German Hodgkin Study Group
Deutsche Hodgkin Studiengruppe

GHSG
www.ghsg.org

Clinical trials for adults

HD21 for advanced stages

Treatment optimization trial in the first-line treatment of advanced stage Hodgkin lymphoma; comparison of 4-6 cycles of escalated BEACOPP with 4-6 cycles of BrECADD

Sponsor

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Sponsor code: Uni-Koeln-1762
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CONTENTS

ABBREVIATIONS

ABVD	Doxorubicin, Bleomycin, Vinblastine, Dacarbazine
AE	Adverse event
ALAT	Alanine Aminotransferase
AMG	Arzneimittelgesetz (German medicines law)
AMH	Anti-Müllerian hormone
AML	Acute myeloid leukemia
Anti-HBs	Anti-Hepatitis-B-Surface
sALCL	systemic Anaplastic Large Cell Lymphoma
AP	Alkaline phosphatase
ASAT	Aspartate Aminotransferase
AVD	Doxorubicin, Vinblastine, Dacarbazine
BAL	Bronchoalveolar lavage
BEACOPP	Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone
BGBl	Bundesgesetzblatt (federal law gazette)
BM	Bone marrow
BOB	Bundesoberbehörde (supreme federal authority)
BrECADD	Brentuximab vedotin, Etoposide, Cyclophosphamide, Doxorubicin, Dacarbazine, Dexamethasone
CD30	Cluster of differentiation
ceCT	Contrast-enhanced computed tomography
CHD	Coronary heart disease
CI	Confidence interval
CR	Complete remission
eCRF	Electronic case report form
COPP	Cyclophosphamide, oncovin, procarbazine, prednisone
CRP	C-reactive protein
CRr	Complete remission with residual changes
CS	Clinical stage
CT	Computed tomography
CTCAE	Common Terminology Criteria of Adverse Events
CTx	Chemotherapy
DHSG	German Hodgkin Study Group
DLCO	Carbon monoxide diffusion capacity
DMC	(independent) Data Monitoring Committee
EBV	Epstein-Barr virus

ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EDTA	Ethylene-diamine-tetra-acetic acid
E-lesion	Extranodal lesion
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of treatment
EPO	Erythropoietin
ESR	Erythrocyte sedimentation rate
Eudra-CT	European Clinical Trials Database
FA	Final analysis
FDG	Fluorodeoxyglucose
FDG PET/CT	Imaging modality for FDG accumulation combining PET and CT for attenuation correction and anatomical correlation of PET findings
FFTF	Freedom from treatment failure
FN	Febrile neutropenia
FS	Fractional shortening
FSH	Follicle-stimulating hormone
γ-GT	γ-glutamyl transferase
GCP	Good Clinical Practice
GCP-V	GCP-Verordnung (German GCP regulations)
G-CSF	Granulocyte colony-stimulating factor
GHSG	German Hodgkin Study Group
GOT	Glutamate oxalacetate transaminase
GPT	Glutamate pyruvate transaminase
Hb	Hemoglobin
HCV	Hepatitis C Virus
HbA1C	Glycated hemoglobin
β-hCG	Beta human chorionic gonadotropin
HIV	Human Immunodeficiency Virus
HL	Hodgkin lymphoma
HRQoL	Health related quality of Life
HR-CT	High resolution computed tomography
ICDO	International Classification on Diseases for Oncology
ICH	International Conference on Harmonization
ICRU	International Commission on Radiation Units and Measurements
IF	Involved Field

IMRT	Intensity Modulated Radiiotherapy
IPS	International Prognostic Score
ITT	Intention to treat
IUD	Intrauterine device
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
LKP	Trial Chairman
LN	Lymph node(s)
LS	Life situation
LT	Late toxicity
LV	Left ventricle
LVEF	Left ventricle ejection fraction
LYSA	Lymphoma Study Association
MDRD	Modification of Diet in Renal Disease
MDS	Myelodysplastic syndrome
MFI	Multidimensional Fatigue Inventory
MMAE	Monomethyl auristatin E
MRT	Magnetic resonance tomography
MT	Mediastinal tumor
NC	No change
NCT	U.S. National Institutes of Health Clinical Trials Database
NHL	Non-Hodgkin lymphoma
NLPHL	Nodular lymphocyte-predominant Hodgkin lymphoma
NMR	Nuclear magnetic resonance
NYHA	New York Heart Association
OS	Overall survival
PCO_2	Carbon dioxide partial pressure
PCR	Polymerase chain reaction
PD	Progressive disease (=PRO)
PEI	Paul-Ehrlich-Institut
PET	Positron emission tomography
PFS	Progression free survival
PML	Progressive Multifocal Leucencephalopathy
PNP	Peripheral neuropathy
PO_2	Oxygen partial pressure
PP	Per protocol
PR	Partial remission

PRO	Progression
PS	Pathological stage
QoL	Quality of life
QTc	Corrected QT interval
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
SUV	Standardized uptake value
TARC	Thymus and activation-regulated chemokine
TCRBCL	T-cell rich B-cell lymphoma
TEE	Transesophageal echocardiography
TMF	Trial master file
TNM	Tumor, nodes, metastases
TRMB	Treatment-related morbidity
TSH	Thyroid-stimulating hormone
VOI	Volumes of interest
WHO	World Health Organization

0 GENERAL INFORMATION

WRITING COMMITEE

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A. Plütschow (Köln)
S. Kreissl (Köln)

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GHSG Honorary Chairman	V. Diehl (Berlin)
GHSG Chairman	Prof. A. Engert (Köln)
Head of the Trial Coordination Center	M. Fuchs (Köln)
Sponsor	University of Cologne

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Switzerland, SAKK	Prof. A. Lohri Dr. A. Moccia
Norway	Dr. A. Fosså

Other participating countries to be done…

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	Priv. Doz. Dr. S. Staar (Bremen)
Advisory	P. Born (patient representative)
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	Prof. H.H. Flechtner (Magdeburg)
	Dr. D. Hasenclever (Leipzig)
	Priv. Doz. Dr. C. Mauz-Körholz (GPOH HD)
	Dr. S. Mathas (Berlin)
	Prof. R. Naumann (Siegen)
	N.N.(DSHNHL, Homburg/Saar)
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	Prof. M. de Wit (ADHOK, Berlin)

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Internal medicine	Prof. A. Hagenbeek (Amsterdam, NL)
	Prof. M. Hutchings (Copenhagen, DK)
Cochrane	Dr. G. Schwarzer (Freiburg)

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	Prof. M. L. Hansmann (Frankfurt)
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	Prof. P. Möller (Ulm)
	Prof. A. Rosenwald (Würzburg)
	Prof. H. Stein (Berlin)

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	M. Fuchs (Köln)
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	R. Scheuvens (Köln)

TRIAL CENTERS

The participating trial centers are listed in the trial master file (TMF), which is kept at the GHSG Trial Coordination Center in Köln and on the GHSG's website, www.ghsg.org.

0.1 DECLARATION

Declaration on the 1st edition

In January 1997, the International Conference on Harmonization issued the “Note for Guidance on Good Clinical Practice” (ICH-GCP). In terms of planning, execution and analyses, the trials of the GHSG conform to the GCP principles and the requirements stipulated in the 16th AMG version. Besides, the trial is based upon the Declaration of Helsinki.

The trial management undertakes to adhere to the Declaration of Helsinki and the GCP principles as well as to the 16th AMG version. The participating centers likewise undertake to adhere to the principles laid out by GCP and competent legislation and confirm this by signing the trial center agreement.

The trial management undertakes to publish the results of the trial following completion of data analyses.

Independent Data Monitoring Committee (DMC)

The DMC that was founded for HD21 advises the trial management on changes and, if required, early termination of the trial. The DMC consists of the following three members:

Statistics	Prof. W. Lehmacher (Köln), Committee Head
	Dr. G. Schwarzer (Freiburg)
Internal medicine	Prof. A. Hagenbeek (Amsterdam, NL)

Signatures

Köln, 29.04.2016



Prof. Dr. Peter Borchmann	Heinz Haverkamp	Prof. Dr. Andreas Engert
Trial Chairman (as representative of the sponsor)	Head Statistician	GHSG Chairman

Declaration for the 2nd edition

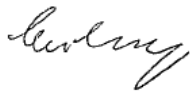
The 2nd edition of the HD21-protocol includes all changes introduced within the scope of the Amendment of 31st May 2016.

Parts of the texts that are no longer valid or that no longer apply after the respective amendment came into effect were deleted without replacement in order to ensure clarity regarding the currently valid trial plan, particularly for new trial centers.

Within the framework of the 1st Amendment specifications of E-Data-Capture procedures were made. Moreover editorial changes were implemented in the protocol.

Signatures

Köln, 31.05.2016


Prof. Dr. Peter Borchmann	Heinz Haverkamp	Prof. Dr. Andreas Engert
Trial Chairman (as representative of the sponsor)	Head Statistician	GHSG Chairman

Declaration for the 3rd edition

The 3rd edition of the HD21-protocol includes all changes introduced within the scope of the Amendment of 19th July 2016.

Parts of the texts that are no longer valid or that no longer apply after the respective amendment came into effect were deleted without replacement in order to ensure clarity regarding the currently valid trial plan, particularly for new trial centers.

Within the framework of the 2nd Amendment the exclusion criterion: Administration of corticosteroids before start of chemotherapy was deleted.

Signatures

Köln, 19.07.2016



Prof. Dr. Peter Borchmann	Heinz Haverkamp	Prof. Dr. Andreas Engert
Trial Chairman	Head Statistician	GHSG Chairman
(as representative of the sponsor)		

Declaration for the 4th edition

The 4th edition of the HD21-protocol includes all changes introduced within the scope of the Amendment of 13th March 2017.

Parts of the texts that are no longer valid or that no longer apply after the respective amendment came into effect were deleted without replacement in order to ensure clarity regarding the currently valid trial plan, particularly for new trial centers.

The 3rd Amendment based on the results of the HD18 trial, the GSHG defines 4 cycles of escalated BEACOPP as new standard of care for PET-2 negative patients, whereas PET-2 positive patients receive 6 cycles of escalated BEACOPP. Only those patients with PET positive tumor residues after completion of chemotherapy are subjected to local radiotherapy with 30 Gy.

After 2 cycles of chemotherapy, a restaging with ceCT (CT-2) and PET-2 is performed in all patients.

Signatures

Köln, 13.03.2017



Prof. Dr. Peter Borchmann	Annette Plütschow	Prof. Dr. Andreas Engert
Trial Chairman (as representative of the sponsor)	Head Statistician	GHSG Chairman

Declaration for the 5th edition

The 5th edition of the HD21-protocol includes all changes introduced within the scope of the Amendment of 24th November 2017.

Parts of the texts that are no longer valid or that no longer apply after the respective amendment came into effect were deleted without replacement in order to ensure clarity regarding the currently valid trial plan, particularly for new trial centers.

Within the framework of the 4th Amendment updates due to a new version of the SmPC and editorial/organizational changes were implemented.

Signatures

Köln, 24.11.2017

Prof. Dr. Peter Borchmann	Annette Plütschow	Prof. Dr. Andreas Engert
Trial Chairman (as representative of the sponsor)	Head Statistician	GHSG Chairman

Declaration for the 6th edition

The 6th edition of the HD21-protocol includes all changes introduced within the scope of the Amendment of 20th March 2018.

Parts of the texts that are no longer valid or that no longer apply after the respective amendment came into effect were deleted without replacement in order to ensure clarity regarding the currently valid trial plan, particularly for new trial centers.

Within the framework of the 5th Amendment updates due to a new version of the SmPC and editorial/organizational changes were implemented. Furthermore, the accompanying clinical scientific investigation was adapted.

Signatures

Köln, 23.05.2018

Prof. Dr. Peter Borchmann	Annette Plütschow	Prof. Dr. Andreas Engert
Trial Chairman (as representative of the sponsor)	Head Statistician	GHSG Chairman

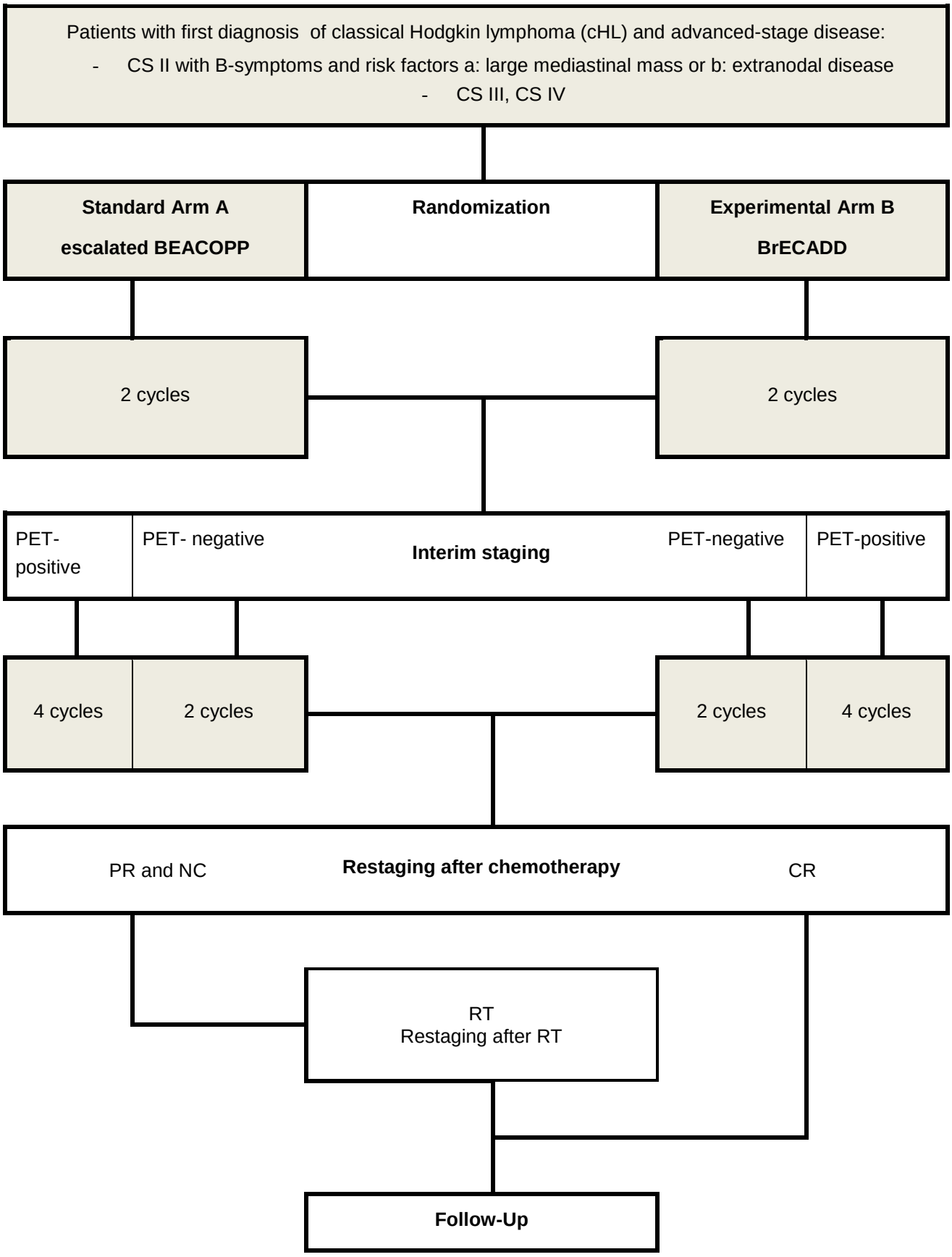
0.2 PROTOCOL SYNOPSIS

SPONSOR	University of Cologne Albertus-Magnus Platz 50923 Köln Represented by: Prof. P. Borchmann (Trial Chairman) Cologne University Hospital Department of Internal Medicine I Kerpener Str. 62 50937 Köln
TRIAL CHAIRMAN	Prof. P. Borchmann
TRIAL SECRETARY	Stefanie Kreissl
HEAD STATISTICIAN	Annette Plütschow
TITLE	Treatment optimization trial in the first-line treatment of advanced stage Hodgkin lymphoma; comparison of 4-6 cycles of escalated BEACOPP with 4-6 cycles of BrECADD.
SCHEDULE	Entry of first patient 01 July 2016 End of recruitment 30 June 2020 Analysis of primary endpoint 01 April 2024 Last patient, last visit 31 December 2025 Subsequent follow-up observation of patients outside the trial
PHASE	III
TRIAL CENTERS	Approx. 250 in Germany and other countries
PRIMARY ENDPOINTS	• Progression-free survival (PFS) • Treatment-related morbidity (TRMB)
SECONDARY ENDPOINTS	• Tumor response (CR rate) • Overall survival (OS) • Infertility rate at 1 year • Second malignancies • Quality of life (QoL) • Frequency of adverse events

	• Therapy adherence
NUMBER OF PATIENTS	1,500
MAIN ENTRY CRITERIA	• Histologically proven classical Hodgkin lymphoma • First diagnosis, no previous treatment, 18 to 60 years of age • Stage IIB with large mediastinal mass and/or extranodal lesions, stage III or IV
MAIN EXCLUSION CRITERIA	• Composite lymphoma or nodular lymphocyte-predominant Hodgkin lymphoma • Previous malignancy (exceptions: basalioma, carcinoma in situ of the cervix uteri, completely resected melanoma TNMpT1) • Prior chemotherapy or radiotherapy • Concurrent disease which precludes protocol treatment • Pregnancy, lactation • Non-Compliance
TREATMENT GROUPS	Patients are randomized to receive chemotherapy with escalated BEACOPP (standard group) or with BrECADD (experimental group). After the first two cycles, a restaging is performed by contrast-enhanced computed tomography (ceCT) and positron-emission tomography (FDG PET/CT) in all patients in order to guide response-adapted continuation of therapy consisting of 4 or only 2 additional cycles of randomized chemotherapy in case of a PET positive or negative staging result, respectively. A second restaging will be performed after completion of chemotherapy; Patients with PET-positive residual disease will receive local irradiation, while patients in complete remission do not receive radiotherapy.
TRIAL DESIGN	Open-label, prospective, multicenter trial with two parallel groups and central stratified randomization (minimization method)
STATISTICAL METHODS	Hierarchical design with two primary endpoints. At first, non-inferiority in terms of PFS will be tested using the 95% confidence interval of the hazard ratio adjusted for stratification factors. If successful, superiority in terms of less serious treatment-related adverse events during treatment will be tested using the Cochran-Mantel-Hanszel test. The intention-to-treat analysis set will be primary analysis set in both cases.

GCP CONFORMITY	This trial is conducted in conformity with the international Guidelines for Good Clinical Practice (ICH-GCP) including the storage of essential documents.
FINANCIAL SUPPORT	The trial is financially supported and brentuximab vedotin is supplied free of charge by Millennium Pharmaceuticals, Inc.

0.3 FLOW SHEET



0.4 ASSESSMENT PLAN (FOLLOW UP SEE SECTION 0)

Examinations	Screening day -28 to day 0	CTx cycle 1 + 2	Interim restaging (d17-21 of the 2nd cycle)[0]	CTx 3rd to 6th cycle	Restaging after chemo-therapy [2]	Restaging after radiotherapy (if indicated) [4]
Inclusion/exclusion criteria	X					
Informed consent	X					
General examinations						
Histology including histology review	X					
Case history	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X
Clinical Examination	X	X	X	X	X	X
Bone marrow biopsy	X[5]				X[3]	X[3]
Laboratory examinations						
Blood count and differential blood count	X	X	X	X	X	X
Clinical chemistry (details see Chapter 5.1.3.2)	X	X[1]	X	X[1]	X	X
Fasting blood sugar	X					
Absolute albumin	X					
LDH	X					
HIV, hepatitis B + C	X					
Thyroid gland: basal TSH	X		X		X	X
In females: ß-hCG	X					
Imaging						
Chest X-ray	X[7]					
CTs of neck, chest and abdomen (with contrast medium)	X		X[3]		X[3]	X[3]

FDG PET/CT	X[6]		X[6]		X[6]	X[6]
NMR (MRT) (if initial staging by means of MRT)	(X)		(X)		(X)	(X)
Examinations for assessment of toxicity						
ECG	X		strongly recommended		X	
Echocardiography	X		strongly recommended		X	
Pulmonary function (Hb, PO_2, PCO_2, DLCO, vital capacity)	X		strongly recommended		X	
Gonadal function	X[8]				X[8]	
Serum sample EDTA	X		X		X	
Quality of Life (QoL)[9]	X		X		X	X

[0] Please complete both, staging and restaging documentation in due course and forward all staging images to the reference panel of the Department for Nuclear Medicine of the University Hospital of Cologne for independent central review.

[1] Clinical chemistry should be done after recovery from the previous cycle and before day 1 of the planned cycle

[2] within 3 weeks after day 21 of the last cycle. Please send all imaging from staging, interim staging and staging after CTx to the reference panel of the Department for Nuclear Medicine of the University Hospital of Cologne for independent central review.

[3] To be performed in all initially involved sites.

[4] In case of no change, progressive disease or any change in therapy deviating from the protocol, the CT-scans have to be transmitted to the reference panel of the Department for Nuclear Medicine of the University Hospital of Cologne without delay. All these events have to be subjected to independent central review.

[5] Not required if bone marrow infiltration was excluded by FDG PET/CT

[6] The procedure is strongly recommended for all patients at baseline and obligatory at interim staging after 2 cycles of chemotherapy and for patients presenting with signs of active tumor after the end of chemotherapy. It is not recommended to be performed after radiotherapy as long as there are no signs of disease progression.

[7] sagittal plane to be performed only if reconstructed CT image is not available and/or does no allow a precise determination of large mediastinal mass.

[8] Assessment of gonadal function is strongly recommended in all patients, but not obligatory.

[9] QoL: If the patient agreed to participate in the quality of life survey, QoL is to be documented on specially designed forms using rating scales. For details, please refer to sections 5.8 and 10.4.

1 STUDY DESIGN FOR ADVANCED STAGES

1.1 INTRODUCTION AND BACKGROUND

With the establishment of polychemotherapy and the continuous advancements in radiotherapy, Hodgkin lymphoma has meanwhile become a malignant oncological disease in adults with one of the best prognoses of all. The outcome improvements in Hodgkin lymphoma patients have been achieved by strict quality standards across all medical disciplines involved in diagnostics and treatment including pathology, radiology, nuclear medicine, radiotherapy and oncology. In the first-line treatment of advanced stage Hodgkin lymphoma there is still a strong need for further optimization regarding treatment-related acute and late toxicities. Therefore, the German Hodgkin Study Group (GHSG) strives to develop a new, modified treatment regimen in order to minimize side-effects while maintaining the response to treatment at the same high level.

1.2 CHOICE OF CHEMOTHERAPY

1.2.1 Standard group (escalated BEACOPP)

The final analysis of the HD9 trial in August 2001 showed for the first time that the escalated BEACOPP chemotherapy regimen provides superior tumor control (HD9 arm C) both in comparison with baseline BEACOPP (HD9 arm B) and in comparison with COPP/ABVD (HD9 arm A). With escalated BEACOPP the early progression rate could be reduced to 2% (baseline BEACOPP 8%, COPP/ABVD 10%; C vs. A and C vs. B with $p<0.001$ respectively). The results for the 5-year FFTF rate were also impressive, amounting to 87% under treatment with escalated BEACOPP compared to 76% under baseline BEACOPP and 69% under COPP/ABVD (C vs. A and C vs. B with $p<0.001$ respectively), and so were the results for the Hodgkin-specific FFTF rate (escalated BEACOPP 91%, baseline BEACOPP 78%, COPP/ABVD 71%, C vs. A and C vs. B with $p<0.001$ respectively). With a 5-year overall survival rate of 91%, escalated BEACOPP was superior to the former standard regimen, COPP/ABVD, which had a 5-year OS of 83% ($p=0.002$), whereas also baseline BEACOPP provided considerably better results (88%) than COPP/ABVD ($p=0.051$).

In the 10-year analysis, which was published in 2009, escalated BEACOPP proved its superiority even more clearly.

Treatment with escalated BEACOPP is associated with greater hematotoxicity, which is clinically manageable though and which is why an increase in the rate of acute toxic deaths during first-line therapy was not observed (escalated BEACOPP 1.7%, baseline BEACOPP 1.5%, COPP/ABVD 1.9%).

With respect to the rate of second malignancies, the follow-up period was too short to draw any conclusions regarding solid tumors. In contrast, regarding the development of second non-Hodgkin lymphomas (NHL), no significant difference was observed (escalated BEACOPP 5/466, baseline BEACOPP 7/469, COPP/ABVD 7/260; p=0.29) [1].

The final analysis of the HD12 trial also showed a comparably low rate of second NHLs (16/1574). The rate of second leukemias was 1.4% (22/1574) and was thus considerably lower than the 5-year rate that had been estimated on the basis of the HD9 trial at 2.5% (95%-CI: 0.8% – 4.2%). With this result, the number of second leukemias under escalated BEACOPP was only slightly higher than under baseline BEACOPP (0.7%, 95%-CI: [0% - 1.7%]) and COPP/ABVD (0.5%, 95%-CI: [0% - 1.5%]). In this connection it should be emphasized that (1) the superior tumor control and survival rates with escalated BEACOPP were maintained despite the increased second leukemia rate, and (2) an increased incidence of second leukemias is also to be expected in patients who were not treated with escalated BEACOPP due to the greater need for high-dose salvage chemotherapy [2].

The subsequent HD15 trial compared the former GHSG standard of 8 cycles of escalated BEACOPP (arm A) with 6 cycles of escalated BEACOPP (arm B) and 8 cycles of BEACOPP-14 (arm C), a time-dense variant of baseline BEACOPP. Its aim was to reduce chemotherapy and the associated side-effects while maintaining treatment results. The HD15 trial was the first to employ positron emission tomography (PET) with ^{18}F- fluoro-deoxyglucose (FDG) for treatment stratification. Patients with residual tumor masses ≥ 2.5 cm after the end of chemotherapy received a PET examination. Patients who showed an increased FDG accumulation in the tissue (PET positive) were then subjected to radiotherapy, while patients without metabolic activity (PET negative) did not receive such therapy.

Two important conclusions could be drawn from the results of the HD15 trial: (1) 6 cycles of escalated BEACOPP are superior to an 8-cycle therapy, and (2) the decision whether a patient should receive radiotherapy or not can be taken based on the PET examination because a high negative prognostic value (94.6%) was established for this method [3, 4].

After the HD15 trial, 6 cycles of escalated BEACOPP became the new GHSG standard for advanced stage Hodgkin lymphoma patients aged ≤ 60 years. Only those patients with PET positive residual tumor masses are subjected to radiotherapy.

The following HD18 trial was guided by FDG PET/CT after 2 cycles of chemotherapy (PET-2) and aimed at a further reduction of chemotherapy for PET-2 negative patients as well as an improved outcome for PET-2 positive patients by addition of the anti-CD20 antibody rituximab to the escalated BEACOPP regimen.

HD18 was an open-label, international, multicenter, prospective, randomized, phase III study for newly diagnosed, advanced stage HL patients aged 18–60 years (ClinicalTrials.gov ID: NCT00515554). PET-2 was performed after two cycles of escalated BEACOPP and centrally assessed by an expert panel. PET-2 positive patients were then randomly assigned to receive additional six cycles of either escalated BEACOPP, or escalated BEACOPP plus rituximab. PET-2 negative patients received additional 6 or 2 cycles of escalated BEACOPP. After the results of the HD15 trial were published in 2012, 6 cycles of escalated BEACOPP were implemented as new standard of care in the HD18 trial.

As reported by Borchmann et al, PFS for PET-2 positive patients was much better than expected exceeding 90% at three years with the use of escalated BEACOPP in both treatment groups. Estimated 3-year PFS was 91.4% for escalated BEACOPP (95% CI: 87.0% to 95.7%), and 93% for escalated BEACOPP plus rituximab (95% CI: 89.4% to 96.6%). There was no benefit of rituximab in combination with escalated BEACOPP in terms of PFS. Based on a futility analysis, the independent data monitoring committee recommended publication of this second planned interim analysis as final result. Thus, six cycles of escalated BEACOPP remains the standard of care for PET-2 positive patients with advanced stage HL [5].

In PET-2 negative patients, 4 cycles of escalated BEACOPP turned out to be non-inferior to 6 or 8 cycles of escalated BEACOPP in terms of PFS (5-year PFS for 8/6x escalated BEACOPP: 90.6% [95% CI: 87.5% to 93.7%]; 5-year PFS for 4 cycles escalated BEACOPP: 92.2% [95% CI: 89.3% to 95.1%]; preliminary data, October 2016). In terms of OS, 4 cycles of escalated BEACOPP were even superior with 5-year estimates of 98.3% (95% CI: 96.9% to 99.7%) for 4x escalated BEACOPP and 95.0% (95% CI: 92.8% to 97.2%) for 8/6x escalated BEACOPP, respectively. Treatment-related morbidity was significantly reduced with 40.8% (95% CI: 36.4% to 45.3%)for 4 cycles of escalated BEACOPP versus 61.4% (95% CI: 54.5% to 68.1%) for 6 cycles and 64.9% (95% CI: 59.1% to 70.4%) for 8 cycles of escalated BEACOPP, respectively. The benefit in terms of toxicity was observed both for organ toxicity of CTC grade III/IV (7.7% versus 13.3% versus 21.5%) and hematological toxicity, defined as anemia, thrombopenia and infections grade 4 (37.3% versus 53.8% versus 58.0%).

Based on these results, the GHSG defines 4 cycles of escalated BEACOPP as new standard of care for PET-2 negative patients with newly diagnosed advanced stage HL. The

implementation of the new standard in the ongoing HD21 trial is central part of the 3rd amendment of the study protocol.

1.2.2 Experimental group (BrECADD)

With the use of escalated BEACOPP, an intensified first line chemotherapy regimen, disease control in advanced stage HL is excellent and can hardly be improved. However, this regimen exposes patients to considerable acute and long term toxicities. Defining the right balance between efficacy and toxicity remains the most important challenge in HL. Thus, minimizing acute and late toxicities without compromising the tumor specific outcome of patients is the major goal of current clinical research.

To reduce the toxicity of the first line treatment, the implementation of targeted drugs into the BEACOPP backbone is a promising strategy. Targeted drugs might replace unspecific cytotoxic drugs, which cause systemic toxicity. For this approach, two modified BEACOPP variants with different degrees of modification have been developed, both combined with brentuximab vedotin, and compared in the “Targeted BEACOPP trial” regarding their efficacy and tolerability.

Brentuximab Vedotin has been chosen for this major modification of our standard regimens, since it is highly active in relapsed patients as single agent and causes less severe toxicities than one would expect to see with conventional chemotherapy [6]. Due to its unique combination of efficacy and tolerability it is an extremely interesting candidate for the improvement of established chemotherapy regimens.

Brentuximab vedotin in classical Hodgkin lymphoma

Brentuximab vedotin is an antibody-drug conjugate consisting of the monoclonal anti-CD30 antibody and the synthetic cytostatic, monomethyl auristatin E (MMAE). After binding of the antibody to the target antigen CD30, which is constantly and almost exclusively expressed by Hodgkin and Reed-Sternberg cells, the conjugate is internalized into the cell and the cytostatic is released enzymatically [7]. By interrupting the mitotic spindle apparatus, the cytostatic arrests the cell cycle, thus leading to apoptosis of the CD30-expressing tumor cells [8].

Pre-clinical trials have already shown a promising activity of brentuximab vedotin, both as monotherapy and in combination with conventional chemotherapy [9]. Based on these findings, a phase I dose escalation trial that included 45 patients with multiply relapsed classical Hodgkin lymphoma or anaplastic large-cell lymphoma was conducted. The results demonstrated a regressive course in 36 out of 42 analyzed patients and a median response duration of at least 9.7 months. The maximum tolerated dose was 1.8 mg/kg administered in 3-week intervals [7].

Following this trial, a phase II trial was initiated with 102 classical Hodgkin lymphoma patients who had developed another relapse after high-dose chemotherapy and autologous stem cell transplantation. The patients were administered 1.8 mg/kg of brentuximab vedotin every 3 weeks in a total of 16 cycles. The response to treatment was comparable to that in the phase I trial and the side-effects were usually mild and clinically manageable [6].

Brentuximab vedotin is currently being tested in combination with AVD chemotherapy in a phase III trial as first-line treatment in classical Hodgkin lymphoma patients (NCT01712490). Apart from that, brentuximab vedotin's role as maintenance therapy after high-dose chemotherapy and autologous stem cell transplantation in high-risk patients with relapsed classical Hodgkin lymphoma was examined within the scope of a randomized phase III trial. The authors showed that early consolidation with brentuximab vedotin after autologous stem-cell transplantation improved progression-free survival in patients with Hodgkin lymphoma with risk factors for relapse or progression after transplantation [10].

In November 2012, brentuximab vedotin was approved for use in Europe for the following indications:

(1) Relapsed and/or treatment-refractory CD30+ Hodgkin lymphoma after autologous stem cell transplantation or after at least two prior therapies in cases where autologous stem cell transplantation was not possible.
(2) Relapsed and/or refractory systemic anaplastic large cell lymphoma (sALCL) after at least one prior chemotherapy.

Modification of the BEACOPP regimen in combination with brentuximab vedotin: BrECADD

Vincristine

Due to the implementation of brentuximab vedotin into the BEACOPP regimen with a maximum dose of 1.8 mg/kg as defined in the phase I trial, it is possible to abandon the agent vincristine from the original BEACOPP regimen. The binding of the anti-CD30 antibody to the vinca alkaloid MMAE causes a selective transport of the cytostatic to the tumor cells and an effective internalization into these cells, thus possibly producing a higher antineoplastic effect while the incidence of vincristine-associated grade 3 and 4 polyneuropathies decreases.

Bleomycin

In a trial conducted by the GSHG in 2004, etoposide was replaced by gemcitabine within the BEACOPP regimen. The number of pulmonary toxicities increased under this treatment,

which is why today the GSHG does not employ bleomycin whenever new agents are being tested within the scope of the BEACOPP regimen [11]. Besides, the role of bleomycin in Hodgkin lymphoma therapy is not yet fully understood and, though occurring only rarely, bleomycin-induced pneumonitis is a serious side-effect. A phase I trial examined the combination of brentuximab vedotin with ABVD versus AVD in the first-line treatment of patients with advanced HL. The combination of brentuximab vedotin with the ABVD regimen has so far resulted in a considerably higher incidence of non-infectious pneumonitides, both compared to the existing data for the conventional ABVD regimen and compared to the combination of brentuximab vedotin and AVD [12]. Based on these data, bleomycin is not used in the new BrECADD regimen.

Etoposide and doxorubicin

Among the late effects of Hodgkin lymphoma therapy, second myelodysplastic syndrome (MDS) and second acute myeloic leukemia (AML) are of particular importance due to their poor prognosis [13]. The risk for developing second MDS or AML correlates with the dose intensity of the administered polychemotherapy regimen. For this reason, the second MDS/AML rate under treatment with escalated BEACOPP is significantly higher than under other chemotherapy regimens [14]. The MDS/AML-inducing effect of chemotherapy is attributed to the alcylating agents (e.g. procarbazine and cyclophosphamide) as well as to the topoisomerase II inhibitors (e.g. etoposide) contained in them [15] [16].

The analysis of the HD15 trial showed that 6 cycles of escalated BEACOPP are equal to 8 cycles of escalated BEACOPP/BEACOPP-14 in advanced stage patients [3]. Based on this result and the assumption that etoposide is a main inductor of these two toxicities, in the BrECADD regimen the etoposide dose is reduced to 150 mg/m^2. At the same time, the anthracycline dose is increased moderately from 35 mg to 40 mg of doxorubicin, thus ensuring that the cumulative effective chemotherapy dose will be maintained.

Prednisone

14-day prednisone therapy is replaced by **4-day dexamethasone therapy**. Thereby it is aimed to reduce of risk for serious infectious during the aplasia phase, which usually commences between day 6 and day 10 of each chemotherapy cycle.

Procarbazine

Oral administration of procarbazine for 7 days is replaced by a 2-day intravenous therapy with dacarbazine on day 2 and on day 3 of each chemotherapy cycle. This treatment measure is aimed to lower the second MDS and AML rate. In addition, with the use of dacarbazine instead of procarbazine it is intended to achieve a reduction in gonadal toxicity [17].

Dose selection

To approximate potential efficacy of new regimens we used the model based effective dose approach [18] that has successfully predicted trial results in HL [19].. Briefly, the method estimates relative potency of drugs within polychemotherpy regimens using a meta-regression of randomized clinical trials. A summary score allows predicting potential usefulness of experimental regimens, in our case with desired efficacy comparable to escalated BEACOPP. Substances without pre-exisiting data were substituted in the model. Using a conservative approach we assumed that brentuximab vedotion at standard dose (1.8 mg/kg/cycle) would only be equally effective as vincristine with dose used in BEACOPP. Dacarbazine contribution was estimated using equivalent procarbazine doses based on results in pediatric HL [17]; exchange of the corticosteroid was handled similarly. Efficacy estimates and known toxicity profiles resulted in two variants of BEACOPP that were evaluated in a phase II trial.

Proof of concept data - results of the Targeted BEACOPP-study

Both modified BEACOPP regimens (BrECADD, i.e. brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone; and BrECAPP, i.e. brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, procarbazine, and prednisone) have recently been tested in the GHSG “Targeted BEACOPP study (NCT01569204). This randomized phase II study evaluated the efficacy as determined by the complete remission rate and the tolerability and feasibility of these new regimens in 104 patients Both escalated BEACOPP variants met the primary efficacy endpoint with a complete remission-rate of 86% for BrECAPP (95%-CI: 73%-94%) and 88% for BrECADD (95%-CI: 77%-96%). The 18-month PFS estimates were 95% (95%-CI: 85%-100%) after BrECAPP and 89% (95%-CI: 77%-100%) after BrECADD. The feasibility of both regimens, BrECAPP and BrECADD, was better than with escalated BEACOPP. Particularly the BrECADD regimen was associated with a favorable toxicity profile with severe organ toxicity rates of 17% for BrECAPP and 4% for BrECADD, respectively.[20]. .Therefore, BrECADD was chosen as experimental treatment for the HD21 study to be compared to the current standard of care - escalated BEACOPP.

1.3 SUMMARY

Escalated BEACOPP is the GHSG’s standard regimen for advanced stage HL patients aged ≤ 60 years due to its superior tumor control. Based on the results of the HD18 trial, the GSHG defines 4 cycles of escalated BEACOPP as new standard of care for PET-2 negative patients, whereas PET-2 positive patients receive 6 cycles of escalated BEACOPP. Only

those patients with PET positive tumor residues after completion of chemotherapy are subjected to local radiotherapy with 30 Gy.

It is currently not yet clear whether the modified BEACOPP regimen combined with brentuximab vedotin is as effective as the current standard treatment and, what's more, less toxic. This is to be determined within the scope of the HD21 trial.

All changes within the new treatment regimen are aimed to reduce the number of acute and late toxicities without impairing treatment success. Due to the implementation of brentuximab vedotin into the BEACOPP regimen with a maximum tolerated dose of 1.8 mg/kg as defined in the phase I trial, it is possible to dispense with the agent of vincristine. The etoposide dose is lowered to 150 mg/m^2 while the anthracycline dose is increased moderately from 35 mg to 40 mg of doxorubicin. 14-day prednisone therapy is replaced by 4-day dexamethasone therapy. Oral administration of procarbazine for 7 days is replaced by a 2-day intravenous therapy with dacarbazine on day 3 and on day 4 of each chemotherapy cycle. Besides, bleomycin is abandoned completely from the chemotherapy regimen because of its higher potential for causing pulmonary toxicity.

Patients are randomized into one of the two treatment groups directly after their inclusion into the trial. Patients in the standard group receive escalated BEACOPP, patients in the experimental group receive BrECADD. After 2 cycles of chemotherapy, a restaging with ceCT (CT-2) and PET-2 is performed in all patients. PET-2 negative patients in both treatment groups receive additional 2 cycles of escalated BEACOPP or BrECADD respectively. PET-2 positive patients continue with additional 4 cylces of chemotherapy.

After completion of chemotherapy, ceCT (CT-4 or CT-6, respectively) is performed as staging examination. FDG PET/CT (PET-4 or PET-6) is obligatory for patients presenting with signs of active tumor, and optional in other cases. PET-4 positive or PET-6 positive patients will receive local radiotherapy with 30 Gy.

2 AIM OF THE HD21 TRIAL

The aim of the HD21 trial is to prove that the new chemotherapy regimen, BrECADD, is non-inferior to BEACOPP as first-line treatment in advanced stage classical Hodgkin lymphoma patients aged ≤ 60. The combination of conventional chemotherapy with brentuximab vedotin is designed to reduce the doses of certain conventional cytostatics in order to reduce the rate of adverse effects while maintaining an equally good response to treatment.

2.1 ENDPOINTS

2.1.1 Primary endpoints

The **primary endpoints** of this trial are the following:

- Progression-free survival (PFS)
- The rate of serious treatment-related toxicities during primary treatment ("treatment related morbity", TRMB). Adverse effects include organ toxicities of CTCAE grade 3 and 4 under chemotherapy that lead to severe and irreversible impairments and severe hematological toxicities of grade 4. Based on the experience from previous studies (HD15, HD18), the following kinds of toxicities are classified as relevant:
    1. Acute non-hematological organ toxicity of CTCAE grade 3 or 4 of the following system organ classes (SOCs):
        - cardiac disorders,
        - gastrointestinal disorders (excluding vomiting, nausea and mucositis),
        - hepatobiliary disorders,
        - nervous system disorders,
        - renal and urinary disorders, and
        - respiratory, thoracic and mediastinal disorders.
    2. Acute hematological toxicity: grade 4 anemia, grade 4 thrombocytopenia, and grade 4 infections.

2.1.1.1 Justification for the co-primary endpoint „treatment related morbidity (TRMB)"

By implementing brentuximab vedotin into the BEACOPP backbone, a new chemotherapy regimen, BrECADD, was designed in order to reduce toxicity of first line treatment while maintaining equally high efficacy as with the current standard of care, escalated BEACOPP. However, treatment related toxicity includes many different types and grades of toxicities. It is this not established as outcome parameter. Therefore, we here introduce a parameter that comprises clinical relevant toxicities during primary chemotherapy. The selection above is based upon the following reasoning.

Ad 1. Acute non-hematological organ toxicity

Organ related toxicities of CTCAE grade 3 or 4 affect around 15% of patients treated with six courses of escalated BEACOPP based on the experience from the HD15 and HD18 trials. By definition, grade 3 or 4 toxicities are associated with severe and/or irreversible symptoms indicating medical intervention up to life threatening consequences/situations. In addition, they can result in treatment postponement and/or dose reduction and might have impact on health related quality of life (HRQoL). Based on experience from previous studies, the following SOC categories were classified as clinically relevant:

- cardiac disorders,
- gastrointestinal disorders (excluding vomiting, nausea and mucositis),
- hepatobiliary disorders,
- nervous system disorders,
- renal and urinary disorders, and
- respiratory, thoracic and mediastinal disorders.

Inflammations of the mucous membranes, alopecia, nausea and vomiting, and drug-induced fever are not considered within the scope of this primary endpoint since they are reversible and can be managed without difficulties.

Ad 2. Acute hematological toxicity

Essentially all patients experience grade 3/4 hematological toxicities after treatment with escalated BEACOPP. Hematological toxicities grade 1-3 are usually easily manageable by haemato-oncologists. We thus do not consider grade 1-3 hematological toxicity being relevant for the co-primary endpoint TRMB. In contrast, grade 4 anemia and thrombocytopenia represent potentially life-threatening events requiring urgent medical intervention and are included into this endpoint. Grade 4 neutropenia is observed in nearly all patients despite obligatory growth factor support. Accordingly, neutropenia is not suited as co-primary endpoint. However, severe neutropenia might result in severe and life threatening infections. With regard to the obvious clinical relevance of grade 4 infections, we included this event into the definition of TRMB.

Toxicities related to Brentuximab Vedotin

The safety profile of brentuximab vedotin is based on available data generated from clinical trials. The most frequently reported, clinically relevant side effects are peripheral sensory neuropathy, reversible hematological toxicity, and infections [6]. All of these are covered by the definition of the co-primary endpoint TRMB. Accordingly, additional toxicities caused by this drug in the BrECADD regimen will be registered. The informative value regarding long term toxicities may be limited within the scope of this trial.

Infertility/gonadal toxicity

Infertility/gonadal toxicity was not included into the co-primary endpoint, as incidence rates and clinical relevance differ significantly within the patient cohort depending on age, sex and individual life situation. Nonetheless, it is an important toxicity for individual patients and was therefore chosen as secondary endpoint. We have planned serum analyses during treatment and follow-up to determine gonadal damage.

Second neoplasia

Incidence rates of sAML/MDS reported for escalated BEACOPP are low ranging from 0-1.5% [3, 21-24]. The same applies for second solid tumors, which usually occur later than 10 years after the end of treatment. Events this late will not be captured within the follow-up of this trial. In a large network meta-analysis on advanced stage HL with more than 10,000 patients, the overall incidence of second neoplasia was too low to allow for testing [25]. Obviously, this outcome parameter is not suited as primary endpoint and was therefore chosen as secondary endpoint.

Grade 5 toxicities

Any grade 5 toxicities are covered by the first primary endpoint PFS and therefore not included into the TRMB endpoint. Nonetheless, fatal events are documented and will be evaluated additionally as secondary endpoint.

2.1.2 Secondary endpoints

The **secondary endpoints** of this trial include:

- CR rate after completion of chemotherapy
- Overall survival
- Infertility rate at 1 year (determined by hormone levels)
- Second malignancies
- Number of serious adverse events within 30 days after end of treatment
- Therapy adherence
- Quality of life before, during and after therapy

3 TRIAL PLAN

3.1 TRIAL DESIGN

In this prospective, multicenter, randomized and open-label trial, patients in the standard group are treated with either 4 or 6 cycles of escalated BEACOPP according to the results of the interim staging (PET-2 negative patients receive 4 cycles of escalated BEACOPP, PET-2 positive patients receive 6 cycles of escalated BEACOPP) . Patients in the experimental group receive either 4 or 6 cycles of the BrECADD chemotherapy regimen, again according to the results of the interim staging (PET-2 negative patients receive 4 cycles of BrECADD, PET-2 positive patients receive 6 cycles of BrECADD).

In both groups, patients with PET positive residual tumor masses at the end of chemotherapy according to PET-4 or PET-6 are subjected to local irradiation with 30 Gy.

Patients without signs of active tumor at restaging after chemotherapy do not receive any further treatment and directly enter the follow-up program.

Assessments from the interim staging and the restaging after chemotherapy (without regard to the number of administered treatment cycles) are rewieved in Cologne.

Standard group: PET-2 negative patients: 4 x escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) + 30 Gy to PET-4 positive residual masses

PET-2 positive patients: 6 x escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) + 30 Gy to PET-6 positive residual masses

Experimental group: PET-2 negative patients: 4 x BrECADD (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone) + 30 Gy to PET-4 positive residual masses

PET-2 positive patients: 6 x BrECADD (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone) + 30 Gy to PET-6 positive residual masses

3.2 RECRUITMENT

It is planned to enter 1500 patients into this trial during a recruitment period of approximately 4 years. About 250 centers in Germany and other countries will participate in the trial.

3.3 DURATION OF THE TRIAL

It is expected that it will take about 7.75 years from the beginning of recruitment to the final analysis of the study question. The last visit of the last recruited patient will take place approximately 5.5 years after the end of the recruitment period resulting in an expected total trial duration of 9.5 years.

3.4 EARLY TERMINATION OF THE TRIAL

3.4.1 Termination of protocol treatment

The patient may discontinue treatment within the trial at any time if they wish to. The treating physician may also decide to terminate treatment within the HD 21 trial due to unacceptable toxicity, progression of disease, serious concurrent disease or pregnancy.

Independently of the above, the statistics section of the GHSG evaluates the completeness of documentation and the administration of protocol treatment. Under certain circumstances they may rate the course of the trial in a certain patient as an early termination of protocol treatment.

In any case, either following a formal or an actual termination, the documentation of the respective patient should be continued.

After termination of protocol treatment, the patient's treatment should be continued according to the universal treatment standard or at the discretion of the treating physician.

3.4.2 Early termination of the trial

The whole trial can be terminated early by the trial chairman, if possible in consultation with the trial steering committee and the data monitoring committee (DMC), if the formal termination criterion concerning the primary endpoint is reached or if the patients' safety appears to be at risk.

3.4.3 Termination in certain trial centers

The clinical trial may be terminated in certain trial centers if the GCP requirements are not met or if the respective centers do not work in compliance with the GCP guidelines (e.g. if documentation forms are not completed after repeated requests to do so).

3.4.4 Termination for other reasons

The trial will be terminated completely if

- there is a considerable impairment in the risk-benefit-ratio for patients,
- the sponsor considers the termination of the trial to be necessary for safety reasons (e.g. at the recommendation of the DMC),
- it is no longer justifiable to use the trial medication,
- the trial proves to be not feasible.

The sponsor will discuss the decision to terminate the trial with the trial steering committee and the head statistician. A consent on the part of the trial steering committee and the head statistician is not essential.

4 ENROLLMENT

4.1 INCLUSION CRITERIA

1. Histologically proven **classical** Hodgkin lymphoma
2. Stage:
   - 2.1 CS (PS) IIB with one or both of the following risk factors:
     - a) Large mediastinal mass (≥ 1/3 of the maximum transverse thoracic diameter)
     - b) Extranodal disease (see definition in section 13.4)
   - 2.2 CS (PS) III; IV
3. Patient has had no previous treatment for HL
4. Age at entry: 18 – 60 years
5. Patient has given their written informed consent to participate in the trial
6. Patient agrees to their personal data and tissue material being used for the study, with due regard for data protection
7. Normal organ function (except for HL-related functional disorders)
   - Leukocyte concentration > 3000/mm3 and thrombocyte concentration > 100,000/ mm3 unless there is known marrow involvement of the disease (e.g. in case of BM infiltration or splenomegaly)
   - Total bilirubin must be < 1.5 x the upper limit of the normal (ULN) unless the elevation is known to be due to Gilbert syndrome.
   - GPT(ALT) or GOT(AST) must be < 3 x ULN(exception: elevated values due to Hodgkin-related liver involvement may be elevated up to 5 times ULN)
   - Creatinine clearance or calculated creatinine clearance > 60 mL/minute (24-hour urine or calculation based on MDRD formula/Cockroft-Goult formula)
   - Hemoglobin must be ≥ 8g/dL.
8. In women: negative pregnancy test within four weeks before trial entry (to be repeated if clinically indicated)
9. Estimated life expectancy > 3 months

4.2 EXCLUSION CRITERIA

1. Incomplete diagnosis of the disease stage

2. Prior or concurrent disease that prevents treatment according to protocol, in particular the following contraindications:

   - Chronic obstructive pulmonary disease with global respiratory insufficiency
   - Status post myocardial infarction, symptomatic coronary heart disease, permanent arrhythmias > grade 2, status post thromboembolic events (deep vein thrombosis, pulmonary embolism, symptomatic cerebrovascular event), left ventricular ejection fraction < 50% **within the last 6 months before start of chemotherapy**

     Exception: chronic stable atrial fibrillation under anticoagulation therapy is NOT an exclusion criterion

   - Cardiac insufficiency NYHA III or IV
   - QTc interval > 480 msec
   - Serious arterial hypertonia despite adequate medication
   - Any active systemic viral, bacterial, or fungal infection requiring systemic antibiotics at time of first study drug dose
   - HIV infection
   - Chronic active or persistent (PCR positive) hepatitis B and/or C
   - Known cerebral or meningeal disease (HL or any other etiology), including signs or symptoms of PML

3. Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) or composite lymphoma

4. Chemotherapy or radiotherapy in medical history

5. Malignant disease within the last 5 years

   (**Exceptions:** basalioma, carcinoma in situ e.g. of the cervix uteri, completely resected melanoma TNMpT1)

6. Pregnancy (to exclude pregnancy it is obligatory to perform a β-hCG serum test at the time of trial entry and prior to first dose of brentuximab vedotin in all female patients except for postmenopausal and surgically sterilized women); lactation

7. ECOG performance status > 2

8. Long-term administration (> 6 months) of corticosteroids (e.g. for chronic polyarthritis) or antineoplastic drugs (e.g. methotrexate)

9. Peripheral neuropathy > CTCAE grade 1

10. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to the protocol.

    Patient's lack of accountability and inability to understand the nature, meaning and consequences of the trial and to formulate their own wishes correspondingly

11. Non-compliance:

    Refusal of blood products during treatment, epilepsy, drug dependency, change of residence to abroad, prior cerebral injury or comparable circumstances that appear to render protocol treatment and/or long-term follow-up impossible

12. General intolerance to any of the agents included in the trial protocol, and known hypersensitivity to recombinant proteins, murine proteins, or to any excipient contained in the drug formulation of brentuximab vedotin

13. Unsafe contraception

Contraceptive methods are considered as safe if they have a Pearl index of ≤ 1%, including (according CTFG guidelines: http://www.hma.eu/ctfg.html):

- Transdermal hormonal contraception
- Contraceptive plaster
- Injectable long-term contraceptives
- Progesterone-releasing implant (Implanon®)
- Progesterone i.m.
- Tubal ligation
- Hormone-releasing intra-uterine device (IUD)
- Oral hormonal contraception, if combined (estrogen and progestogen containing)

Not reliable are methods such as:

- Progestogen-only Oral hormonal contraception
- Preservative plus spermicidal
- Single-barrier methods such as vaginal pessary, condom, female condom
- Rhythm methods
- Basal body temperature method
- Coitus interruptus
- Double barrier method

Please note:

Male patients must commit to effective contraception by means of barrier methods during the whole duration of the trial until 6 months after they last received trial medication or must completely abstain from sexual intercourse.

Female patients must commit to effective contraception by means of safe methods as described above during the whole duration of the trial until 6 months after they last received trial medication or must completely abstain from sexual intercourse.

14. Patients who have a relationship of dependence or employer-employee relationship to the sponsor or the investigator

15. Commitment to an institution on judicial or official order

16. Participation in another interventional trial that could interact with this trial

5 INDIVIDUAL TRIAL PROCEDURE

5.1 DIAGNOSIS AND STAGING

5.1.1 Confirmation of diagnosis by the pathologist

Upon suspicion of a lymphoma, the treating physician arranges for a biopsy to be made. The histological examination of the biopsy is usually performed by a local pathologist (primary pathologist). The histological diagnosis is to be established on the biopsy of a lymph node or, as the case may be, of another primarily involved organ. The biopsy should include an entire lymph node, if possible, or a sufficient portion of tissue. Fine needle biopsies are not appropriate. Such biopsies have proved to be not suitable for diagnosing HL because they are only of little representative value.

If the suspected diagnosis of Hodgkin lymphoma is confirmed, a complete clinical staging is to be conducted immediately. When the patient consents to participate in the trial and is qualified based on the inclusion and exclusion criteria as defined in the trial protocol, he or she is reported to the Trial Coordination Center.

To check the primary histological diagnosis, the primary pathologist sends the biopsy tissue (at least 12 paraffin slides and, if available, tissue in formalin) immediately and complete, together with the name of the trial, to **one of the eight pathology review centers listed in chapter 9.1** and reports the respective pathology review center to the GHSG Trial Coordination Center. The GHSG will then provide the pathology review center with the corresponding basic patient data.

After completion of the pathology review (see chapter 14.1), the diagnosis is communicated to the GHSG Trial Coordination Center on the histopathological review form, as well as via post to the primary pathologist. It should take no longer than three weeks for the pathology review diagnosis to be established. If this deadline has passed, a reminder is sent from the GHSG Trial Coordination Center to the respective pathology review center. If by then the pathology review center has not received any biopsy tissue, missing material will be requested from the primary pathologist by the Trial Coordination Center.

Should the diagnosis ‘Hodgkin lymphoma’ be altered following the pathology review, the patient will be removed from the trial. In this case, the review pathologist will immediately inform the Trial Coordination Center as well as the primary pathologist. The treating physician will be informed by the Trial Coordination Center.

5.1.2 Staging and allocation to a trial

The staging criteria are the same as in the previous trial generation

<table>
<tr><th colspan="2" rowspan="2"></th><th colspan="4">Stage</th></tr>
<tr><th>IA, IB, IIA</th><th>IIB</th><th>IIIA</th><th>IIIB, IV</th></tr>
<tr><td rowspan="5">Risk factors</td><td>None</td><td colspan="2">Early-stage favorable HL</td><td rowspan="5" colspan="2">HD21</td></tr>
<tr><td>≥ 3 LN areas</td><td rowspan="4" colspan="2">Early-stage unfavorable HL</td></tr>
<tr><td>elev. ESR</td></tr>
<tr><td>large MT</td></tr>
<tr><td>E-lesions</td></tr>
</table>

5.1.3 Baseline toxicity and staging examinations

5.1.3.1 Diagnosis of clinical stage

The examinations for clinical staging (see chapter 5.1.3.4) should be completed within 14 days. Adherence to this deadline should be ensured by carefully planning the appointment schedule from diagnosis onwards. Due to time constraints, it is advisable to perform the bone marrow biopsy immediately after confirmation of diagnosis.

5.1.3.2 Case history and laboratory diagnostics

The case history must be taken thoroughly, including all clinical symptoms, particularly any **B symptoms** that might be present. The patient's general status is documented based on the **ECOG performance status**. Besides, the patient must be questioned regarding potential pre-existing and concurrent conditions and infectious mononucleosis in their medical history as well as regarding other hematological and non-hematological disorders in their own medical history and in that of family members.

The following laboratory diagnostics are **obligatory**:

- ESR
- TSH
- Fasting blood sugar

- Blood count with differential distribution
- Clinical chemistry (gamma-GT, GOT (ASAT), GPT (ALAT), AP, bilirubin, creatinine, urea, uric acid, Na, K, Ca)
- Albumin (absolute value preferred to electrophoresis)
- Lactate dehydrogenase (LDH)
- HIV1/2 antibody screening test
- Hepatitis B (anti-Hbs, anti-Hbc), hepatitis C (anti-HCV)
- In females: pregnancy test (in the serum)

5.1.3.3 Physical examination

The examination of the body is to be conducted carefully, including peripheral lymph nodes, spleen, liver and the abdominal region. All involved sites, i.e. all sites that are involved from a clinical perspective, have to be documented, even if there is no histological confirmation.

5.1.3.4 Obligatory instrumental/imaging examinations for staging

For an exact diagnosis of the disease stage the following examinations are **obligatory**:

- **Computed tomography** with contrast (ceCT) medium of neck, thorax and abdomen. At the time of trial inclusion the CT images may not be older than 4 weeks.
- **Chest X-ray** sagittal plane only (to be performed only, if reconstructed CT image is not available and/or does no allow a precise determination of large mediastinal mass).
- **Bone marrow** biopsy (results not mandatory for enrollment) unless bone marrow involvement is excluded by PET/CT
- **Clinically suspect** extranodal involvements or organ involvements must be clarified with adequate methods (e.g. bone X ray if bone involvement is suspected or MRT). Histological confirmation is recommended.

5.1.3.5 Optional examinations for staging

The following additional instrumental examinations may be employed for staging diagnostics depending on the individual case:

- Ultrasound of neck and abdomen
- Histological confirmation of ambiguous results in the imaging examinations
- NMR (MRT) if a pericardium or myocardium infiltration or osseous involvement is suspected

5.1.3.6 FDG PET/CT

FDG PET/CT of the whole trunk of the **body is strongly recommended** if available in concordance with the Lugano classification [26]. Images of the lower extremities are only required if ceCT scan indicates a primary tumor there. Please refer to section 5.5 and the EANM Guidelines [57]. When FDG PET/CT is performed as optional examination in addition to or in combination with ceCT, the investigator should include the results in the restaging documentation and include the PET-scans in the material provided for central review.

5.1.4 Examinations to assess toxicity before start of treatment

In this trial the following pre-therapy examinations are required in order to determine the patient's general suitability for therapy and in order to record their initial status to enable assessing treatment-related toxicities that may occur later on:

Obligatory:

- ECG; echocardiography
- Pulmonary function (Hb, PO_2, PCO_2, DLCO, vital capacity)
- Thyroid function: basal TSH

Optional:

- Further cardiac diagnostics (e.g. long-term ECG, TEE) if ECG and/or echocardiography is abnormal
- Gonadal function: strongly recommended
- Females: documentation of menstruation history; FSH, LH, estradiol, anti-Müllerian hormone,
- Males: FSH, LH, testosterone, inhibin B
  Spermiogram if family planning still open

The examinations required to document late toxicities during follow-up are described in chapter 5.6.2.

Female patients should discuss preventive measures regarding fertility with a gynecologist.

Male patients have to be informed about the possibility of pre-treatment sperm cryoconservation.

5.2 PATIENT BRIEFING AND TERMINATION OF PROTOCOL TREATMENT

When all routine staging examinations have been completed and the patient is qualified for HD21, they will be briefed about the trial. The briefing should include the following main points:

title and aim of the trial, kind of treatment, side-effects, reason for randomization, passing on of data and material samples, insurance, the ethical committee's vote of approval as well as the patient's freedom to decide. **Chapter 15** contains a detailed description of the verbal patient briefing. Copies of the Information for Patients brochure and the Declaration of Consent form are handed out to the patient.

The patient may give their written informed consent to participation in the trial and randomization **24 hours after the personal briefing at the earliest**. The signed original consent form is kept in the trial site file (if required, additional copies may be kept in the patient's files). The patient receives a copy of each document.

The patient may revoke their consent to participate in the trial at any time.

Termination of protocol treatment can be effected at the patient's wish and/or by the treating physician because of unacceptable toxicity, disease progression, serious concurrent disease or pregnancy.

However, the documentation has to be continued even after termination of protocol treatment provided that the patient does not withdraw their consent to further documentation.

5.3 ENROLLMENT INTO THE TRIAL

5.3.1 Reporting procedure

If, after completion of staging, the patient is qualified for the trial and gives their written informed consent to participate, mandatory baseline data should be recorded in the EDC system. When documentation is complete and signed the corresponding “enrollment report” should be printed and sent by fax to the Trial Coordination Center in Cologne together with the documents indicated on the report. For that, it is essential to send the enrollment report with all mandatory details including a phone number. The patient will be registered into the trial and the respective trial center will receive a confirmation mail that the data has been entered in the EDC system, including the CaseID of the patient and the randomization result.

A copy of the primary histology report is mandatory as well.

Trial Coordination Center Cologne:

Phone: +49 221 / 478 - 88200

Fax: +49 221 / 478 - 88188

The patient must be asked to permit the Trial Coordination Center to contact them personally in the event that no information regarding their current state of remission or no quality of life forms have been received for a longer time period. The patient’s address is to be recorded on the consent form and be transcribed to the enrollment report if applicable.

5.3.2 Randomization

When a patient is reported to the Trial Coordination Center for enrollment, they will be randomized to one of the trial groups. The reporting or treating physician will be informed about the randomization result immediately by email. There is no blinding in this trial.

5.4 TREATMENT

5.4.1 Trial medication

The chemotherapy drugs administered in the HD21 trial – doxorubicin, bleomycin, brentuximab vedotin, cyclophosphamide, darcarbazine, dexamethasone, etoposide, procarbazine, prednisone and vincristine – are authorized for Hodgkin lymphoma treatment and have been tested in several clinical trials.

For details concerning the storage and handling of chemotherapeutics as well as known intolerances, the information provided by the manufacturer or product information should be consulted.

The sponsor will inform the participating centers should any new findings concerning intolerance emerge within the scope of this trial.

The administration of trial medication has to be documented in such way that the charge number, the time of administration as well as the administered amount are clearly identifiable (e.g. chemotherapy plan, patient's file, etc.).

5.4.1.1 Additional information on the trial medication

All components of the escalated BEACOPP regimen as well as the substances dacarbazine and dexamethasone are resale products. Therefore, additional production or labeling measures are not necessary.

The substance brentuximab vedotin is produced by Millennium Pharmaceuticals, Inc. for the HD21 trial and is labeled in accordance with the GCP requirements (GCP-V). It will be dispatched by Almac Clinical Services.

5.4.2 Administration of chemotherapy

Chemotherapy should begin immediately after the patient has been enrolled. For patients under 40 years of age this usually means that the chemotherapy can be started immediately. For patients over 40 years of age, or in younger patients at the disrection of the treating physician, a 4-day pre-phase treatment with 40 mg of dexamethasone may be scheduled. It is usually administered in an outpatient setting, apart from the first cycle for which hospitalization is recommended. Treatment is continued at full dosage according to schedule, provided that on the planned day of continuation the **leukocyte count is ≥ 2500/mm^3 or** the neutrophilic **granulocyte count is ≥ 1500/mm^3** and the **thrombocyte count is ≥ 80,000/mm^3** with a rising trend (after reaching the nadir). If these values are not attained, a treatment delay and dose reduction strategy will be put into effect (see **chapter 5.4.2.8**).

During the administration of escalated BEACOPP and BrECADD blood values have to be monitored at regular intervals. It is recommended to perform blood tests 2-3 times on day 8-15 (expected nadir).

5.4.2.1 Schedule and duration of chemotherapy

Standard group:

- 4 cycles of escalated BEACOPP (bleomycin, etoposide, cyclophosphamide, doxorubicin, vincristine, procarbazine, prednisone) for PET-2 negative patients
- 6 cycles of escalated BEACOPP (bleomycin, etoposide, cyclophosphamide, doxorubicin, vincristine, procarbazine, prednisone) for PET-2 positive patients

Experimental group:

- 4 cycles of BrECADD (brentuximab vedotin, cyclophosphamide, etoposide, doxorubicin, dacarbazine, dexamethasone) for PET-2 negative patients
- 6 cycles of BrECADD (brentuximab vedotin, cyclophosphamide, etoposide, doxorubicin, dacarbazine, dexamethasone) for PET-2 positive patients

The individual cycles are repeated on **day 22**. Thus, the planned chemotherapy duration is 77 days for PET-2 negative patients and 119 days for PET-2 positive patients.

Escalated BEACOPP treatment regimen (full dose=dose level 4)

Cyclophosphamide*	**1250 mg/m^2**	**i.v.**	**day 1**	**over 60 min**
Doxorubicin	**35 mg/m^2**	**i.v.**	**day 1**	**over 30 min**
Etoposide or Etoposide phosphate**	**200 mg/m^2**	**i.v.**	**day 1 - 3**	**over 60 min**
Procarbazine	**100 mg/m^2**	**p.o.**	**day 1 - 7**	
Prednisone	**40 mg/m^2**	**p.o.**	**day 1 - 14**	
Vincristine	**1.4 mg/m^2 (max. 2 mg)**	**i.v.**	**day 8**	**i.v. bolus**
Bleomycin***	**10 mg/m^2**	**i.v.**	**day 8**	**i.v. bolus**
Peg. G-CSF recommended (e.g. Neulasta ®)	**6 mg**	***s.c.***	***on day 4***	

Repeat on day 22

Escalated BrECADD treatment regimen (full dose=dose level 4)

Brentuximab vedotin	**1.8 mg/kg**	**i.v.**	**day 1**	**over 30 min**
Cyclophosphamide *	**1250 mg/m^2**	**i.v.**	**day 2**	**over 60 min**
Doxorubicin	**40 mg/m^2**	**i.v.**	**day 2**	**over 30 min**
Etoposide or Etoposide phosphate**	**150 mg/m^2**	**i.v.**	**day 2 - 4**	**over 60 min**
Dacarbazine	**250 mg/m^2**	**i.v.**	**day 3 - 4**	**over 120 min**
Dexamethasone	**40 mg**	**p.o.**	**day 2 - 5**	
Peg. G-CSF recommended (e.g. Neulasta ®)	**6 mg**	***s.c.***	***on day 5***	

Repeat on day 22

When it comes to calculating the right chemotherapy doses, in both treatment groups there is no body surface limit constituting the maximum dose limit.

The dose of brentuximab vedotin is calculated upon the current body weight of the patient up to a limit of 100 kg. **Patients weighing > 100 kg receive the maximum dose of 180 mg.**

*Additional administration of Uromitexan is obligatory. The patient should ingest 2.5 l of fluid on the day of administration.

**Etoposide phosphate as etoposide-equivalent dose: 113 mg etoposide phosphate is equivalent to 100 mg etoposide. This difference is due to different molecular weights.

***N.B.: Bleomycin-induced pneumonitis** or pulmonary fibrosis is not predictable and often difficult to diagnose. Therefore, a chest X-ray or HR CT and a lung function test should be arranged at the slightest suspicion of it.

The following factors are associated with an increased risk:

- Older patient
- Cumulative bleomycin dose > 300-400 mg
- Mediastinal irradiation
- Administration of extra oxygen
- Renal insufficiency
- Additional administration of other pulmonary toxic substances

Since there are no histological or clinical findings classified as pathognomonic for bleomycin-induced pneumonitis, the diagnosis is based on the assessment of the clinical, radiological and/or histological findings in their entirety after excluding other differential diagnoses.

A considerable fall in vital capacity can be interpreted as a sign of toxicity. In this case, it is imperative that no further bleomycin is administered. Later resumption of bleomycin administration is justified only if the suspicion of bleomycin-induced toxicity has proved unfounded.

In case of doubt, bleomycin administration should be discontinued to prevent a fulminant, treatment-resistant course of bleomycin-induced pneumonitis.

5.4.2.2 Administration of brentuximab vedotin

Brentuximab vedotin is administered as a 30-minute infusion on day 1 of each cycle. A pre-medication before the first administration of brentuximab vedotin is not intended on a routine basis. Should the patient show grade 1 or 2 reactions during or after infusion, in the following cycles they receive a pre-medication before the administration of brentuximab vedotin according to SmPC.

In case of grade 3 or grade 4 reactions, treatment with brentuximab vedotin **can be continued** in combination with an adequate pre-treatment. The respective decision has to be taken by the treating physician on site.

Before the first infusion is initiated, adrenaline and diphenhydramine hydrochloride as well as all necessary measures for treating a serious anaphylactic reaction should be kept ready.

Brentuximab Vedotin might cause interactions when co-administered with medical products metabolized through the CYP3A4 route (CYP3A4 inhibitors/inducors). Detailed information is listed in the SmPc of Adcetris.

For details see: **http://medicine.iupui.edu/clinpharm/ddis/clinical-table**

5.4.2.3 Administration of G-CSF

Administration of a G-CSF product is **obligatory in both treatment groups**. As an alternative to daily G-CSF, the pegylated form can be used (see the following section). [27].

- **Escalated BEACOPP:** Daily administration of G-CSF in each escalated BEACOPP cycle from **day 4** onward.
- **BrECADD:** Daily administration of G-CSF in each escalated BEACOPP cycle from **day 5** onward.

The administration of G-CSF is to be discontinued when the leukocyte count, after reaching the nadir, is over 1000/mm^3 on 3 successive days. Chemotherapy is to be continued no earlier than 48 hours after G-CSF was discontinued.

5.4.2.4 Administration of pegylated G-CSF

Pegylated G-CSF can be used as an alternative to daily G-CSF.

- **Escalated BEACOPP:** 1 x pegylated G-CSF at a dose of 6 mg s.c. on **day 4** of each cycle
- **BrECADD:** 1 x pegylated G-CSF at a dose of 6 mg s.c. on **day 5** of each cycle

5.4.2.5 Safety examinations during chemotherapy

During chemotherapy, safety assessments as outlined in 0.4 will be performed and documented regularly. For each cycle, laboratory values and abnormal findings will be documented in the hematology and CTCAE toxicities sections of the respective eCRF. Laboratory values and results from toxicity examinations are also to be documented in the respective sections of the restaging forms.

It is recommended to monitor the following parameters during chemotherapy:

- 2-3x/week: leukocytes, thrombocytes, hemoglobin

At the end of each cycle (day 19-22), the following additional laboratory examinations are recommended:

- leukocytes, thrombocytes, hemoglobin, creatinine, uric acid, bilirubin, gamma GT, GOT, GPT

5.4.2.6 Supportive therapy

An **antibiotic prophylaxis** with **Cotrim-forte** (trimethoprim/sulfametaxolole) is obligatory. It has to be given 3x/week (Mon-Wed-Fri) **during the whole duration of chemotherapy.**

Apart from that, in the phase of aplasia an **intensified antibiotic prophylaxis** with quinolones (e.g. Ciprofloxacin) is **recommended**.

If fever occurs, the patient should see their treating physician immediately. At the weekend or at nighttime, the patient should visit the local hospital.

Antiemetic treatment should primarily be performed using **5-HT3 receptor antagonists**. In case of persisting nausea antiemetic treatment may be intensified, including steroids if indicated.

For prophylaxis of **hemorrhagic cystitis** under treatment with cyclophophamide, **Uromitexan** is given on **day 1** of **escalated BEACOPP** and on **day 2** of **BrECADD**.

Besides, **adequate supply of fluids (i.v./oral) of at least 2.5 l/day** must be assured. Treatment with allopurinol and H_2-receptor blockers should be considered depending on the individual case.

Tumor lysis syndrome is a potentially severe complication of chemotherapeutic treatment characterized by rapid development of hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia and acute renal failure. It typically occurs shortly after initiation of treatment, when neoplastic cells are killed rapidly and intracellular components are released into the peripheral blood. Especially patients with large tumor burden are at higher risk for the development of tumor lysis. To prevent and early detect tumor lysis close laboratory monitoring and clinical observation are mandatory. The management of tumor lysis syndrome includes sufficient hydration, control of electrolyte disturbances up to hemodialysis in case of anuric renal failure or other life-threatening complications.

5.4.2.7 Administration of erythrocyte concentrates

Erythrocyte concentrates may be transfused for treatment of anemia if the treating physician considers this necessary in view of the clinical symptoms.

If the Hb level is > 10 g/dl and neither symptoms nor coronary heart disease are present, transfusion is usually not indicated. However, this has to be decided by the treating physician on site.

The number of the transfused concentrate units must be documented for each cycle.

Further supportive measures are generally not recommended. Should any additional medication become necessary from a clinical point of view, this should be documented in detail including indication, date and administered dose.

Steroids other than the products and doses defined in this protocol should only be administered in a situation of emergency.

The following particulars have to be documented: the number of hospitalized days and days in intensive care, number of days with febrile neutropenia, administration of blood products (erythrocytes, thrombocyte concentrates) as well as the administration of G-CSF.

5.4.2.8 Treatment postponement and dose reduction

1. In both groups treatment is always to be continued punctually and at full dosage, provided that the following conditions are fulfilled after the blood values have reached the nadir:

   - Leukocytes ≥ 2.500/mm^3 or

     Neutrophilic granulocytes ≥ 1.500/mm^3

     AND

   - Thrombocytes ≥ 80.000/mm^3

2. Should the critical values not be reached on the planned day of treatment continuation, therapy is postponed and blood values should be tested again after 3, 7, 10 and 14 days. As soon as above-quoted critical values have been fulfilled, treatment is resumed according to the strategies described below.
3. Within the **escalated BEACOPP** regimen the chemotherapeutics bleomycin and vincristine are administered on day 8 even if leukopenia, thrombocytopenia and/or anemia are present, provided that patients do not show any signs of infection. If non-

hematological events occur (fever, infection or signs of infection, etc.), the application of bleomycin and vincristine on day 8 is omitted without substitution.

4. If serious unexpected non-hematological side-effects of CTCAE grade 3 or 4 occur, treatment should not be continued until the patient has recovered to CTCAE ≤ grade 1.
5. In case of peripheral neuropathies under **BrECADD** therapy, the brentuximab vedotin dose has to be adjusted as follows:

Severity of peripheral sensory or motor neuropathy (signs and symptoms)	**Dose adjustment**
Grade 1 (asymptomatic; only clinical or diagnostic finding; no need for treatment; paresthesia and/or loss of deep tendon reflexes)	Continuation of protocol treatment
Grade 2 (mild symptoms; limited activity in daily life) Grade 3 (pronounced symptoms; self-care in daily life is only possible to a limited degree)	Discontinuation of treatment until symptoms have subsided to ≤ grade 1 level or initial state, then continuation of treatment with a reduced dose of 1.2 mg/kg every 3 weeks
Grade 4 (life-threatening; treatment must be initiated immediately)	Termination of Brentuximab vedotin treatment
Grade 5 (death)	

Should the patient show signs of progressive multifocal leukoencephalopathy (PML), this has to be reported promptly to the Trial Coordination Center of the GHSG. In this case treatment must be discontinued immediately.

5.4.2.9 Indications for dose reduction

Dose reduction for escalated BEACOPP and BrECADD has to follow a predefined de-escalation scheme which is based upon the occurrence of toxic events in the previous cycles. Once a dose level has been reduced, in the following course of therapy no doses must exceed this reduced level.

The following are regarded as **toxic events**:

- leukopenia for more than 4 days (leukocytes < 1000/mm^3)
- thrombocytopenia on one or more days (thrombocytes < 25.000/mm^3)
- Infection CTCAE grade 4
- Other CTCAE grade 4 toxicities, e.g. mucositis
- Treatment delay of more than 2 weeks due to inadequate recovery of blood values

If one or more toxic events occur in a given cycle, the dose in all following cycles has to be reduced by one dose level.

If toxicity events occur in two successive cycles, the doses are reduced to baseline level.

In case of a treatment delay of up to 2 weeks, a dose reduction is not necessary.

5.4.2.10 Dose levels for escalated BEACOPP

Treatment always begins at full dose (see escalated BEACOPP treatment regimen, chapter 5.4.3.1). Should a dose reduction be necessary, the following dose levels are to be used:

Escalated BEACOPP

Full dose, dose level 4

Cyclophosphamide	1250 mg/m^2	i.v.	Day 1
Doxorubicin	35 mg/m^2	i.v.	Day 1
Etoposide	200 mg/m^2	i.v.	Day 1-3

Dose level 3

Cyclophosphamide	1100 mg/m^2	i.v.	Day 1
Doxorubicin	35 mg/m^2	i.v.	Day 1
Etoposide	175 mg/m^2	i.v.	Day 1-3

Dose level 2

Cyclophosphamide	950 mg/m^2	i.v.	Day 1
Doxorubicin	35 mg/m^2	i.v.	Day 1
Etoposide	150 mg/m^2	i.v.	Day 1-3

Dose level 1

Cyclophosphamide	800 mg/m^2	i.v.	Day 1
Doxorubicin	35 mg/m^2	i.v.	Day 1
Etoposide	125 mg/m^2	i.v.	Day 1-3

Baseline BEACOPP

Cyclophosphamide	650 mg/m^2	i.v.	Day 1
Doxorubicin	25 mg/m^2	i.v.	Day 1
Etoposide	100 mg/m^2	i.v.	Day 1-3

5.4.2.10.1 Examples of dose reduction for escalated BEACOPP:

Example 1

Cycle	1	2	3	4	5	6
Dose level	4	4	4	**3**	3	3
Toxicity	no	no	**yes**	no	no	

Example 2

Cycle	1	2	3	4	5	6
Dose level	4	4	4	**3**	3	**2**
Toxicity	no	no	**yes**	no	**yes**	

Example 3

Cycle	1	2	3	4	5	6
Dose level	4	4	**3**	3	2	**baseline**
Toxicity	no	**yes**	no	**yes**	**yes**	

5.4.2.11 Dose levels for BrECADD

<u>Full dose, dose level 4</u>

Cyclophosphamide	1250 mg/m^2	i.v.	Day 2
Doxorubicin	40 mg/m^2	i.v.	Day 2
Etoposide	150 mg/m^2	i.v.	Day 2-4

<u>Dose level 3</u>

Cyclophosphamide	1100 mg/m^2	i.v.	Day 2

Doxorubicin	40 mg/m^2	i.v.	Day 2
Etoposide	125 mg/m^2	i.v.	Day 2-4

Dose level 2

Cyclophosphamide	950 mg/m^2	i.v.	Day 2
Doxorubicin	40 mg/m^2	i.v.	Day 2
Etoposide	100 mg/m^2	i.v.	Day 2-4

Dose level 1

Cyclophosphamide	800 mg/m^2	i.v.	Day 2
Doxorubicin	40 mg/m^2	i.v.	Day 2
Etoposide	100 mg/m^2	i.v.	Day 2-4

baseline BrECADD

Cyclophosphamide	650 mg/m^2	i.v.	Day 2
Doxorubicin	35 mg/m^2	i.v.	Day 2
Etoposide	100 mg/m^2	i.v.	Day 2-4

5.4.2.11.1 Examples of dose reduction strategies for BrECADD

Example 1

Cycle	1	2	3	4	5	6
Dose level	4	4	4	**3**	3	3
Toxicity	no	no	**yes**	no	no	no

Example 2

Cycle	1	2	3	4	5	6
Dose level	4	4	4	**3**	3	**2**
Toxicity	no	no	**yes**	no	**yes**	

Example 3

Cycle	1	2	3	4	5	6
Dose level	4	4	4	**3**	**Baseline**	**baseline**
Toxicity	no	no	**yes**	**yes**	No	

5.4.2.12 Intolerance

In case of drug-specific intolerance (e.g. vincristine neuropathy, procarbazine allergy), single drugs may be dropped from the regimen without substitution. The reason for a deviation from protocol treatment always has to be recorded.

5.4.3 Documentation of side-effects

Exact documentation of side-effects by the treating physician is absolutely necessary. It has to be based on the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 of 29 May 2009 (see trial site file). The evaluation of side-effects according to these criteria has to be performed individually for each treatment cycle. Side-effects of 1-5 are documented in the chemotherapy section. The documentation of serious adverse events (SAEs) is described in section 6.2.1.

5.4.3.1 Febrile neutropenia

If the patient develops febrile neutropenia (FN) under treatment, this is to be documented in the chemotherapy section or the respective chemotherapy cycle. FN is defined as:

- ANC <1000/mm^3

  and
- a single temperature of >38.3 degrees C or a sustained temperature of >=38 degrees C for more than one hour.

If the patient has to be hospitalized due to febrile neutropenia, the number of hospitalized days has to be documented in the chemotherapy section.

5.4.4 Radiotherapy

Additional radiotherapy after completion of chemotherapy will be recommended by the review panel (see 5.6) for patients presenting with PET-4 or PET-6 positive residues. However, the decision and organization of the radiotherapy is up to the discretion of the treating physician on site. For recommendations concerning dose and duration of radiotherapy please refer to current guidelines with high evidence such as the S3-guideline for Hodgkin Lymphoma.

5.5 RESTAGING

Restagings are performed after 2 chemotherapy cycles (interim staging, CT-2/PET-2), after completion or early termination of chemotherapy (restaging after chemotherapy, CT-4/PET-4 or CT-6/PET-6) and at the end of radiotherapy if given (restaging after radiotherapy). A restaging should also be performed during therapy or follow-up whenever a disease progression or relapse is being suspected.

The remission criteria are defined in detail in chapter 13.5.

Procedure

Each restaging always includes an examination of all initially involved lymph nodes or organs using adequate methods. In case of doubt, histological confirmation should be sought.

If FDG PET/CT is performed for restaging, the examination should cover the whole trunk of the body; images of the lower extremities are only required if a primary tumor was located there. Please refer to section 14.2 and the EANM Guidelines for technical details. The FDG-PET scans are evaluated by the PET facility that performs the examination. The visual criteria adapted from Meignan et al. [28] should be used as described in section 13.6. The treating oncologist holds the organizational responsibility and arranges for the PETs and CTs taken before start of chemotherapy and for restagings to be sent to the “Department for Nuclear Medicine” of the University Hospital of Cologne. **As the restaging results determine the further course of treatment, the documentation for each restaging should be completed in due course and the respective CT- and PET- scans have to be transmitted to the reference panel without delay.** These images and the documentation of the restaging in the eCRF serve the review specialists as a basis for independent response evaluation (see section 5.6).

Obligatory examinations

- Interim case history (B symptoms)
- Clinical examination (size of lymph nodes, spleen, liver)
- Laboratory tests:
    - Differential blood count
    - Clinical chemistry (electrolytes, gamma-GT, GOT (ASAT), GPT (ALAT), bilirubin, creatinine, urea, uric acid, Na, K, Ca)
- ceCT of all initially involved sites
- NMR (MRT) monitoring if:
    - ✓ NMR was performed for initial staging, e.g. if a pericardium or myocardium infiltration or osseous involvement was suspected

- FDG PET/CT according to EANM guidelines if one of the following applies:
    - ✓ Restaging after 2 cycles
    - ✓ Restaging after completion of chemotherapy **and** signs of active tumor according to ceCT

Optional FGD PET/CT examination

When FDG PET/CT is performed as optional examination in addition to or in combination with ceCT, the investigator should include the results in the restaging documentation and include the PET-scans in the material provided for central review.

Please note:

FDG PET/CT is not recommended at final restaging after radiotherapy because of a high probability of false PET-positive findings.

5.5.1 Restaging in case of suspected disease progression

If a disease progression (POD) is suspected, an unscheduled ceCT-based restaging should be performed and documented. If a POD is confirmed by ceCT, all relevant imaging scans have to be transmitted to the reference panel of the Department for Nuclear Medicine of the University Hospital of Cologne for independent central review. Individual recommendation on salvage treatment will be given by a panel oncologist if the panel confirms POD.

5.5.2 Interim restaging (CT-2/PET-2)

The interim staging after the first two cycles of randomized chemotherapy mainly aims at the early detection of progressive disease as well as an individual treatment recommendation which is based on the early response assessment.

In case the interim restaging shows a primarily progressive disease under chemotherapy, the Trial Coordination Center should be contacted to discuss how to proceed and which alternative treatment options there are.

Patients who are confirmed to be PET-2 negative will receive only 2 more cycles of chemotherapy irrespective of the treatment group. PET-2 positive patients continue with 4 additional cycles of chemotherapy.

In case that a patient is no longer qualified for the trial according to the central review, study therapy will be terminated and reasons for treatment termination have to be documented by the investigator.

Schedule

In both treatment groups the interim restaging (CT-2/PET-2) takes place in the last week of the 2nd chemotherapy cycle, preferably between days 17 and 21, days 14 to 17 are also acceptable. **Performance of FDG PET/CT should not delay therapy.**

Obligatory examinations: FDG PET/CT is required in addition to the ceCT for all patients. Other obligatory restaging examinations are listed above (section 5.5), please also refer to the assessment plan (section 0.4)

5.5.3 Restaging after chemotherapy

This restaging serves to determine and review the chemotherapy outcome and to guide further therapy. No additional therapy will be recommended in cases of complete remission. In case of PET-4 or PET-6 positive residues, additional radiotherapy will be suggested by the review panel. If the restaging result is inadequate response of progressive disease the Trial Coordination Center should be contacted to discuss individual treatment options.

Schedule In both treatment groups, the restaging after chemotherapy including ceCT and FDG PET/CTtakes place within 3 weeks after day 21 of the last chemotherapy cycle without regard to the number of chemotherapy cycles applied.

After central review of the restaging images and documentation, the panel will provide the investigator with a treatment recommendation.

Subsequently (not earlier) the patient should be seen by the radiotherapist in case that additional radiotherapy is planned.

Obligatory examinations

Obligatory restaging examinations are listed above (section 5.5), please also refer to the assessment plan (section 0.4).

FDG PET/CT in addition to the ceCT is obligatory in case of residual lesions (> 1.5 cm).

5.5.4 Restaging after Radiotherapy

After completion of radiotherapy, a **CT-based restaging** will be performed in order to evaluate the therapy outcome**. FDG PET/CT is not recommended** due to an expected high rate of false positive findings after radiotherapy.

Schedule

The restaging after radiotherapy is to be conducted **not earlier than 6 weeks after completion of radiotherapy**.

Obligatory examinations

Obligatory restaging examinations are listed above (section 5.5), please also refer to the assessment plan (section 0.4)

5.6 PANEL REVIEW

The PET review assessment is always conducted by two experienced nuclear-medical specialists and is established by consensus. Nuclear-medical specialists, radiotherapists, oncologists, and diagnostic radiologists are welcome to take part in the respective review assessments. The panel meetings for the PET review assessments take place at weekly intervals. If necessary, shorter intervals can be agreed upon.

The imaging information from the FDG PET/CTs and ceCTs taken before start of treatment and for restaging has been made available to them, and they also have the image interpretation by the primary PET facility that performed the examination at hand. PET scans can only be evaluated if emission images and attenuation-corrected emission images (on CD, X-ray film or hardcopies) as well images with at least 2 levels have been provided. Please refer to section 14.2 for technical procedures for the FDG PET/CT examination.

The PET review assessment is performed visually and qualitatively and is documented on the respective e-CRF.

If the nuclear-medical specialists assess an FDG accumulation as vital tumor tissue, it is obligatory to consult a radiotherapist to evaluate whether there is an indication for irradiation and to determine the sites of irradiation. The sites of irradiation are defined on the basis of the initial CT images and those taken after 2 and 4/6 cycles of chemotherapy as well as the PET-2 and PET-4/-6 images.

If the CT images taken after 4/6 cycles of chemotherapy indicate an inadequate or lacking response to treatment, it is obligatory to consult an oncologist.

The treating oncologist and the GHSG Trial Coordination Center will be informed on whether the PET prerequisites have been fulfilled, the PET result according to the Deauville criteria

[28], chemotherapy response according to the remission criteria (see 13.5) and the resulting recommendation regarding radiotherapy or salvage therapy, where applicable.

5.7 FOLLOW-UP

After end of treatment and completion of the definitive restaging, patients have to be seen for follow-up examinations at regular intervals. The longer treatment dates back, the longer are the intervals between the individual follow-up examinations. The follow-up examinations until the timepoint Last Patient Last Visit (LPLV) are part of the trial protocol. Every single patient will be followed up at least for five years. The follow-up examinations beyond this period are part of standard follow-up care in tumor patients.

5.7.1 Follow-up assessments

In every follow-up examination, the state of remission and toxicities, if applicable, are to be documented.

Please note:

After the definite restaging at the end of treatment including radiotherapy if applicable, routine examinations do not include CTs, provided that a CR has been achieved after end of treatment.

5.7.1.1 Table of assessments

Examination times	1st year			2nd to 5th year	Later than 5th year
	Month 3*	Month 6*	Month 12*	Every 6 months	Every year
Clinical Examination	**X**	**X**	**X**	**X**	**X**
Case history	**X**	**X**	**X**	**X**	**X**
Laboratory examinations					
Differential blood count	**X**	**X**	**X**	**X**	**X**
TSH	**strongly recommen-ded**	**strongly recommen-ded**	**strongly recommen-ded**	**strongly recommended**	**strongly recommen-ded**
Fertility (FSH, LH, estradiol, testosterone, anti-Müllerian hormone, inhibin B)			**strongly recommen-ded**	**strongly recommended** [1) 2)]	
Menstruation history/ spermiogram			**strongly recommen-ded**	**strongly recommended** [1) 2)]	
Echocardiography			**strongly recommen-ded**	**strongly recommended** [1) 2)]	
ECG			**strongly recommen-ded**	**strongly recommended** [1) 2)]	
Serum sample			**X**	**X** [1) 2)]	
Computed tomography [3)]			**If clinically indicated**		
Pulmonary function			**strongly recommen-ded**		
Abdominal ultrasound	**strongly recommen-ded**		**strongly recommen-ded**	**strongly recommended** [4)]	**strongly recommen-ded**
QoL [5)]	**X**	**X**	**X**	**X** [4)]	**X**

* months from end of chemotherapy (day 21 of last cycle) irrespective of radiotherapy

[1)] 24 months after end of chemotherapy [2)]) 60 months after end of chemotherapy [3)]) further CTs are recommended depending on findings [4)]) examination once a year

[5)] If the patient agreed to participate in the quality of life survey, QoL is to be documented on specially designed forms using rating scales (see 5.8).

5.7.1.2 Assessments in case of suspected relapse

After the restaging at the end of treatment including radiotherapy if applicable, routine examinations do not include CTs, provided that a CR has been achieved after end of treatment. If a relapse is suspected, all necessary examinations (including CT) should be performed for clarification. If a relapse is confirmed, all relevant imaging scans have to be transmitted to the reference panel of the Department for Nuclear Medicine of the University Hospital of Cologne for independent central review.

5.7.1.3 Toxicity assessments

The documentation of treatment-related toxicity is an essential part of the follow-up examinations and includes a detailed case history exploration, a physical examination and some **strongly recommended** instrumental/imaging examinations and laboratory analyses.

The following examinations are to be performed:

- **Pulmonary function test (strongly recommended** follow-up examination at 1 year after end of chemotherapy and always if an impaired pulmonary function is suspected). If a treatment-related pneumonitis is suspected, a HR-CT has to be performed and, if necessary, further diagnostic measures (BAL)
- **Thyroid diagnostics (strongly recommended** follow-up examination)
- **Echocardiography and ECG (strongly recommended** follow-up examinations) at the following times after end of chemotherapy: 12 months, 24 months, 60 months

Further examination for the purpose of toxicity monitoring are indicated particularly if conspicuous findings appeared within the scope of the initial staging, e.g. further cardiac diagnostic examinations (such as long-term ECG, TEE) in case of abnormal ECG and/or echocardiography.

5.7.1.4 Optional fertility assessments

Schedule:

Gonadal function assessment is strongly recommended during follow-up at 12 months, 24 months and 60 months after end of chemotherapy

Recommendet assessments:

Females: menstruation history; FSH, LH, β-estradiol, anti-Müllerian hormone

Males: FSH, LH, testosterone, inhibin B.

5.8 QUALITY OF LIFE (QOL) ASSESSMENT

If the patient agreed to participate in the quality of life survey, QoL is to be documented on specially designed forms using rating scales. The GHSG provides validated questionnaires in German. Other countries may need different questionnaires. Organization of QoL assessment is thus in the repsonsibilty of the national representative. Please refer to section 10.4 for a more detailed description of the QoL assessment methods.

Schedule: These forms have to be completed by the patients themselves before the start of chemotherapy, after the 2nd cycle and after completion of chemotherapy and, if applicable, after the end of radiotherapy (see 0.4 and 5.7.1.1). Until 2 years after end of chemotherapy, further QoL documentation is required at the same time points as each follow-up visit (3, 6, 12, 18 and 24 months after end of chemotherapy). Thereafter, further documentation is required on an annual basis at the follow-up examination.

6 ADVERSE EVENTS

In the following, the classification as well as the documentation and reporting of adverse events are described.

Therapeutic consequences of adverse events are dealt with in section 5.4.2. Please refer to sections 0.4, 5.4.2.5, and 5.7.1.3 for required toxicity examinations before, during and after treatment.

N.B.: Bleomycin-induced pneumonitis, which may occur as a side-effect, is described in detail in section 5.4.2.1.

6.1 DEFINITIONS

Adverse event

"An adverse event is any detrimental event that occurs in a person who was administered an investigational drug and that does not necessarily stand in a causative relation to this treatment." (GCP-V art.3 (6))

Concurrent diseases:

In this connection, also a worsening of a previously existing disease is to be considered as an adverse event. However, a measure that is taken in order to treat a previously existing disease and that was planned before the patient was enrolled into the trial is not to be considered as an adverse event.

Pregnancy:

If a participating patient becomes pregnant, in terms of this trial this is considered as an adverse event for reasons of drug safety. If pregnancy occurs in a patient of this trial, the respective case has to be reported immediately (see section 6.2.4).

Adverse reaction

"An adverse reaction is any detrimental and unintentional reaction to an investigational drug, independent of the administered dose." (GCP-V art.3 (7))

Serious adverse event or serious adverse reaction

"A serious adverse event or a serious adverse reaction is any adverse event or reaction that is fatal or life-threatening, that necessitates or prolongs hospitalization, or that leads to a permanent or severe disability or invalidity, or to a congenital anomaly or birth defect." (GCP-V art. 3 (8))

Unexpected adverse reaction

"An unexpected adverse reaction is an adverse reaction that does not correspond to the existing information on the investigational drug in terms of the nature and severity of this reaction." (GCP-V art.3 (9))

The currently existing information on the respective investigational product is stated in the latest summary of product characteristics (SmPCs), which is to be used as a reference.

6.1.1 Evaluation of adverse events

See section 6.1 for definitions.

The degree of severity is evaluated as follows:

- mild
- moderate
- severe
- life-threatening

The evaluation is to be based on the official CTCAE version 4.0 (of 29 August 2009).

For each occurring event an assessment of causality has to be performed:

- Not evaluable It is not possible to assess whether there is a relation with the administered investigational drug(s) or not.
- Not evaluated An event that was reported as adverse event, but for which a relation with the administered investigational drug(s) was not established at the time of reporting because further data were necessary or are currently being compiled.
- No relation An event on which there is sufficient information available to assume that there is no relation with the investigational drug.
- Possible relation An event that follows a matching chronological course after administration of the investigational drug, or that follows a known or expected scheme of response to the suspect investigational drug, but which could also have been caused by a number of other factors.
- Probable relation An event that follows a matching chronological course after administration of the investigational drug, that follows a known or expected scheme of response to the suspect investigational drug and disappears after the administration is discontinued or reduced to a lower dose and that cannot be explained by the known clinical condition of the patient.
- Certain relation An event that follows a matching chronological course after administration of the investigational drug, or an event due to which the concentration of the investigational drug in the body tissues or fluids is measured, that follows a known or expected scheme of response to the suspect investigational drug and that

disappears after the administration is discontinued or reduced to a lower dose and reappears after repeated exposure.

6.1.2 Serious adverse events

Adverse events are rated as serious in the following cases:

- Every case of death, independent of the cause of death, occurring during protocol-conform therapy or within 30 days after end of chemotherapy
- Life-threatening
- Events that lead to a permanent or severe disability or invalidity
- Events that necessitate hospitalization or prolong a hospital stay
- Congenital anomaly or birth defect
- Second malignant tumors
- Events rated as “medically significant”. This applies to events that are not directly fatal or life-threatening and that do not necessitate immediate hospitalization but some kind of medical or surgical intervention to prevent any of the above-mentioned consequences. Examples for such events:
  - Allergic bronchospasms requiring intensive treatment in an ICU or at home
  - Blood dyscrasias or spasms not requiring hospitalization
  - Abuse of medicinal products or addiction to medicinal products
  - Transmission of infectious agents through medicinal transfusion products (e.g. prion proteins)

A **life-threatening** event in the above-mentioned connection is an event in which the patient is in mortal danger **at the time it occurs**. This does not refer to an event which hypothetically might have caused death if it were more severe.

A hospital stay is any stay in a hospital as an inpatient for at least one night. A hospitalization that has already been planned before the first administration of the investigational drug is not considered as a serious adverse event.

All events occurring up to 30 days after end of chemotherapy have to be reported. Events occurring after this time period have to be reported if they are rated to be **at least possibly related** to chemotherapy.

The following events have to be reported at any time they occur, as there is always a possible causal relationship to chemotherapy: neuropathy, myelodysplastic syndrome, secondary malignancies and progressive multifocal leukencephalopathy.

6.1.3 Suspected cases of unexpected serious drug side-effects

A **SUSAR (suspected unexpected serious adverse reaction)** is a case in which the occurrence of a serious adverse reaction that could not be expected is suspected (there is **at least a possible relation** to the administered protocol medication), and the nature and severity of this reaction do not correspond to the existing information on the respective investigational drug. The reaction is rated as serious and a relation between the investigational drug and the reaction is considered to be possible. The existing information on the respective investigational drug can be found in the summary of product characteristics (SmPCs) of the respective drug, since all drugs used in this trial are officially licensed for Hodgkin lymphoma treatment.

Special attention must be paid to the potential occurrence of **progressive multifocal leukencephalopathy (PML)** since PML cases have been reported in connection with the administration of brentuximab vedotin.

Should a patient show signs of progressive multifocal leukoencephalopathy (PML), this has to be reported promptly to the Trial Coordination Center of the GSHG, and therapy must be discontinued immediately.

6.2 DOCUMENTATION AND EVALUATION OF ADVERSE EVENTS

6.2.1 Documentation

Every adverse event (grade 1-5) has to be documented, independent of the investigator's opinion of whether there is a causative relation with therapy or not.

Unexpected adverse events are to be documented on the respective eCRF ((S)AE form). Documentation includes the nature of the event, beginning, duration, severity/grade and causality.

Signs and symptoms as well as changes in the laboratory values should be documented in summary as a single adverse event. Unusual laboratory values have to be assessed by the investigator regarding their clinical relevance and – if they are assessed to be relevant – they have to be documented as an adverse event.

All adverse events have to be tracked until they have subsided or stabilized.

All adverse events that are not rated as unexpected (see section 6.1) have to be documented in the CTCAE toxicities section of the eCRF.

6.2.2 Obligation to report

The investigator has to report every serious adverse event and every pregnancy directly after they become known (within one working day) to the following address:

Studienleiter / Trial Chairman
Deutsche Hodgkin Studiengruppe (GHSG)
Prof. P. Borchmann
Gleueler Str. 269
50935 Köln
Tel.: +49 221 / 478-88180
Fax: +49 221/478-88188

Every SAE has to be reported immediately using an SAE form which has to be sent to the stated address.

If the required information is not available at that time, tracking reports have to be sent in later. In cases of death, a copy of the autopsy report should also be forwarded.

Sponsor Reporting toTakeda Pharmacovigilance or designee

The sponsor has to report every serious adverse event and every pregnancy directly (within 24 hours of becoming aware of the event) to the following: SAE and Pregnancy Reporting Contact Information, Fax#: 1 202 315-3560, E-mail:takedaoncocases@cognizant.com

6.2.3 Exceptions from the obligation to report

The following serious adverse events do not have to be reported within the scope of this trial:

- Severe or unexpected adverse events that occur after registration of the patient, but before start of treatment
- Hospitalization in connection with the therapeutic measures of the trial (administration of investigational drug, blood transfusions)
- Cases of death due to the primary disease (Hodgkin lymphoma) with the exception of death occurring after first dose of brentuximab vedotin up to 30 days after the end of chemotherapy (as defined in 6.1.2.)

At regular intervals, the trial chairman informs the respective investigator of the trial centers about all reported adverse events. The investigators will be informed immediately should any serious adverse events occur that were unknown so far and for which a causal relation with the trial medication cannot be ruled out.

6.2.4 Documentation and reporting of suspected unexpected serious adverse reactions (SUSARs), pregnancies and changes of the risk-benefit-ratio

Independent of the suspected causal relation, every serious adverse event that occurs in the course of the trial has to be documented on the SAE form.

After the occurrence of an SAE becomes known, the investigator has to inform the trial chairman (representative of the sponsor) immediately. Exept from this are the events mentioned in section 6.2.3.

The investigator also has to report cases of pregnancies that occur during the course of the clinical trial and their outcome.

The trial chairman evaluates all occurring SAEs and decides whether they are to be rated as unexpected (according to chapter 6.1.3).

6.2.4.1 Notification to the ethical committee and the appropriate authority

The trial chairman reports any case of a severe unexpected adverse reaction that occurs during the course of the clinical trial to the appropriate BOB (supreme federal authority in Germany) as well as to the responsible ethical committee.

The legal regulations stipulated in the GCP-V are being adhered to.

Outside Germany, the respective national sponsor representatives have to ensure that such events are reported to the appropriate foreign authorities.

<u>Fatal and life-threatening SUSARs</u>

The appropriate BOB and the responsible ethical committee have to be informed immediately on all fatal and life-threatening SUSARs, at the latest within 7 calendar days after it becomes known that the minimum criteria for an immediate reporting of such cases by the trial chairman (as sponsor representative) have been fulfilled. In all cases of fatal and life-threatening SUSARs that occur, further relevant information will be investigated upon. These information will also be communicated to the appropriate BOB as well as to the responsible ethical committee.

<u>Non-fatal and non-life-threatening SUSARs</u>

The appropriate BOB and the responsible ethical committee also have to be informed immediately on all non-fatal and non-life-threatening SUSARs, not later than 15 calendar days after it becomes known that the minimum criteria for an immediate reporting by the trial chairman (as sponsor representative) have been fulfilled. Further relevant information has to be communicated as soon as possible.

In case that the available information is incomplete at the time when the SUSAR is reported to the Trial Coordination Center, the reporting physician and other sources will be contacted for further information that is required for analyzing the case adequately.

Reporting of changes regarding the risk-benefit-ratio

If circumstances arise that necessitate a revision of the risk-benefit-ratio, the sponsor informs the responsible ethical committee about these within 15 calendar days, including:

- Individual case reports of expected serious adverse reactions with unexpected outcome
- An increase in the frequency of suspected serious adverse reactions that are rated as clinically relevant
- Suspected cases of serious unexpected adverse reactions that occurred after the respective patient had already concluded the clinical trial
- Events in connection with the trial execution or the development of the investigational drug that can possibly harm the safety of the participating patients

6.2.4.2 Notification to the Data Monitoring Committee

The DMC will be informed about all occurring SAEs, SUSARs and other circumstances as listed in section 6.2.4.1.

6.2.4.3 Notification to the investigators

The sponsor will inform the investigators about all occurring SUSARs, including any relevant further information, within the time limits stipulated by the appropriate authority.

Should any new information arise that differs from the information the investigators were provided with, the sponsor will inform all investigators about this.

6.2.5 Annual report on the safety of trial participants

The sponsor submits an annual report on the safety of trial participants to the appropriate BOB (supreme federal authority) and to the responsible ethical committee. This report complies with ENTR/CT 3 and includes all available relevant information regarding the respective period under report. This report includes:

- Report on the safety of trial participants of the respective clinical trial
- List of all suspected cases of serious adverse reaction (including all SUSARs) that occurred in the respective clinical trial

- List that summarizes the suspected cases of serious adverse reactions (grouped according to organ system, treatment group and type of the adverse reaction) that occurred in the respective clinical trial

The period for the submission of the annual report on the safety of trial participants starts on the day on which the trial is approved by the appropriate authority. This date is a cut-off date for the data that is to be included in the annual report. The sponsor submits the report within the statutory time period.

6.2.6 Known adverse drug reactions

-All adverse drug reactions or side-effects listed in the product information

6.2.7 Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product.

A medication error is a preventable event that involves an identifiable patient and leads to inappropriate medication use, which may result in patient harm since a product complaint is not in and of itself an Adverse Event. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not.

Individuals who identify a potential product complaint situation should immediately contact Takeda (see below) and report the event. Please report by copy the responsible project managerand quality manager of the GHSG.

Pending response the medication must be put under quarantine.

Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Takeda Quality representative.

For Product Complaints or Medication Errors

Phone: 1-844-662-8532
Email: GlobalOncologyMedinfo@takeda.com

Product complaints in and of themselves are not AEs. If a product complaint or medication error results in an SAE, an SAE form should be completed and sent to Millennium as detailed above (see sections 1.2 and 6.2.2).

7 STATISTICS

7.1 OBJECTIVES

Primary objective of the trial is to demonstrate non-inferior efficacy of six cycles of BrECADD compared to six cycles of escalated BEACOPP, each followed by radiotherapy to PET-positive residual lesions, in terms of progression free survival (efficacy objective).

If non-inferior efficacy can be shown, the co-primary objective is to further demonstrate reduced toxicity of the BrECADD treatment compared to the escalated BEACOPP treatment measured by treatment-related morbidity (TRMB objective).

7.2 STUDY DESIGN

The trial is an open-label, prospective, multicenter phase III trial with two parallel groups with central randomization using stratified minimization. It is designed with two primary endpoints that will be tested hierarchically to account for multiplicity. No interim analysis is planned.

7.3 RANDOMIZATION AND STRATIFICATION

Patients are allocated to the BrECADD and escalated BEACOPP groups in a 1:1 ratio. Chance allocation is performed by the GHSG Trial Coordination Center before initiation of treatment, according to the minimization method including a random element [29]. This method endeavors to maintain a balance between treatment groups with respect to factors that might influence results. To this end, stratification will be performed using the following factors:

1.	Country	country of enrolment
2.	Age	$<$ 45 years
		$\geq$ 45 years
3.	Sex	male
		female
4.	IPS	0-2
		3-7

7.4 ENDPOINT DEFINITIONS

7.4.1 Primary endpoints

Progression-free survival (PFS) is the time from the date randomization until the date of the first occurrence of one of the events mentioned below, and is censored at the date of the last information on tumor status, if none of these events have occurred.

The following count as events:

- progression of disease,
- relapse,
- death from any cause

The exact time of occurrence of an event is to be documented on the respective case report form. The date of progression/relapse will always be the diagnosis date (date biopsy taken, if available) even if it is not diagnosed at a scheduled visit.

PFS reflects tumor growth and is thus particularly suitable for a comparison between treatment groups, in which the differences between the individual groups become apparent after a good initial response to chemotherapy.

Treatment related morbidity (TRMB) is defined as any CTCAE organ toxicity of grade 3 or 4 or severe hematological toxicity of grade 4 during primary chemotherapy (including a period of 30 days after the last chemotherapy dose) of the following SOC categories as documented on the CTCAE toxicities section of the eCRF:

- cardiac disorders grade 3 or 4,
- gastrointestinal disorders grade 3 or 4 (excluding vomiting, nausea and mucositis),
- hepatobiliary disorders grade 3 or 4,
- nervous system disorders grade 3 or 4,
- renal and urinary disorders grade 3 or 4,
- respiratory, thoracic and mediastinal disorders grade 3 or 4,
- anemia grade 4,
- thrombocytopenia grade 4, and
- infections grade 4.

7.4.2 Secondary endpoints

Overall survival (OS) is calculated from the date of initial staging until the date of death, and, if the patient is alive, is censored at the date of last information including follow-up visits and quality of life questionnaires.

Tumor response (final treatment outcome) is the rate of complete remissions (CR) at the restaging after primary study treatment including radiotherapy if applicable (remission criteria see section 13.5). Patients with unknown tumor status after primary treatment and patients receiving a different treatment will be handled according to GHSG SOPs.

Further secondary endpoints are defined in section 10.3 and 10.4.

7.5 TRIAL PARAMETERS AND ASSUMPTIONS

7.5.1 Expected recruitment

The HD18 trial accrued around 300 patients in the first year of recruitment and around 400 patients in each following year since then. We expect a similar recruitment for the HD21 trial. While patients with NLPHL were included in HD18 they only account for 3.5% of patients, a rate not compromising expected rates for HD21. Thus a recruitment period of three years will expectedly lead to 1,100 patients; each additional quarter would yield 100 patients. Considering participation of the LYSA (Lymphoma Study Association), it will be sufficient to include the largest 100 centers in Germany, based on recruitment of the ongoing trials HD18 (GHSG) and AHL 2011 (LYSA, ClinicalTrials.gov identifier NCT01358747).

Based on data of HD18, we expect that 85-90% of the patients may be included in a per-protocol (PP) analysis set.

7.5.2 Estimation of the 5-year PFS rate in the escalated BEACOPP group

The final analysis of the HD15 trial with a median follow-up for PFS of four years demonstrated a 4- year PFS of 91.0% and a 5-year PFS of 90.6% after six cycles of escalated BEACOPP for the subgroup of patients with classical Hodgkin lymphoma in the intention to treat analysis set. Thus, we assume a 5-year PFS of 90.5% for the HD21 trial.

7.5.3 Assumed efficacy of BrECADD

BREACDD has been tailored with the intent to be a replacement of escalated BEACOPP with equal anti-tumor efficacy. Therefore the sample size calculation assumes equal efficacy of both treatment groups with a true difference in 5-year PFS of zero (i.e. a hazard ratio of one).

7.5.4 Definition of the non-inferiority margin for the 5-year PFS rate

Clinically relevant inferiority has been defined as an absolute difference of 6 percentage points in 5-year PFS, i.e. a 5-year rate of 84.5% for the BrECADD group. This margin corresponds to a hazard ratio of BrECADD vs. escalated BEACOPP ($HR_{BrECADD/BEACOPP}$) of ln(0.845)/ln(0.905)=1.69 for the sample size calculation. If a reduction in efficacy of this size can be excluded, the experimental group will be considered non-inferior.

7.5.4.1 Justification of the margin

The selection of the non-inferiority margin is based upon a combination of statistical reasoning and clinical judgment. It has been discussed within the GHSG panel consisting of experts in the field as well as patient representatives. Different aspects contributed to the selection of 6% as acceptable lower margin for non-inferiority. First, PFS differences do not necessarily translate into OS differences, since patients might be rescued by a second line treatment. Accordingly, differences in PFS might be acceptable to a certain degree. In fact, alternative and worldwide-acknowledged treatment strategies accept PFS differences of 20% compared to escalated BEACOPP assuming that this will not result in OS differences [21]. However, a 20% PFS difference results in 20% more patients (i.e. 30% in total) being in need of high dose chemotherapy. Although there are no reliable data on the toxicity and outcome of this intervention, there was a consensus amongst the panel members that this large number of patients undergoing high dose chemotherapy and its toxicities is not acceptable when using an intensive regimen up front. We thus decided to use a clearly smaller margin than 20%, a third of that was considered tolerable at most. A margin of 6% margin allows the successful conduct of the study regarding the patient number we need to conclude non-inferiority: reducing the margin from six to five percentage points would increase the number of required events by an infeasible 25%. In summary, the GHSG agreed that the 6% margin is justified taking the assumed benefit in terms of a better tolerability into account.

7.5.5 Estimation of the TRMB rate in the escalated BEACOPP group

The following table shows toxicity rates from patients treated with 6 cycles of escalated BEACOPP from interim data from the HD18 trial.

TRMB component	**HD18 (6 cycles n=492, CTCAE V.3)**	**HD18 (4 cycles, n=496, CTCAE V.3)**
organ toxicity grade 3 or 4	16.7%*	7.7%
anemia grade 4	10.2%	
thrombocytopenia grade 4	47%	37.9%
infection grade 4	1.6%	
Any of the above	58.3% (55.6% without anemia)	41.3%

*) single toxicities ranging between 0.8% (heart) and 9.8% (nervous system)

Since hepatobiliary toxicities during treatment were not recorded in the HD18 trial and the grade 4 anemia definition was changed from “Hb <6.5 g/dl” to “life threatening” between CTCAE versions 3 and 4, we assume that the total treatment related morbidity rate will range between 55% and 65% in patients treated with 6 cycles and between 39% and 48% in patients treated with 4 cycles of escalated BEACOPP. In the HD18 trial, 25% of all recruited patients were PET-2 positive with an FDG uptake higher than in the liver parenchyma. Thus, we assume that between 51% and 61% of patients treated with BEACOPP will experience one or more TRMB events.

7.5.6 Expected TRMB rate in the BrECADD group

Final analysis data from the targeted BEACOPP phase II trial show that 14 of 52 patients treated with 6 cycles BrECADD were affected by TRMB (26.9%, exact 95% CI 16% to 41%).Despite the wide confidence interval due to small numbers, we expect that the true TRMB rate will be at least by 10 percentage points less than with BEACOPP.

7.6 TEST DESIGN

7.6.1 Non-inferior efficacy in the BrECADD treatment group

To assess non-inferior efficacy of the BrECADD group the two-sided 95% confidence interval (CI) for the $HR_{BrECADD/BEACOPP}$ derived from a Cox regression incorporating the stratification factors from randomization will be examined. This corresponds to a one-sided significance level of $\alpha = 0.025$.

The following hypotheses will be considered:

Null hypothesis	H_{01} :	$HR_{BrECADD/BEACOPP} \geq 1.69$
Alternative hypothesis	H_{A1} :	$HR_{BrECADD/BEACOPP} < 1.69$

If the upper margin of the CI is lower than 1.69, non-inferiority is demonstrated. The primary analysis set will be the ITT analysis set.

7.6.2 Lower TRMB rate in the BrECADD treatment group

TRMB rates will be compared between groups using a Cochran-Mantel-Haenszel test adjusting for the same stratification factors if and only if non-inferior efficacy of the BrECADD group can be established (a priori ordering of hypotheses). Therefore no adjustment for multiplicity of the significance level is required. The following hypotheses for difference will be considered:

Null hypothesis	H_{02} :	$TRMB_{BEACOPP} = TRMB_{BREACDD}$
Alternative hypothesis	H_{A2} :	$TRMB_{BEACOPP} \neq TRMB_{BREACDD}$

BrECADD will be considered superior if the two-sided test is significant at a two-sided level of $\alpha = 0.05$ and if the TRMB rate in the BrECADD group is lower. The primary analysis set for this objective will be the ITT analysis set.

7.6.3 Power considerations

Both primary endpoints are to be investigated with a power $1-\beta$ of at least 90% each. The combined power should not fall short of 80% when using the primary (ITT) analysis set.

7.7 SAMPLE SIZE ESTIMATION

7.7.1 Non-inferior efficacy in the BrECADD treatment group

The required sample size is calculated assuming an exponential model without stratification factors and the confidence interval being calculated using normal approximation [30]. With

the conditions from section 7.5 and the test design outlined in section 7.6, the required number of failure events at a one-sided significance level of α = 0.025 and a power of 90% is 154. To observe this number 1,481 patients are required within a recruitment period of 48 months with an additional follow-up of 42 months. Thus the trial objective may be reached if 1,500 patients are recruited with a total duration of recruitment plus follow-up of 7.5 years if the assumptions are correct.

7.7.1.1 Robustness of the sample size estimate

The following table shows the resulting power of the trial under different assumptions for 5-year PFS for both the (primary) ITT and (secondary) PP population, respectively. It is assumed that 85% of all patients will be eligible for the PP analysis.

Scenario	5-year PFS	Non-inferiority margin (HR)	Non-inferiority margin (5- year PFS)	Power for ITT analysis set (n=1,500)	Power for PP analysis set (n=1,275)
Baseline scenario					
1	90.5%	1.69	6%	90.4%	85.3%
Robustness scenarios					
2	91%	1.69	5.7%	88.8%*	83.4%
3	91.5%	1.69	5.4%	87.0%$	81.2%
4	90%	1.69	6.3%	91.7%	87.0%
5	89%	1.69	6.9%	93.9%	89.9%

*) 90% with 3 additional months of follow-up

$) 90% with 7 additional months of follow-up

Scenario 1 is the original sample size calculation for the trial. The last column shows that the (secondary) PP analysis of this endpoint will have a power above 85% when the same set of hypotheses H_{01} and H_{A1} is considered. If the 5-year PFS rate is 0.5 percentage points better than expected, observing the necessary number of PFS events will require three additional months of follow-up (2) to achieve a power of 90%. Seven additional months are required if the the 5-year PFS rate is 1 percentage point better than estimated (3). If the 5-year PFS rate is lower than expected by 0.5 or 1.5 percentage points, it will become easier to establish non-inferiority with the margin of 1.69 for the hazard ratio (4, 5).

Thus the trial is feasible without an increase in recruitment under different scenarios if additional follow-up is accepted in case the observed 5-year PFS rate is higher than

anticipated. Alternatively, the number of patients may be increased by 50-150 patients without increasing the total study duration in these situations (details not included in table). The power to analyse the PP population will be above 80% in all scenarios covered.

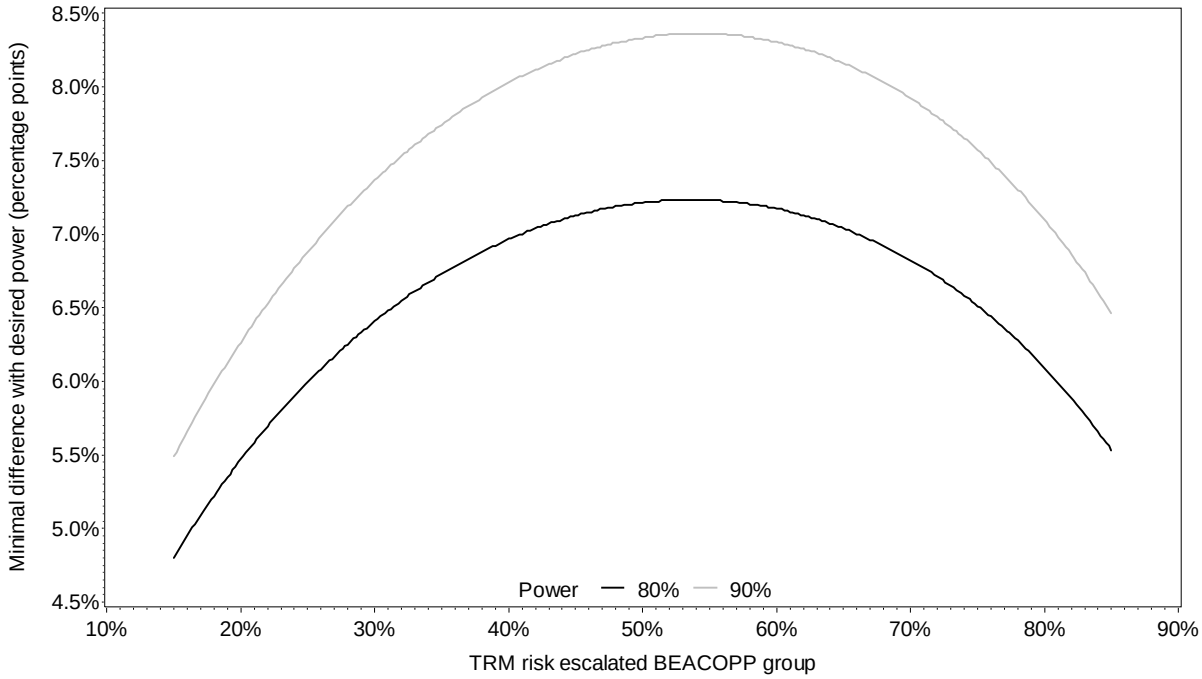
If recruitment is lower than expected, the total trial duration will have to be increased to be able to reach the trial objective.

7.7.1.2 End of recruitment

If the recruitment takes a faster or slower course than expected, the principal investigator, in consultation with the Data Monitoring Committee (DMC), has to decide on when to end the recruitment period.

7.7.2 Lower TRMB rate of the BrECADD treatment group

The following figure shows the TRMB risk reduction in percentage points that may be shown with 1,500 patients with both 80% and 90% power (unadjusted Chi²-test for a conservative power estimate).



The figure shows that while the difference that may be shown depends on the TRM risk in the standard BEACOPP group, all reductions of at least 7.25 percentage points will result in a power of 80% and above, while a reduction of at least 8.4 percentage points will yield a power of at least 90%. Since we hope for a reduction of at least 10 percentage points, it is sufficient to derive the sample size for the trial from the efficacy endpoint only.

7.7.3 Combined power

The combined power for the entire trial is the product of the powers for both primary endpoints if both are independent from each other. Thus, using the primary ITT analysis set, the chances of successfully achieving both trial objectives is at least 0.9 * 0.9 = 0.81 if the upper CI limit of the $HR_{BrECADD/BEACOPP}$ for PFS is less than 1.69 and the TRM rate in the BrECADD group is at least 8.4 percentage points lower than in the BEACOPP group. If the reduction in the TRM rate is at least 9.5% (power 95.8%), combined power will be 0.9 * 0.958 = 0.862, i.e. above 85%.

7.8 ANALYSIS METHODS

Data will be summarized with respect to demographic and baseline characteristics, safety observations and measurements as well as efficacy parameters. The available data are illustrated by means of tables and graphs. Wherever applicable, statistically measured values that characterize the distribution and two-sided 95% confidence intervals calculated for descriptive comparisons between groups will be shown. Details for each parameter will be defined in a statistical analysis plan based on the requirements stipulated by ICH E3 and the CONSORT statements. It is to be finalized prior to the first analysis of the study endpoints.

7.8.1 Populations for analysis

The **full analysis set (FAS)** consists of all patients randomized into the trial. It will be used for statistical monitoring.

The **intention-to-treat (ITT) analysis set** includes all patients from the FAS whose initial diagnosis of HL has not been revoked by the reference pathology panel. Patients originally considered as having cHL but considered NLPHL after reference pathology review remain in the ITT set.

The **per-protocol (PP) analysis set** consists of all ITT set patients who violated no inclusion and exclusion criteria and were treated in conformity with the trial protocol. Treatment deviations considered relevant for exclusion are

- change of treatment groups;
- less than five complete cycles of chemotherapy or more than 7 cycles;
- administration of any antineoplastic substance that is not part of the treatment regimen randomized.
- irradiation of a PET-negative patient (irradiation of bone lesions endangering stability is allowed based on the discretion of the trial center); or
- lack of irradiation if radiotherapy was recommended by the PET panel.

Patients with any of these deviations will be excluded from the PP analysis set unless the treatment deviation is caused by treatment toxicity, progression of disease or death.

The analyses of both primary endpoints (see section 7.4.1) will be performed within both the PP and the ITT analysis set. For the purpose of non-inferiority studies, ITT analyses alone are not sufficiently conservative. Jones et al. therefore recommend to perform both ITT and PP analyses and to carefully analyze those patients who were excluded from the PP set [31]. The ITT analysis set will be the primary set for both primary endpoints with the PP analysis serving as a supportive sensitvity analysis. For trial results to be convincing, results will have to be concordant.

7.8.2 Monitoring of recruitment

In order to identify possible recruitment problems at an early stage, the accumulated number of recruited patients is regularly compared to the recruitment rate expected for the trial.

7.8.3 Statistical safety monitoring

Safety analyses are performed for all patients on a regular basis. In these analyses, the frequency of the following parameters is monitored:

- tumor-related events (progression, relapse),
- deaths,
- acute toxicities of grade 3/4,
- SAEs / SUSARs,
- Second malignancies, and
- results of futility assessments

The results of the safety analyses will be submitted to the DMC (see section 8.2.4) by the responsible statistician. The safety analysis concept and procedures are described in detail in the statistical monitoring manual. The manual contains definitions of the parameters and the times of analysis. It also describes the evaluation strategies and information exchange with the DMC.

7.8.4 Final analysis

The cumulated number of PFS events is recorded at regular intervals and used for determining the time of analysis.

According to the sample size calculation, a sufficient number of events will have occurred after 7.5 years (4 years of recruitment followed by 3.5 years of follow-up (see section 7.7.1). Taking into account that additional time will be needed to complete the documentation and to deal with queries, and that there will be 1-year follow-up intervals from the fifth year onwards, the final analysis will probably be performed 3.75-4 years after end of recruitment.

The GHSG Trial Coordination Center will compile a comprehensive report on the final analysis. This report is to be completed within three months after the final analysis and will form the basis for the report to the legal authorities.

7.8.4.1 Specific preplanned analyses

Sensitivity of PFS to the censoring rule

To better assess the impact of patients receiving anticancer treatment without evidence of objective progression, the primary efficacy analysis will be supplemented with an analysis using a different censoring rule for PFS in the ITT analysis set. In addition to the patients outlined in section 7.4.1, patients will also be censored in case of

- administration of any antineoplastic substance that is not part of the treatment regimen randomized. or
- irradiation of a PET-negative patient (irradiation of bone lesions endangering stability is allowed based on the discretion of the trial center).
- treatment with more than 7 cycles of chemotherapy;
- change of treatment groups;

Homogeneity of effects

Planned subgroup analyses for both primary endpoints will include presentation of effect by Ann Arbor stage, IPS groups, age groups, and gender using forest plots.

TRM

Single components of the TRM endpoint will also be presented separately including 95% confidence intervals for the differences between groups.

7.8.5 Follow-up analyses

All subsequent analyses, which are planned to take place at intervals of five years after the final analysis, will be carried out based on the statistical analysis plan for the trial.

7.9 EARLY TERMINATION STRATEGY

The principal investigator is responsible to decide whether to stop the whole trial. In case of concern, he will receive detailed information from the Data Monitoring Committee (see section 8.2.4) that will serve as a basis for this decision.

This information, amongst others, includes data on the course of recruitment, balance of patient characteristics, execution of therapy, frequency of acute toxicities and SAEs and the distribution of events in the individual trial groups.

However, since not only statistical factors but also medical, ethical and organizational aspects must be considered when deciding on terminating the trial, an early termination of the trial cannot be completely formalized beforehand.

8 DOCUMENTATION AND MONITORING

8.1 DATA COLLECTION

Study data will be collected using eCRFs accessed by a web browser. Use of the system requires a personal login created by acromion only available to named study personnel that have been trained for the system. Data may be entered by either the investigator or a person authorized to conduct the documentation (e.g. trial assistant). Correctness of the documentation in the Marvin database always has to be confirmed by an investigator by digital signature.

Enrolling new patients into the trial starts with adding a new case in the EDC system. The first item to be completed is the confirmation that a signed and dated informed consent is present followed by entry of baseline data required for randomization.

From this information a report will be created that has to be printed, completed by hand and then sent to the GHSG TCC by fax together with the last histology report and documents that may be required for scientific component projects if applicable.

If the data provided is complete and consistent, the GHSG TCC will assign a CaseID to the patient as permanent study specific identification followed by randomization. Both items will be entered into the EDC system by TCC personnel and the system then sends a confirmation to the treating physician by email that the patient has been successfully enrolled.

Only after enrollment all further eCRFs for the documentation will become available in the EDC system with the patient now being identified by CaseID. All visits should be documented and signed in a timely manner.

A manual both for the EDC system in general as well as instructions on enrollment, data entry and entry conventions, digital signatures and the query process will be available from the starting page of the EDC application after login. .

8.2 MEASURES FOR SAFEGUARDING DATA QUALITY

8.2.1 Monitoring

In order to assure a high quality standard regarding the trial execution and collected data, all trial centers will be visited by monitors at regular intervals.

The monitors compare the data of a random selection of patients on the eCRFs as fully as possible to the source data. The extent and procedures of the monitoring measures are described in detail in a separate monitoring manual. In this manual, all trial-related issues are

explained, and the minimum extent of the monitoring activities is specified on corresponding forms.

All investigators have to agree to these monitoring visits at their trial center. The purpose of these visits is in particular

- to check if the statutory standards are met,
- to evaluate the progress of the trial,
- to control whether the trial protocol is adhered to,
- to discuss problems, including AEs,
- to check if the eCRFs are fully and accurately filled in,
- to validate the eCRFs by comparing them to the original data,
- to check how the trial medication is handled.

For each visit the monitor will draw up a monitoring report that documents the progress of the trial and all occurring problems.

The monitor is entitled to compare eCRFs with original documents (e.g. clinical record, ECG, laboratory reports) in due consideration of the data protection regulations. The monitor is obligated to maintain confidentiality. For the purpose of trial-related monitoring, the investigators have to give the monitor direct access to original data/documents.

The GHSG reserves the right to pay a certain trial center additional or more frequent monitoring visits if the center has shown irregularities or problems with the execution of the trial.

Shortly after a monitoring visit, the written follow up-letter will be sent to the respective trial center.

8.2.2 Audits / Inspections

The aim of an audit is to assure the validity of data and the credibility of the trial. For this purpose, the sponsor may commission persons who are otherwise not involved in the trial (auditors). The auditors have the right to examine all trial-related records (in particular the trial protocol, eCRFs, patient files, documentation of trial medication, trial-related correspondence).

The sponsor and all participating centers have committed themselves to support inspections by the appropriate authorities and on-site inspections by ethical committees and to allow the persons who have been commissioned to perform such inspections direct access to the original documents.

All persons who carry out audits or inspections are obligated to treat patient data confidentially.

8.2.3 Statistical monitoring

8.2.3.1 Safety analyses

Intensive safety analyses of all patients are performed on a regular basis.

The procedure is described in detail in chapter 7.8.3.

8.2.3.2 Course of recruitment

In order to identify potential recruitment problems at an early stage, the accumulated number of recruited patients is regularly compared to the expected recruitment rate for the trial.

If the recruitment takes a faster or slower course than expected, the sponsor has to decide on when to end the recruitment period.

8.2.4 Data Monitoring Committee

The Data Monitoring Committee (DMC) is responsible for a continuous evaluation of the

- progress of the trial,
- safety of patients,
- serious adverse events (SAEs), and
- results of futility assessments,

and it has to give corresponding recommendations to the trial chairman. For this purpose, the GHSG Trial Coordination Center will regularly provide the DMC with all information it requires (see chapter 7.8.2 and 7.8.3). The individual responsibilities and processes will be described in detail in the DMC charter based on SOPs of the GHSG Trial Coordination Center. The charter will include decision rules on when to stop the trial for futility.

The DMC for this trial consists of the following experts:

Prof. Dr. Hagenbeek, Uetrecht, Netherlands

Prof. Dr. W. Lehmacher, Köln

Dr. G. Schwarzer, Freiburg

Prof. M. Hutchings (Copenhagen)

None of these experts is involved in the execution of this trial.

8.3 DOCUMENTATION

All trial-relevant data are to be recorded on the provided eCRF within a short period of time by the responsible investigator, sub-investigator or study assistant.

8.3.1 Data management

The GHSG Trial Coordination Center checks documentation for completeness and plausibility and violations of the study protocol.

9 REVIEW PANELS

9.1 PATHOLOGY REVIEW

Histological confirmation of diagnosis is an indispensable precondition for including a patient into the trial. In Germany, eight pathology review centers are available for confirmation of diagnosis. These review centers have extensive experience in the field of lymph-node pathology and have access to all required immunohistological and molecular biological techniques and reagents.

The pathology reviews have to be performed by one of the following eight pathology review centers:

Prof. Dr. med. A. C. Feller Hämathologie Lübeck Konsultations- und Referenzzentrum für Lymphom- und Knochenmarkdiagnostik	Maria-Goeppert-Str.9a 23562 Lübeck Tel.: +49 451/580 840 0 Fax: +49 451/580 840 17
Prof. Dr. med. Falko Fend Universitätsklinikum Tübingen Institut für Pathologie	Liebermeisterstr. 8 72076 Tübingen Tel: +49 7071/29-82266 Fax: +49 7071/29-2258
Prof. Dr. med. M. L. Hansmann Konsultations- und Referenzzentrum für Lymphknoten- und Hämatopathologie Universitätsklinikum Frankfurt Dr. Senkenberg. Institut für Pathologie	Haus 6 Theodor Stern Kai 7 60590 Frankfurt Tel: +49 69/6301 5364 Fax: +49 69/6301 5241
Prof. Dr. W. Klapper Leiter Institut für Pathologie Sektion Hämathopathologie Lymphknotenregister der Universität Kiel	Michaelisstr. 11 24105 Kiel Tel.: +49 431/500 15716 Fax: +49 431/500 15714

Prof. Dr. med. P. Möller Direktor des Pathologisches Instituts Universitätsklinik Ulm	Oberer Eselsberg M 23 89069 Ulm Tel.: +49 731/502 3321 Fax: +49 731/502 3884
Prof. Dr. med. German Ott Robert-Bosch-Krankenhaus Abteilung für Pathologie	Auerbachstr. 110 70376 Stuttgart Tel: +49 711/8101-3390 Fax: +49 711/8101-3619
Prof. Dr. med. A. Rosenwald Direktor des Pathologischen Instituts der Universität Würzburg	Josef Schneider Str. 2 97080 Würzburg Tel.:+49 931/31 81199 Fax: +49 931/31 81224
Prof. Dr. med. H. Stein Pathodiagnostik Berlin Berliner Referenzzentrum für Lymphom- und Hämatopathologe	Komturstr. 58-62 12099 Berlin Tel.: +49 30/236084-210 Fax: +49 30/236084-219

For participating countries:

After prior agreement with the sponsor (GHSG) a local expert pathologist can be determined. The GHSG Histopathological Review Form (according to chapter 17.1) must be used for documentation.

10 SCIENTIFIC COMPONENT PROJECTS

10.1 ACCOMPANYING CLINICAL SCIENTIFIC INVESTIGATIONS

10.1.1 Background

The prognosis of Hodgkin lymphoma has improved markedly, especially through the introduction of aggressive polychemotherapy treatment regimens (e.g. escalated BEACOPP). Nevertheless, some patients suffer a relapse or treatment-related toxicities (e.g. second malignancies, cardiac dysfunctions or infertility). Therefore, it seems important to identify in advance those patients who have an increased risk for suffering treatment failure or treatment-related toxicity. The knowledge of genetic, serological and molecular markers could help to identify such patient groups and to treat them individually in the future in view of these risks (intensification versus detoxification).

To estimate the prognosis different clinical and laboratory parameters are applied. The best prognostic tool is currently the International Prognostic Score, which was established with the help of GHSG data [32]. Several other laboratory parameters might also have a predictive value for survival [33]. However, data documenting this has so far only been generated by small and mainly non-controlled studies and are therefore not sufficiently validated for clinical application.

Hence, the predictive value of these biological markers, which were identified on the basis of a small number of samples, and the predictive value of new markers should be confirmed through studies with a large number of patients. There will be histopathological studies that determine the protein and RNA expression of different molecules in paraffin or frozen tissue sections by means of immunohistochemistry to answer routine and scientific questions. Apart from that and depending on technical feasibility, also RNA expression studies by means of gene chip analyses or comparable technologies, such as real-time PCR, will be carried out. In addition, there will be further investigations on the concentration of a number of potential prognostic markers in the patients' serum. Beside cytokines and soluble proteins, these markers also include the DNA of the Epstein-Barr virus and possibly further viral components that are currently not measured on a routine basis. These markers will be evaluated with regard to their suitability as monitoring parameters for early indication of treatment response and treatment failure under treatment conditions.

The scientific component project is reserved only for german sites due to organizational reasons.

10.1.2 Submission of material

From every trial participant who has given consent to participation in the scientific co-projects, blood samples will be taken as follows (only German Sites).

Samples have to be collected according to the following schedule.

The samples may be tested for immunogenicity. The samples have to be sent to the address stated below.

Schedule for the submission of laboratory material:

Point in time	**Purpose**	**Material**
Before start of treatment	Scientific co-investigation Late toxicity	10 ml serum 10 ml EDTA 20ml blood plasma
Interim restaging After 2 cycles	Scientific co-investigation Late toxicity	10 ml serum 10 ml EDTA 20ml blood plasma
Restaging after end of chemotherapy	Scientific co-investigation Late toxicity	10 ml serum 10 ml EDTA 20ml blood plasma
12 months after EOT	Scientific co-investigation Late toxicity	10 ml serum 20ml blood plasma
24 months after EOT	Scientific co-investigation Late toxicity	10 ml serum 20ml blood plasma
60 months after EOT	Scientific co-investigation Late toxicity	10 ml serum 20ml blood plasma
120 months after EOT	Scientific co-investigation Late toxicity	10 ml serum 20ml blood plasma

Kits containing the necessary specialized cell free DNA drawing tubes will be provided to the trial centers and should be used for all patients who participate in the scientific co-projects. For cell free DNA collection the special cfDNA tube provided in this kit **has to be used**, but all tubes necessary for the respective timepoints are provided within the kit for convenience. Please post the samples using the provided packaging material together with the completed dispatch note **on the day of taking** to to following address:

Uniklinik Köln
Labor für Immuntherapie
Raoul Michels GB 16, UG
Kerpener Str. 62
50937 Köln
Deutschland

10.1.3 Genetic investigations

With the aid of the patients' blood and tissue samples collected in this trial, further genetic DNA analyses can be conducted in the future. The precise extent, study question and design of these investigations are currently not clearly defined yet. However, it is likely that in the future, genetic markers will help to enable a further individualized and risk-adapted treatment. But only if genetic investigations are combined with clinical disease-related and personal patient data, it will be possible to obtain useful study results. By means of genetic investigations it will also be possible to analyze aspects regarding the genetic basis of Hodgkin lymphoma and the hereditability of the disease ("familial Hodgkin lymphoma"). In the HD21 trial, such investigations will be carried out in individual cases. It is also planned to determine within the HD21 trial whether it is possible to identify any genetic changes that are associated with an increased risk for the development of cardiac toxicity or infertility.

Note regarding the declaration of consent:

Corresponding results can only be communicated to patients if they have given their consent to being contacted by the GHSG directly. "Results" means the results of the genetic investigation as a whole, not the individual analysis of each patient.

10.2 ANTI-DRUG ANTIBODY MEASUREMENT

In addition to the accompanying clinical scientific investigations as explained in the study protocol (chapter 10.1), further immunogenicity samples will be taken from patients receiving brentuximab vedotin for the determination and measurement of anti-drug antibodies (HAHA, HAHA-1, HAHA-2, HAHA-3). Primary objective of this investigation is to identify the ratio of patients with positive detection of these antibodies. To answer this question blood samples of 100 patients are required. Samples will be taken in a number of selected University hospitals in Germany.

10.2.1 Submission of material

From every trial patient who has given consent to participation in this specific scientific co-project, blood samples will be taken as follows.

Before start of treatment, after cycle 1, after cycle 2 and after cycle 6 OR at termination if treatment is terminated before cycle 6 a serum sample (5ml) has to be taken from the patient.

In order to guarantee a correct sample collection, please see sample collection information below:

10.2.2 Immunogenicity samples

Materials:

Collection tube: One 5.0mL Serum Separator Tube (SST, Gold cap)

Transport tube: Four 2mL polypropylene cryovial

Transfer pipettes

Procedure:

1. Draw blood using standard venipuncture technique into a 5.0 mL serum separator tube.
2. Invert 5 times and then allow samples to clot for 30 minutes at room temperature.
3. Centrifuge for 10 minutes at approximately 1,000 xg.
4. Remove serum using a transfer pipette and transfer into cryovials. Transfer approximately .5mL into HAHA, HAHA-1, and HAHA-2 2mL polypropylene cryovials. Transfer the remaining serum into the HAHA-3 2mL polypropylene cryovial.
5. Freeze and store cryovials at -70 C°.

The samples have to be shipped directly to Covance on dry ice to the address stated below

Lab Support/Specimen Management

Immunochemistry Services

Covance Laboratories, Inc.

3635 Concorde Parkway; Suite # 100

Chantilly, VA. 20151

10.3 SURVEY OF LATE TOXICITIES

10.3.1 Background

Due to the continuous improvement of the results in Hodgkin lymphoma treatment, it is becoming increasingly important to reduce late toxicities while retaining treatment efficacy. In the HD21 trial the toxicity profiles of 6 cycles of escalated BEACOPP and 6 cycles of BrECADD are compared to each other. Recording late effects, especially pulmonary and cardiac toxicities as well as those that impair fertility, is another important aim of this trial.

10.3.1.1 Cardiac toxicities

Cardiac diseases rank among the most frequently occurring causes of death in long-term survivors of Hodgkin lymphoma. The measures required for treatment of Hodgkin lymphoma may induce cardiac dysfunctions such as systolic and diastolic pumping dysfunctions to the point of manifest coronary heart disease. Cardiomyopathy, myocardial infarct, coronary heart disease, valvular dysfunctions or arrhythmia may also be sequelae of Hodgkin lymphoma therapy. Such toxicities are caused by anthracyclines, particularly in combination with active substances such as cylophosphamide, bleomycin, etoposide or vincristine. If the patient has received mediastinal irradiation before or within the scope of Hodgkin lymphoma treatment, this is another risk factor for the development of a myocardial lesion. Further risk factors are diabetes mellitus and hypertonia, sex (female) and age (< 15 and > 65 years) [34, 35].

It is important to determine from when on relevant events can be detected and from when on therapeutic interventions seem useful. This can only be answered by collecting further information on the course of the disease. Apart from that, genetic material will be collected to detect potential genetic risk factors. If such risk factors can be defined for Hodgkin lymphoma, this may enable the development of an individual risk profile and a treatment approach adjusted and individualized accordingly, both in terms of first-line HL therapy and in terms of therapeutic strategies for subclinical and clinical dysfunctions.

10.3.1.2 Pulmonary toxicities

The cyctostatic agent bleomycin, which is used in Hodgkin lymphoma therapy across all disease stages, may lead to considerable lung parenchym damage both during chemotherapy and afterwards. Administration of bleomycin can induce a dose-dependent interstitial pneumonitis with transformation to pulmonary fibrosis (see chapter 5.4.2.1). In rare

cases, a dose-independent acute alveolitis may occur [36, 37]. Higher pulmonary toxicity is to be expected only at a cumulative bleomycin dose of > 400 mg. The incidence of bleomycin-related toxicities chiefly depends on the total given dose, the age of the patient, previous pulmonary diseases, accompanying radiotherapy and combination with other chemotherapy drugs. The combination of bleomycin-containing polychemotherapy and irradiation of the thorax also increases the risk of pulmonary toxicities [38].

The development of a bleomycin lung is not predictable and can occur after the first administration of bleomycin.

Pulmonary function can only serve as a reference parameter, but not for early detection of a bleomycin lung. A significant correlation between DLCO or vital capacity and a bleomycin lung could not be demonstrated [39]. The best way to early detect a bleomycin lung is to record clinical symptoms and to perform chest X-ray examinations in case lung toxicity is suspected.

Upon suspicion of chemotherapy- or radiotherapy-induced pneumonitis, a high-resolution CT should be performed as standard imaging method.

10.3.1.3 Investigations on fertility

Most Hodgkin lymphoma patients are young and often still childless at diagnosis. Sterility caused by a disturbed ovarian function or spermatogenesis is a frequently observed side-effect of treatment that often leads to a long-term impairment of the patient’s quality of life.

Fertility disturbances after chemotherapy are mainly caused by alkylating agents. The degree and duration of spermatogenesis damage are dose-dependent. The available data demonstrate a rate of azoospermia between 96% and 100%, with recovery rates between 12% and 20% after 2 years.

Kreuser reports an infertility rate of 87% (13/15) after 4 cycles of COPP/ABVD. No recovery of spermatogenesis was observed in these patients [40].

Oligospermia and azoospermia have likewise been observed after ABVD. Viviani et al. reported azoospermia in 33% of the patients after ABVD and oligozoospermia in 21%. Within 18 months, spermatogenesis completely regenerated in all observed patients [41].

Since many patients already show a damaged spermatogenesis with oligospermia and azoospermia before treatment, the possibility of in vitro fertilization (IVF) is limited. For patients with severe dyspermia before and after treatment, intracytoplasmic spermatozoa injection (ICSI) is currently the most efficient reproduction technique. It has demonstrated high rates of fertilization even with poor initial parameters [42].

Patients should always be informed about the possibility of pre-treatment sperm cryoconservation.

Most treatment compounds that are germ cell damaging in males often lead to a damage of the ovary in females as well. In female patients the main adverse effect of chemotherapy is temporary or persistent amenorrhea with subsequent sterility. After MOPP chemotherapy, for example, amenorrhea occurs in 45-80% of cases. These large variations are due to the varying age of patients.

An amenorrhea rate of 77% was reported following treatment with COPP/ABVD [40]. While permanent ovarian insufficiency is observed in only 30% of patients under 30 years of age, this rate increases to 80% in patients over 30. In contrast, ABVD appears to have less gonadal toxicity. Bonadonna (1984) reported no cases of amenorrhea or disturbance of menstruation in 24 patients receiving ABVD [43]. After 8 cycles of escalated BEACOPP the amenorrhea rate is about 50%, according to data of the GHSG. In the respective studies patients over 30 years were also affected more often [44].

Since cytotoxicity does not only affect the germ cells but also the supporting, hormonally active theca and granulosa cells, this frequently results in decreased levels of the circulating estrogen with menopausal symptoms and subsequent psychic and vegetative disturbances [40]. Apart from the respective treatment regimen and number of cycles, the extent of ovarian insufficiency mainly depends on the patients' age. Recent studies proved the anti-Müllerian hormone (AMH) to be the most sensitive parameter for a reduced ovarian reserve after HL treatment [45]. If treatment-related ovarian insufficiency occurs, early hormonal substitution therapy is a possibility that has to be discussed, among other things for prophylaxis of osteoporosis.

10.3.1.4 Second malignancies

10.3.1.4.1 MDS and AML

Compared to other second malignancies, second AML and MDS show a considerably shorter period of latency, and with an incidence of 0.5 – 2% they are comparably rare. About 25% of cases develop during the first year and about 80% within 5 years after Hodgkin lymphoma therapy [13, 46].

The risk of second AML to occur depends on various factors such as the patient's age at the time of diagnosis and the administered drugs. Apart from different risk factors such as the patient's age at the time of diagnosis and the agents used for therapy, the risk for developing second MDS or AML correlates with the dose intensity of the administered polychemotherapy regimen. The MDS/AML-inducing effect of chemotherapy is attributed to the alkylating agents (e.g. procarbazine and cyclophosphamide) as well as to the

topoisomerase II inhibitors (e.g. etoposide) contained in the regimen [15] [16]. The prognosis of second leukemias is very unfavorable and even treatment with allogenic stem cell transplantation failed to improve it to a decisive degree. In a retrospective study by Josting et al. the overall survival rate after 2 years was 8% [13].

10.3.1.4.2 Non-Hodgkin lymphomas

Second non-Hodgkin lymphomas (NHL) usually occur 5-10 years after treatment. Their cumulative incidence is approximately 4-5% [47]. In the majority of cases these are diffuse B-cell lymphomas, which more often involve extranodal sites compared to primary NHL.

The prognosis of second NHLs is overall less favorable than that of primary NHLs. However, about 25% of patients attain long-term survival with standard chemotherapy [48].

10.3.1.4.3 Solid tumors

In an analysis of 1449 patients in four successive trial generations that was carried out by the European Organisation of Research and Treatment of Cancer (EORTC), the relative risk of death due to second solid tumors lay markedly above the rate for the normal population, even 10 and 15 years after the primary disease, although Hodgkin-related deaths became much less frequent in this time period [49]. In all studies with at least 15 years of follow-up, the incidence of solid tumors was 2-3 times higher than that of leukemias or second non-Hodgkin lymphomas [47]. Radiotherapy or combined modality are the greatest risk factors for the development of second solid tumors. The prognosis of second solid tumors does not appear to differ from that of the corresponding primary tumor entities.

10.3.2 Aims of the toxicity survey

The main aim of the toxicity investigation is to survey all relevant late toxicities as precisely and longitudinally in time as possible.

The frequency and severity of late toxicities are to be documented and related to the treatment administered within the HD21 trial. In addition, possibilities for early detection of late toxicities are to be investigated.

10.3.2.1 Execution and documentation of the toxicity survey

10.3.2.1.1 Examinations regarding cardiac toxicity

Cardiac toxicity is examined by the standard procedures, echocardiography (LVEF) and ECG.

Examination times:

Echocardiography and ECG are to be performed before start of treatment, after 2 cycles of chemotherapy, at the time of restaging after chemotherapy, 12 months after end of chemotherapy as well as 2 and 5 years after end of chemotherapy.

10.3.2.1.2 Examinations regarding pulmonary toxicity

The best way to early detect a bleomycin lung is to record clinical symptoms, combined with high-resolution CT scans as standard imaging procedure. Independently thereof, in HD21 the lung function is to be tested and documented, not only before and during treatment but also after end of chemotherapy.

The lung function is to be examined **12 months after end of chemotherapy**. If there is no pathological finding in the examination 1 year after end of chemotherapy, further monitoring examinations are not necessary. If there is a pathological finding, annual monitoring examinations (lung function and, when indicated, chest X-ray and/or CT) are to be performed.

If bleomycin-induced toxicity is clinically suspected in a respective patient, this must be documented.

10.3.2.1.3 Examinations regarding fertility

To survey gonadal damage, spermiogram or menstrual history and hormone determinations should be part of the regular follow-up examinations. In case of pathological findings, these have to be documented.

Examination times: spermiogram or menstrual history as well as FSH, LH, β-estradiol or testosterone, AMH and inhibin B are strongly recommended **before start of treatment**, **at the time of restaging after end of chemotherapy** as well as **12 months after end of chemotherapy**. It is to be decided at the discretion of the treating physician, in consultation with the patient, if and when further examinations should be performed.

10.3.2.1.4 Documentation of second malignancies

Second malignancies are to be recorded as in the previous trials. The documentation must include the date of diagnosis and the type of second malignancy (leukemia/MDS, NHL, solid tumor). In addition, a copy of the histological findings report dealing with the second malignancy has to be submitted, if required (after consultation with the Trial Coordination Center).

10.4 ASSESSMENT OF QUALITY OF LIFE

10.4.1 Measuring instruments

The analyses of HD10-12 and the latest developments in questionnaire design have lead to some modifications in terms of the quality of life assessment.

The EORTC-QLQ-C30 [50] remains to be the core questionnaire in terms of health-related quality of life in cancer patients. However, our analyses as well as those of other study groups showed that the 5 scales postulated by the Mental Fatigue Inventory (MFI) cannot be replicated. Besides, there is a new EORTC module available for recording fatigue (EORTC-QLQ-FA13). Therefore, instead of the 20 questions contained in the MFI, we will now employ the 13 questions of EORTC-QLQ-FA13. This questionnaire was specifically developed for use in combination with EORTC-QLQ-C30. It was recently approved for use in clinical trials and its three dimensions were confirmed by an international trial [51].

In view of the importance and frequency of peripheral neuropathies (PNP) in connection with aggressive polychemotherapy regimens like BEACOPP, the formerly used single item regarding sensation disorders is not sufficient anymore. Therefore, an EORTC module for recording chemotherapy-induced peripheral neuropathies will be employed [52]. This questionnaire has good psychometric properties and demonstrated a very high test-retest reliability in recent studies [53]. Another reason for recording PNPs more precisely is the previous clinical experience gained with brentuximab vedotin: despite the favorable side-effect profile of this single agent, PNPs are presumably the most serious toxicity brentuximab vedotin may induce.

10.4.2 Neurotoxicity, gonadal toxicity and fatigue as main focus in the quality of life analysis

There are precise analysis algorithms for the questionnaires and modules employed in this trial, and in many cases also age- and gender-specific reference values for the average population in Germany are available [54]. The reference values facilitate the interpretation and classification of the results. They are not absolutely necessary for the direct comparison of both treatment groups, but as regards the EORTC-QLQ-C30 they permit an individual adjustment for the respective age and gender of the patients.

The existing data on the toxicity of both polychemotherapy regimens leads to the following hypotheses: compared to the standard group (BEACOPP), in the experimental group (BrECADD) there should be less reports of sensory PNP symptoms and possibly less fatigue during therapy. We regard fatigue as a subjective correlate of the overall burden for the organism due to tumor mass, toxicity and the resulting psychic and social consequences.

The corresponding statistical hypotheses for the acute phase during therapy (T) are as follows:

1. Sens. PNP: H1: $PNP_{Exp, T} < PNP_{Control, T;}$ H0: $PNP_{Exp, T} \geq PNP_{Control, T}$
2. Fatigue: H1:$\Delta FA_{Exp, T} < \Delta FA_{Control, T}$ H0: $\Delta FA_{Exp, T} \geq \Delta FA_{Control, T}$

ΔFA is the mean deviation from the age- and gender-specific reference value for fatigue [54] and PNP is the mean value of the sensory subscale of EORTC-QLQ-CIPN20.

Apart from that it will be tested whether the survivors of the experimental group will also report less late toxicity and a better quality of life after the acute phase. This should apply for chemotherapy-induced PNPs and should reflect in the sensory subscale of EORTC-QLQ-CIPN20. Furthermore, it is to be expected that the BrECADD regimen has a lower gonadal toxicity than BEACOPP due to the absence of procarbazine [55]. Should it be possible to achieve a broad improvement in tolerability with BrECADD, less cancer-related fatigue, and, accordingly, lower fatigue values should be verifiable in survivors. Our analyses of previous trials show that in most cases the recovery process is largely complete 2 years after end of chemotherapy. This is why the comparison of late toxicity was planned for this point in time.

The statistical hypotheses at 2 years after chemotherapy (2y) are in summary:

1. Sens. PNP: H1: $PNP_{Exp, 2y} < PNP_{Control, 2y}$ H0: $PNP_{Exp, 2y} \geq PNP_{Control, 2y}$
2. Fatigue: H1: $\Delta FA_{Exp, 2y} < \Delta FA_{Control, 2y}$ H0: $\Delta FA_{Exp, 2y} \geq \Delta FA_{Control, 2y}$
3. Fertility H1: $AM_{Exp, 2y} < AM_{Control, 2y}$ H0: $AM_{Exp, 2y} \geq AM_{Control, 2y}$

ΔFA is the mean deviation from the age- and gender-specific reference value for fatigue [54], PNP is the mean value of the sensory subscale of EORTC-QLQ-CIPN20, and AM stands for amenorrhea rate.

In the analysis of acute and longterm results there will be an adjustment for known and potential confounders and for the baseline values of the variables before treatment.

In addition, all function and symptom scales of EORTC-QLQ-C30 as well as the single items for both treatment groups will be described over time, and their deviations from the reference values will be visualized using heat maps. These and other statistics used in this context are descriptive and will report confidence intervals to compare and determine the accuracy of the estimates.

10.4.3 Execution of the quality of life survey in Germany

In addition to the instruments described above, a baseline form for sociodemographic characteristics is to be completed when entering the trial.

When a patient is entered into the trial, the Trial Coordination Center enquires whether the patient has already received or completed and returned the baseline form and first QoL

questionnaire before start of treatment. These documents have to be sent to the Trial Coordination Center. Further questionnaires are to be completed after 2 and 6 cycles of chemotherapy and after end of radiotherapy if applied.

If the patient has consented to being contacted directly by the Trial Coordination Center, post baseline questionnaires are sent directly to the patient. Otherwise, the QoL questionnaire is to be forwarded by the treating physician.

During the follow-up period, the Trial Coordination Center dispatches the QoL questionnaires at the respective examination times (3, 6, 12, 18 and 24 months after end of chemotherapy and annually thereafter). The patient should complete the questionnaires and send them back to the Trial Coordination Center. The patient may also hand over the completed questionnaires to his treating physician, who forwards them to the Trial Coordination Center.

11 ETHICAL ASPECTS

11.1 DECLARATION OF HELSINKI

The trial is executed in accordance with the Declaration of Helsinki (revised version of the 48th General Assembly of the World Medical Association, Somerset West, Republic of South Africa, October 1996) [56].

11.2 ETHICAL COMMITTEE

The trial cannot begin until the supreme federal authority and the responsible ethical committee have given their approval. The written vote of approval by the ethical committee and the permission by the supreme federal authority are stored in the trial master file. Every participating center receives a copy of both documents, which are to be deposited in the trial site file by the respective investigator.

All centers that would like to take part in this trial have to provide details on their qualification, especially with regard to the availability of technical equipment, facilities and staff for executing the trial as well as with regard to experience in executing similar clinical trials, pursuant to art.7 (3) and art.8 (5) of the German GCP regulations (GCP-V).

For this purpose, the investigator has to provide the sponsor with the following documents, which will then be sent to the involved ethical committees for assessment:

- CVs of the investigator and of all of their representatives, including details on their experience with medical trials in general
- Information regarding their experience with medical trials concerning this indication and, if available, proof of qualification
- List of staff available for the execution of the trial
- List of all institutions that are also involved in the trial for diagnostics, treatment etc.

Before the HD21 trial documents were submitted to the appropriate ethical committee and to the supreme federal authority, the sponsor (represented by the trial chairman) registered the trial with the European clinical trials database (EudraCT) and applied for a EudraCT number.

The EudraCT number for HD21 is: 2014-005130-55

This number has to be stated with all official documents related to HD21.

Pursuant to GCP-V art.7, the trial protocol and all related documents were then presented to the appropriate ethical committee for assessment. At the same time, all essential trial documents were submitted to the supreme federal authority (Paul-Ehrlich-Institut, PEI).

This trial protocol was approved by the appropriate ethical committee of the University of Cologne.

Apart from that, the protocol will be submitted to the appropriate foreign authorities for approval of the trial in other countries. This will be carried out by the respective national representatives of the sponsor.

11.3 PROTOCOL AMENDMENTS

Amendments to the trial plan have to be agreed upon with all persons who signed the trial plan.

According to GCP-V art.10, the responsible ethical committee and the supreme federal authority have to be informed about any intended protocol amendments and, if required, a new vote of approval/permission of both has to be awaited. Amendments that require to be approved by the ethical committee/supreme federal authority may not be implemented until both institutions have given their approval.

This includes amendments to the approved trial protocol that may

- harm the safety of the involved persons,
- require additional data collection or analyses for which the patient information documents and/or the consent form have to be altered,
- influence the interpretation of the scientific documents on which the trial is based upon, or the validity of the trial results,
- change the management or execution of the trial in a decisive way,
- reduce the quality or safeness of the investigational drugs,
- change the risk assessment for the environment of a clinical trial that includes genetically modified organisms.

Such changes may only be made if the ethical committee and the appropriate supreme federal authority have given their approval.

11.4 PATIENT BRIEFING

Before a patient is entered into the trial (enrollment), the treating physician has to inform him/her on the nature of the trial, its aims and the expected advantages as well as possible risks.

11.5 DECLARATION OF CONSENT

Every patient must give a written declaration of consent to participate in the trial. The patient must be given sufficient time and the chance to decide on their participation in the trial and to clarify open questions before any measures relating to the trial are taken.

The consent form has to be signed by the patient and the investigator or a sub-investigator. If the patient is unable to sign the consent form personally, a witness is required to confirm by their signature that the patient has been briefed and consents to participation in the trial.

The formatting and header of the consent form may be adapted to the standard of the respective trial center. Upon request, the final versions of the forms are to be submitted to the ethical committee for evaluation.

Two copies of the Information for Patients and Declaration of Consent are needed for each patient. One copy remains with the investigator (in the trial site file), the other is handed over to the patient.

11.6 LEGAL REGULATIONS

The trial conforms to the regulations of the applicable version of the “Deutsches Arzneimittelgesetz” (German medicines law) as well as to the applicable version of the “Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen” (regulation concerning the application of good clinical practice in clinical testing of medicines on human subjects), also called “GCP-Verordnung” or “GCP-V”.

The trial conforms to the applicable version of the legal specifications stipulated in the “Strahlenschutzverordnung” (regulation on radiation protection) and the “Richtlinie Strahlenschutz” (guideline on radiation protection).

The trial chairman must have at least two years of experience in the conduction of clinical trials investigating medicines.

The trial protocol was approved by the appropriate supreme federal authority (Paul-Ehrlich-Institut, PEI) on **03. May 2016**.

Pursuant to AMG art.67, all investigators are obliged to report their participation in a clinical trial to the appropriate local surveillance authority, according to the specifications stipulated in GCP-V art.12, before the first patient is entered into the trial.

Trial centers outside Germany have to adhere to the corresponding national legal regulations of the respective country.

11.7 INSURANCE FOR TRIAL SUBJECT/PATIENTS

Insurance protection for the patients participating in this trial in Germany is provided by HDI Gerling Mainz, insurance policy no. 57 010309 03010, tel. 0211 / 7482-5404.

11.8 TRIAL CENTERS

Before patients can be recruited, every participating center must declare its willingness to enter patients into the trial according to protocol, to administer treatment according to protocol and to fully document each patient by returning the signed trial center agreement to the Trial Coordination Center. An ethics vote for each participating center must be present.

12 ORGANIZATION

12.1 DATA PROCESSING AND STORAGE

12.1.1 Hardware and Software

Trial data are captured with eCRFs, defined and provided by Acromion GmbH, Frechen. All clinical data are stored in “Marvin”, a validated trial management system. This trial management software has been developed by XClinical GmbH based on Java technology and is designed as a web application. Marvin can be used with every usual web browser, so no additional software installations at local sites are needed. A validated installation of Marvin need to be installed on current x86 processors, running a Debian operating system having at least 2GB RAM and 100GB free hard disk space. Marvin systems for productive services are being installed on validated data centers only.

12.1.2 Data security and back-up

Datacenters of XClinical comply with German legal requirements in terms of data security (redundancy, connectivity, power supply) and data privacy protection. All operations are performed within a virtual private network with encrypted data transfer (secure shell).

Backups of instances are performed regularly (typically a 2 hour interval). Backups are done as database dump on the hard drive and can be restored by the database system. No additional software is required.

For every project running on a particular server, a separate physical server (called “standby-server”) automatically keeps a copy of all installation files and database backups. The backups are synchronized as soon as they are finished on the production machine serving as well as an offsite backup. In case of an emergency, the project can be restored and started on the standby server within typically 15 minutes.

12.1.3 Data validation

A multilevel data validation plan was conceived in order to guarantee the correctness and consistency of data. The data is checked during data entry using both consistency checks (type of data, permitted range of values, etc.) and plausibility of data through a comparison with previously entered data of the respective patient (cross checks). Impossible values (e.g. dates in the future) will be rejected; values deemed implausible require a commentary. Only complete forms may be digitally signed. All alterations of data are recorded in an audit trail.

A 5-digit-number (CaseID) forms the patient key. This number is allocated automatically by the TCC data base (sequence definition) when the patient is enrolled into the trial. This

guarantees not only that the patient key is unique, but also that there is no logical connection between patient key and personal data. Exchange of data is only performed using the patient key.

12.1.4 Data analyses and archiving

For the purpose of interim and final analyses, pseudonymized data files will be extracted from the database into statistical packages (SPSS, SAS) to be analyzed by the GHSG Trial Coordination Center.

Paper documentation forms are stored at the Trial Coordination Center in appropriate filing cabinets that are kept locked.

The accompanying clinical scientific investigations are performed with anonymized samples by the laboratory of the Cologne University Hospital or a contract laboratory.

The trial chairman stores hard copies and electronic files of the interim and final reports.

All documentation forms, consent forms and other important trial documents are stored for at least 10 years, pursuant to GCP-V art.13 (10).

12.1.5 Data protection

The regulations of the German data protection law are adhered to. Pursuant to the data protection regulations, it will be ensured that all examination material and data are pseudonymized in an adequate way before they are used for scientific purposes.

The trial participants will be informed about the transfer of their pseudonymized data to the recipients stated in the GCP-V, pursuant to the obligations regarding documentation and reporting stipulated in GCP-V art.12 and art.13. Persons who do not consent to this will not be included into the trial.

The procedures concerning the storage of data are specified in a data protection plan.

12.2 PROTOCOL AMENDMENTS

Protocol amendments or additions can be decided upon by the trial chairman for reasons of ethics or safety on the basis of the available trial data or information from newly published literature.

Any protocol amendment is to be

- presented to the trial steering committee and review board/DMC for their information,

- submitted to the ethical committee and the supreme federal authority (BOB) if the risk for patients has to be recalculated (pursuant to GCP-V art.10 (1),
- communicated immediately in writing to all participating centers,
- recorded in the protocol logbook, with date.

12.3 FINANCING AND INSURANCE

The company Millennium Pharmaceuticals Inc. provides financial support for this trial and provides the investigational drug, brentuximab vedotin, available for use within this trial free of charge.

A patient insurance for the patients in this trial has been procured. The conditions of insurance can be obtained from the GHSG Trial Coordination Center.

12.4 AGREEMENT ON PUBLICATION

Analyses and publications (lectures, articles, etc.) of data and information connected with the present quality assurance protocol may only be made in consultation with the trial chairman. The trial chairman holds the responsibility for the final analysis.

The final analysis must be published regardless of the trial results.

13 DEFINITIONS

13.1 ECOG PERFORMANCE STATUS

The ECOG index assesses the performance status of the patient with regard to physical and social factors:

0: normal activity, without symptoms
1: light work possible, with symptoms
2: self-care possible, < 50% of the time bedridden
3: limited self-care possible, 50% of the time in bed or armchair
4: in need of full care

13.2 DISEASE STAGE (ANN ARBOR MODIFIED)

The determination of the disease stage is based on the results of the required diagnostics. The following definition corresponds largely with that of Ann Arbor, but deviates in certain points (stage IV, extranodal disease).

CS: clinical staging (without laparotomy)
PS: pathological staging after invasive diagnostics

Stage I: nodal involvement in a single region (I,N) or a single localized extranodal involvement (I,E)

Stage II: nodal involvement (II,N) and/or localized extranodal involvements (II,E) in two or more regions on one side of the diaphragm

Stage III nodal involvement (III,N) and/or localized extranodal involvements (III,E) on both sides of the diaphragm

Stage IV disseminated involvement of one or more extralymphatic organs with or without involvement of lymph nodes

Lymphatic tissue: lymph nodes, spleen, thymus, Waldeyer's ring

Organs: N = lymph nodes H = liver S = spleen L = lung
M = bone marrow O = bone D = skin P = pleura

Constitutional symptoms:

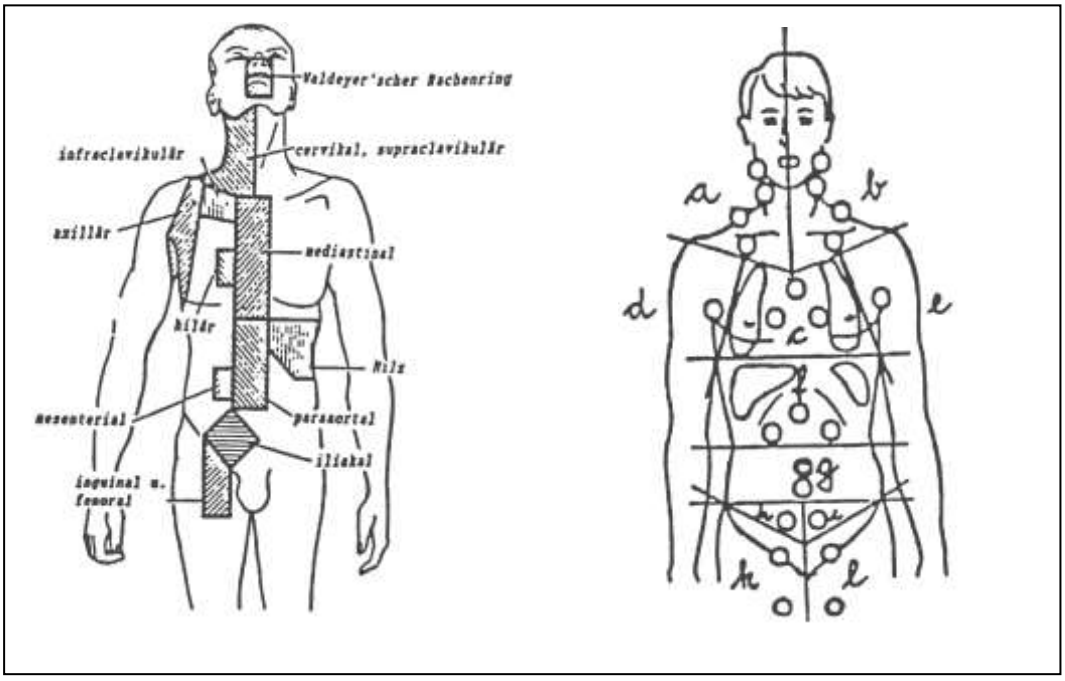
The stages I to IV are given the suffix B if one or more of the following general symptoms are present, and the suffix A if all of these symptoms are absent. The general symptoms are:

- Fever over 38°C that cannot be attributed to anything else
- Night sweats (with change of bed-linen) that cannot be attributed to anything else
- Loss of weight of more than 10% of body weight within 6 months that cannot be attributed to anything else

13.3 LYMPH NODE REGIONS AND LYMPH NODE AREAS

The differences between lymph node regions, whereby the stage of disease is defined, and lymph node areas, whereby the risk factor (≥3 LN areas) is defined, are shown in the following illustration. The accompanying table shows LN regions compared to LN areas in summary and includes the coding scheme for nodal involvement.

N.B.: the definition of lymph node AREAS used in this context is not identical with that of lymph node REGIONS according to Ann Arbor. A lymph node area may include several lymph node regions.



Regions Areas

Figure: Illustration of lymph node regions for determination of the disease stage and lymph node areas for determination of the risk factor (≥3 LN areas).

Table: Summary of regions (a) and areas (b) with allocation of the codes for nodal involvement

(a) Lymph node regions for the determinination of the stage of disease

Region		Lymph node	Code
Waldeyer's ring	right left	Waldeyer's ring	1 2
cervical-supraclavicular	right	high cervical/nuch./subm. cervical supraclavicular	3 5 7a
cervical-supraclavicular r	left	high cervical./nuch./subm. cervical supraclavicular	4 6 8a
infraclavicular	right	Infraclavicular LN	7b
infraclavicular	left	Infraclavicular LN	8b
axillar	right	axillar LN	9
axiliar	left	axillarLN	10
mediastinal		upper mediastinum lower mediastinum	11a 11b
pulmonary hilum	right left	hilar LN of the lung	12 13
spleen		spleen splenic hilum	19 20
mesenterial		mesenterial LN	18
paraaortic		coeliac LN paraaortic LN	17b 21
iliac	right	Iliac LN	22
iliac	left	Iliac LN	23
inguinal / femoral	right	inguinal / femoral LN	24
inguinal / femoral	left	inguinal / femoral LN	25
other		hepatic portal	17a

(b) Lymph node areas for the determination of the risk factor

Area	Lymph node		Code
a	right	Waldeyer's ring high cervical/nuchal/subm LN cervical LN supraclavicular LN infraclavicular LN	1 3 5 7a 7b
b	left	Waldeyer's ring high cervical/nuch/subm LN cervical LN supraclavicular LN infraclavicular LN	2 4 6 8a 8b
c		mediastinal LN: upper mediastinum lower mediastinum hilar LN of the lung,, right hilar LN of the lung, left	 11a 11b 12 13
d	right	axillar LN	9
e	left	axillar LN	10
f		upper abdominal LN: hepatic portal coeliac LN spleen splenic hilum	 17a 17b 19 20
g		lower abdominal LN: mesenterial LN paraaortic LN	 18 21
h	right	iliac LN	22
i	left	iliac LN	23
k	right	inguinal / femoral LN	24
l	left	inguinal / femoral LN	25

13.4 EXTRANODAL DISEASE, BULK, LARGE MEDIASTINAL MASS, ELEVATED ESR

Extranodal disease (E-lesions)

Definition: localized involvement of extralymphatic tissue (either by direct intrusion from a neighboring lymph node or by close anatomic connection). Also two or more E-lesions are compatible with stage II or III.

Bulky disease (measured by CT)

Bulky disease is present in case of

massive involvement of one lymph node with > 5 cm in the greatest diameter, or

conglomerate tumor > 5 cm in the greatest diameter, or

mediastinal tumor > 5 cm in diameter (hili and pericard not included in measurements).

Large mediastinal mass

Definition: ≥ 1/3 of the maximum transverse thoracic diameter of the thorax (measured in CT reconstruction, alternatively in sagittal chest X-ray image posterior-anterior in an upright position,). The maximum transverse thoracic diameter is measured in a posterior-anterior image at the level of the diaphragm from the insides of the ribs.

Mediastinal involvement

When defining irradiation regions, an involvement of the upper mediastinum, which is solely located above the tracheal bifurcation, has to be differentiated from an involvement of the lower, infrabifurcal mediastinum. If the involvement is located exactly at the level of the tracheal bifurcation, the entire mediastinum is classified as being involved.

Elevated (or high) ESR

Definition: ESR≥ 50 mm/h with A symptoms, ESR≥ 30 mm/h with B symptoms

13.5 REMISSION CRITERIA

The following remission criteria are obligatory for the restagings after the end of chemotherapy and the end of radiotherapy, if applicable. They should be applied analogously for the interim restaging **[26]**.

Complete remission (CR)

A complete remission has been attained if one of the following conditions is met:

- Complete radiologic response with regress of all residual masses to ≤ 1.5 cm in the largest diameter in absence of signs of active lymphoma

- Complete metabolic response (score 1-3) with or without residual masses in absence of clinical signs of active lymphoma

A CR implies that, apart from protocol treatment, no further therapeutic measures are necessary.

Partial remission (PR)

A partial remission has been attained if the following conditions are met:

- Continuing presence of lymphoma tissue (clinical, radiological) in absence of complete metabolic response (score 1-3)
- Absence of new lesions
- No lymphoma has grown by more than 25% in the largest diameter
- Shrinkage of the majority (at least half) of large involved lymph nodes and localized measurable organ manifestations (with more than 3 cm in diameter) by more than 50% compared with the initial status. If no lesion had more than 3 cm in diameter: shrinkage of the two largest involved lesions by more than 50% in greatest diameter. Shrinkage of a large mediastinal mass (if present) by more than 50% in the maximum transverse diameter.
- Absence of clinical signs of active lymphoma

At interim, these findings suggest responding disease. At end of treatment, these findings indicate residual disease.

No Change (NC)

No change applies if the following conditions are met:

- Continuing presence of lymphoma tissue (clinical, radiological) in absence of complete metabolic response (score 1-3)
- Absence of new lesions
- No lymphoma has grown by more than 25% in the largest diameter
- Shrinkage criteria for PR not satisfied

No change also applies in case of presence of clinical signs of active lymphoma.

Progressive disease (PD)

Progressive disease applies if any of the following conditions are met:

- Appearance of new lesions
- Increase of at least one known lesion by more than 25% diameter

In case of progressive disease, further treatment is usually necessary.

Progression and Relapse

A relapse is defined as the appearance of new tumor lesions or the reappearance of initial lesions or B-symptoms following CR at least three months after end of treatment. If the interval is shorter the event is classified as a progression.

In case of relapse or progression, a renewed histological assessment is recommended.

13.6 VISUAL CRITERIA FOR DESCRIBING AND INTERPRETING FDG ACCUMULATIONS

(adapted from Meignan et al. [28]).

Score	PET finding	Interpretation
1	No FDG uptake	PET negative
2	FDG uptake lower or same as in the mediastinal blood pool	PET negative
3	FDG uptake higher than in the mediastinal blood pool but lower or the same as in the liver parenchyma	PET negative
4	FDG uptake higher than in the liver parenchyma	PET positive
5	FDG uptake into a new lesion, increasing FDG uptake into known tumor tissue, progression*	PET positive

*) exclusion criterion for continuation of protocol treatment

14 TECHNICAL PROCEDURES

14.1 PROCEDURE FOR THE PATHOLOGICAL REVIEW OF DIAGNOSIS

As described in section 5.1.1, the primary pathologist is asked by the treating physician to send the patient's biopsy material (paraffin block preferably and, if available, lymph node tissue in formalin; otherwise at least 12 slides) complete and without delay to one of the six German pathology review centers for review of the diagnosis and report the respective review center to the GHSG Trial Coordination Center. The GHSG will then provide the review center with name, date of birth and the respective trial.

With his written consent to participation in the trial, the patient agrees to the forwarding of his material to one of the pathology review centers. The primary pathologist only incurs the postage costs if at all.

The pathology review for confirmation of diagnosis includes the following examinations: see Appendix 17

After completion of the pathology review examinations and interpretation of the results according to the WHO classification system, the following particulars will be communicated to the GHSG Trial Coordination Center on the histopathological review form, as well as via post to the primary pathologist:

pathology review diagnosis, including

- ICD-O code,
- diagnostic immunophenotype, and
- identification code of the pathology review center.

It should take no longer than 3 weeks for the pathology review diagnosis to be established. If this deadline has passed, a reminder is sent from the GHSG Trial Coordination Center to the respective pathology review center. If by then the review center has not received any biopsy tissue, missing material will be requested from the primary pathologist by the Trial Coordination Center.

Quality assurance and improvement of pathology review diagnostics

For the purpose of quality assurance, the pathology review diagnoses of all cases in which it has been difficult to establish a differential diagnosis will be reexamined and likewise a sufficient sample (about 15%) of the entire cases. These quality controls are performed by the heads or deputy heads of all pathology review centers in panel meetings in which the respective cases are reexamined at the microscope together. The panel members may be of

the same opinion right from the beginning, so the panel diagnosis is obvious in this case. Given initial differences of opinion, the diagnostic criteria will be discussed using a multiple view microscope. This procedure leads to a consistent diagnostic standard of the six pathology review centers and facilitates a reliable evaluation of the dependability of the diagnostic criteria. Another aim of this procedure is to identify risk factors in order to be able to better predict the prognosis for a patient and the treatment outcome for a certain lymphoma subtype at the time of pathology review.

14.2 PROCEDURES FOR THE PET EXAMINATION

14.2.1 Patient preparation

Patients must fast for 6 hours prior to the PET examination; only carbohydrate-free drinks are permitted (e.g. water). Parenteral nutrition or glucose-containing infusions should be discontinued at least 4 hours before the PET examination.

Before the application of FDG, it is recommended to determine the blood glucose level with a validated and calibrated instrument and to calculate the SUV with and without blood glucose correction. With a normal blood glucose level of 5 mmol/l the uncorrected and corrected blood glucose levels are the same. Please note that many bedside methods are not sufficiently precise for SUV correction.

Poorly controlled diabetes mellitus (HbA1c < 7.5% or a fasting blood sugar > 200mg/dl) is an exclusion criterion for the PET examination. During the FDG injection and the following FDG uptake phase the patient should rest to minimize FDG uptake in the muscles. Besides, hypothermia should be prevented to keep the FDG uptake in the brown fat tissue low.

In case of unexpectedly high blood glucose levels, the examining PET facility may optionally administer short-acting insulin (e.g. 2 units), provided that the patient can be monitored and emergency care measures are kept ready.

The following recommendations apply for patients with diabetes mellitus:

1. Diabetes mellitus type II (under oral medication)
    - The PET examination should be performed in the late morning.
    - The fasting time as stated above should be adhered to.
    - Oral medication should be taken as usual.

2. Diabetes mellitus type I and insulin-dependent diabetes mellitus type II

    - A normal blood glucose level is ideal for the PET examination and should be aimed at; the treating physician should discuss this with the patient beforehand.
    - The PET examination should be performed in the late morning.
    - After breakfast at 7:00 a.m., the patient should administer their usual amount of insulin. After this, they should not have any food or carbohydrate-containing drinks.

Immediately before the examination at the respective PET facility, the blood glucose level of the patient should be checked again to avoid complications due to overly low or high blood sugar values.

- The blood sugar value has to be measured **BEFORE** the administration of FDG. For this purpose a glucose meter or a comparable bedside method can be used.
- The measuring instruments must have been approved and inspected every year.The examination has to be performed using a PET scanner with a full ring detector or a technical equivalent. Double-head coincidence gamma cameras are not appropriate.

14.2.2 Measuring instruments

The examination has to be performed using a PET scanner with a full ring detector or a technical equivalent. Double-head coincidence gamma cameras are not appropriate.

14.2.3 Measurement field

The measurement field should include the trunk of the body (neck, chest, abdomen, pelvis). Images of the lower extremities are only required if a primary tumor is located there.

The use of whole body techniques is advantageous.

14.2.4 Acquisition technique

Static, absorption-corrected emission tomograms of the trunk of the body (neck, chest, abdomen, pelvis) that allow for a qualitative and quantitative analysis of pathological uptake sites are to be produced. For the lower extremities, emission scans are adequate. Emission scans of the trunk are to begin 60 minutes after injection.

14.2.5 Post Processing/quantification

Iterative reconstruction is to be used as standard method. Pathological uptake sites have to be assessed quantitatively (e.g. standardized uptake value, metabolic rate for glucose).

It is recommended to analyze at least one of the following parameters in addition to the SUVmax. The following 3D VOIs are common:

- SUVA41 (3D Isocontur at 41% of the SUVmax, corrected for the A41 background)
- SUV50 (3D Isocontur at 50% of the SUVmax)
- SUVA50 (3D Isocontur at 50% of the SUVmax, corrected for the A50 background)

A (semiautomatic) VOI may be more difficult to prepare in case of a low nuclide uptake in the tumor tissue as well as in case of a high background or in regions with a high physiological nuclide uptake such as heart and bladder. Therefore, VOIs have to be examined visually in any case, and the assessment has to be done manually where necessary.

14.2.6 Quality control

The recommendations for tumor imaging with FDG drawn up by the quality management working group of the European Association for Nuclear Medicine should be adhered to [57].

14.2.7 Procedures for the performance of contrast-enhanced computed tomography (ceCT)

To optimize the assessment of the lymphoma volume using computed tomography, the following technical criteria should be aimed at:

- spiral CT technique;
- administration of an intravenous contrast medium for all examinations;
- oral contrast medium for abdominal CT;
- spiral CT neck (collimation/table shift/increment): 5/6/4;
- spiral CT thorax: 5/8/4;
- spiral CT abdomen: 8/10/8.

Computed tomography should be considered technically inadequate:

- with a layer thickness > 1 cm and a table shift > 1.5 cm;
- without or with too weak intravenous contrasting so that blood vessels cannot be differentiated reliably from neighboring lymphoma tissue;
- without or with too weak oral contrasting so that the intestine cannot be differentiated reliably from neighboring lymphoma tissue.

15 PATIENT BRIEFING AND CONSENT

15.1 GUIDE TO PATIENT BRIEFING

The patient briefing is to contain all the points 1 to 5 described below. A witness is required only if the patient is illiterate.

15.1.1 The trial

Short explanation of the trial title, vote of approval of the ethical committee, randomization, insurance, aim of the trial, experimental procedures, procedure and advantages of the trial, transfer of data and test samples, freedom of decision. Information that the patient does not incur any additional trial-related costs apart from potential travel expenses for the PET examination.

15.1.2 Nature of the disease

Short description of symptoms, clinical matters, response to treatment and prognosis as well as age distribution and the prognosis of untreated disease.

Important: It has to be mentioned that Hodgkin lymphoma is one of the best-treatable malignancies in adults.

15.1.3 Protocol:

A. Target group:

Patients in advanced stages (stage IIB with large mediastinal mass or extranodal disease; stage III (lymph-node involvement both above and below the diaphragm); stage IV (organ involvement: lung (disseminated), liver, bone marrow).

B. Therapy:

Depending on the interim staging (PET-2) chemotherapy with 4/6 cycles of escalated BEACOPP or 4/6 cycles of BrECADD, patients with PET positive residual tumor masses receive local radiotherapy with 30 Gy. Patients with PET negative residual tumor masses independent of size do not receive additional radiotherapy.

C. Aim:

The aim of this clinical trial is to reduce the toxicity of treatment while maintaining the chances of cure by means of a new combination of conventional chemotherapeutics and a new antibody-drug conjugate, brentuximab vedotin.

D. Effects:

Lessening of symptoms such as night sweats, fever, weight loss, itching, swollen lymph nodes; improvement of general condition; cure.

E. Possible side-effects:

Changes in blood values which may be associated with an increased risk of infection and bleeding, mucous inflammations in the mouth, throat and esophageal areas, nausea, vomiting, loss of hair (partial), loss of appetite, sleeplessness, temporary or long-term side-effects in various organs (lung, kidney, spinal cord, heart, sexual glands), second malignancies.

15.1.4 Transfer of test samples:

For purposes of diagnosis confirmation, tissue samples will be forwarded to a review pathologist. For purposes of clinical scientific co-investigations, blood samples will be examined in various laboratories, provided that the patient has given their written consent to this.

15.1.5 Patient's freedom of decision:

The patient may reconsider their decision to participate in the trial at any time. If the patient refuses to participate in the trial, they are free to decide on the kind of their further treatment.

15.1.6 Follow-up examinations:

It is to be explained to the patient that regular monitoring examinations over a time span of many years are required in their own interest and especially in the interest of future patients. The results of these examinations will be reported to the Trial Coordination Center.

The patient has to be informed that also quality of life and late toxicities that might possibly occur will be surveyed, and that they will have to complete corresponding forms (QoL questionnaires) at regular intervals.

They have to be told that the Trial Coordination Center may write to them directly, if they have agreed thereto. If so, the patient will receive quality of life questionnaires from the Trial Coordination Center at regular intervals and will be reminded of the need to return the questionnaires promptly.

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17 APPENDIX

17.1 HISTOPATHOLOGICAL REVIEW FORM

German Hodgkin Study Group
Deutsche Hodgkin Studiengruppe

GHSG
www.ghsg.org

Hodgkin lymphoma – Histopathological Review

GHSG; Gleueler Straße 269-273; D-50935 Köln; **Fax:+49(0)221 478 88188 Köln**

(to be filled in by the reference pathologist and to be sent by fax with a written report to the study center)

Surname: First name:

Date of birth: . . *(dd.mm.yy)* Registration number: *(if known)*

Organisational aspects

Referring pathology: _____

Histology number of referring pathology: _____

Histology number of reference pathology: _____

Date of review: . . *(dd.mm.yy)*

Tissue type and quality

Localisation: _____

☐ Core needle biopsy ☐ surgical biopsy ☐ other, specify:

Tissue quality: ☐ average ☐ poor | Parrafin block available: ☐ no ☐ yes | Kryomaterial available: ☐ no ☐ yes

Unstained slides available for review: ☐ no ☐ yes, _____

Stained slides available for review: ☐ no ☐ yes, _____

Blocks available for review: ☐ no ☐ yes, _____

Blocks stored at reference center: Berlin *(indicate number)* **TMA-suitable:** ☐ no ☐ yes

Nucleic acids stored at reference center: **DNA:** ☐ no ☐ yes | **RNA:** ☐ no ☐ yes

Diagnosis

Classical Hodgkin Lymphoma (ICD-C 81)

☐ nodular sclerosis
☐ mixed cell (ICD-C 81.2)
☐ lymphocyte depleted (ICD-C 81.3)
☐ nodular lymphocyte rich (ICD-C 81.4)
☐ other
☐ without subtyping

Comment: _____

Nodular lymphocyte predominant Hodgkin Lymphoma (ICD-C 81.0)

☐ typical ☐ atypical Comment: _____

DIAGNOSIS OF HODGKIN LYMPHOMA COULD NOT BE CONFIRMED

☐ no malignant tumor comment: _____
☐ other lymphoma please specify: _____
☐ other malignant tumor please specify: _____

Immunohistochemistry of the neoplastic cells (mandantory antibodies for all entities):

CD20:	☐ -	☐ +	☐ ++	☐ +++	☐ n.i	☐ n.d
CD3:	☐ -	☐ +	☐ ++	☐ +++	☐ n.i	☐ n.d
CD30:	☐ -	☐ +	☐ ++	☐ +++	☐ n.i	☐ n.d
CD15:	☐ -	☐ +	☐ ++	☐ +++	☐ n.i	☐ n.d
PAX5:	☐ -	☐ +	☐ ++	☐ +++	☐ n.i	☐ n.d
LMP1:	☐ -	☐ +	☐ ++	☐ +++	☐ n.i	☐ n.d

Other antibodies: _____

"n.i" = not interpretable; "n.d" = not done; "-" = negative; "+" = few positive cells; "++" = significant number of cells positive; "+++" = most or all cells positive

17.2 BRENTUXIMAB VEDOTIN PHARMACY MANUAL

Brentuximab vedotin Pharmacy Manual

Introduction

The Pharmacy Manual is a reference guide for pharmacists participating in Investigator Initiated Studies with Brentuximab Vedotin. This manual does not replace the protocol.

Brentuximab vedotin Pharmacy Procedures (IV and SC)

1) Formulation

The drug product is labeled brentuximab vedotin. Brentuximab vedotin for Injection is a sterile, preservative-free, white to off-white lyophilized cake for reconstitution for IV administration. brentuximab vedotin for Injection is supplied by Millennium Pharmaceuticals, Inc. in single-use, Type 1 borosilicate glass vials with FluroTec®-coated butyl rubber stoppers and aluminum seals. Each vial of the product contains brentuximab vedotin , trehalose, sodium citrate, and polysorbate 80. The lyophilized product, after reconstitution with 10.5 mL sterile Water for Injection, USP, yields 11 mL of brentuximab vedotin solution (5 mg/mL concentration after reconstitution).

2) Packaging and Labeling

Vials of study treatment will be packaged as one single-use vial per carton (kit). Each kit will contain 1 vial of investigational product.

3) Storage Conditions

Vials containing study treatment must be refrigerated at 2-8 °C in a secure location (e.g., locked room) accessible only to the pharmacist, the investigator, or a duly designated person.

Study treatment does not contain preservatives; therefore, opened and reconstituted vials of study treatment must be used on the same day when stored under refrigeration at 2-8 °C. Reconstituted study treatment should not be stored at room temperature. It is recommended that study treatment vials and solutions be protected from direct sunlight until the time of use. **Reconstituted vials must not be shaken.**

4) Directions for the use (DFU) of brentuximab vedotin

Recommended safety measures for handling and preparation include masks, protective clothing, gloves, and vertical laminar airflow safety cabinets.

Study treatment vials are single-use containers. Any partially used vials or diluted dosing solutions are to be discarded using appropriate institutional drug disposal procedures.

Study treatment must be reconstituted with the appropriate amount of Sterile Water for Injection, USP (see Pharmacy Manual for details). GENTLY swirl the vial until the contents are completely dissolved. **The vial must not be shaken or vigorously swirled;** excess agitation may cause aggregate formation. Visually inspect the reconstituted drug product for any particulate matter and discoloration.

The appropriate amount of reconstituted study treatment will be withdrawn from the vial(s) and diluted in a 150-250 mL infusion bag containing 0.9% Sodium Chloride Injection, USP.

There are no known incompatibilities between study treatment and polyvinyl chloride (PVC), polyolefin, polyethylene, and ethylene vinyl acetate (EVA) bags. These bags should be gently inverted to mix the solution. **The bags must not be shaken;** excess agitation may cause aggregate formation. Prior to administration, the reconstituted and diluted drug product should be inspected visually for any particulate matter and discoloration.

The formulation contains no preservative and is intended for single use only; infusion solutions should be prepared and transferred using aseptic technique in a biosafety hood.

Dose preparation instruction is as follows for 50-mg vials:

1. Remove the plastic flip-off caps from the necessary number of vials.

2. Reconstitute lyophilized study treatment by adding 10.5 mL Sterile Water for Injection, USP, to the vial, directing the stream at the side of the vial.

3. GENTLY swirl vial until the contents are completely dissolved. **THE VIAL MUST NOT BE SHAKEN OR VIGOROUSLY SWIRLED AS EXCESS AGITATION MAY CAUSE AGGREGATE FORMATION.** Slight "bubbling" of the solution upon reconstitution may be observed. Settle the reconstituted vial for a minute to allow them to dissipate.

4. The reconstituted product should be a colorless, clear to slightly opalescent solution with no visible particulates, with a total volume of 11 mL (5 mg/mL)

5. Withdraw the appropriate amount of reconstituted study treatment for Injection and dilute in a 150-250mL infusion bag (polyvinyl chloride, polyolefin, polyethylene, or ethylene vinyl acetate) containing 0.9% Sodium Chloride Injection, USP.

6. Gently invert the infusion bag (as applicable); DO **NOT SHAKE.**

Diluted study treatment for Injection must be utilized the same day as it is prepared

17.3 RESPONSIBLE PERSONS

Trial chairman

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