Change history

Version Nr	Version date	Modified without version change	Description, comments	Control
4.0	25.08.2015		Amended version	
5.0	31.08.2017	x	Adapted to new Swissethics Template Change of principal investigators at participating sites For clarification - information for adjustment of D_{LCO} for hemoglobin using Dinakara equation was added Clarify the number of participants Analysis of screening failure patients revealed that many patients had HTCTI scores higher than 3 due to reduced D_{LCO}. This special parameter is not routinely analyzed prior to high-dose Clarification that any maintenance treatment after ASCT is allowed and does not lead to exclusion of patient(s) from analysis. Delete pregnancy test on day Day 80 to 120 Clarification of events not to be reported as AEs Clarification that the German Version of HCT-CI score listed in protocol version 2.0 is not used in this trial. HCT-CI score from Sorror 2013 is used instead. Clarification that EORTC QLQ-C30 (Version 3.0) is used Clarify handling of obese patients regarding dosing of treatment Clarify that the the BSA (body surface area) is calculated using the.DuBois Method Delete Appendix 5: Declaration of Helsinki, add as a reference	

A randomized phase II trial comparing BeEAM with BEAM as conditioning regimen for autologous stem cell transplantation (ASCT) in lymphoma patients (BEB-trial).

Clinical Study Protocol

Study Type:	Clinical trial investigating the chemotherapeutic compound Bendamustine (Ribomustin®) in lymphoma patients.
Study Categorisation:	Risk category according to LHR: category B
Study Registration:	EudraCT2014-003629-16
Study Identifier:	BEB-trial
Sponsor, or Principal Investigator:	This is an investigator initiated trial (IIT); Sponsor is Prof. Dr. med. Thomas Pabst; Associate Professor; Department of Medical Oncology; University Hospital/Inselspital; 3010 Bern; Switzerland. Phone +41 31 632 84 30; Fax +41 31 632 34 10; Email: *thomas.pabst@insel.ch*; Coordinating investigator for the entire trial is: Prim. Univ. Prof. Dr. Felix Keil; Hanusch Krankenhaus der Wiener Gebietskrankenkasse; 3. Medizinische Abteilung; Heinrich Collin-Straße 30; 1140 Wien; Tel.: +43 1 910 21 – 85411; Fax.: +43 1 910 21 – 85419; E-Mail: *felix.keil@wgkk.at*
Investigational Product:	Bendamustine hydrochloride (Ribomustin®)
Protocol Version and Date:	Version 05, 31.08.2017, incl. Amendment 2

Signature Page(s)

Study number	EudraCT2014-003629-16
Study Title	A randomized phase II trial comparing BeEAM with BEAM as conditioning regimen for autologous stem cell transplantation (ASCT) in lymphoma patients (BEB-trial).

The Sponsor and trial statistician have approved the protocol version 05 (dated 31/08/2017), and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm if applicable and the local legally applicable requirements.

Sponsor:

Prof. Dr. Thomas Pabst; Department for Medical Oncology; University Hospital/Inselspital; 3010 Berne.

Place/Date	Signature

Local Principal Investigator at study site*:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Site ……..

Principal investigator ……..

Place/Date	Signature

*Note: In multicentre studies, this page must be individually signed by all participating Local Principal Investigators.

Table of Contents

STUDY SYNOPSIS

Sponsor / Sponsor-Investigator	This is an investigator initiated trial (IIT); Sponsor is Prof. Dr. med. Thomas Pabst; Associate Professor; Department of Medical Oncology; University Hospital/Inselspital; 3010 Berne; Switzerland. Phone +41 31 632 84 30; Fax +41 31 632 34 10; Email: thomas.pabst@insel.ch; Coordinating investigator for the trial is: Prim. Univ. Prof. Dr. Felix Keil; Hanusch Krankenhaus der Wiener Gebietskrankenkasse; 3. Medizinische Abteilung; Heinrich Collin-Straße 30; 1140 Wien; Tel.: +43 1 910 21 – 85411; Fax.: +43 1 910 21 – 85419; E-Mail: felix.keil@wgkk.at
Study Title:	A randomized phase II trial comparing BeEAM with BEAM as conditioning regimen for autologous stem cell transplantation (ASCT) in lymphoma patients (BEB-trial).
Short Title / Study ID:	Bendamustine for autologous transplant.
Protocol Version and Date:	Version 05: 31/08/2017
Trial registration:	EudraCT2014-003629-16
Study category and Rationale	Risk category according to LHR: category B. Bendamustine is licensed in Switzerland for the treatment of lymphoma patients; in this study, it is used as a part of a conditioning regimen before autologous transplant in lymphoma patients.
Clinical Phase:	Randomized prospective non-blinded clinical phase II trial investigating the drug bendamustine hydrochloride.
Background and Rationale:	BCNU containing BEAM is one of the most commonly used conditioning regimens in lymphoma patients treated with autologous stem cell transplantation (ASCT). One of the most frequently observed non-hematological complications of high-dose BCNU containing regimens is pulmonary toxicity, with a reported incidence varying from 2% to 64%. Pulmonary fibrosis is developing months or years after treatment with BCNU. Acute lung injury with a toxic inflammatory reaction after high-dose BCNU in ASCT might result in irreversible impairment of pulmonary function, and, generally, these effects are not reported in clinical trials, which typically focus on overall survival (OS) and progressionfree survival (PFS). Although treatment related mortality in ASCT is usually low, pulmonary toxicity might result in significant morbidity and in late deaths because of impairment of pulmonary function and or impairment of the right heart because of pulmonary hypertension. Thus, replacing BCNU by a promising cytotoxic compound - such as bendamustine - might result in better PFS without the impairment of lung function. Thus, a head-to-head comparison of BeEAM with BEAM with a focus on acute and late toxicity and on PFS - is an unmet clinical need to improve results in lymphoma patients receiving ASCT. As older patients with higher comorbidity scores might also profit from ASCT, a less toxic regimen might also improve clinical results in this age cohort.

Objective(s):	• *Primary objective:* To show a clinically meaningful reduction of lung toxicity - defined as a a decrease of the diffusion capacity of the lung for carbon monoxide (D_{LCO}) by 20% or more from baseline before ASCT - from 25% of patients in the BEAM group to 4% of patients in the BeEAM group at 3 months after ASCT. Use Dinakara equation for adjusting DLCO for hemoglobin • *Secondary objectives:* To assess acute and late toxicity/adverse events (CTCAE 4.0) during entire study period To assess the hematologic engraftment after 3 months To assess early and late lung toxicity by pulmonary function tests, spiroergometry, $D_{LCO,}$ HRCT and venous BGA after 3 and 12 months. To perform cardiac assessment by ECHO/ECG To assess the quality of life prior to ASCT and 3 and 12 months thereafter. To assess overall survival and progression free survival after 12 months and then yearly.
Outcome(s):	To show a clinically meaningful reduction of lung toxicity - defined as a reduction of the DLCO by at least 20% - from 25% of patients in the BEAM group to 4% of patients in the BeEAM group at 3 months after ASCT.
Study design:	Randomized open-label prospective phase II trial
Inclusion / Exclusion criteria:	• Key inclusion criteria: Mantle cell lymphoma (MCL) in first or second remission or second chemosensitive relapse Diffuse large B-cell lymphoma (DLBCL) in first remission or second remission or second chemosensitive relapse Follicular lymphoma (FL) in second remission or second chemosensitive relapse Aged between 18 years and 75 years Neutrophils ≥ 1000/µl; Platelets ≥ 100 x 10^9/L • Key exclusion criteria: Acute infection Relevant co-existing disease excluding a treatment according to protocol HCTCI > 5 (Use Dinikara equation for adjusting DLco for hemoglobin) Concurrent malignant disease with the exception of basalioma/spinalioma of the skin or early-stage cervix carcinoma, or early-stage prostate cancer. Previous treatment for other malignancies (not listed above) must have been terminated at least 24 months before registration and no evidence of active disease must be documented since then. Lack of patient cooperation to allow study treatment as outlined in this protocol Pregnancy or lactating female patients Major coagulopathy or bleeding disorder Major surgery less than 30 days before start of treatment Contraindications and hypersensitivity to any of the active chemotherapy compounds

Measurements and procedures:	Two high-dose chemotherapy regimens (BeEAM versus BEAM) used for conditioning treatment before autologous stem cell transplantation will be compared in a 1:1 randomization. The experimental arm is the BeEAM regimen. The BEAM regimen is the control treatment. Both regimens use the three drugs etoposide, cytarabine and melphalan at identical doses and at identical days. The only difference is the replacement of the standard drug BCNU (carmustin; given in the BEAM group at day -6) by the experimental drug bendamustine (given in the BeEAM group at days -7 and -6). Lung toxicity will be assessed by venous blood gas assessment, thereby assessing the diffusion capacity of the lung for carbon monoxide (D_{LCO}), and by spiroergometry . This analysis will be performed before ASCT, as well as 3 months and 12 months after ASCT. BeEAM chemotherapy regimen consisting of bendamustine intravenously on days −7 and −6 at 200 mg/m^2; cytarabine, 400 mg/m^2 intravenously daily from day −5 to day−2; etoposide, 200 mg/m^2 intravenously daily from day −5 to day −2; and melphalan, 140 mg/m^2 intravenously on day −1 before reinfusion of autologous stem cells will be compared with the standard BEAM regimen with carmustine 300 mg/m^2 on day -6, followed by the EAM regimen as described above, in a randomized phase II trial. Toxicity and efficacy will be compared.
Study Product / Intervention:	The experimental treatment group is treated according to the BeEAM regimen. The BeEAM chemotherapy regimen is consisting of bendamustine intravenously on days −7 and −6 at 200 mg/m2; cytarabine, 400 mg/m2 intravenously daily from day −5 to day−2; etoposide, 200 mg/m2 intravenously daily from day −5 to day −2; and melphalan, 140 mg/m2 intravenously on day −1 before reinfusion of autologous stem cells.
Control Intervention (if applicable):	The standard (control) treatment group is treated according to the BEAM regimen. The BEAM chemotherapy regimen is consisting of BCNU (carmustine) 300 mg/m2 on day -6; cytarabine, 400 mg/m2 intravenously daily from day −5 to day−2; etoposide, 200 mg/m2 intravenously daily from day −5 to day −2; and melphalan, 140 mg/m2 intravenously on day −1 before reinfusion of autologous stem cells.
Number of Participants with Rationale:	Applying a statistical power of 80% and a two-sided significance level of 5%, 49 evaluable patients will be needed in each group to show a clinically meaningful reduction of events (lung toxicity defined as a reduction of the DLCO by at least 20% compared to baseline), i.e. from 25% of patients in the BEAM group to 4% of patients in the BeEAM group. Thus, a total of 108 evaluable patients is needed. Expecting a rate of ineligible patients of 10%, a total of 108 patients is needed, with 54 patients in each of the two arms.
Study Duration:	The total study duration is 36 months.
Study Schedule:	First-Participant-In (planned): January 2015 Last-Participant-Out (planned): December 2018

Investigator(s):	• For Vienna / Austria: Prim. Univ. Prof. Dr. Felix Keil; Hanusch Krankenhaus der Wiener Gebietskrankenkasse; 3. Medizinische Abteilung; Heinrich Collin-Straße 30; 1140 Wien; Tel.: +43 1 910 21 – 85411; Fax.: +43 1 910 21 – 85419; E-Mail: felix.keil@wgkk.at • For Linz / Austria: OÄ Dr. Veronika Buxhofer-Ausch, Ordensklinikum - Krankenhaus der Elisabethinen Linz, Interne 1 - Hämato-Onkologie, , Fadingerstrasse 1, A-4020 Linz, Veronika.Buxhofer-Ausch@ordensklinikum.at; Telefon: +43 732 7676 4409, Fax: +43 732 7676 4418 • For Berne / Switzerland: Prof. Dr. Thomas Pabst; Department for Medical Oncology; University Hospital/Inselspital;; 3010 Berne; Phone +41 31 632 84 30; Fax +41 31 632 34 10; Email: thomas.pabst@insel.ch • For Zurich / Switzerland: Dr. Antonia Müller; Klinik für Hämatologie; Universitätsspital Zürich; Rämistrasse 100; CH-8091 Zürich; Tel. +41 442555371; Fax. +41 442554560; Email: AntoniaMaria.Mueller@usz.ch
Study Centres:	2 centres in Austria: Vienna; Linz 2 centres in Switzerland: Berne; Zurich

Statistical Considerations:	This study involves two treatment arms and applies a 1:1 randomization, additionally considering the stratification for lymphoma subtypes: diffuse large B-cell lymphoma versus mantle cell lymphoma versus follicular lymphoma. No interim analysis is planned, and all calculations will be performed per evaluable patient. The primary endpoint is to show a clinically meaningful reduction of events (lung toxicity defined as a reduction of the D_{LCO} by at least 20%) at three months, i.e. from 25% of patients in the BEAM group to 4% of patients in the BeEAM group. Arm A is the experimental arm (BeEAM chemotherapy), and arm B is the standard arm (BEAM chemotherapy). The null hypothesis is that the lung toxicity determined at three months is equal in both arms ($LT3_A = LT3_B$). The aim of the study is to ultimately show 20% less lung toxicity of the experimental (BeEAM) arm, with $LT3_A < LT3_B$. Based on previous reports, we anticipate observing lung toxicity in the standard (BEAM) arm in 25% ($LT3_B$). Our hypothesis is that the experimental (BeEAM) arm will show lung toxicity in only 4% or less of the patients ($LT3_A$), thus a difference of at least 20 percentage points. Thus, the superiority margin in the proposed prospective randomized study is 0.20, i.e. the reduction of lung toxicity is considered a success compared to the standard (BEAM) arm if its lung toxicity rate is more than 20 percentage points better. With $LT3_A$ and $LT3_B$ being the (true) success rates in the BeEAM arm and in the BEAM arm, respectively, the hypotheses are: H0: LT BeEAM chemotherapy is > 0.04 when LT BEAM is 25%. H1: LT BeEAM chemotherapy is ≤ 0.04 when LT BEAM is 25%. Applying a statistical power of 80% and a two-sided significance level of 5%, 49 evaluable patients will be needed in each group to show a clinically meaningful reduction of events (lung toxicity defined as a reduction of the DLCO by at least 20%), i.e. from 25% of patients in the BEAM group to 4% of patients in the BeEAM group using Fishers Exact Test. Thus, a total of 108 evaluable patients are needed. Expecting a rate of ineligible patients of 10%, a total of 108 patients is needed, with 54 patients in each of the two arms. The significance level actually achieved by this design is 0.0497. All statistical analysis for sample size calculations were performed using the software package nQuery Advisor 7.0. For statistical analysis of this study, continuous endpoints will be summarized using descriptive statistics including mean, median, standard deviation, first and third quartiles, minimum and maximum values, and where appropriate by graphical techniques (e.g. histogram, box plot). For categorical endpoints, the number and percentage of patients in each category will be summarized. Where appropriate, a two-sided 95% confidence interval for the proportion will be reported. The primary endpoint in the two groups will be tested using Fishers Exact Test.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCPas well as all national legal and regulatory requirements.

STUDY SUMMARY IN LOCAL LANGUAGE

Lymphome sind bösartige Lymphdrüsen-Erkrankungen. Die häufigsten Lymphom-Typen umfassen dass Diffus Grosszellige B-Zell-Lymphom (DLBCL), das Mantelzelllymphom (MCL) und das follikuläre Lymphom (FCL). Patienten mit diesen Lymphom-Erkrankungen in erster oder zweiter Remission stellen die häufigste Indikation dar zur Hochdosis-Chemotherapie mit autologer Stammzell-Transplantation (ASCT), oft und zunehmend häufiger dabei mit endgültiger Heilung als Ziel.

Das häufigste Hochdosis-Chemotherapie Schema vor autologer Transplantation ist das BEAM-Schema. Es setzt sich aus vier Chemotherapeutika zusammen (BCNU, Etoposid, Cytarabin, Melphalan), deren Anfangsbuchstaben zum BEAM-Schema zusammengefasst werden. Eine der häufigsten Organ-Schädigungen dieser intensiven Therapie wird durch das Medikament BCNU verursacht; es handelt sich dabei um eine Lungenschädigung, die sich in den Monaten nach der ASCT mit zunehmender Atemnot und Husten äussert, und in einer Lungenfibrose enden kann. Das Ausmass dieser Lungenschädigung variiert beträchtlich, und sie kommt in 2 bis 64% aller Patienten vor. Die Lebensqualität kann dadurch nachhaltig und dauerhaft geschädigt sein, was bei kurativen Situationen umso belastender ist.

Das Medikament Bendamustin wird mit gutem Erfolg heute bei verschiedenen Lymphom-Typen eingesetzt, und seine Wirksamkeit in der Lymphom-Therapie ist bestens belegt. Vor allem aber verursacht Bendamustin keine Lungenschädigung. Erste Erfahrungen mit Bendamustin anstelle von BCNU – im sogenannten BeEAM Schema – zeigen nun, dass dieses Schema durchaus wirksam und gut toleriert wird, aber die Lungenschädigung nach der BEAM-Therapie nicht zu verursachen scheint. Im BeEAM Schema ersetzt also Bendamustin das BCNU, während die drei anderen Medikamente in gleicher Dosierung und Reihenfolge verabreicht werden

In der vorliegenden Studie an vier Zentren (Bern und Zürich in der Schweiz; Wien und Linz in Österreich) soll nun randomisiert in einem 1:1 Vergleich zwischen diesen beiden Schemas gezeigt werden, dass eine Hochdosis-Chemotherapie nach dem BeEAM-Schema signifikant weniger Lungenschädigung verursacht zum Zeitpunkt drei Monate nach ASCT (<4%) als nach dem BEAM-Schema (>25%). Die klinisch relevante Lungenschädigung soll dabei definiert werden als eine Abnahme der Diffusionskapazität der Lunge für Kohlenmonoxid (D_{LCO}) um mindestens 20% zum Zeitpunkt drei Monate nach ASCT. Gleichzeitig wird die Wirksamkeit dieser beiden Schemas verglichen. Total sind 54 Lymphom-Patienten (DLBCL, MCL oder FCL in erster oder zweiter Remission) in jedem Behandlungsarm geplant, mit einer Studiendauer von 36 Monaten.

ABBREVIATIONS

AE	Adverse Event
AGES	Arzneimittelbehörde in Oesterreich
ASCT	Autologous stem cell transplantation
ASR	Annual Safety Report
BCNU	1,3-Bis(2-chloroethyl)-1-nitrosourea, Carmustine
BEAM	BCNU-Etoposide-Cytarabin-Melphalan
BeEAM	Bendamustine-Etoposide-Cytarabine-MelphalanBlood gas analysis
BGA	Blood gas analysis
BSA	Body Suface Area
CBV	Cyclophosphamide-BCNU-Etoposide
CEC	Competent Ethics Committee
CRF	Case Report Form
ClinO	Ordinance on Clinical Trials in Human Research *(in German: KlinV, in French: OClin)*
eCRF	Electronic Case Report Form
CTCAE	Common terminology criteria for adverse events
DLBCL	Diffuse large B-cell lymphoma
D_{LCO}	Diffusing capacity of the lung for carbon monoxide
DSMC	Data safety monitoring committee
ECG	Electrocardiography
ECHO	Echocardiography
FCL	Follicular lymphoma
FEV_1	Forced expiratory volume in first second
FVC	Forced vital capacity
GCP	Good Clinical Practice
HCTCI	hematopoietic cell transplantation comorbidity index
HDCT	High-dose chemotherapy
IB	Investigator's Brochure
H1	Alternative hypothesis
HFG	Humanforschungsgesetz (Law on human research)
HRCT	High-resolution computed tomography
IMP	Investigational Medicinal Product
IIT	Investigator-initiated Trial
IPI	international prognostic index
IPS	Idiopathic pneumonia syndrome
ISO	International Organisation for Standardisation
ITT	Intention to treat
KlinV	Verordnung über klinische Versuche in der Humanforschung *(in English: ClinO, in French OClin)*
MCL	Mantle cell lymphoma
NHL	Non Hodgkin's lymphoma

OClin	Ordonnance sur les essais cliniques dans le cadre de la recherche sur l'être humain *(in German : KlinV, in English : ClinO)*
RBC	Red blood cell
SPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TRM	Treatment related mortality
QoL	Quality of life

STUDY SCHEDULE

Study Periods	Screening	Treatment / Intervention		
Visit	1	2	3	4[3]
Time (days)	-28 to -8	-7 until dismissal	80-120	350-400
Patient information & informed consent	x			
Height / weight / BMI	x			
Medical history	x			
In- /exclusion criteria	x			
Physical examination	x	x	x	x
HCTCI score	x			
ECOG score	x	x	x	x
Vital Signs	x	x	x	x
Hematology (complete blood counts with differential)	x	x	x	x
Routine serum biochemistry (according to center policy)	x	x	x	x
Pregnancy Test	x			
Randomization	x			
ECG	x		x	x
Echocardiography	x		x	x
Pulmonary function (FEV_1 & FVC), D_{LCO}[1]	x		x	x
Spiroergometry	x		x	x
Response (CT, MR or PET) thorax/abdomen [2,4]	x		x	x
VBGA	x		x	x
HR-CT chest	x		x	x
QoL (EORTC Q30)	x		x	x
CTCAE 4.0 toxicity score		x	x	x
Engraftment, neutrophil and platelet recovery		x		
Days until platelets >50 G/L			x	
Number of CD34+ cells used		x		
RBC & platelet transfusions		x		
Days of T>38.0°; number of febrile episodes		x	x	
Administer study medication		x		
Adverse Events		x	x	x

[1]Adjusted D_{LCO} = measured D_{LCO} / (0.06965 x Hb)

[2] The selection of the radiologic assessment is at the discretion of the center and the treating physician

[3] Patients withdrawn from protocol are documented for a total of 12 months. All patients terminating study treatment before 12 months will be analyzed until the last documented follow-up.

[4] After the 12 months control, assessments will be done once per year after that as routine follow-up assessments. If relapse is suspected, CT, MR or PET-CT assessments are recommended. The follow-up is performed at the discretion of the center; if relapse or progression of lymphoma is suspected, standard radiological examination has to be performed.

1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor,

Prof. Dr. Thomas Pabst (Sponsor)

Department for Medical Oncology

University Hospital/Inselspital

3010 Bern
Tel: +41 31 632 84 30
Fax: +41 31 632 34 10
E-Mail: thomas.pabst@insel.ch

1.2 Principal Investigator(s)

Prim. Univ. Prof. Dr. Felix Keil (Coordinating Investigator)

Hanusch Krankenhaus der Wiener Gebietskrankenkasse
3. Medizinische Abteilung
Heinrich Collin-Straße 30
1140 Wien
Tel: +43 1 910 21 - 85411
Fax: +43 1 910 21 - 85419
E-Mail: felix.keil@wgkk.at

Prof. Dr. Thomas Pabst (Principal Investigator for Switzerland)

Department for Medical Oncology

University Hospital/Inselspital

3010 Bern
Tel: +41 31 632 84 30
Fax: +41 31 632 34 10
E-Mail: thomas.pabst@insel.ch

1.3 Statistician ("Biostatistician")

Univ. Prof. DI Dr. Andrea Berghold

Institut für Med. Informatik, Statistik und Dokumentation

Medizinische Universität Graz

Auenbruggerplatz 2

8036 Graz

Tel: +43/316/385-4261

Fax: +43/316/385-3590

E-Mail: andrea.berghold@medunigraz.at

1.4 Laboratory

Not applicable; No central specific laboratory analyses are planned in this trial.

1.5 Monitoring institution

For Berne and Zurich, Switzerland: Monitoring will be performed by the Clinical trial Unit (CTU) of the University of Berne, Switzerland.

For the two Austrian centres: Mag.Dr. Judith Schuster, Groisbach 47, A-2534 Alland, Tel: +43 664 3934498, Fax: +43 2258 2047, E-Mail: j.schuster@medtest.at

1.6 Data Safety Monitoring Committee

not applicable; no DSMC is needed for this trial.

1.7 Any other relevant Committee, Person, Organisation, Institution

Not applicable

2. ETHICAL AND REGULATO RY ASPECTS

Before the study will be conducted, the protocol, the proposed patient information and the consent form as well as other study-specific documents will be submitted to the Competent Ethics Committee (CEC) in Berne (leading CEC for Switzerland) and to the competent authorities (Swissmedic and to the Austrian competent authorities) in agreement with local legal requirements, for formal approval. Any amendment to the protocol will as well be approved (if legally required) by these institutions.

The decision of the CEC and Swissmedic/foreign competent authority concerning the conduct of the study will be made in writing to the Sponsor before commencement of this study. The clinical study can only begin once approval from the required authoritiy has been received. Any additional requirements imposed by the authorities shall be implemented.

2.1 Study registration

The study is registered in a registry listed in the WHO International Clinical Trials Registry Platform (ICTRP, http://www.who.int/ictrp/en/) (http://clinicaltrials.gov). In addition,it is registered in a national language in the Swiss Federal Complementary Database (http://www.kofam.ch)

2.2 Categorisation of study

This clinical trial falls into Category B since the investigational compound Bendamustine is approved in Switzerland for the treatment of lymphoma patients. In this trial, Bendamustine is used for the treatment of lymphoma patients, but it is used as a part of a high-dose chemotherapy regimen (BeEAM regimen), thus outside its approved indication.

2.3 Competent Ethics Committee (CEC)

The responsible investigator at each site ensures that approval from an appropriately constituted Competent Ethics Committee (CEC) is sought for the clinical study.

All changes in the research activity and all unanticipated problems involving risks to humans will be reported including in case of planned or premature study end and the final report. No changes will be made to the protocol without prior Sponsor and CEC approval, except where necessary to eliminate apparent immediate hazards to study participants.

Premature study end or interruption of the study is reported within 15 days. The regular end of the study is reported to the CEC within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter 2.10.

2.4 Competent Authorities (CA)

The Sponsor will obtain approval from the competent authority (e.g. Swissmedic) before the start of the clinical trial.

All changes in the research activity and all unanticipated problems involving risks to humans will be reported including in case of planned or premature study end and the final report. No changes will be made to the protocol without prior Sponsor and CEC approval, except where necessary to eliminate apparent immediate hazards to study participants.

Premature study end or interruption of the study is reported within 15 days. The regular end of the study is reported to the CEC within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter 2.10.

2.5 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

2.6 Declaration of interest

No conflicts of interest are reported

2.7 Patient Information and Informed Consent

Participants will be comprehensively informed about the study and consent is sought from each participant; no compensation for study participation is made in this trial. The investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment.

The participant will be informed that his/her medical records may be examined by authorised individuals other than their treating physician.

All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study. Enough time needs to be given to the participant to ask questions and decide whether to participate or not.

The patient information sheet and the consent form will be submitted to the CEC to be reviewed and approved. The formal consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any study procedure.

The participant will read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The original consent form will also be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.

2.8 Participant privacy and confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.

For data verification purposes, authorised representatives of the Sponsor (-Investigator), a competent authority (e.g. Swissmedic), or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.9 Early termination of the study

The Sponsor (and any competent authority) may terminate the study prematurely according to certain circumstances for example:.

- ethical concerns,
- insufficient participant recruitment,
- when the safety of the participants is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise,
- early evidence of benefit or harm of the experimental intervention

2.10 Protocol amendments

The Principle-Investigator and Sponsor are allowed to amend the protocol or to provide suggestions for a protocol amendment. Substantial amendments are only implemented after approval of the CEC and CA respectively.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the CEC/CA. Such deviations shall be documented and reported to the sponsor and the CEC/CA as soon as possible.

All Non-substantial amendments are communicated to the CA as soon as possible if applicable and to the CEC within the Annual Safety Report (ASR) .

3. BACKGROUND AND RATIO NALE

3.1 Background and R ationale

Autologous stem cell transplantation (ASCT): High-dose chemotherapy (HDCT) followed by ASCT is considered the treatment of choice for relapsed/refractory lymphomas. On the basis of the results of the PARMA study group trial, high-dose chemotherapy followed by ASCT has become the standard of care for patients with relapsed, chemo-sensitive aggressive lymphoma[1] and it is the treatment of choice in patients relapsing with follicular lymphoma and Hodgkin's disease[2] [3] [4]. Worldwide, about 11'000 patients are treated with ASCT per year because of relapsing lymphoma. The BEAM chemotherapy regimen is the most frequently used conditioning regimen since more than thirty years. Thus, challenging this established regimen is of high clinical relevance.

Several chemotherapy preparative regimens are used in ASCT, and the chemotherapeutic agents are selected because of activity against particular lymphoma subtypes; however, there has not been a single adequately powered randomized clinical trial to support the superiority of one regimen against another. Therefore, regimens are frequently chosen by institutional preference, and most of them contain (among others) with BCNU as in the BEAM (BCNU, etoposide, cytarabine, melphalan) or in the CBV regimens (cyclophosphamide, BCNU, and etoposide [VP-16]), with these two representing the most frequently used ASCT preparative regimens for patients with lymphoma.

The "delayed" Idiopathic Pneumonia Syndrome (IPS) and toxicity of BCNU after ASCT: Toxic pneumonia with interstitial infiltration and impairment of the diffusion capacity of the lung is a recognized complication of HDCT regimens containing BCNU.[5] The idiopathic pneumonia syndrome (IPS) clinically presents with dyspnea or cough[6], decreased reduction of the diffusion capacity of carbon monoxide of the lung (D_{LCO}), and radiological signs of interstitial infiltration. This IPS after ASCT differs from that observed after allogeneic SCT as its onset occurs later (median onset at day 45 vs. day 19 after allogeneic SCT) and its usually better clinical outcome. Although mortality is significantly lower compared with IPS after allogeneic SCT (with a less than 10% mortality rate) and IPS is responsive to steroid therapy,[7] it is associated with significant morbidity and late toxicity or long term impairment of pulmonary function which might adversely affect the quality of life in patients otherwise cured from their underlying disease.

The underlying mechanism of BCNU-associated pulmonary toxicity is not entirely clear. Oxidative stress and glutathione dysfunction, as well as immune-mediated injury have been implicated as causative factors. The delayed presentation after ASCT may be consistent with initial tissue injury followed by pneumonia progression at the time of lymphocyte recovery. Toxicities of BCNU containing regimens, such as BEAM, result in the incidence of IPS of between 2% and up to 64%,[8,28,29] depending on the BCNU dose, pre-treatment modalities, and co-morbidity of the patient. Furthermore, results from the Bone Marrow Transplant Survivor Study showed a relative risk of death not related to relapse of 2.27 (95% confidence interval 1.42-3.64) for patients receiving ASCT for hematologic malignancies with BCNU based regimens[9,10]

Although treatment related mortality in ASCT is low, undetected late toxicity might impair long term results and quality of life in patients receiving ASCT. Lane et al showed in a population of patients with lymphoma treated with high-dose CBV and ASCT[11] a 31% median reduction in D_{LCO} three months after treatment. In addition to the BCNU dose, prior mediastinal radiation and a total dose of BCNU exceeding 1000 mg were identified as significant risk factors for developing IPS induced pneumonia.[12] In addition, in 20% of patients receiving BCNU less than 750 mg, an IPS incidence of 20% was observed. The delayed median onset of symptoms (50 days post-ASCT) may not be detected in an outpatient setting as the focus on posttransplant investigation is usually focusing on hematological recovery and disease free survival. However, delayed pulmonary toxicity should be documented and BCNU sparing regimens might be of clinical relevance; in addition, new promising combinations of cytotoxic agents may increase response rate and decrease late toxicity after ASCT. In summary, a BCNU-induced reduction of D_{LCO} of 20% might ultimately not cause treatment related mortality, but it might affect quality of life by impaired long-term pulmonary function.

Recently, replacement of BCNU by Lemustine[13] showed a trend towards reduced TRM. The causes of death at day 100 in the BEAM group (TRM at day 100 was 4.67%) were pneumonia (n=3), sepsis (1), relapse (1), myocardial infarction (1) and TRM after dismissal of hospital (1). In the LEAM group (TRM at day 100 was 1.8%), there was only one single death from pneumonia.

Although the dose of BCNU in the BEAM protocol is lower (300 mg/m^2) than in the CBV protocol (600 mg/m^2), it might have a significant impact on deterioration of pulmonary function as BEAM is frequently used as a rescue therapy before ASCT in relapse of lymphoma patients and, thus, the total dose of infused BCNU might exceed the critical threshold of 1000 mg/m^2.

3.2 Investigational Product and Indication

The potential role of Bendamustine in treating relapsed lymphoma patients in combination with Etoposide, Ara C and Melphalan (BEAM): Bendamustine combines the alkylating activity of the mustard group with the antimetabolite activity of the purine analogue.[14,15] Bendamustine was studied in several entities of B-cell neoplasms and demonstrated significantly superior efficacy compared with standard therapies in the treatment of relapsed chronic lymphocytic leukemia[16] (CLL) and indolent NHL and myeloma.[17,18] Rummel et al have demonstrated that bendamustine was highly effective in indolent lymphoma such as follicular lymphoma (FCL) and mantle cell lymphoma (MCL). Compared to CHOP chemotherapy, the toxic profile was somewhat preferable, and in mantle cell lymphoma better response rates were seen.[19,20] The BRIGHT study confirmed the non-inferiority of a immunochemo-therapy with Rituximab-Bendamustine when compared with R-CHOP or R-CVP in indolent lymphoma or mantle cell lymphoma.[21]

3.3 Evidence of clinical activity of Bendamustine from previous studies

Recently, Visani et al have shown that Bendamustine, coupled with fixed doses of Etoposide, Cytarabine, and Melphalan (ie, BeEAM) in the conditioning regimen for ASCT for resistant/relapsed lymphoma (HD and NHL) patients is highly active and resulted in promising results concerning safety and efficacy.[22] No treatment mortality was observed and no relevant pulmonary toxicity was seen. Non-hematological toxicity was moderate, and most prominent toxicities were gastroenteritis grade 3 to 4 in 34% and mucositis grade 3 to 4 in 35%, respectively. No grade 3 to 4 cardiac toxicity or toxic pneumonia was observed. Engraftment was rapid and trilinear, and stable hematopoiesis was observed. BeEAM was very effective, with 81% of patients in complete response after a median observation time of 18 months. A recent update of this study showed that at 41 months still 72% of the patients are still in complete remission and the 3-year PS was 75%.[31] Four patients showed a first remission ever with the Bendamustine containing regimen. In 35 patients treated at the Vienna centre according to the Visani BeEAM protocol, these encouraging data of Visani et al could be reproduced; similar toxicities and rapid and stable engraftment were observed.[23] Finally, the combination of Bendamustine with sequential application of high-dose Cytarabine was reported to improve the response rates in relapsing lymphomas.[24,25] In conclusion, it seems promising to integrate Bendamustine in myelobablative regimens in ASCT, but a randomized clinical trial is lacking so far.

3.4 Evidence for selecting Bendamustine as a component of a high-dose chemotherapy regimen:

Since ASCT remains an important component of therapy for lymphomas, any improvement in conventional chemotherapy is warranted. Although there is currently an increasing focus on so-called targeted therapies, standard chemotherapy should be improved in clinical trials and it is mandatory that BEAM or CBV regimen are challenged in new clinical trials. Recently, it has been shown that the EAM regimen (thus omitting BCNU) is not sufficient to obtain equal response rates if compared with BEAM and poorer disease control resulted in impaired DFS.[26] Thus, it might be detrimental for patients just to eliminate BCNU without an appropriate substitution. Replacing BCNU by Bendamustine with its potential to eradicate residual or treatment-resistant lymphoma cells could be a promising clinical approach and should be investigated in a randomized phase II clinical trial comparing standard BEAM with BeEAM.

Although transplant related mortality is generally low in ASCT, long term cardio-pulmonary toxicity might be underestimated.[27] Almost all patients with lymphoma receive anthracyclins as first line treatment or later in reinduction chemotherapy and some of them are treated with bleomycin containing regimen followed by a combination of BCNU; thus, both pulmonary and cardiac toxicity with impairment in cardiopulmonary function might deteriorate over the years after ASCT. Any additional pulmonary toxicity by BCNU may result in impaired diffusion capacity of the lung[28] with deterioration of oxygenation and possible increase in right heart blood pressure. This may result in myocardial insufficiency. Many late effects are not documented and about 50 percent of patients eligible for ASCT achieve long term remission or even cure. Thus, prevention of late cardio-pulmonary toxicity is of particular interest for these patients.

Treatment of lymphoma patients usually is performed in highly specialized hematological centres, and after achieving stable remission, such patients are typically no longer seen by transplant physicians. Thus, late toxicities with pulmonary or cardiac impairment[29] are often not documented. A replacement of BCNU by bendamustine might be an attractive concept as so far no specific cardio-pulmonary toxicity of bendamustine is known. As cited above, bendamustine is a highly active component in the treatment of follicular or aggressive lymphomas and - in combination with high-dose cytarabine - very efficient in the treatment of relapsing mantle cell lymphoma.[25] Therefore, the high-dose cytarabine containing EAM might be the ideal combination for cytotoxic drugs with Bendamustine. In our multicenter academic trial, we plan to compare the standard BEAM protocol with BeEAM thereby replacing BCNU and to document early and late effects of BCNU on cardio-pulmonary function.

Justification and definition of primary endpoint: The pulmonary diffusion capacity is the prominent tool to assess lung specific toxicity and it is assessed by the single breath carbon monoxide method D_{LCO}. It demonstrates the ability to absorb alveolar gases into the capillary blood flow, representing the function of the alveolar membrane, and it is affected by hemoglobin level, cardiac output, and distribution of diffusion capacity, ventilation and perfusion. As the hemoglobin level is relevant for interpretation of D_{LCO} and since changes of D_{LCO} as a function of hemoglobin will be documented, D_{LCO} will be evaluated before ASCT (baseline), 3 months after ASCT when recovery of erythropoietin can be expected, as well as 12 months after ASCT. D_{LCO} will be adjusted according to the Dinikara equation[34]: Adjusted D_{LCO} = measured D_{LCO} / (0.06965 x Hb)

A 20 % reduction of D_{LCO} can be interpreted as a significant impairment of pretransplant values. It has been shown that post transplant D_{LCO} showed lower values in patients receiving toxic lung chemotherapy, with maximum effects observed around 100 days after ASCT.[30] We expect significantly fewer patients with lung specific toxicity measured by D_{LCO} defined as a decrease by at least 20% from baseline value in the BeEAM group (4%) compared to the BEAM group (25%).

Other standardized spirometric parameters as forced expiratory volume in first second (FEV_1) and forced vital capacity (FVC) seem not to be affected 3 months after ASCT. On the other hand, impaired lung function has been predictive for IPS after SCT and is recommended as a pre-transplant control in many centers and a parameter for the hematopoietic cell transplantation comorbidity index (HCTCI). Therefore, we will perform FEV_1 and FVC before ASCT as well as 3 and 12 months after ASCT to demonstrate possible differences in the decline of pulmonary function in BeEAM versus BEAM treated patients.

Additionally, VBGA,spiroergometry as well as cardiac assessments (ECHO and ECG) will be performed before (baseline) as well as 3 months and 12 months after ASCT to evaluate the functional cardio-pulmonary status of the patients before and after ASCT.

3.5 Dose Rationale for Bendamustine in the BeEAM regimen

Visani et al have reported their experience with the BeEAM regimen thereby replacing BCNU with Bendamustine. They have used bendamustine at 200mg/m^2 on days -7 and -6 before ASCT. In this study we use this (same) bendamustine dosage given the promising experience both for efficacy and tolerance with this dosage.

3.6 Explanation for choice of comparator (or placebo)

Based on our clinical experience using the BeEAM regimen as well as on the report of Visani et al, a randomized clinical trial comparing the standard conditioning regimen (BEAM) with the experimental BeEAM regimen appears a clinical need to demonstrate non-inferiority of the BeEAM regimen as well as better pulmonary tolerance.

3.7 Risks / Benefits

Routinely performed high-dose chemotherapy with ASCT is associated with significant side effects requiring detailed information of the patient. Usually, it is associated with a hospitalization of at least 3 weeks. A particular side effect of the commonly used BEAM chemotherapy regimen is its (early or late occurring) pulmonary toxicity. It is usually caused by the chemotherapy component BCNU. In this study, we investigate whether the use of Bendamustine instead of BCNU might decrease the rate of pulmonary toxicity observed after BEAM conditioning.

Bendamustine might affect the duration until hematologic recovery, which has to be carefully monitored during the study. Bendamustine might increase or cause other organ dysfunction or toxicities, and therefore, such observations will have to be comprehensively collected and reported in this study.

No competing trials are currently reported.

3.8 Justification of choice of study population

This study does not involve vulnerable participants (e.g. minors, adolescents, participants incapable of judgement or participants under tutelage, emergency treatment of unconscious patients or others). The age limits are between 18 and 75 years.

4. STUDY OBJECTIVES

4.1 Overall Objective

This study aims to demonstrate that replacing the chemotherapeutic drug BCNU by Bendamustine within the four-drug chemotherapy regimen BEAM reduces the occurrence of early and late pulmonary toxicity in lymphoma patients undergoing high-dose chemotherapy with autologous stem cell transplantation.

4.2 Primary Objective

This study intends to show a clinically meaningful reduction of lung toxicity - defined as a decrease of the diffusion capacity of the lung for carbon monoxide (D_{LCO}) by 20% or more from baseline before ASCT - from 25% of patients in the BEAM group to 4% of patients in the BeEAM group at 3 months after ASCT. Use Dinakara equation for adjusting D_{LCO} for hemoglobin [34]. Adjusted D_{LCO} = measured D_{LCO} / (0.06965 x Hb)

4.3 Secondary Objectives

This study intends

- to assess acute and late toxicity/adverse events (CTCAE 4.0) during the entire study period
- to assess the hematologic recovery and engraftment after 3 months
- to assess early and late lung toxicity by pulmonary function tests, spiroergometry, D_{LCO}, HRCT and venous BGA performed before ASCT, 3 and 12 months after ASCT.
- to perform cardiac assessment by ECHO/ECG before, 3 and 12 months after ASCT
- to assess the quality of life prior to ASCT, 3 and 12 months thereafter.
- to assess overall survival and progression free survival after 12 months and then yearly as routine follow-up assessments.

4.4 Safety Objectives

The study aims to assess early- and long-term pulmonary and cardiac toxicity of the new regimen replacing the chemotherapeutic compound BCNU by Bendamustine within the polychemotherapy BEAM regimen as compared to the standard BEAM regimen in lymphoma patients undergoing high-dose chemotherapy with autologous stem cell transplantation. Any other acute or late adverse event will be recorded in the CRFs.

5. STUDY OUTCOMES

5.1 Primary Outcome

A clinically meaningful reduction of lung toxicity is defined as a reduction of the D_{LCO} by at least 20% from baseline before ASCT.

5.2 Secondary Outcomes

Acute and late toxicity/adverse events are assessed according to the CTCAE 4.0 during the entire study period.

Hematologic engraftment after ASCT is defined as the first day of neutrophils rising above 0.5 G/l, and of platelets rising above 20 G/L in the absence of platelet transfusions in the previous 3 days.

Overall survival is defined as the time from ASCT until death of any cause or date of last follow-up.

Progression free survival is defined as the time from ASCT until first recurrence of lymphoma or date of last follow-up whatever occurs first.

5.3 Other Outcomes of Interest

Not applicable

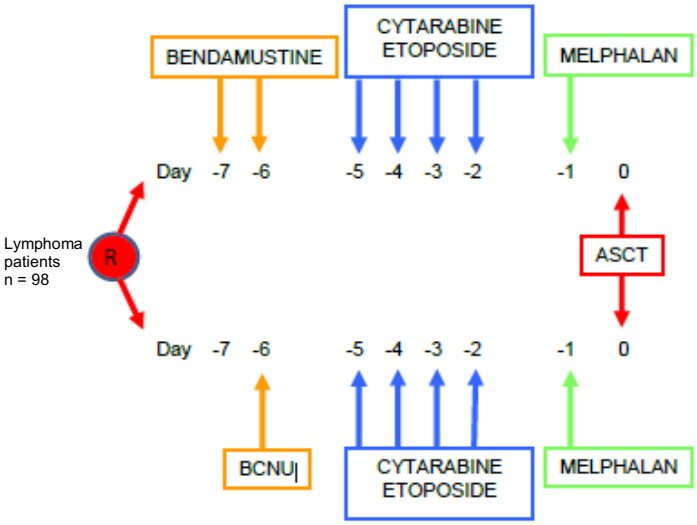
5.4 Safety Outcomes

This study intends to assess cardiac and pulmonary toxicities associated with high-dose chemotherapy before autologous stem cell transplantation. Patients will be screened for the occurrence of such toxicities by pulmonary and cardiac assessments at specified time points during the study protocol.

6. STUDY DESIGN

6.1 General study design and justification of design

A schematic diagram of trial design, procedures and stages



Bendamustine	200 mg/m^2 d -7, -6
or BCNU	300 mg/m^2 d -6
Cytarabine	400 mg/m^2 d -5 to -2
Etoposide	200 mg/m^2 d -5 to -2
Melphalan	140 mg/m^2 d -1

This is a randomized parallel open-label prospective phase II trial investigating chemosensitive lymphoma patients in first or second remission considered clinically fit to undergo high-dose chemotherapy with autologous stem cell transplantation. Lymphoma types include mantle cell lymphoma, diffuse large B-cell lymphoma or follicular lymphoma.

Two high-dose chemotherapy regimens (BeEAM versus BEAM) used for conditioning treatment before autologous stem cell transplantation will be compared in a 1:1 randomization (see trial diagram above). The experimental arm is the BeEAM regimen. The BEAM regimen is the control treatment. Both regimens use the three drugs etoposide, cytarabine and melphalan at identical doses and at identical days. The only difference is the replacement of the standard drug BCNU (carmustine; given in the BEAM group at day -6) by the experimental drug bendamustine (given in the BeEAM group at days -7 and -6).

Lung toxicity will be assessed by spiroergometry, as well as by assessing the diffusion capacity of the lung for carbon monoxide (D_{LCO}) and venous BGA. This analysis will be performed before ASCT, as well as 3 months and 12 months after ASCT.

BeEAM chemotherapy regimen consisting of Bendamustine intravenously on days −7 and −6 at 200 mg/m^2; cytarabine, 400 mg/m^2 intravenously daily from day −5 to day−2; etoposide, 200 mg/m^2 intravenously daily from day −5 to day −2; and melphalan, 140 mg/m^2 intravenously on day −1 before reinfusion of autologous stem cells will be compared with the standard BEAM regimen with carmustine 300 mg/m^2 on day -6, followed by the EAM regimen as described above, in a randomized phase II trial. Toxicity and efficacy will be compared.

There will be 49 evaluable patients needed in each group to show a clinically meaningful reduction of events (lung toxicity defined as a reduction of the D_{LCO} by at least 20% from baseline vaule), i.e. from 25% of patients in the BEAM group to 4% of patients in the BeEAM group, at three months. Thus, a total of 108 evaluable patients are needed. Expecting a rate of ineligible patients of 10%, a total of 108 patients is needed, with 54 patients in each of the two arms.

The anticipated study duration will be 36 months.

Patients will be assessed for cardio-pulmonary toxicity before ASCT, as well as 3 and 12 months after ASCT. Thereafter, patient follow-up will be performed clinically once per year.

6.2 Methods of minimising bias

This is a 1:1 randomized parallel open-label prospective phase II trial investigating chemosensitive lymphoma patients in first or second remission considered clinically fit to undergo high-dose chemotherapy with autologous stem cell transplantation. Patients will be stratified for lymphoma subtypes.

6.2.1 Randomisation

Randomisation is centrally performed in this trial by the “Institut für Med. Informatik, Statistik und Dokumentation; Medizinische Universität Graz; Auenbruggerplatz 2; 8036 Graz; phone: +43/316/385-4261; fax: +43/316/385-3590; E-Mail: andrea.berghold@medunigraz.at)“. The web-based randomization software („Randomizer for Clinical Trials“, www.randomizer.at) will be applied. Patients can be registered 24 h / 7 days.

6.2.2 Blinding procedures

Not applicable; this is an open-label trial.

6.2.3 Other methods of minimising bias

Not applicable

6.3 Unblinding Procedures (Code break)

Not applicable; this is an open-label trial.

7. STUDY POPULATION

7.1 Eligibility criteria

Participants fulfilling all of the following inclusion criteria are eligible for the study:

- Informed Consent as documented by signature (Appendix Informed Consent Form)
- Chemosensitive diffuse large B-cell lymphomas (DLBCL), follicular lymphomas (FL), and mantle cell lymphomas (MCL) in first or second remission
- Aged between 18 years and 75 years
- Neutrophils ≥ 1000/µl; Platelets ≥ 100 x 10^9/L

The presence of any one of the following exclusion criteria will lead to exclusion of the participant:

- Acute uncontrolled infection
- Other clinically significant concomitant disease states (e.g., renal failure, hepatic dysfunction, cardiovascular disease, etc.) excluding a treatment according to this protocol
- HCTCI > 5 (Use Dinikara equation for adjusting DLco for hemoglobin)
- Concurrent malignant disease with the exception of basalioma/spinalioma of the skin or early-stage cervix carcinoma, or early-stage prostate cancer. Previous treatment for other malignancies (not listed above) must have been terminated at least 24 months before registration and no evidence of active disease must be documented since then.
- Known or suspected non-compliance excluding participation to the treatment as outlined in this protocol
- Inability to follow the procedures of the study, e.g. due to language problems, psychological disorders, dementia, etc. of the participant,
- Major coagulopathy or bleeding disorder
- Major surgery less than 30 days before start of treatment
- Contraindications to the class of drugs under study, known hypersensitivity or allergy to class of drugs or the investigational product
- Women who are pregnant or breast feeding; Women with the intention to become pregnant during the course of the study,
- Lack of safe contraception, defined as: Female participants of childbearing potential, not using and not willing to continue using a medically reliable method of contraception for the entire study duration, such as oral, injectable, or implantable contraceptives, or intrauterine contraceptive devices, or who are not using any other method considered sufficiently reliable by the investigator in individual cases. Female participants who are surgically sterilised / hysterectomised or post-menopausal for longer than 2 years are not considered as being of child bearing potential.
- Participation in another study with investigational drug within the 30 days preceding and during the present study,
- Previous enrolment into the current study,
- Enrolment of the investigator, his/her family members, employees and other dependent persons.

7.2 Recruitment and s creening

Participants are recruited to this study by screening lymphoma patients routinely referred to one of the study centres for autologous stem cell transplantations. No specific advertisement for this study is performed. Screening procedure is outlined in section 9.3.1. No payment or compensation is given to study participants.

7.3 Assignment to study groups

Randomization is centrally performed in this trial by the Institut für Med. Informatik, Statistik und Dokumentation; Medizinische Universität Graz; Auenbruggerplatz 2; 8036 Graz; phone: +43/316/385-4261; fax: +43/316/385-3590; E-Mail: andrea.berghold@medunigraz.at. The web-based randomization software („Randomizer for Clinical Trials“, www.randomizer.at) will be applied. Patients can be registered 24 h / 7 days.

Stratification is performed for lymphoma subtypes. If an already registered patient is later found not to completely fulfill the inclusion/exclusion criterias, he/she will be documented on the enrollment-log at the centre. The exclusion of this patient will be reported to the coordinating investigator and to the sponsor. The patient will

not be included in the final analysis, and his/her patient number will not be replaced by another patient.

7.4 Criteria for withdrawal / discontinuation of participants

- withdrawal of informed consent by the participant
- lack of compliance of the participant to follow the study procedures
- relevant protocol violation
- lost to follow up
- Unacceptable toxicity or death

Any participant has the right to withdraw the consent to participation in this trial at any time. Details of the time and the circumstances of the withdrawal have to be recorded in the patient charts and in the CRFs. The treating physician can withdraw the patient from the study if considered necessary. Again, the time and the circumstances of the withdrawal have to be recorded in the patient charts and in the CRFs. Patients withdrawn from this protocol are documented for a total of 12 months. All patients terminating study treatment before 12 months will be analyzed until the last documented follow-up.

8. STUDY INTERVENTION

8.1 Identity of Investigational Prod ucts (treatment)

Two high-dose chemotherapy regimens (BeEAM versus BEAM) used for conditioning treatment before autologous stem cell transplantation will be compared in a 1:1 randomization. The experimental arm is the BeEAM regimen. The BEAM regimen is the control treatment. Both regimens use the three drugs etoposide, cytarabine and melphalan at identical doses and at identical days. The only difference is the replacement of the standard drug BCNU (carmustin; given in the BEAM group at day -6) by the experimental drug Bendamustine (given in the BeEAM group at days -7 and -6).

Lung toxicity will be assessed by spiroergometry, as well as by assessing the diffusion capacity of the lung for carbon monoxide (D_{LCO}) and venous BGA. This analysis will be performed before ASCT, as well as 3 months and 12 months after ASCT.

BeEAM chemotherapy regimen consisting of Bendamustine intravenously on days −7 and −6 at 200 mg/m^2; Cytarabine, 400 mg/m^2 intravenously daily from day −5 to day−2; Etoposide, 200 mg/m^2 intravenously daily from day −5 to day −2; and Melphalan, 140 mg/m^2 intravenously on day −1 before reinfusion of autologous stem cells will be compared with the standard BEAM regimen with Carmustine 300 mg/m^2 on day -6, followed by the EAM regimen as described above, in a randomized phase II trial. Toxicity and efficacy will be compared.

8.1.1 Experimental Interven tion (treatment)

Investigational arm:	**BeEAM**	
Bendamustine	200mg/m^2	days -7 and -6
Etoposide	200mg/m^2	days -5, -4, -3, -2
Cytarabine	400mg/m^2	days -5, -4, -3, -2
Melphalan	140mg/m^2	day -1

8.1.2 Control Intervention (standard treatment)

Standard arm:	**BEAM**	
BCNU	300mg/m^2	day -6
Etoposide	200mg/m^2	days -5, -4, -3, -2
Cytarabine	400mg/m^2	days -5, -4, -3, -2
Melphalan	140mg/m^2	day -1

8.1.3 Packaging, Labelling and Supply (re -supply)

Bendamustine will be provided in single brown glass vials containing 25 mg or 100 mg of bendamustine hydrochloride (HCl) powder.

Labeling of bendamustine is performed by the manufacturer in accordance to GMP and the local regulatory requirements.

Each vial will be affixed with a label describing the protocol number, patient number, content of each vial, dosage form, and route of administration, lot number, expiration date, storage conditions, and the Sponsor's name.

Packaging and shipping will be according to the manufacturer's standards and local regulations.

Upon receipt of bendamustine by the study site/ pharmacy personnel should check for damage and verify proper quantity, identity, and integrity. Any complaints and deviations from the delivery notes have to be reported to the monitor upon discovery.

Ordering and distribution of Bendamustine to the study sites will be performed country-specific.

Switzerland: Mundipharma Medical Company will receive orderings for bendamustine study medication via a specific fax ordering form. Distribution of bendamustine will be performed by Alloga Switzerland to the pharmacy of Swiss study sites.

For each Swiss study site, a stock of study medication will be provided in advance which has to be replenished

by fax-order sent to Mundipharma Medical Company (Switzerland).

Appropriate fax ordering forms and fax numbers are provided in the Investigator Study File.

Austria: Mundipharma GmbH (Austria) will be responsible for providing study medication directly to the pharmacy of the study sites.

Note: Drug supply has to be ordered by fax for each patient prior to treatment start.

Appropriate fax ordering forms and fax numbers are provided in the Investigator Study File.

Commercial products will be used for the comparator BCNU as well as for the EAM regimen.

8.1.4 Storage Conditions

Storage of Investigational Product: The investigational product will be stored at < 25°C and protected from light in a secure location accessible only by authorized personnel. All drug supplies are to be used only for this protocol and not for any other purpose.

8.2 Administration of experimental and control interventions

8.2.1 Experimental Intervention - high -dose chemotherapy BeEAM (with Bendamustine)

Bendamustin: Before administration, bendamustine powder must be dissolved in sterile water for injection and then immediately diluted in 500 ml of 0.9% sodium chloride. Once reconstituted, bendamustine is chemically and physically stable in conventional polyethylene i.v. bags and infusion sets for 3.5 hours at room temperature (25°C/60% relative humidity) or for maximally 2 days under refrigerated conditions (2º-8ºC) and is photostable. From a microbiological point of view, the solution should be used immediately. If not used immediately, in-use storage times and conditions prior use are the responsibility of the user. Because compatibility studies have not been performed, bendamustine should not be combined with other agents or solutions (e.g. glucose).

Bendamustine dose will be given at a dose of 200mg/m^2 at days -7 and -6, and the dose will be calculated according to the BSA (body surface area) using the.DuBois Method. No dose capping (e.g. for under-weight or over-weight patients) will be performed. The BSA has to be determined only once at screening. Bendamustine is administered by i.v. infusion over 120 minutes. An in-line filter is not required for administration.

As bendamustine is a mildly to moderately emetogenic drug, premedication with antiemetic drugs is advised (e.g. a 5-HT3 receptor antagonist).

Bendamustine is not considered to be a vesicant when diluted and administered as recommended. However, if bendamustine extravasates during infusion, it might cause some irritation to affected tissues (follow instructions of SmPC in case of extravasation).

Vials are for single use only. Vials used for one subject may not be used for any other subject.

Partly unused or expired medication can be destroyed by the pharmacy at the study site according to local guidelines, but only after monitor's approval. The destruction shall be either documented by completing the drug return or the drug destruction log.

Etoposide at a dose of 200mg/m^2 will be administered as single i.v. Infusion over 30 minutes at days -5, -4, -3 and -2 before stem cell re-transfusion. No dose capping (e.g. for under-weight or over-weight patients) will be performed. Antiemetics, hydration and supportive care are according to local hospital guidelines.

Cytarabine at a dose of 400mg/m^2 will be administered as single i.v. Infusion over 30 minutes at days -5, -4, -3 and -2 before stem cell re-transfusion. No dose capping (e.g. for under-weight or over-weight patients) will be performed. Antiemetics, hydration and supportive care including konjunctival prophylaxis are according to local hospital guidelines.

Melphalan at a dose of 140mg/m^2 will be administered as single i.v. Infusion over 60 minutes at day -1 before stem cell re-transfusion. No dose capping (e.g. for under-weight or over-weight patients) will be performed. Antiemetics, extensive hydration, control of renal function and supportive care are according to local hospital guidelines.

8.2.2 Control Intervention - high -dose chemotherapy BEAM (with BCNU)

BCNU at a dose of 300mg/m^2 will be administered as a single i.v. Infusion over 120 minutes at day -6 before stem cell re-transfusion. No dose capping (e.g. for under-weight or over-weight patients) will be performed. Antiemetics, hydration and supportive care are according to local hospital guidelines. The prophylactic administration before BCNU infusion of an antihistamin (e.g. clemastin 2mg i.v.), of steroids (solumedrol 125mg i.v.) and of akineton (1mg-2.5mg i.v. depending on body weight) is recommended or according to local hospital

guidelines.

Etoposide at a dose of 200mg/m^2 will be administered as single i.v. Infusion over 30 minutes at days -5, -4, -3 and -2 before stem cell re-transfusion. No dose capping (e.g. for under-weight or over-weight patients) will be performed. Antiemetics, hydration and supportive care are according to local hospital guidelines.

Cytarabine at a dose of 400mg/m^2 will be administered as single i.v. Infusion over 30 minutes at days -5, -4, -3 and -2 before stem cell re-transfusion. No dose capping (e.g. for under-weight or over-weight patients) will be performed. Antiemetics, hydration and supportive care including konjunctival prophylaxis are according to local hospital guidelines.

Melphalan at a dose of 140mg/m^2 will be administered as single i.v. Infusion over 60 minutes at day -1 before stem cell re-transfusion. No dose capping (e.g. for under-weight or over-weight patients) will be performed. Antiemetics, extensive hydration, control of renal function and supportive care are according to local hospital guidelines.

8.3 Dose modifications

No discontinuation of (one or several) study compounds or dose modification of the allocated interventions is allowed by this protocol for a given trial participant. Dosing of study treatment in obese patients (body mass index BMI > 35) is recommended to be adapted as follows: ad half of the overweight to normal weight (height in cm minus 100; eg. height 170 cm then normal weight is 70 kg) and adjust treatment dose for that.

8.4 Compliance with study intervention

According to the intention-to-treat principle, non-compliant patients will not be excluded from the analysis. Non-compliant patients will be documented for a total of 60 months.

All patients terminating study treatment before 12 months will be analyzed until the last documented follow-up.

8.5 Data Collection and Follow -up for withdrawn participants

Any participant has the right to withdraw the consent to participation in this trail at any time. Details of the time and the circumstances of the withdrawal have to be registered in the patient charts and in the CRFs. The treating physician can withdraw the patient from the study treatment if considered necessary. Again, the time and the circumstances of the withdrawal have to be registered in the patient charts and in the CRFs. Patients withdrawn from this protocol are documented for a total of 12 months. All patients terminating study treatment before 12 months will be analyzed until the last documented follow-up.

If patients withdraw their consent to this study, their study data will be anonymized after completion of the study analysis.

8.6 Trial specific preventive measures

Not included in this trial will be female participants of childbearing potential, which are not using and not willing to continue using a medically reliable method of contraception for the entire study duration, such as oral, injectable, or implantable contraceptives, or intrauterine contraceptive devices, or who are not using any other method considered sufficiently reliable by the investigator in individual cases. Female participants who are surgically sterilised / hysterectomised or post-menopausal for longer than 2 years are not considered as being of child bearing potential.

Men should not father a chilld during and up to 12 months after the trial intervention.

8.7 Concomitant Intervent ions (treatments)

No specific recommendations are made excluding specific medication not allowed during study treatment. Maintenance treatment after ASCT is allowed within this protocol but has to be documented in medical records and case report form

8.8 Supportive treatment during neutropenia after ASCT

- All patients receive G-CSF (filgrastim) 5 µg/kg b.w. starting at day +6 after ASCT
- Platelet infusions are given < 10.000/µl; or in case of fever or coagulopathy if platelets are <20.000 µl

- Red cell transfusions if Hb < 8 /dL. Packed RBCs and platelet transfusions should be given to maintain a hemoglobin level > 8 g/dL and a platelet count > $10x10^9$/L.
- Fungal prophylaxis with 400mg of fluconazole p.o. ought be given once per week.
- Cotrimoxazole prophylaxis three times a week for 3 weeks after ASCT, and Acyclovir prophylaxis twice daily 500mg p.o. for three months will be administered to the patients or according to the hospital policy.
- Daily clinical assessment and documentation of toxicities exceeding grade 2 during neutropenia.

8.9 Study Drug Accountability

The investigational product is Bendamustine. Accordingly, Bendamustine is provided free of charge for all patients in this study by the company Mundipharma and all Bendamustine sent to the sites must be accounted for. All other components of the polychemotherapy conditioning before ASCT are considered standard of care, and they are reimbursed by the insurance of the patients.

The investigator is responsible for the control of application and handling of the drugs as requested per protocol.

Adequate records of receipt, administration, storage, destruction or return of the study drugs have to be maintained. All logs have to be completed by the study site staff in a timely manner, and thus should be kept current.

All records, logs and study drugs (used and un-used) at the site have to be available for the inspection at any time.

Upon termination of the study, all logs have to be completed and returned to the monitor to be passed to the Sponsor. Copies thereof, have to be maintained by the study site.

8.10 Return or Destruction of Study Drug

Bendamustine Dispensing and Accounting: All Bendamustine sent to the site must be accounted for. In addition, the amount (in mg) of Bendamustine dispensed for each patient must be recorded on an Investigational Product Accountability Log and the amount (in mg) administered documented on the case report form (CRF). An accurate record of the date and amount of Bendamustine dispensed to each patient must be available for inspection at any time. Partially used vials may be destroyed per institutional guidelines and documented. All unopened and unused vials of Bendamustine will be destroyed upon completion of the study or if drug expires unless otherwise directed by the Sponsor. The study site will document all receipt, complete destruction, and return (if applicable) of Bendamustine.

9. STUDY ASSESSMENTS

9.1 Study flow chart / table of study procedures and assessments / Study Schedule

Study Periods	Screening	Treatment / Intervention		
Visit	1	2	3	4[3]
Time (days)	-28 to -8	-7 until dismissal	80-120	350-400
Patient information & informed consent	x			
Height / weight / BMI	x			
Medical history	x			
In- /exclusion criteria	x			
Physical examination	x	x	x	x
HCTCI score	x			
ECOG score	x	x	x	x
Vital Signs	x	x	x	x
Hematology (complete blood counts with differential)	x	x	x	x
Routine serum biochemistry (according to center policy)	x	x	x	x
Pregnancy Test	x			
Randomization	x			
ECG	x		x	x
Echocardiography	x		x	x
Pulmonary function (FEV_1 & FVC), D_{LCO}[1]	x		x	x
Spiroergometry	x		x	x
Response (CT, MR or PET) thorax/abdomen [2] [4]	x		x	x
VBGA	x		x	x
HR-CT chest	x		x	x
QoL (EORTC Q30)	x		x	x
CTCAE 4.0 toxicity score		x	x	x
Engraftment, neutrophil and platelet recovery		x		
Days until platelets >50 G/L			x	
Number of CD34+ cells used		x		
RBC & platelet transfusions		x		
Days of T>38.0°; number of febrile episodes		x	x	
Administer study medication		x		
Adverse Events		x	x	x

[1] Adjusted D_{LCO} = measured D_{LCO} / (0.06965 x Hb)

[2] The selection of the radiologic assessment is at the discretion of the center and the treating physician

[3] Patients withdrawn from protocol are documented for a total of 12 months. All patients terminating study treatment before 12 months will be analyzed until the last documented follow-up.

[4] once per year after that as routine follow-up assessments. If relapse is suspected, CT, MR or PET-CT assessments are recommended. The follow-up is performed at the discretion of the center; if relapse or progression of lymphoma is suspected, standard radiological examination has to be performed.

9.2 Assessments of outcomes

9.2.1 Assessment of primary outcome

The primary outcome – thus, to show a clinically meaningful reduction of lung toxicity - will be assessed by measuring the diffusion capacity of the lung for carbon monoxide (D_{LCO}) at baseline before ASCT, as well as 3 months and 12 months after ASCT. Since this is an open-label trial, assessment of the primary endpoint cannot occur in a blinded manner.

9.2.2 Assessment of secondary outcomes

- To assess acute and late toxicity/adverse events (CTAE 4.0) during the entire study period by clinical assessment
- To assess the hematologic engraftment after 3 months by determining hemoglobin, leukocyte and platelet counts at three months after ASCT
- To assess early and late lung toxicity by pulmonary function tests, spiroergometry, D_{LCO} and HRCT and venous BGA performed at baseline before ASCT, as well as 3 months and 12 months after ASCT.
- To perform cardiac assessment by ECHO/ECG at baseline before ASCT, as well as 3 months and 12 months after ASCT.
- To assess the quality of life assessed at baseline before ASCT, as well as 3 months and 12 months after ASCT using the EORTC-Q30 questionnaire.
- To assess overall survival and progression free survival after 12 months and then yearly as routine follow-up assessments.

9.2.3 Assessment of safety outcomes

9.2.3.1 Adverse events

For AE definition and procedures, see section 10.

9.2.3.2 Laboratory parameters

See Study Schedule 9.1.

9.2.4 Assessments in participants who p rematurely stop the study

According to the intention-to-treat principle, non-compliant patients will not be excluded from the analysis. Non-compliant patients will be documented for a total of 12 months.

All patients terminating study treatment before 12 months will be analyzed until the last documented follow-up.

Any participant has the right to withdraw the consent to participation in this trail at any time. Details of the time and the circumstances of the withdrawal have to be registered in the patient charts and in the CRFs. The treating physician can withdraw the patient from the study treatment if considered necessary. Again, the time and the circumstances of the withdrawal have to be registered in the patient charts and in the CRFs. Patients withdrawn from this protocol are documented for a total of 12 months. All patients terminating study treatment before 12 months will be analyzed until the last documented follow-up.

If patients withdraw their consent to this study, their study data will be anonymized after completion of the study analysis.

9.3 Procedures at each visit

9.3.1 Screening visit (Day -28 to -8):

- Written informed consent
- Height and weight
- Complete medical history (lymphoma histology and localisation, IPI, date of diagnosis, relapse(s), prior treatment(s) (first and second line) and response before ASCT
- Pregnancy test
- Physical examination
- hematopoietic stem cell transplantation comorbidity score (HCT-CI) [33] (see Appendix 4)
- ECOG Score (see Appendix 2), body mass index (BMI),

- ECG
- Echocardiography
- Pulmonary function tests (FEV_1 and FVC) and evaluation of D_{LCO}
- Spiroergometry
- Venous BGA
- Hematology (complete blood counts with differential)
- Routine serum biochemistry (according to the centres policy)
- Disease assessment and CT Staging (or MRI or CT-PET) of abdomen/thorax at discretion of the center
- HR-CT chest
- QoL (EORTC Q30, Version 3.0) (see Appendix 5)

All screening procedures should be performed within 4 weeks prior to start of study treatment

9.3.2 Assessments during ASCT (Day -7 until day of hospital discharge

- Date of ASCT and date of engraftment
- Number of CD34+ cells transplanted
- Unit number of infused red blood cell (RBC) and platelet transfusions
- Time to platelet recovery > 20x 10^9/L and > 50x 10^9/L
- Time to recovery of ANC > 0,5x10^9/L
- Number of days of temperature > 38.0° and number of febrile episodes
- Duration in days of platelets Plt < 50x 10^9/L since day of ASCT
- Assessment of CTCAE 4.0 highest toxicity score observed during ASCT until dismission from hospital (see Appendix 1)

9.3.3 Assessments three months after ASCT (Day 80 to 120)

- Physical examination
- ECOG Score
- ECG
- Echocardiography
- Pulmonary function tests (FEV_1 and FVC) and evaluation of D_{LCO}
- Spiroergometry
- Venous BGA
- Hematology (complete blood counts with differential)
- Routine serum biochemistry (according to the centres policy)
- Disease assessment and CT staging (or MRI or CT-PET) of abdomen/thorax at discretion of the center
- HR-CT chest
- Acute and late toxicity/adverse events (CTCAE 4.0)
- Engraftment/best response (at 3 months after ASCT)
- QoL (EORTC Q30)
- Number of days of temperature > 38.0° C, and number of febrile episodes

9.3.4 Assessments after one year (Day 350 to 4 00)

- Physical examination
- ECOG Score
- ECG
- Echocardiography
- Pulmonary function tests (FEV_1 and FVC) and evaluation of D_{LCO}
- Spiroergometry
- Venous BGA

- Hematology (complete blood counts with differential)
- Routine serum biochemistry (according to the center policy)
- Disease assessment and CT staging (or MRI or CT-PET) of abdomen/thorax at discretion of the center
- HR-CT chest
- Acute and late toxicity/adverse events (CTCAE 4.0)
- QoL (EORTC Q30)

Any relapse or death or other reason for study discontinuation will be reported as soon as known. The remission status will be assessed using the RECIST-Criteria Version 1.1. (see Appendix 3) at three months and 12 months after ASCT, and once per year after that as routine follow-up assessments. If relapse is suspected, CT, MR or PET-CT assessments are recommended. The follow-up is performed at the discretion of the center; if relapse or progression of lymphoma is suspected, standard radiological examination has to be performed.

9.4 Response criteria

- See Appendix 3 attached

10. SAFETY

10.1 Drug studies

This is a Category B trial. During of the study, all serious adverse events (SAEs) until d100 after ASCT are collected, fully investigated and documented in source documents and case report forms (CRF). Study duration encompassed the time from when the participant signs the informed consent until the last protocol-specific procedure has been completed, including a safety follow-up period.

Adverse Events have to be reported in case report forms from the time the participant is randomised until 30 days after ASCT. Serious Adverse Events have to be reported in case report forms from the time the participant signs the informed consent until 100 days after ASCT

Adverse Events have to be reported, with the exception of:

- A pre-existing condition that does not increase in severity; the pre-existing condition should be reported on the baseline concomitant diseases CRF
- AEs of CTCAE grade ≤2
- Abnormal laboratory values that have been recorded as being not clinically significant by the investigator in the source documents
- Progression of the disease under study; complications as a result of disease progression remain reportable Adverse Events
- Alopecia
- Nausea/vomiting/loss of appetite
- Hematological toxicities
- Diarrhoea
- Weight loss not exceeding 10% of body weight before HDCT/ASCT
- Febrile neutropenia
- Other expected AEs during HDCT

10.1.1 Definition and assessment of (serious) adverse events and other safety related events

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study procedure. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. [ICH E6 1.2]

Laboratory test value abnormalities should not be recorded in the AE section of the CRF as AEs unless they are considered clinically significant as defined below. Any treatment-emergent abnormal laboratory result that is clinically significant should be recorded as a single diagnosis in the AE section of the CRF. Clinical significance is defined as meeting one or more of the following conditions:

- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment

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

- results in death,
- is life-threatening,
- requires in-patient hospitalization or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious. [ICH E2A]

SAEs should be followed until resolution or stabilisation. Participants with ongoing SAEs at study termination (including safety visit) will be further followed up until recovery or until stabilisation of the disease after termination.

Assessment of Causality

Both Investigator and Sponsor make a causality assessment of the event to the study drug, based on the criteria listed in the ICH E2A guidelines:

Relationship	Description
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Unexpected Adverse Drug Reaction

An “unexpected” adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator’s Brochure for drugs that are not yet approved and Product Information for approved drugs, respectively).

Suspected Unexpected Serious Adverse Reactions (SUSARs)

The Sponsor evaluates any SAE that has been reported regarding seriousness, causality and expectedness. If the event is related to the investigational product and is both serious and unexpected, it is classified as a SUSAR.

Assessment of Severity

To document the severity grades, the “Common Terminology Criteria for Adverse Events CTCAE Version 4.0” terminology will be used.

10.1.2 Reporting of serious adverse events (SAE) and other safety related events

All SAEs and other relevant safety related events until d100 after ASCT have to be reported by the local investigator immediately to the Prinicipal Investigator and Sponsor within 24h of knowledge. The appropriate fax-numbers and email addresses are provided on the SAE-reporting form.

SAEs of all patients, who received study medication in this trial, have to be reported to the Sponsor until d100 after ASCT

Excluded from the reporting are as follows:

- All planned surgeries or hospitalizations known at the time of study initiation,
- All routinely required hospitalizations for chemo- and radiotherapy as well as for ASCT,
- Progression or death due to the underlying malignancy. Hematological toxicities
- Expected SAEs during HDCT

10.1.3 Reporting to the manufacturer of bendamustine hydrochloride:

The Sponsor will supply Mundipharma (i.e.Mundipharma Research GmbH & Co.KG, Germany, Mundipharma Medical Company, Switzerland and Mundipharma Ges. m.b.H., Austria) with

- A copy of all SAEs until d100 after ASCT within 24 hours of being aware of the event regardless of whether or not the event is listed in the reference document (Product Information).
- A copy of all pregnancy reports within 24 hours of being aware of the event.
- A copy of all SUSARs within one business at the time of the submission to the regulatory authorities, the ECs and investigators
- A copy of the ASR at the time of the submission to the regulatory authorities and the ECs.

The appropriate and actual fax-numbers and email addresses are provided in the separate Safety Data Exchage Agreement (SDEA) agreement with Mundipharma.

10.1.4 Reporting of SAEs

All SAEs must be reported immediately and within a maximum of 24 hours to the Sponsor and Principal Investigator of the study by using the SAE reporting form. The Sponsor and Principal Investigator will re-evaluate the SAE and return the form to the site.

10.1.5 Reporting of Deaths

SAEs resulting in death are reported to the local Ethics Committee (via local Investigator) and to AGES (via Principal Investigator for Austrian centers) within 7 days.

The other in the trial involved Ethics Committees receive SAEs resulting in death in Switzerland via Sponsor within 7 days.

10.1.6 Reporting of SUSARs

A SUSAR needs to be reported to the local Ethics Committee (local event via local Investigator) and to Swissmedic for category B and C studies (via Sponsor for Swiss centers) and to AGES (via Principal Investigator for Austrian centers) within 7 days, if the event is fatal, or within 15 days (all other events).

This is a multi-centre trial: The Sponsor must inform all investigators participating in the clinical study of the occurrence of a SUSAR. All in the trial involved Ethics Committees will be informed about SUSARs in Switzerland via Sponsor and in Austria via Principal Investigator according to the local reporting requirements, directives and timelines.

10.1.7 Reporting of Safety Signals

All suspected new risks and relevant new aspects of known adverse reactions that require safety-related measures, i.e. so called safety signals, must be reported to the Sponsor and Principal Investigator within 24 hours. The Sponsor (for Swiss centers) or the Principal Investigator (for Austrian centers) must report the safety signals within 7 days to the local Ethics Committee (local event via local investigator) and to Swissmedic (for Swiss centers) as well as to AGES in Austria (for Austrian centers).

This is a multi-centre trial: The Sponsor must immediately inform all participating investigators about all safety signals. The other in the trial involved Ethics Committees will be informed about safety signals in Switzerland via the Sponsor and in Austria via the Principal Investigator.

10.1.8 Reporting and Handling of Pregnancies

Pregnant participants must immediately be withdrawn from the clinical study. Any pregnancy during the treatment phase of the study and within 6 months after discontinuation of study medication will be reported to the Sponsor within 24 hours. The course and outcome of the pregnancy should be followed up carefully until birth of the child, and any abnormal outcome regarding the mother or the child should be documented and reported according to local reporting requirements, directives and timelines.

10.1.9 Periodic reporting of safety (ASR)

The ASR (annual safety report) is submitted once a year to the local Ethics Committee and to Swissmedic via the Sponsor and to AGES (via the Principal Investigator for Austrian centers). Since this is a multi-centre trial, the annual ASR contains information from all sites including information from sites outside of Switzerland. The Sponsor is responsible for the data collection and preparation of the ASR, and submits it to the participating Investigators. The participating Investigators submit it to the local Ethics committees.

10.1.10 Follow up of (Serious) Adverse Events

The follow up of participants terminating the study (either regularly or prematurely) with reported ongoing SAE, or any ongoing AEs of laboratory values or of vital signs being beyond the alert will be documented until resolution or death of the patient. All adverse events (AE) (until 30 days after ASCT) including all serious adverse events (SAE) (until d100 after ASCT) are collected, fully investigated and documented in the source document and appropriate case report form (CRF) during the entire study period, i.e. from patient's informed consent until the last protocol-specific procedure, including a safety follow-up period.

11. STATISTICAL METHODS

11.1 Hypothesis

The hypothesis of this study is to show a clinically meaningful reduction of lung toxicity - defined as a reduction of the D_{LCO} by at least 20% from baseline value- from 25% of patients in the standard group to 4% of patients in the experimental group at 3 months after autologous stem cell transplantation in lymphoma patients. The standard group of patients is treated with the BEAM high-dose chemotherapy regimen whereas the experimental group is treated with the BeEAM regimen.

11.2 Determination of Sample Size

This study involves two treatment arms and applies a 1:1 randomization, additionally considering the stratification for lymphoma subtypes: diffuse large B-cell lymphoma versus mantle cell lymphoma versus follicular lymphoma. No interim analysis is planned, and all calculations will be performed per evaluable patient. The primary endpoint is to show a clinically meaningful reduction of events (lung toxicity defined as a reduction of the D_{LCO} by at least 20%) at three months, i.e. from 25% of patients in the BEAM group to 4% of patients in the BeEAM group.
Arm A is the experimental arm (BeEAM chemotherapy), and arm B is the standard arm (BEAM chemotherapy). The null hypothesis is that the lung toxicity determined at three months is equal in both arms ($LT3_A = LT3_B$). The aim of the study is to ultimately show less lung toxicity of the experimental (BeEAM) arm, with $LT3_A < LT3_B$.
Based on previous reports, we anticipate observing lung toxicity in the standard (BEAM) arm in 25% ($LT3_B$). Our hypothesis is that the experimental (BeEAM) arm will show lung toxicity in only 4% or less of the patients ($LT3_A$), thus a difference of at least 20 percentage points. Thus, the superiority margin in the proposed prospective randomized study is 0.20, i.e. the reduction of lung toxicity is considered a success compared to the standard (BEAM) arm if its lung toxicity rate is more than 20 percentage points better.

With $LT3_A$ and $LT3_B$ being the (true) success rates in the BeEAM arm and in the BEAM arm, respectively, the hypotheses are:

H0: LT BeEAM chemotherapy is > 0.04 when LT BEAM is 25%.

H1: LT BeEAM chemotherapy is ≤ 0.04 when LT BEAM is 25%.

Applying a statistical power of 80% and a two-sided significance level of 5%, 49 evaluable patients will be needed in each group to show a clinically meaningful reduction of events (lung toxicity defined as a reduction of the D_{LCO} by at least 20%), i.e. from 25% of patients in the BEAM group to 4% of patients in the BeEAM group using Fishers Exact Test. Thus, a total of 108 evaluable patients is needed. A drop-out rate of 10% is expected, thus 54 patients are supposed to be included in each arm.

The significance level actually achieved by this design is 0.0497. All statistical analysis for sample size calculations were performed using the software package nQuery Advisor 7.0.

For statistical analysis of this study, continuous endpoints will be summarized using descriptive statistics including mean, median, standard deviation, first and third quartiles, minimum and maximum values, and where appropriate by graphical techniques (e.g. histogram, box plot). For categorical endpoints, the number and percentage of patients in each category will be summarized. Where appropriate, a two-sided 95% confidence interval for the proportion will be reported. The primary endpoint in the two groups will be tested using Fishers Exact Test. Progression free survival and overall survival will be assessed using Kaplan-Meier plots and log-rank test.

11.3 Statistical criteria of termination of trial

Given the existing (own and by others) data on the promising tolerance and efficacy of the experimental treatment (BeEAM chemotherapy), no stopping rules or discontinuation criteria are planned in this trial for individual participants, for parts of the trial and for the entire trial.

11.4 Planned Analyses

All analyses will be performed per patient treated. All other statistical testing will be two-tailed at the 5% level of significance.

The final analysis of the study will be initiated 12 months after inclusion of the last study patient. No subgroup analysis is planned. No interim analysis is planned.

Safety analysis will be performed at the end of the study. No data safety monitoring board is planned in this study.

Analysis of demographics and baseline characteristics: Continuous measurements (e.g. age) will be summarised using n, mean, standard deviation (SD), median, minimum and maximum while discrete measurements (e.g. sex) will be summarised using frequency counts and percentages. No formal statistical testing will be performed on these data.

Randomization is centrally performed in this trial by the Institut für Med. Informatik, Statistik und Dokumentation; Medizinische Universität Graz; Auenbruggerplatz 2; 8036 Graz; phone: +43/316/385-4261; fax: +43/316/385-3590; E-Mail: andrea.berghold@medunigraz.at. The web-based randomization software („Randomizer for Clinical Trials“, www.randomizer.at) will be applied. Patients can be registered 24 h / 7 days.

11.4.1 Datasets to be analysed, analysis populations

All patients randomised to treatment who have taken at least one dose of study medication will be considered evaluable and will be included in the evaluation of safety.

Three populations will be defined:

(1) The intention to treat (ITT) population. The ITT set includes all randomized patients in the groups to which they were randomly assigned, regardless of their adherence with the entry criteria, regardless of the treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from the protocol. The evaluation of efficacy will be based on the intention to treat (ITT) population.

(2) The per protocol (PP) population. The PP set includes all patients who fulfil the protocol in the terms of the eligibility, interventions, and outcome assessment. The PP set will be used for assessing sensitivity.

(3) All patients randomized to treatment who have taken at least one dose of study medication will be considered evaluable and will be included in the safety population for the evaluation of safety data.

The evaluation of efficacy will be based on two analysis sets, the full analysis (intent-to-treat) set and the per protocol set. The full analysis set is the primary population and will be those patients in the safety population who satisfy all inclusion criteria and who have efficacy data for the primary parameter recorded for baseline and at least one post baseline period assessment. The per protocol set will be those patients in the full analysis set who have no major protocol violations.

11.4.2 Primary Analysis

This is a superiority trial. Specifically, a clinically meaningful reduction of lung toxicity - defined as a reduction of the D_{LCO} by at least 20% from baseline value- from 25% of patients in the standard group to 4% of patients is anticipated in the experimental BeEAM group as compared to the standard BEAM group at 3 months after autologous stem cell transplantation.The primary endpoint D_{CLO} at baseline and three months will be compared using Fishers Exact Test.

11.4.3 Secondary Analyses

For the description of quantitative variables, median and mean values will be used as well as standard deviations, minimum and maximum values. For qualitative variables such as hematologic recovery and engraftment after three months, percentages and absolute frequency will be indicated.

Early and late lung toxicity by pulmonary function tests, spiroergometry, $D_{LCO,}$ venous BGA and HRCT, cardiac assessment by ECHO/ECG and quality of life assessment performed before ASCT, 3 and 12 months after ASCT as well as response rates (CR; PR) at three and 12 months will be compared using Fishers Exact Test tests. Survival rates (OS; PFS) after 12 months.

11.4.4 Interim analyses

No interim analysis planned.

11.4.5 Safety analysis

Acute and late toxicities will be graded and described using the highest grade observed.

11.4.6 Deviation(s) from the original statistical plan

No major deviation(s) from the original statistical plan are to be expected.

11.5 Handling of missing data and drop -outs

A drop-out rate of 10% is expected, thus 54 patients are supposed to be included in each of the two treatment arms.

12. QUALITY ASSURANCE AN D CONTROL

The following procedures guarantee quality of trial conduct:

- Reviews of protocol and forms according to standard operating procedures
- Paper data forms will be entered into a database at the site of Prim. Univ. Prof. Dr. Felix Keil; Hanusch Krankenhaus der Wiener Gebietskrankenkasse; 3. Medizinische Abteilung; Heinrich Collin-Straße 30; 1140 Wien
- Computerized and manual consistency checks will be performed.
- Data review by the primary local investigatoror a delegated person (all forms will be reviewed and checked on medical content)
- Safety monitoring
- Validation of database and statistical analysis
- Accountability of study drugs
- Requirements for potential sub-investigators for participation: signed and dated CV.

12.1 Data handling and record keeping / archiving

Source data are kept available for auditing and monitoring by the Sponsor or Sponsor delegates or competent authorities.

12.1.1 Case Report Forms

Study data will be recorded on paper case report forms (p-CRF). For each enrolled study participant a CRF is maintained. CRFs will be kept current to reflect subject status at each phase during the course of study. Participants will not be identified in the CRF by name or initials and birth date. Appropriate coded identification, e.g. participant number will be used (e.g. combination of initials and year of birth).

A defined study nurse will be identified to be authorized to perform CRF entries, and it will be assured that any authorized person can be identified.

12.1.2 Specification of source documents

Source data will be available at the site to document the existence of the study participants. Source data will include the original documents relating to the study, as well as the medical treatment and medical history of the participant.

12.1.3 Record keeping / archiving

All study data will be archived in the center for a minimum of 10 years after study termination or premature termination of the clinical trial. The investigator will retain copies of the patient trial records (CRFs, patient informed consent statement, laboratory printouts, drug transportation and destruction forms, and all other information collected during the trial) and documentation until at least 10 years after the termination of the trial. In the event that the investigator retires or changes employment, custody of the records may be transferred to another suitable person who will accept responsibility for those records. Notice of such transfer will be given in written to the EC.

12.2 Data management

12.2.1 Data Management System

Study data will be recorded on paper case report forms (p-CRF). For each enrolled study participant a CRF is maintained. CRFs will be kept current to reflect subject status at each phase during the course of study. Participants will not be identified in the CRF by name or initials and birth date. Appropriate coded identification,

e.g. participant number will be used (e.g. combination of initials and year of birth).

12.2.2 Data security, access and back -up

It is planned to use Excel-Database to enter data collected via p-CRF. Access to database information will be restricted to sponsor, to data management team and to responsible statistician Prof. Berghold. Changes to database entries as well as user information will be documented using audit trial function of Excel-Database. Backup-files will be made after each data entry session. Data entries will only be made by authorized personnel of data management team. Patient data are entered anonymously using unique patient identification number and not using full name or complete date of birth. Key (patient identification log) to get information about patient identity is only available at treatment site of patient. The key will not be available to sponsor (with exception of patient data from site of sponsor) and third parties.

12.2.3 Analysis and archiving

All study data will be archived in the center for a minimum of 10 years after study termination or premature termination of the clinical trial. The investigator will retain copies of the patient trial records (CRFs, patient informed consent statement, laboratory printouts, drug transportation and destruction forms, and all other information collected during the trial) and other relevant documentation (protocol, contracts etc.) until at least 10 years after the termination of the trial. In the event that the investigator retires or changes employment, custody of the records may be transferred to another suitable person who will accept responsibility for those records. Notice of such transfer will be given in written to the Sponsor and CEC.

12.2.4 Electronic and central data validation

Computerized and manual consistency checks will be performed.

12.3 Monitoring

The clinical trial unit (CTU) in Berne will perform monitoring of this trial in Switzerland and Mag. Dr. Judith Schuster will be responsible for monitoring in Austria. The monitors will be allowed to inspect the various records of the trial in accordance with local requirements. The monitor will maintain patient confidentiality. Source data verification of the following data will be performed for every patient:

- Informed consent
- Inclusion/exclusion criteria
- Serious Adverse Events (SAE)
- Primary endpoint
- Accountability of study drugs

12.4 Audits and Inspections

Regulatory authorities and delegates of the local Ethic Committees have the right to perform inspections and to verify original data. The investigators are obliged to actively participate during an audit or inspection. They have to ensure that all required source data and collected patient data are made available during an audit or inspection and that adequate facilities are provided for the audit or inspection. Access to source data verification has to be provided within a reasonable peiod of time, In case of an announcement of an inspection, the investigator has to inform the Sponsor promptly.

12.5 Confidentiality, Data Protection

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws.

All patients will be informed as to the strict confidentiality of their patient data, which will not be handed over to non-authorized third parties. However, they will also be informed and have given written informed consent that their medical records (anonymised data) may be reviewed for trial, scientific or monitoring purposes by authorized individuals other than their treating physicians.

12.6 Storage of biological material and related health data

No samples are stored in this study, and no biobank will be involved in this study.

13. PUBLICATION AND DISS EMINATION POLICY

Sponsor and Principal/Coordinating Investigator will commonly publish the data of the trial in a peer-reviewed journal within 12 months after study completion, All study data collected will be kept confidential by all investigators prior to publication. Release of any abstract, manuscript or presentation will be shared and discussed between the Sponsor-, Principal/Coordinating Investigator and Co-investigators. The companies supplying the study medications have the right to review manuscripts and abstracts prior to submission for publication as defined in the separate agreements.

The Sponsor agrees to inform the companies supplying the study medication about any impending publication and release of any abstract, relating to the outcome of the trial. Without prejudice to the Sponsor's autonomy in respect to the publication of the results of the trial, the Sponsor agrees to provide to the companies the proposed manuscript in advance at least thirty and abstracts at least fourteen days before. The Supplier may propose changes to the text up to twenty-eight days from receipt of the manuscript and up to twelve days from receipt of the abstract. The Sponsor shall respond in good faith to any reasonable and justified requested revisions of the manuscript, always provided that Sponsor shall have the final say in deciding on the contents and wording of the text. The Sponsor shall give appropriate acknowledgement to the Supplier's or its Associates employees, if applicable, in the publication.

14. FUNDING AND SUPPORT

14.1 Funding

This study is supported in Switzerland by grants from the „Gemeinnützige Stiftung Empiris“ in Zürich and a grant from the company Mundipharma Medical Company. Bendamustine hydrochloride is provided free of charge by the company Munidpharma Medical Company in Switzerland and Mundipharma Ges. m.b.H. in Austria.

14.2 Other Support

No other support is available for this study.

15. INSURANCE

The Inselspital Berne is sponsor of this study. The insurance for patients in Switzerland will be provided by the Sponsor, and a separate insurance solution is defined for the Austrian centers. A copy of the certificate is filed in each investigator site file and the trial master file.

16. APPENDICES

16.1 Appendix 1: Toxizitätskriterien nach CTCAE 4.0

CTC adverse events version v4.0 : http://ctep.cancer.gov/reporting/ctcnew.html

Adverse event/ Toxizitäts -Grad	1 gering – Leicht	2 mäßig – deutlich	3 stark – ausgeprägt	4 lebensbedrohlich
Neutropenie	< LLN – 1500/mm³	< 1500 – 1000/mm³	< 1000 – 500/mm³	< 500/mm³
Thrombopenie	< LLN – 75.000/mm³	< 75.000 – 50.000/mm³	< 50.000 – 25.000/mm³	< 25.000/mm³
Anämie	Hb < LLN – 10.0 g/dl	Hb 10.0 – 8.0 g/dl	Hb 8.0 – 6.5 g/dl	Hb < 6.5 g/dl
Nausea	Appetitsverlust ohne Veränderung der normalen Essgewohnheiten	Nahrungsaufnahme etwas vermindert- , Kein Gewichtsverlust	Unzureichende orale Kalorien bzw. Flüssigkeitszufuhr ; i.v. Flüssigkeits-zufuhr, parenterale Ernährung > 24h	Lebensbedrohliche Konsequenzen
Erbrechen	1 Episode in 24 h	2 – 5 Episoden in 24 h; i.v. Flüssigkeitszufuhr < 24 h	6 oder mehr Episoden in 24 h; i.v. Flüssigkeits-zufuhr bzw. parenterale Ernährung > 24 h	Lebensbedrohliche Konsequenzen
Diarrh oe	Anstieg auf < 4 Stühle pro Tag über baseline	Anstieg auf 4-6 Stühle pro Tag über baseline; i.v. Flüssigkeitszufuhr < 24 h; beeinträchtigt Alltagsaktivitäten nicht	Anstieg über 7 Stühle pro Tag über baseline; i.v. Flüssigkeitszufuhr > 24 h; stationäre Aufnahme; beeinträchtigt Alltagsaktivitäten	Lebensbedrohliche Konsequenzen d. Diarrhoe
Fatigue	Leichte Fatigue; stärker als bei baseline	Mäßige Fatigue; beeinflusst Ausübung einiger Aktivitäten	Schwere Fatigue; Alltagsaktivitäten beeinträchtigt	Inaktivierend
Mukositis klin. Untersuchung	Erythem der Schleimhaut	Nicht konfluierende Ulzerationen od. Pseudomembranen	Konfluierende Ulzerationen od. Pseudomembranen; Blutung bei Minimaltrauma	Gewebsnekrose; signifikante spontane Blutung; lebensbedrohliche Konsequenzen
Neuropathie Sensorisch	Abgeschwächte Sehnenreflexe oder Parästhesien; keine Funktions-Einschränkung	Veränderung der Sensorik od. Parästhesien; Funktions-Einschränkung, jedoch Alltagsaktivität nicht beeinträchtigt	Veränderung der Sensorik od. Parästhesie; Alltagsaktivität beeinträchtigt	Inaktivität

Infektion – Febrile Neutropenie	---	---	Bestehende febrile Neutropenie	Lebensbedrohliche Konsequenzen (z.B. septischer Schock, Hypotension, Acidose, Nekrose)
Allergien	Transienter Rush Fieber< 38°	Rush, Urtikaria, Dyspnoe Fieber>38°	Symptomatische Bronchospasmen die intravenöse Medikation erfordern, Hypotension	Anaphylaxie
Schmerzen	Leicht, keine Funktionseinschränkung	Mittel mit Funktionseinschränkung	Schwer mit massiver Funktionseinschränkung	
Dysphagia	Symptomatisch, kann normale Ernährung zu sich nehmen	Symptomatisch, mit veränderten Ess- und Schluckgewohnheiten; i.v. Flüssigkeitszufuhr < 24 h	Symptomatisch mit stark veränderten Ess- und Schluckgewohnheiten; i.v. Flüssigkeits zufuhr, parenterale Ernährung >24 h	Lebensbedrohliche Konsequenzen (z.B. Obstruktion, Perforation)
Gewichtsverlust	5 – < 10 % von Baseline	10 – < 20 % von Baseline; Zusatzernährung indiziert	> 20 % von Baseline; PEG-Sonde oder parenterale Ernährung indiziert	___
Soor	___	Lokalisiert; lokale Therapie nötig	i.v. Intervention nötig; Radiologischer oder operativer Eingriff nötig	Lebensbedrohliche Konsequenzen (z.B. septischer Schock, Hypotonus, Acidose, Nekrose)

16.2 Appendix 2: Performance status scale (ECOG)

0 normale Aktivität möglich ohne Einschränkung

1 Einschränkung bei körperlich anstrengender Tätigkeit aber leichte Tätigkeiten möglich und keine Bettlägerigkeit

2 nicht arbeitsfähig, selbständig, tagsüber weniger als 50% Ruhe bzw. Hinlegen erforderlich

3 Selbstversorgung sehr eingeschränkt möglich, tagsüber mehr als 50% Ruhe bzw. Hinlegen erforderlich, Pflege bzw. Hilfe erforderlich

4 bettlägerig und völlig pflegebedürftig

5 tot

16.3 Appendix 3: Remissionsbeurteilung RECIST

Nach RECIST: response evaluation criteria in solid tumors Version 1.1.
(Eisenhauer EA, Therasse P, Bogaerts J, et al.: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). In: Eur. J. Cancer. 45, Nr.2, Januar 2009, S.228–47)
Messbare Läsionen (Target lesions): in mindestens einer Dimension messbar und ≥ 10mm im längsten Durchmesser(LD) im CT (2 CT-Schichtdicke) oder klinisch oberflächlich (Foto), ≥ 20 mm LD im Thorax-Röntgen; Lymphknoten ≥ 15 mm im kurzen Durchmesser (KD)
Nicht-messbare Läsionen (Non-target lesions): kleiner 10mm im CT, osteoblastische Knochenläsionen(Szintigraphie, PET oder Konv. RÖ), leptomeningeale Erkrankung, Ascites, Pleuraerguß, Perikarderguß, Lymphangiose, zystische Läsionen

- Ausgangsmessung muss innerhalb 4 Wochen vor Therapiebeginn erfolgen
- Gleiche Methode der Messung sollte im Verlauf verwendet werden
- Radiologische Methoden werden vor klinischen Methoden bevorzugt
- Ultraschall sollte nur in wenigen Fällen herangezogen werden (zB LK Größe)
- Zytologie oder Histologie unterscheidet in manchen Fällen zwischen PR und CR
- Bei neuen Ergüssen entscheidet Zytologie zwischen PD und SD/PR/CR

Tumorlast: Basisuntersuchung: Alle messbaren Läsionen bzw. wenn multipel: die größten und/oder am besten messbaren Läsionen (target lesions) - maximal 5 Läsionen (≤ 2 pro Organ) insgesamt.
Summe der längsten Durchmesser aller target lesions.

Target lesions:

Komplette Remission (CR):	Verschwinden aller extranodalen Herde, alle Lymphknoten sind im KD < 10 mm;
Partielle Remission (PR):	mindestens 30% Verminderung der Summe der längsten Durchmesser der target lesions im Vergleich zum Ausgangsbefund.
Progredienz (PD):	mindestens 20% Vergrößerung der Summe der längsten Durchmesser der target lesions (in Beziehung zum besten Meßergebnis seit Beginn der Therapie) oder Auftreten von 1 oder mehr neuen Läsionen
Stabile Erkrankung (SD):	zwischen PR und PD

Non-target lesions:

CR:	Verschwinden aller Läsionen,
Incomplete response/SD:	Persistieren einer oder mehrerer Läsionen
PD:	Ein oder mehrere neue Läsionen und/oder eindeutige Progredienz einer non-target lesion

16.4 Appendix 4: HCT-CI score [33]

Comorbidity	*Explanation*	*HCT-CI score*
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1
Cardiac	Coronary artery disease, congestive heart failure, myocardial infarction or EF≤50%	1
IBD	Crohn's disease or ulcerative colitis	1
Diabetes	Requiring treatment with insulin or oral hypoglycemics	1
CVD	Transient ischemic attack or cerebrovascular accident	1
Psychiatric disturbance	Depression or anxiety requiring psychiatric consult or treatment	1
Hepatic, mild	Chronic hepatitis, bilirubin >ULN to 1.5 × ULN, or AST/ALT >ULN to 2.5 × ULN	1
Obesity	Patients with a body mass index >35 kg/m^2	1
Infection	Requiring treatment after day 0	1
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	2
Peptic ulcer	Requiring treatment	2
Moderate/severe renal	Serum creatinine >2 mg 100 mL, on dialysis, or prior renal transplantation	2
Moderate pulmonary	DLCO and/or FEV1 66–80% or dyspnea on slight activity	2
Prior solid tumor	Treated at any time point in the patient's history, excluding non-melanoma skin cancer	3
Heart valve disease	Except mitral valve prolapse	3
Severe pulmonary	DLCO and/or FEV1 ≤65% or dyspnea at rest or requiring oxygen	3
Moderate/severe hepatic	Liver cirrhosis, bilirubin >1.5 × ULN, or AST/ALT >2.5 × ULN	3

Abbreviations: AST/ALT=aspartate aminotransferase/alanine aminotransferase; CTD=connective tissue disease; CVA=cerebrovascular disease; DLCO=diffusion capacity of carbon monoxide; EF=ejection fraction; FEV1, force expiratory volume in 1 second; HCT-CI=hematopoietic cell transplantation-specific comorbidity index; IBD=inflammatory bowel disease; RA=rheumatoid arthritis; SLE=systemic lupus erythmatosis; ULN=upper limit of normal.

16.5 Appendix 5: Fragebogen zur Lebensqualität EORTC QLQ -C30 (Version 3.0)

UPN: ……. ☐ vor ASCT ☐ 3 Monate nach ASCT ☐ 12 Monate nach ASCT

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.

		überhaupt 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:

		überhaupt 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

Bitte wenden

Während der letzten Woche:

		überhaupt nicht	wenig	mäßig	sehr
15.	Haben Sie erbrochen?	1	2	3	4
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 Zeitunglesen 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

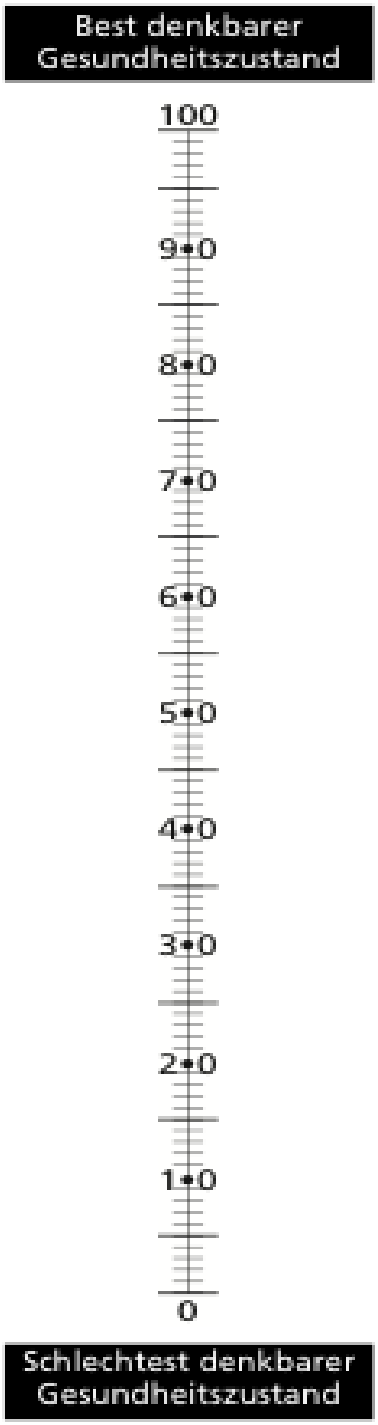
30. Wie würden Sie insgesamt Ihre Lebensqualität während der letzten Woche einschätzen?

1	2	3	4	5	6	7
sehr schlecht						ausgezeichnet

Um Sie bei der Einschätzung, wie gut oder wie schlecht Ihr Gesundheitszustand ist, zu unterstützen, haben wir eine Skala gezeichnet, ähnlich einem Thermometer. Der best denkbare Gesundheitszustand ist mit einer „100“ gekennzeichnet, der schlechteste mit „0“.

Wir möchten Sie nun bitten, auf dieser Skala zu kennzeichnen, wie gut oder schlecht Ihrer Ansicht nach Ihr persönlicher Gesundheitszustand ist, indem Sie einen horizontalen Strich auf der Skala setzen.

Ihr aktueller Zustand



17. REFERENCES

[1] Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy sensitive non Hodgkin's lymphoma. N Engl J Med 1995;333:1540-1545.

[2] Gisselbrecht C, Glass B, Mounier N, et a. lSalvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 2010 28:4184–4190.

[3] Gribben JG, Linch DC, Singer CR, et al. Successful treatment of refractory Hodgkin's disease by high-dose combination chemotherapy and autologous bone marrow transplantation. Blood 1989;73:340-344.

[4] Sureda A. et al. Autologous and allogeneic stem cell transplantation in Hodgkin's lymphoma. Hematol Oncol Clin North Am. 2007;21:943–960.

[5] Durant JR, Norgard MJ, Murad TM, et al. Pulmonary toxicity associated with bischloroethylnitrosourea (BCNU) Ann Intern Med. 1979;90:191–194.

[6] Weaver CH, Appelbaum FR, Petersen FB. High-dose cyclophosphamide, carmustine, and etoposide followed by autologous bone marrow transplantation in patients with lymphoid malignancies who have received dose-limiting radiation therapy. *J Clin Oncol* 1993;11:1329–1335.

[7] Kalaycioglu M, Kavuru M, Tuason L, Bolwell B. Empiric prednisone therapy for pulmonary toxic reaction after high-dose chemotherapy containing carmustine (BCNU) Chest. 1995;107:482–487.

[8] van Besien K, Tabocoff J, Rodriguez M, et al. High-dose chemotherapy with BEAC regimen and autologous bone marrow transplantation for intermediate grade and immunoblastic lymphoma: durable complete remissions, but a high rate of regimen related toxicity. Bone Marrow Transplant 1995;15:549-555.

[9] Bhatia S, Robinson LL,Francisco L, et al. Late mortality in survivors of autologous hematopoietic-cell transplantation: report from the Bone Marrow Transplant Survivor Study. Blood 2005;105:4215-4222.

[10] Reece DE, Nevill TJ, Sayegh A, et al. Regimen-related toxicity and non-relapse mortality with high-dose cyclophosphamide, carmustine (BCNU) and etoposide (VP16-213) (CBV) and CBV plus cisplatin (CBVP) followed by autologous stem cell transplantation in patients with Hodgkin's disease. Bone Marrow Transplant 1999;23:1131-1138.

[11] Lane AA, Armand P, Feng Y. Risk factors for development of pneumonitis after high-dose chemotherapy with cyclophosphamide, BCNU and etoposide followed by autologous stem cell transplant. *Leuk Lymphoma* 2012;53:1130–1136.

[12] Weaver CH, Appelbaum FR, Petersen FB. High-dose cyclophosphamide, carmustine, and etoposide followed by autologous bone marrow transplantation in patients with lymphoid malignancies who have received dose-limiting radiation therapy. *J Clin Oncol* 1993;11:1329–1335.

[13] Sven Armin Sommerfeld et al:. Safety and Efficacy Of Lomustine (CCNU) Substituting Carmustine (BCNU) In Conditioning For Autologous Haematopoietic Stem Cell Transplantation In Lymphoma. A Retrospective Analysis Of Two Patient Cohorts Over a Ten Year Period.

[14] Rummel MJ, Chow KU, Hoelzer D, et al. In vitro studies with bendamustine: Enhanced activity in combination with rituximab. Semin Oncol 2002;29:12–14.

[15] Leoni LM, Bailey B, Reifert J, et al. Bendamustine (Treanda) displays a distinct pattern of cytotoxicity and unique mechanistic features compared with other alkylating agents. Clin Cancer Res 2008 ;14:309–317.

[16] Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol 2009;27:4378-4384.

[17] Ogura M,Ando K, Taniwaki M,et al. Feasibility and pharmacokinetic study of bendamustine hydrochloride in combination with rituximab in relapsed or refractory aggressive B cell non-Hodgkin's lymphoma. Cancer Sci 2011;102:1687–1692.

[18] Al-Batran SE, Kim SZ Rummel MJ, et al. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma. J Clin Oncol 2005;23:3383–3389.

[19] Rummel MJ, Niederle N, Maschmeyer G, et al. Study group indolent Lymphomas (StiL). Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 2013;381:1203-1210.

[20] Rummel MJ,Al-Batran SE, Kim SZ, et al. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma. J Clin Oncol 2005;23:3383–3389.

[21] Flinn I, Jagt R, Burke J et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first line treatmetof indolent NHL or MCL: the BRIGHT study. Blood 2014;123:2944-2952.

[22]Visani G, Malerba L, Isidori A et al. BeEAM before ASCT is safe and effective for resistant /relased lymphoma patints. Blood 2001; 118:12.

[23] Nösslinger T, Keil f et a: Respons rate and toxicity in Lymphoma patients transplanted with the Visani Benda EAM Protocol DGHO : 2013 Abstract.

[24] Castegnaro S, Visco C, Chieregato K, et al. Cytosine arabinoside potentiates the apoptotic effect of bendamustine on several B- and T-cell leukemia/lymphoma cells and cell lines. Leuk Lymphoma 2012;53:2262–2268.

[25] Visco C, Castegnaro S, Chieregato K, et al. The cytotoxic effects of bendamustine in combination with cytarabine in mantle cell lymphoma. Blood Cells Mol Dis 2012;48:68–75.

[26] Loke J, Ward P, Mahendra S et al. Outcome of EAM conditioned ASCT for lymphoma. A matched pair retrospective single-centre study analysis. Bone Marrow Transplant2013;1486-1487.

[27] Puig N, de la Rubia J, Remigia MJ, et al. Morbidity and transplant-related mortality of CBV and BEAM preparative regimens for patients with lymphoid malignancies undergoing autologous stem-cell transplantation. Leuk Lymphoma 2006;47:1488–1494.

[28] Alessandrino EP, Bernasconi P, Colombo A, et al. Pulmonary toxicity following carmustine-based preparative regimens and autologous peripheral blood progenitor cell transplantation in hematological malignancies. Bone Marrow Transplant. 2000;25:309–313.

[29] Gianni L, Herman EH, Lipshultz SE, et al. Anthracycline cardiotoxicity: from bench to bedside. J Clin Oncol. 2008;26:3777–3784.

[30] Bhalla KS,Wilczynski SW, Abushamaa AM, Petros WP, McDonald CS, Loftis JS, Chao NJ, Vredenburgh JJ, Folz RJ. Pulmonary Toxicity of Induction Chemotherapy Prior to Standard or High-dose Chemotherapy with Autologous Hematopoietic Support. Am J Respir Crit Care Med 2000;161:17–25.

[31] Visani G, Stefani PM, Capria S, et al. Bendamustine, etoposide, cytarabine, and melphalan (BeEAM) followed by autologous stem cell transplantation produce a three-year progression-free survival of 75% in heavily pretreated Hodgkin and Non-Hodgkin lymphoma. ASH Annual Meeting Abstracts 2013:2134.

[32] Clark J, Schwartz et al. Risk factos for airflow obstruction in recipients of bone marrow transplants. Ann Intern Med 1987;107:648-656.

[33] Sorror, M. L. (2013). How I assess comorbidities before hematopoietic cell transplantation. Blood, 121(15), 2854–2863. http://dx.doi.org/10.1182/blood-2012-09-455063

[34] Shibasaki Y, et al. The Dinakara equation for adjusting DLCO for hemoglobin in the HCT-CI is superior to the Cotes equation for predicting high-risk patients in allogeneic hematopoietic stem cell transplantation. Am J Hematol. 2016 May;91(5):E296. doi: 10.1002/ajh.24318. Epub 2016 Apr 6.

[35] Declaration of Helsinki (as amended in Tokyo, Venice, Hong Kong, Somerset West, Edinburgh, Seoul and Fortaleza, and clarified in Washington and Tokyo). 2013,