90 000/mm^3

Therapieaufschub: bei ANC < 1 500/mm^3 und Thrombozyten < 90 000/mm^3 Verzögerung Start nächster Zyklus (max. 14 Tage) Therapieabbruch: bei Therapieverzögerung > 4 Wochen siehe auch Studienprotokoll

Wechselwirkungen:	Protonenpumpeninhibitoren (PPI) können die MTX-Ausscheidung verzögern und so zu erhöhtem MTX Plasmaspiegel führen, daher wird empfohlen, PPI 2 Tage vor bis 2 Tage nach der MTX-Gabe zu pausieren (ggf. durch H_2-Blocker, Tepilta® ersetzen). Ebenfalls Vorsicht ist bei der gleichzeitigen Anwendung von MTX und NSAIDs oder Antibiotika (ß-Lactam-Antibiotika, Sulfonamide, Trimetoprim, Tetracycline, Ciprofloxacin) angezeigt. 2 Tage vor und 2 Tage nach MTX-Gabe keine Kontrastmittelgabe.
Erfolgsbeurteilung:	nach 2 bzw. 4 Zyklen: MRI (Schädel), bei positiver Diagnose: CSF-Untersuchung, Augenuntersuchung (Spaltlampenmikroskopie), nach Zyklus 4 zusätzlich: MMSE, QOL Wiederholung: d22; nach 2. Zyklus Stammzellharvest, insgesamt maximal 4 Zyklen
Literatur:	Studienprotokoll Matrix-Studie
Zuständiger Oberarzt:	Prof. Finke, Universitätsklinikum Freiburg, Innere Medizin I, gcp@oncoconsult.de

060507_ MATRix-Studie High Dose Consolidation Arm B: HDT-ASCT *Indikation: ZNS-NHL* *ICD-10: C85.9*

BCNU/Thiotepa

Chemotherapie

Tag	zeitl. Ablauf	Substanz	Dosierung	Trägerlösung (ml)	Appl.	Inf.-dauer	Bemerkungen
-6	0	Carmustin (BCNU)	400 mg/m²	500 ml Glucose 5%	i.v.	1h	unter Lichtschutz
-5	0	Thiotepa	5 mg/kg	Glucose 5%	i.v.	2h	12h Abstand zwischen beiden Gaben
-5	+12h	Thiotepa	5 mg/kg	Glucose 5%	i.v.	2h	12h Abstand zwischen beiden Gaben
-4	0	Thiotepa	5 mg/kg	Glucose 5%	i.v.	2h	12h Abstand zwischen beiden Gaben
-4	+12h	Thiotepa	5 mg/kg	Glucose 5%	i.v.	2h	12h Abstand zwischen beiden Gaben

Diese Zytostatikatherapie birgt letale Risiken. Die Anwendung darf nur durch erfahrene Onkologen/Hämatologen und entsprechend ausgebildetes Pflegepersonal erfolgen. Die Dosisberechnung und Anforderung obliegt der Verantwortung des bestellenden Arztes und muss in jedem Fall sorgfältig überprüft werden. Die Herausgeber übernehmen keine Verantwortung für die Chemoanforderung.

Tag 0 periphere Stammzelltransplantation (≥ 5x10^6 CD34$^+$ Zellen/kgKG)

Therapieablauf:

Induktion:

2 Zyklen MATRix → Stammzell-Harvest → 2 Zyklen MATRix
(= 4 Zyklen MATRix insgesamt)

Konsolidierung:

2 Zyklen R-DeVIC Arm A	Hochdosistherapie mit BCNU/Thiotepa + PBSCT ArmB

Cave: Aprepitant ist moderater Inhibitor und Induktor von CYP3A4 (siehe auch Fachinformation)
zusätzliche Vorsicht bei Etoposid, Vinorelbin, **Docetaxel**, Paclitaxel, Irinotecan und Ketoconazol
Keine gleichzeitge Gabe mit Pimozid, Terfenadin, Astemizol und Cisaprid.
Gleichzeitige Gabe mit Rifampicin, Phenytoin, Carbamazepin oder anderen CYP3A4 Induktoren sollte vermieden werden
Reduktion der üblichen Dosis bei Dexamethason p.o. um 50%.
Die Wirksamkeit oraler Kontrazeptiva kann bis 2 Monate nach der letzten Aprepitant Gabe vermindert sein.

Heparin/VOD Prophylaxe bis Entlassung nach PBSZT; nicht bis Tag +30 nach PBSZT nötig, ausser länger erwägen bei Leberfunktionsstörung/Leberschaden

Memo: Thiotepa wird im Schweiß abgesondert. Zur Vermeidung einer toxisch bedingten Erythrodermie (besonders axillär und inguinal) häufig mit nassem Waschlappen abwaschen (keine Seife bis einschl. am Tag nach der Thiotepa-Gabe)

Carmustin - Dosierung bei Übergewicht (hierzu Rücksprache mit Studienzentrale voernehmen!) auf idealisiertes Körpergewicht (**IBW**) beziehen damit die Körperoberfläche berechnen: Männer: IBW = 50,0kg + 2,3 x ((Größe in cm : 2,53) - 60)
Frauen: IBW = 45,5kg + 2,3 x ((Größe in cm : 2,53) - 60)
Bei **massivem Übergewicht (reales KG >15kg über IBW)**, gilt das angepaßte Körpergewicht:
AIBW: berechnetes IBW + 0,4 x (reales KG - berechn. IBW)
Wenn reales Körpergewicht (KG) < IBW gilt das reale Körpergewicht

Zyklustag	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Carmustin														
Thiotepa														
autologe SZT														

Obligate Prä- und Begleitmedikation

Tag	zeitl. Ablauf	Substanz	Dosierung	Trägerlösung (ml)	Appl.	Inf.-dauer	Bemerkungen
-6	-1h	Aprepitant/Emend®	125 mg		p.o.		
-6	-30min	Glucose 5%	1000 ml		i.v.	12h	
-5,-4	1-0-0-0	Aprepitant/Emend®	80 mg		p.o.		
-6,-5,-4	-30min	Heparin/Liquemin®	15000 IE		i.v.	24h	kontinuierlich ab Tag -6; Reduktion bei Thrombozyten < 30 000/µl; während Busulfan pausieren
-6	-30min	Dexamethason	12 mg		i.v.	B	

-6	-30min	Granisetron/Kevatril®	1 mg	i.v.	B	
-6	+11h30min	NaCl 0,9 %	1000 ml	i.v.	12h	
-5,-4	-30min, +11h30min	Glucose 5%	500 ml	i.v.	4h	
-5,-4	-30min, +11h30min	Granisetron/Kevatril®	1 mg	i.v.	B	
-5,-4	-30min, +4h, +11h30min, +16h	Dexamethason	8 mg	i.v.	B	
-5,-4	+3h30min, +15h30min	NaCl 0,9 %	1000 ml	i.v.	8h	
1-30	1-1-1-1	Aciclovir/Zovirax®	200 mg	p.o.		Infektionsprophylaxe; bis Tag 30
-6-25	1-0-0-0	Fluconazol/Diflucan®	200 mg	p.o.		ab Aufnahme kontinuierlich
-6,-5,-4,-3,-2	1-0-1-0	Cotrimoxazol/Cotrim®forte	960 mg	p.o.		ab Aufnahme bis d-2; bei stabilem Engraftment Mo, Mi, Fr 0-1-0-0

Erstellt:	25.10.2013
Bedarfsmedikation:	Kalium/Kalinor®, $NaHCO_3$ 50 ml/2h Infusion, Metoclopramid/Paspertin®, Famotidin/Pepdul®, Analgesie, Antibiose, Allopurinol, Antikonvulsiva, Dexamethason, Granisetron, Sedativa, Solu-Decortin 50mg i.v. vor und während Rituximab
Kontrollen:	siehe Studienprotokoll: ECOG, Gewicht, Vitalzeichen, körperliche und neurologische Untersuchung, Blutbild, Serumelektrolyte, Kreatinin, eGFR, EKG, Ganzkörperplethysmographie, Begleitmedikation, Nebenwirkungen
Dosisreduktion:	siehe Studienprotokoll: **nicht hämatologische Toxizitäten:** Dosisreduktion laut Fachinformation
Cave:	keine gleichzeitige Anwendung von Thiotepa und CYP3A4-Inhibitoren (z.B. Itraconazol, Voriconazol und Posaconazol, Makrolid-Antibiotika)
Summendosis:	Carmustion: erhöhtes Risiko der Toxizität bei kumulativer Geamtdosis > 1 000mg/m²
Therapieabbruch:	bei Therapieverzögerung > 4 Wochen siehe auch Studienprotokoll
Erfolgsbeurteilung:	60 Tage nach Randomisierung: MRI (Schädel), bei positiver Diagnose: CSF-Untersuchung, Augenuntersuchung (Spaltlampenmikroskopie)
Literatur:	Studienprotokoll Matrixstudie
Zuständiger Oberarzt:	Prof. Finke, Universitätsklinikum Freiburg, Innere Medizin I, gcp@oncoconsult.de

060507_ MATRix-Studie High Dose Consolidation Arm B: HDT- ASCT Busulfan-Variante ***Indikation: ZNS-NHL*** ***ICD-10: C85.9***

Busulfan/Thiotepa

Chemotherapie

Tag	zeitl. Ablauf	Substanz	Dosierung	Trägerlösung (ml)	Appl.	Inf.-dauer	Bemerkungen
-8	0	Busulfan	3.2 mg/kg		i.v.	3h	Polycarbonatfreies Infusionsbesteck
-7	0	Busulfan	3.2 mg/kg		i.v.	3h	Polycarbonatfreies Infusionsbesteck
-5	0	Thiotepa	5 mg/kg	Glucose 5%	i.v.	2h	12h Abstand zwischen beiden Gaben
-5	+12h	Thiotepa	5 mg/kg	Glucose 5%	i.v.	2h	12h Abstand zwischen beiden Gaben
-4	0	Thiotepa	5 mg/kg	Glucose 5%	i.v.	2h	12h Abstand zwischen beiden Gaben
-4	+12h	Thiotepa	5 mg/kg	Glucose 5%	i.v.	2h	12h Abstand zwischen beiden Gaben

Diese Zytostatikatherapie birgt letale Risiken. Die Anwendung darf nur durch erfahrene Onkologen/Hämatologen und entsprechend ausgebildetes Pflegepersonal erfolgen. Die Dosisberechnung und Anforderung obliegt der Verantwortung des bestellenden Arztes und muss in jedem Fall sorgfältig überprüft werden. Die Herausgeber übernehmen keine Verantwortung für die Chemoanforderung.

Tag 0 periphere Stammzelltransplantation (≥ 5x10^6 CD34$^+$ Zellen/kgKG)

Therapieablauf:

Tag -8, -7:	Busulfan
Tag -6:	Therapiepause
Tag -5, -4:	Thiotepa

Dosierung **Busulfan** auf idealisiertes Körpergewicht (**IBW**) beziehen
damit die Körperoberfläche berechnen: Männer: IBW = 50,0kg + 2,3 x ((Größe in cm : 2,53) - 60)
Frauen: IBW = 45,5kg + 2,3 x ((Größe in cm : 2,53) - 60)
Bei **erheblichem Übergewicht (reales KG >15kg über IBW)**, gilt das angepaßte Körpergewicht:
AIBW: berechnetes IBW + 0,25 x (reales KG - berechn. IBW)
Wenn reales Körpergewicht (KG) < IBW gilt das reale Körpergewicht

Heparin/VOD Prophylaxe bis Entlassung nach PBSZT; nicht bis Tag +30 nach PBSZT nötig, ausser länger erwägen bei Leberfunktionsstörung/Leberschaden

Memo: Thiotepa wird im Schweiß abgesondert. Zur Vermeidung einer toxisch bedingten Erythrodermie (besonders axillär und inguinal) häufig mit nassem Waschlappen abwaschen (keine Seife bis einschl. am Tag nach der Thiotepa-Gabe)

Obligate Prä- und Begleitmedikation

Tag	zeitl. Ablauf	Substanz	Dosierung	Trägerlösung (ml)	Appl.	Inf.-dauer	Bemerkungen
-9,-8,-7,-6	1-0-1-0	Levetiracetam/ Keppra®	500 mg		p.o.		
-9,-8,-7,-6,-5	1-1-0-0	Bromazepam/Lexotanil®	1.5 mg		p.o.		
-9,-8,-7,-6,-5	0-0-1-0	Bromazepam/Lexotanil®	3 mg		p.o.		
-8,-7,-6,-5,-4	-30min	Heparin/Liquemin®	15000 IE		i.v.	24h	kontinuierlich ab Tag -8; Reduktion bei PTT > N oder Thrombozyten < 50 000/µl; während Busulfan-Gabe pausieren
-8,-7	-30min	NaCl 0,9 %	2000 ml		i.v.	24h	kontinuierlich
-8,-7	-30min	KCl 7,45% (1mmol K$^+$/ml)	ml		i.v.		bei Bedarf nach Wert in Bewässerung
-8,-7	-30min	Granisetron/Kevatril®	3 mg		i.v.	B	
-5,-4	-30min, +11h30min	Glucose 5%	500 ml		i.v.	4h	
-5,-4	-30min, +11h30min	Granisetron/Kevatril®	1 mg		i.v.	B	
-5,-4	-30min, +4h, +11h30min, +16h	Dexamethason	8 mg		i.v.	B	
-5,-4	+3h30min, +15h30min	NaCl 0,9 %	1000 ml		i.v.	8h	
1-30	1-1-1-1	Aciclovir/Zovirax®	200 mg		p.o.		Infektionsprophylaxe; bis Tag 30

-9-25	1-0-0-0	Fluconazol/Diflucan®	200 mg	p.o.	ab Aufnahme kontinuierlich
-9,-8,-7,-6,-5,-4,-3,-2	1-0-1-0	Cotrimoxazol/Cotrim®forte	960 mg	p.o.	ab Aufnahme bis d-2; bei stabilem Engraftment Mo, Mi, Fr 0-1-0-0

Erstellt:	25.10.2013
Bedarfsmedikation:	Kalium/Kalinor®, $NaHCO_3$ 50 ml/2h Infusion (nicht parallel zu Busulfan oder Thiotepa), Metoclopramid/Paspertin®, Famotidin/Pepdul®, Analgesie, Antibiose, Allopurinol, Antikonvulsiva, Dexamethason, Granisetron, Sedativa
Kontrollen:	siehe Studienprotokoll: ECOG, Gewicht, Vitalzeichen, körperliche und neurologische Untersuchung, Blutbild, Serumelektrolyte, Begleitmedikation, Nebenwirkungen
Dosisreduktion:	siehe Studienprotokoll: **nicht hämatologische Toxizitäten:** Dosisreduktion laut Fachinformation
Cave:	keine gleichzeitige Anwendung von CYP3A4-Inhibitoren (z.B. Itraconazol, Voriconazol und Posaconazol, Makrolid-Antibiotika); Wegen einer möglichen Abnahme der Busulfan-Metabolisierung ist bei Einnahme von Paracetamol vor (weniger als 72h) oder gleichzeitig mit der Anwendung von Busulfan Vorsicht geboten.
Therapieabbruch:	bei Therapieverzögerung > 4 Wochen siehe auch Studienprotokoll
Erfolgsbeurteilung:	60 Tage nach Randomisierung: MRI (Schädel), bei positiver Diagnose: CSF-Untersuchung, Augenuntersuchung (Spaltlampenmikroskopie)
Literatur:	Studienprotokoll Matrixstudie
Zuständiger Oberarzt:	Prof. Finke, Universitätsklinikum Freiburg, Innere Medizin I, gcp@oncoconsult.de

060507_ MATRix-Studie Conventional Consolidation Arm A: R- DeVIC *Indikation: ZNS-NHL* *ICD-10:C85.9*

Dexamethason/Etoposid/Ifosfamid/Carboplatin

Chemotherapie

Tag	zeitl. Ablauf	Substanz	Dosierung	Trägerlösung (ml)	Appl.	Inf.-dauer	Bemerkungen
0	0	Rituximab	375 mg/m²	500 ml NaCl 0,9%	i.v.	initial 50mg/h	
1-3	0	Dexamethason	40 mg		i.v.	15min	oder p.o. morgens bzw. 1h vor folgender CTx
1	+15min	Carboplatin	300 mg/m²	250 ml Glucose 5%	i.v.	1h	
1	+1h15min	Ifosfamid	1500 mg/m²	500 ml NaCl 0,9%	i.v.	2h	
2-3	+15min	Ifosfamid	1500 mg/m²	500 ml NaCl 0,9%	i.v.	2h	
1	+3h15min	Etoposidphosphat	100 mg/m²	250 ml NaCl 0,9%	i.v.	2h	Menge entspricht Etoposidanteil
2-3	+2h15min	Etoposidphosphat	100 mg/m²	250 ml NaCl 0,9%	i.v.	2h	Menge entspricht Etoposidanteil

Diese Zytostatikatherapie birgt letale Risiken. Die Anwendung darf nur durch erfahrene Onkologen/Hämatologen und entsprechend ausgebildetes Pflegepersonal erfolgen. Die Dosisberechnung und Anforderung obliegt der Verantwortung des bestellenden Arztes und muss in jedem Fall sorgfältig überprüft werden. Die Herausgeber übernehmen keine Verantwortung für die Chemoanforderung.

CTx mit FN-Risiko von 10-20%: Vorgehen bei der G-CSF-Gabe

- nach CTx: 1x tgl. 5µg/kg Filgrastim s.c. bei Leukozyten < 1 000/µl bis >1 000/µl
- Wenn unter Einbeziehung **individueller Risikofaktoren für den Patienten**

FN-Risiko ≥ 20% =>G-CSF-Primärprophylaxe erwägen/durchführen.

- Nach durchgemachter febriler Neutropenie, in folgenden Zyklen => **G-CSF-Sekundärprophylaxe**

G-CSF-Primär- bzw. Sekundärprophylaxe:
Entweder 24h nach CTx einmal Pegfilgrastim/Neulasta® 6mg s.c. - **Oder**: d6 nach CTx Filgrastim/Neupogen® 5µg/kg/d s.c. bis zum Durchschreiten des Nadir

Zyklustag	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	
Rituximab																							Wdh.
Dexamethason																							
Carboplatin																							
Ifosfamid																							
Etoposidphosphat																							

Therapieablauf:

Induktion:
2 Zyklen MATRix → Stammzell-Harvest → 2 Zyklen MATRix
(= 4 Zyklen MATRix insgesamt)

Konsolidierung:

2 Zyklen R-DeVIC Arm A	Hochdosistherapie mit BCNU/Thiotepa + PBSCT ArmB

Obligate Prä- und Begleitmedikation

Tag	zeitl. Ablauf	Substanz	Dosierung	Trägerlösung (ml)	Appl.	Inf.-dauer	Bemerkungen
0	-1h	Paracetamol	1000 mg		p.o.		
0	-30min	NaCl 0,9%		500 ml	i.v.		
0	-30min	Clemastin/Tavegil® 2mg (bzw. Dimetinden/Fenistil® 1ml/10kg KG)	2 mg		i.v.	B	
0	-30min	Dexamethason	8 mg		i.v.	B	vor Rituximab-Erstgabe obligat; bei Folgegaben in Abhängigkeit von Verträglichkeit
1-4	-30min	NaCl 0,9 %		3000 ml	i.v.	24h	im Wechsel mit Glucose 5%

1-4	-30min	Glucose 5%		1000 ml	i.v.	24h	im Wechsel mit NaCl 0,9%
1-3	-30min	Granisetron/Kevatril®	1 mg		i.v.	15min	Bei Emesis: Dosiserhöhung auf 3mg
1-4	-	NaHCO3 (8,4%)	100 ml		i.v.	24h	1mmol/ml; Urin-pH-Wert muss > 7,4 liegen, während Carboplatin und Mesna pausieren
1-3	-	Heparin/Liquemin®	15000 IE		i.v.	24h	kontinuierlich;Reduktion bei Thrombozyten < 30 000/µl, während Carboplatin und Ifosfamid pausieren
1	+1h15min, +5h15min, +9h15min	Mesna/Uromitexan®	300 mg/m²		i.v.	B	
2-3	+15min, 4h15min, +8h15min	Mesna/Uromitexan®	300 mg/m²		i.v.	B	
1-28	0-1-0-0	Cotrimoxazol/Cotrim®forte	960 mg		p.o.		Montag, Mittwoch, Freitag
1-28	1-1-1-1	Aciclovir/Zovirax®	200 mg		p.o.		kontinuierlich, bei Auftreten von Mukositis ≥ Grad 2

Erstellt: 01.08.2013
Bedarfsmedikation: Metoclopramid/Paspertin®, Famotidin/Pepdul® mite, Sucralfat/Ulcogant®
FN-Risiko: 10-20% --> je nach Risikoabwägung als Primärprophylaxe, bei FN im 1. Zyklus als Sekundärprophylaxe, siehe Kurzfassung Leitlinien G-CSF
Kontrollen: siehe Studienprotokoll: ECOG, Gewicht, Vitalzeichen, körperliche und neurologische Untersuchung, Blutbild, Serumelektrolyte, Kreatinin, eGFR, EKG, Begleitmedikation, Nebenwirkungen
Dosisreduktion: siehe Studienprotokoll: **hämatologische Toxizitäten:** schwerwiegende Neutropenie, schwerwiegende Thrombopenie Grad 4: Carboplatin, Ifosfamid und Etoposid Dosisreduktion auf 70%; **nicht hämatologische Toxizitäten:** Dosisreduktion laut Fachinformation
Therapieabbruch: bei Therapieverzögerung > 4 Wochen siehe auch Studienprotokoll
Erfolgsbeurteilung: 30 Tage nach Behandlungsende (Bildgebung)
Wiederholung: d22
Literatur: Studienprotokoll Matrix-Studie; Motomura K et al. Leuk Lymphoma. 2011 Nov;52(11):2069-75
Zuständiger Oberarzt: Prof. Finke, Universitätsklinikum Freiburg, Innere Medizin I, gcp@oncoconsult.de

Appendix 9 Leucovorin rescue sheet, Freiburg

Leukovorin Rescue: Matrix-Studie

Name:	Größe (cm):		**Protokoll:**	HD MTX	**Diagnose:** ZNS- NHL
Vorname:	Gewicht (kg):		Zyklus:		**Datum:**
Geb.-Dat.:	KO (m^2):	NUM!	Tag:		**Signatur Arzt:**

Leukovorin Applikation

Stunde nach MTX-Beginn	Datum	Uhrzeit	MTX-Spiegel	applizierte LV-Dosis
Stunde 0 - Start MTX-Infusion				
Stunde 4 - Ende MTX-Infusion				
Stunde 24: 1.LV- Applikation				
24h				
30h				
36h				
42h				
48h				
54h				
60h				
66h				
72h				
78h				
84h				
90h				
96h				
102h				
108h				
114h				
120h				

Bestimmung MTX-Spiegel / Leukovorin-Dosierung nach MTX-Spiegel

Stunde nach MTX-Beginn	Datum	Uhrzeit	**Mtx-Spiegel (µmol/l)**	falls Mtx-Spiegel (µmol/l)	LV-Dosis [mg/m²]	LV- Dosis absolut (mg)	Dauer LV-Rescue
4h				-	-	-	Spitzenspiegel
24h				<8,5	15	NUM!	bis Tag 6
				8,5-12	90	NUM!	
				12,1-18	150	NUM!	
				>18	300	NUM!	
42h				<3,0	15	NUM!	bis Tag 6
				3,0-11	90	NUM!	
				11,1-21	150	NUM!	
				>21	300	NUM!	
48h				<1,8	15	NUM!	bis Tag 6
				1,9-2,8	30	NUM!	
				2,9-8,5	90	NUM!	
				8,6-18	150	NUM!	
				>18	300	NUM!	
72h				<1,8	15	NUM!	bis Tag 6
				1,9-2,8	30	NUM!	
				2,9-9,8	90	NUM!	
				9,9-19	150	NUM!	
				>19	300	NUM!	
96h	Vorgehen wie bei Stunde 72						

ggf. weitere MTX- Spiegelbestimmung bei Stunde 120,144,168

Bemerkungen

1. Weiß hinterlegte Felder:
normaler MTX-Spiegelverlauf
Grau hinterlegte Felder:
Cave: Abweichung von normalem MTX-Spiegelverlauf

2. Zeitangaben beziehen sich auf den Beginn der MTX- Infusion.
Start der LV-Rescue ist:
- 24h nach MTX-Beginn bei normalem Spiegelverlauf
- sofort bei
klin. Toxizitätszeichen (auch unter regelrechtem MTX- Spiegelverlauf, z.B. bei Infektionen und schweren Entzündungen) od. MTX-Spiegeln> 1000 µmol/l nach Ende d. MTX-Durchlaufes; die **LV- Dosis** muss dabei auf das **2-(bis4-) fache** erhöht werden. Auf ausreichend Diurese achten.

3. Leukovoringabe bei normalem und erhöhtem MTX-Spiegel während des gesamten Rescues **alle 6h.**
Bei erhöhtem MTX-Spiegel **zusätzlich Differenz zwischen** zuvor gegebener LV-Dosis und neu berechneter LV-Dosis sofort einmalig und bei der folg. LV-Gabe erhöhte, berechnete LV-Dosis bis zum nächsten Spiegelmessungs**ergebnis** geben.

4. Bei **stark erhöhten MTX-Spiegeln:**
Gabe von Carboxypeptidase G2 als Antidot mögl.; Infos über Apotheke

5. Bei LV-Dosen > 20mg/kg KG:
Gabe in 250ml NaCl 0,9% über 1h

6. Strikte Urin- Alkalisierung:
Urin-pH> 7,4; Kontrolle bei jeder Miktion

ProtNr. 060507_xxx
Stand: 20.05.2009

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