**European Network-Paediatric Hodgkin Lymphoma Study Group (EuroNet-PHL)**

**Second International Inter-Group Study for Classical Hodgkin Lymphoma in Children and Adolescents**

- No radiotherapy in patients with adequate response at first restaging after two cycles of chemotherapy
- Randomised comparison between standard COPDAC-28 and intensified DECOPDAC-21 chemotherapy in patients in intermediate and advanced stages and adequate response after two cycles of OEPA
- Randomised comparison between COPDAC-28 plus standard radiotherapy and intensified DECOPDAC-21 plus late response assessment based radiotherapy in patients in intermediate and advanced stages and inadequate response after two cycles of OEPA

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Confidentiality

The content of the protocol and the case report forms must be treated confidentially and may not be imparted to uninvolved persons without consent of the study chairpersons neither in oral nor in written form.

Important information

The protocol was written by the clinical board members to the best of their knowledge and belief. Nevertheless mistakes can never be completely excluded.

Therefore every doctor is responsible for checking the treatment plans of the protocol before treating a patient.
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1 GENERAL INFORMATION

On February 10th, 2012 in Dublin the clinical board of EuroNet-PHL and the national chairpersons of the participating study groups (see section 1.1) agreed on the design of a second European protocol in children and young people with classical Hodgkin’s lymphoma (EuroNet-PHL-C2), which is described in this protocol. Further study groups are encouraged to join. The EuroNet-PHL-C2 trial is a multinational inter-group trial, involving national study groups.

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<td><strong>Alexander Fossà, MD</strong></td>
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### Radiology

<table>
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<td>Dr. D. Stoevesandt and Prof. Dr. Rolf Peter Spielmann</td>
<td>Universitätsklinik und Poliklinik für Diagnostische Radiologie</td>
</tr>
<tr>
<td></td>
<td>Ernst-Grube-Straße 40</td>
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<td></td>
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### Nuclear medicine

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<td>Universitätsklinikum Leipzig</td>
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<td><a href="mailto:regine.kluge@medizin.uni-leipzig.de">regine.kluge@medizin.uni-leipzig.de</a></td>
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### 1.2.3 Central Review Board for Staging and Response Assessment (Austria)

#### Central review coordinator

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<td>St. Anna Kinderspital, Zentrum f. Kinder und Jugendheilkunde Kinderspitalgasse 6 A-1090 Wien, Austria</td>
</tr>
<tr>
<td></td>
<td>Tel +43-1-401704780, Fax +43-1-401707430</td>
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<tr>
<td></td>
<td><a href="mailto:andishe.attarbaschi@stanna.at">andishe.attarbaschi@stanna.at</a></td>
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#### Radiology

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<td>Primarius Dr. Karoly Lakatos</td>
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<tr>
<td></td>
<td>Tel 01/40170 – 2300, Fax 01/40170 – 7000</td>
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<td><a href="mailto:karoly.lakatos@stanna.at">karoly.lakatos@stanna.at</a></td>
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|-------------|--------------------------------------------------------------------------------|
2 PROTOCOL SIGNATURES

Confirmation of the Final Protocol

The final protocol has been approved by:

Authorised representative of the sponsor and coordinating investigator:

Prof. Dr. Dieter Körholz

Date: 27.07.2015

Responsible Biometrician:

Dr. Dirk Hasenclever

Date: 27.07.2015
3 TRIAL SYNOPSIS

3.1 Title

3.2 Trial Design
The EuroNet-PHL-C2 trial is an international, multicentre, randomised controlled trial.

3.3 Aims
To reduce the indication for radiotherapy (RT) in newly diagnosed patients with classical Hodgkin lymphoma without compromising cure rates. To investigate a chemotherapy intensification randomisation in intermediate and advanced classical Hodgkin lymphoma (HL) to compensate for reduction in RT.

3.4 General Trial Strategy
EuroNet-PHL-C2 is a comprehensive treatment strategy for all first line classical Hodgkin Lymphoma (cHL) patients under 18 years (under 25 years in UK, Italy and France). The overall strategy is risk stratified (defining chemotherapy) and response adapted (defining radiotherapy) to tailor the amount of treatment to the individual patient and decrease long term complications.

- Radiotherapy indication will be restricted.

Patients with a negative PET scan after two cycles of OEPA chemotherapy (Early Response Assessment – ERA) will not receive radiotherapy. The threshold for negative PET scan at ERA shifts from the previously used Deauville 1 and 2 = negative (as in the C1 trial) to Deauville 1, 2 and 3 = negative, thereby increasing the number of negative patients without indication for RT.

- Chemotherapy Randomisation

All intermediate (TL-2) and advanced stage (TL-3) patients will be randomised between respectively 2 or 4 standard COPDAC-28 or intensified DECOPDAC-21 consolidation chemotherapy cycles. To avoid delayed consolidation, randomisation has to be performed before ERA and as soon as the TL-assignment is confirmed by central review. Therefore two randomised sub-studies arise based on the ERA PET response:
Patients with adequate response at ERA do not receive radiotherapy - a randomised controlled chemotherapy comparison to show that intensified DECOPDAC-21 consolidation chemotherapy improves EFS as compared to standard COPDAC-28.

Patients with inadequate response at ERA - a randomised controlled chemotherapy-radiotherapy comparison - to show that DECOPDAC-21 combined with radiotherapy restricted to sites that remain FDG-PET positive at the end of all chemotherapy (Late response assessment – LRA) has comparable EFS compared to COPDAC-28 plus standard involved node radiotherapy as in the C1 trial.

- Risk stratification is refined

Former treatment groups (TG) of the EuroNet-PHL-C1 trial are reassigned into treatment levels (TL) by shifting early stage patients (former TG-1) with risk factors into TL-2.

- Semi-quantitative ‘qPET’

Results of semi-quantitative qPET are formally integrated into the response assessment.

3.4.1 Primary Objectives

3.4.1.1 Randomised

1. To increase event-free survival in ERA PET-negative intermediate and advanced stage patients (TL-2 and TL-3) without radiotherapy by using intensified consolidation chemotherapy (DECOPDAC-21).

2. To demonstrate in ERA PET-positive TL-2 and TL-3 patients that the combination of intensified consolidation chemotherapy (DECOPDAC-21) plus restricted field RT to sites that remain FDG-PET positive at the late response assessment (LRA) is comparable to the standard consolidation chemotherapy (COPDAC-28) plus standard involved node radiotherapy.

3.4.1.2 Non-randomised

3. To further reduce the radiotherapy indication in early stage patients by increasing the threshold for a positive FDG PET scan at early response assessment (ERA) to Deauville 4+ while still preserving a 5 year EFS estimate at a target of 90% or above.
3.4.2 Secondary Objectives


2. For ERA PET-positive patients to compare the LRA PET-positivity rates after consolidation chemotherapy with COPDAC-28 or DECOPDAC-21.

3.4.3 Tertiary Objective

1. Description of treatment delivery and study logistics as quality endpoints.

3.5 Outcome Measures

3.5.1 Primary Efficacy Endpoint

- Event-free survival (EFS) defined as time from start of treatment until the first of the following events:
  - progression/relapse of disease
  - secondary malignancy
  - death from any cause.

3.5.2 Secondary Endpoints

- **Efficacy**: overall survival (OS), progression-free survival (PFS)
- **Safety**: CTC (common toxicity criteria) grading during any individual treatment element including assessment of osteonecrosis
- **Quality**:
  - Time from day of PET imaging until decision on response category at ERA or LRA, respectively
  - Time from last day of chemotherapy to first day of radiotherapy in patients with radiotherapy indication
  - Time from last dose of prednisone/prednisolone in OEPA to start of the first consolidation cycle
  - Duration of chemotherapy
  - Chemotherapy dose actually administered divided by scheduled total dose for each drug
  - Discontinuation or substitution rate for each drug
  - Time from FDG-Injection to start of PET acquisition
3.6 Trial Population

EuroNet-PHL-C2 is open to patients with untreated classical Hodgkin’s lymphoma under 18 years of age. There may be country-specific lower age limits. In Australia, France, Italy, New Zealand and UK the upper age limit can be raised under 25 years of age (on the date of written informed consent) for patients treated within specific teenage-young adult (TYA) cancer units.

3.7 Sample Size

At least 2200 patients will be enrolled.

3.8 Main Inclusion and Exclusion Criteria

3.8.1 Inclusion Criteria

- histologically confirmed primary diagnosis of classical Hodgkin’s lymphoma
- patients under 18 years of age on the date of written informed consent. In specialized Teenage and Young Adult (TYA) units in Australia, France, Italy, New Zealand and UK patients up to under 25 years of age can also be enrolled. Lower age limits will be country specific according to national laws or formal insurance requirements that may preclude very young patients.
- written informed consent of the patient and/or the patient’s parents or guardian according to national laws
- negative pregnancy test within 2 weeks prior to starting treatment for female patients with childbearing potential
3.8.2 Exclusion Criteria

Patients with one or more of the following criterion are excluded:

- prior chemotherapy or radiotherapy for other malignancies
- pre-treatment of Hodgkin's lymphoma (except for 7-10 days steroid pre-phase of a large mediastinal tumour)
- diagnosis of lymphocyte-predominant Hodgkin's lymphoma
- other (simultaneous) malignancies
- contraindication or known hypersensitivity to study drugs
- severe concomitant diseases (e.g. immune deficiency syndrome)
- known HIV-positivity
- residence outside the participating countries where long term follow-up cannot be guaranteed
- pregnancy and/or lactation
- patients who are sexually active and are unwilling to use adequate contraception during therapy and for one month after last trial treatment
- current or recent (within 30 days prior to date of written informed consent) treatment with another investigational drug or participation in another interventional clinical trial

3.9 Trial Duration

The recruitment period is expected to last six years (in Germany a maximum of five years for insurance reasons). The follow-up period will be five years after start of treatment. Individual trial participation ends with a last visit 60 months after start of treatment. After the individual end of study, the patients enter a follow-up observational protocol (late effects registry outside the EuroNet-PHL-C2-trial).

The EuroNet-PHL-C2-trial formally ends with the last visit of the last patient.

3.10 Treatment Summary

Please also see trial – flow diagrams (Fig. 1 and 2).

EuroNet-PHL-C2 is risk adapted with stage and risk factors defining the treatment level (TL) and it is response adapted with response to chemotherapy defining the radiotherapy indication.
Patients are risk stratified into one of three Treatment Levels (TL)

- TL-1, TL-2 and TL-3 for low, intermediate and advanced HL respectively.

Patients in TL-1 are not randomised, but patients in TL-2 and TL-3 are randomised between standard COPDAC-28 versus intensified DECOPDAC-21 as soon as the TL is confirmed.

### 3.10.1 INDUCTION THERAPY

All patients start their treatment with two cycles of OEPA chemotherapy. This is followed by the Early Response Assessment (ERA) including FDG-PET.

### 3.10.2 POST INDUCTION THERAPY

**Patients with Adequate Response (AR) at ERA** - (PET negative = Deauville Score 1, 2 or 3) - do NOT receive radiotherapy. Consolidation chemotherapy by TL is as follows:

- TL-1 receive 1 COPDAC-28 (not randomised)
- TL-2 receive 2 COPDAC-28 (standard) or 2 DECOPDAC-21 (intensified chemotherapy) (randomised)
- TL-3 receive 4 COPDAC-28 or 4 DECOPDAC-21 (randomised)

**Patients with Inadequate Response (IR) at ERA** - (PET positive = Deauville Score 4 or 5) - receive consolidation chemotherapy/radiotherapy.

- TL-1 receives standard radiotherapy (20 Gy) to all initially involved sites after two OEPA cycles.
- TL-2 and TL-3 radiotherapy indication is refined by the chemotherapy randomisation.
- TL-2 receive 2 COPDAC-28
- TL-3 receive 4 COPDAC-28

Plus standard involved node radiotherapy (20 Gy). A 10 Gy boost will be delivered to Late Response Assessment (LRA) PET-positive sites.

**Intensified Chemotherapy Arm**
- TL-2 receive 2 DECOPDAC-21
- TL-3 receive 4 DECOPDAC-21

Plus Radiotherapy (30 Gy) only to LRA PET-positive sites. If the LRA FDG PET scan is negative then RT is omitted completely.

---

**Figure 1:** Flow Diagram for Patients in TL-1
Figure 2: Flow Diagram for Patients in TL-2/TL-3

3.11 Financial Support of the Sponsor

Deutsche Krebshilfe e.V./Dr. Mildred Scheel Foundation
### 4 ABBREVIATIONS

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<tr>
<td>AE</td>
<td>Adverse Event</td>
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<td>AIEOP</td>
<td>Associazione Italiana di Emato-Oncologia Pediatrica</td>
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<td>ALAT</td>
<td>Alanine-Amino-Transferase</td>
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<td>AMG</td>
<td>German Drug Law (Arzneimittelgesetz)</td>
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<td>AML</td>
<td>Acute Myeloid Leukaemia</td>
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<td>AP</td>
<td>Alkaline Phosphatase</td>
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<td>AR</td>
<td>Adequate Response</td>
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<td>Aspartate-Amino-Transferase</td>
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<td>ASR</td>
<td>Annual Safety Report</td>
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<td>BfArM</td>
<td>Bundesinstitut für Arzneimittel und Medizinprodukte (German Competent Authority)</td>
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<td>B (B-symptoms)</td>
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<td>Degree Celsius (temperature dimension unit)</td>
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<td>Ca</td>
<td>Calcium</td>
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<tr>
<td>CD</td>
<td>Compact Disc</td>
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<td>c-HL</td>
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<td>CIOMS</td>
<td>Council for International Organisations of Medical Sciences</td>
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<td>Cm</td>
<td>Centimeter</td>
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<td>Cytomegalovirus</td>
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<td>CNS</td>
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<td>DCOG</td>
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DD  Differential diagnosis

Chemotherapy cycle: Dacarbazine, Etoposide, Doxorubicin,

DECOPDAC-21  Cyclophosphamide, Vincristine, Prednisone/Prednisolone

DFS  Disease-Free Survival

DICOM  Digital Imaging File Format

DMC  Data Monitoring Committee

DNA  Deoxyribonucleic Acid

DOX  Doxorubicin

DTIC  Dacarbazine

EBV  Epstein Barr Virus

EC  Ethics Committee

ECG  Electrocardiogram

Echo  Echocardiogram

EEG  Electroencephalogram

EFS  Event-Free Survival

E.g.  example given

E-lesions  Extranodal Lesions by Contiguous Involvement

ENT  Ear, Nose and Throat

ERA  Early Response Assessment

ESR  Erythrocyte Sedimentation Rate

et al.  et altra (and others)

ETO  Etoposide

Eudra-CT  European Clinical Trials Data Base

EuroNet  European Network

EuroNet-PHL-C2  European Network for Paediatric Hodgkin Lymphoma-Classical

Hodgkin-2

FDG-PET  Fluoro-Deoxyglucose-Positron Emission Tomography

Fig.  Figure

FSH  Follicle Stimulating Hormone

fT4  Free Tetra-Iodothyronine

GCP  Good Clinical Practice

GGT  Gamma-Glutamyl-Transferase

GMP  Good Manufacturing Practice

GOT  Synonyme for ASAT (Aspartate-Amino-Transferase)
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l’Enfant et de l’Adolescent

SmPC Summary of medical Product Characteristics
Sono Sonography, Ultrasound
SOP Standard Operating Procedure
SST Secondary Solid Tumour
T2-STIR Fat Saturated T2-weighted Spin Echo Sequence (MRI)
SUSAR Suspected Unexpected Serious Adverse Drug Reaction
SUV Standardised Uptake Value
T1-Flash T1-weighted Gradient Echo Sequence (MRI)
T2-TIRM Fat Saturated T2-weighted Spin Echo Sequence (MRI)
TL Treatment Level
TMF Trial Master File
TOX Toxicity
T1-SE T1-weighted Spin Echo Sequence (MRI)
TSH Thyroid Stimulating Hormone
TYA Teenage and Young Adult
UK United Kingdom
vs. versus
WB-MRI Whole Body MRI
WHO World Health Organisation
VCR Vincristine
VZV Varicella Zoster Virus
X-ray Two-dimensional Radiogram
ZKS Leipzig – Clinical Trial Centre Leipzig (Zentrum für Klinische Studien Leipzig – KKS)
5 BACKGROUND AND RATIONALE

5.1 Prior Experience of DAL/GPOH-HD and EuroNet-PHL Trials

The present study builds on the experience of eight successive DAL/GPOH-HD/EuroNet-PHL study generations. The first trial started in 1978. Since then treatment of paediatric Hodgkin’s lymphoma (HL) has stepwise been optimised thereby establishing the current standard of care in the participating countries.

From the second study generation (DAL-HD-82) onwards the backbone of the treatment strategy has been constituted and changes have evolved gradually.

Patients have been stratified into three treatment groups (TG-1, TG-2 and TG-3) according to Ann Arbor stage (TG-1: I A/B and II A; TG-2: IIEA/B, IIIEA, IIB or IIIA; TG-3: IIIEB, IIIEA/B, IIIB or IVA/B). All patients have started treatment with two intensive induction chemotherapy cycles. First, the OPPA cycle comprised the standard induction treatment; later the OEPA cycle was used.

Patients in TG-2 and TG-3 have received two or four consolidation chemotherapy cycles respectively. First, the COPP cycle comprised the standard consolidation treatment; later the COPDAC cycle was used. Note: COPDAC is now called COPDAC-28 to underline that it is administered as a 28-day cycle in contrast to the experimental DECOPDAC-21, a 21-day cycle.

After end of chemotherapy all patients previously received involved field radiotherapy (RT), later involved-node RT was administered in selected cases only based on response assessment, initially CT-MRI and later FDG PET response.

The DAL-HD-82 trial achieved 3.5-year DFS rates of 99%, 96% and 87% in TG-1, TG-2 and TG-3 respectively and due to these excellent results, was for a long time regarded as the gold standard of care in paediatric HL (Schellong et al., 1986).

Treatment optimisation since then focused on the reduction of long-term sequelae particularly:

- Male infertility attributed to the gonadotoxicity of procarbazine.
- Long term effects of radiotherapy
  - radiotherapy-induced secondary malignancies
  - cardiovascular complications following the combination of anthracyclines and radiotherapy to the mediastinum.
5.2 Prevention of Male Infertility

Over several study generations procarbazine was completely eliminated from the chemotherapy. Inferior results in DAL-HD-85 showed that procarbazine could not be omitted without compromising efficacy (Schellong et al., 1988). The replacement of procarbazine by etoposide (changing OPPA to OEPA induction chemotherapy) in the DAL-HD-90 trial solved the problem for TG-1 patients without loss of efficacy (Schellong et al., 1999). The substitution of procarbazine by dacarbazine (changing COPP to COPDAC consolidation chemotherapy) in the GPOH-HD-2002 trial has been shown to be less haematotoxic and COPDAC equally effective as COPP so procarbazine is no longer used in any TG (Mauz-Körholz et al., 2010). The results of the fourth interim analysis of the EuroNet-PHL-C1 trial (November 2013) are consistent with the GPOH-HD-2002 findings. Early fertility data of the randomised comparison between COPP and COPDAC within EuroNet-PHL-C1 suggest that the OEPA-COPDAC regimen has no major gonadotoxic effect in males (see Fig. 3).

Figure 3: Effect of COPP on FSH Levels

FSH serum levels of male patients enrolled onto the Euronet-PHL-C1 trials and randomised to COPP or COPDAC chemotherapy as well as of male patients in TG-1 who received neither COPP nor COPDAC were transformed into a Z-Score. The mean FSH values in a normal population correspond to zero on the
y-axis. FSH values are depicted in units of the standard deviation. FSH levels in all patients who received COPP were above the mean, while in patients receiving COPDAC the FSH distribution was similar to those patients who neither received COPP nor COPDAC. The differences between FSH-values after COPP and COPDAC are statistically significant (p< 0.01).

Female patients with HL treated with COPP chemotherapy are at risk for premature ovarian insufficiency and/or premature menopause (Kreuser et al., 1987). Fertility data of young women after OEPA-COPDAC treatment are not yet available. However, EuroNet-PHL-C1 showed that OEPA-COPDAC is equally effective to OEPA-COPP but less hematotoxic. Thus, chemotherapy with OEPA-COPDAC will be the standard chemotherapy for all patients in EuroNet-PHL-C2.

5.3 Reduction of Radiotherapy

The development of secondary malignancies after successful HL treatment is of major concern. The rate of secondary haematological malignancies (which are largely chemotherapy related) mostly occurring one to ten years after therapy is very low in previous DAL-HD trials. The estimated risk after 15 years is about 1% for the patients in the trial series DAL-HD-78 to DAL-HD-90 (Schellong et al., 1997). This did not change after the introduction of etoposide (Schellong 1998, Schellong and Riepenhausen 2002).

On the other hand, the risk of non-haematological radiotherapy related secondary tumours increases after a latency period of 20 years and above. The cumulative risk of secondary solid tumours (SSTs) for the DAL/GPOH-HD study patients has been 5.7% after 20 years (standard error (SE) 1.5%). It increased to 11% (SE 2%) after 22 years. The overall survival (OS) has been 94% after 20 years and dropped to 87% after 24 years (Schellong and Riepenhausen 2002; Schellong et al., 2004). The drop in OS after 20 years reflects the major impact of SST on OS. These results are almost identical to the 20-year risk for solid tumours reported by the American Late Effects Study Group (LESG). In their study the SST-rate increased steeply between 20 and 30 years. After 30 years the cumulative rate of secondary malignant tumours approached 25% (Bhatia et al., 2003). Radiation therapy has been attributed as being the most important risk factor for the development of SSTs (O’Brian et al., 2010; Castellino et al., 2011).

The standard radiotherapy dose in DAL-HD-82 was reduced from 25 or 35 Gy to 20 Gy in GPOH-HD95 and GPOH-HD-2002 (Schellong et al., 1988; Dörrfel et al. 2003; Mauz-Körholz et al. 2010). Radiotherapy associated side effects seem to be dose dependent (Schellong 2010; Castellino et al. 2011). However, a significant number of SSTs may still occur at lower radiation doses (O’Brian et al. 2010).
The concerns regarding the late morbidity and particularly late mortality of RT has driven the goal of reduction in RT exposure in our paediatric trials. The concept of response-adapted omission of radiotherapy was first introduced in the GPOH-HD95 trial. Radiotherapy was omitted in patients with complete remission (CR) determined at the end of chemotherapy by CT/MRI. Event-free survival after 5 years was 88% for all patients; overall survival was 97% (Dörffel et al., 2003). In TG-1 there was no significant EFS difference between patients with (94%) and without (97%) radiotherapy. Therefore, omission of radiotherapy in TG-1 CR patients was considered the standard treatment. However, in TG-2 and TG-3 omission of radiotherapy for CR patients led to a significant decrease in EFS (without irradiation 79%, with irradiation 91%). Therefore radiotherapy for patients in TG-2 and TG-3 remained the standard approach in GPOH-HD-2002.

In EuroNet-PHL-C1, early response assessment (ERA) with FDG-PET was introduced after 2 cycles of OEPA. ERA adequate response (AR) was defined as metabolic remission (FDG-PET negative according to IHC criteria) combined with at least partial morphologic remission (PR). Patients with adequate response (AR) did not receive radiotherapy. AR was achieved in about 50% of all trial patients (TG-1: 63.7%, TG-2: 50.2% and TG-3: 33.3%).

According to the fourth interim analysis of EuroNet-PHL-C1 based on 1978 patients the event-free survival (EFS) curves of irradiated and non-irradiated patients are superimposable (Fig. 4).

![Event-free Survival of Children and Adolescents with Classical Hodgkin Lymphoma Treated with/without Radiotherapy Within EuroNet-PHL-C1—Results of the Fourth Interim Analysis](image)

**Figure 4:** Event-free Survival of Children and Adolescents with Classical Hodgkin Lymphoma Treated with/without Radiotherapy Within EuroNet-PHL-C1—Results of the Fourth Interim Analysis
The elimination of radiotherapy in half of the patient population is considered a major success of the EuroNet-PHL-C1 trial.

5.4 Changes in EuroNet-PHL-C2

5.4.1 New Treatment Level Assignment

The EuroNet risk stratification into treatment groups (TG) for early, intermediate and advanced stages have been compared to the stratification in the adult setting. The German Hodgkin Lymphoma Study Group (GHSG) and the EORTC (European Organisation for Research and Treatment of Cancer; Tubiana 1989) use similar strata. Marked differences were noted when comparing our EuroNet-PHL stratification to that of the GHSG (see Fig. 5). About half of our TG-1 patients would be classified into intermediate stage in the adult setting. About 1/3 of our TG-2 patients would be regarded as advanced stage in the adult setting.

![Figure 5: Treatment Stratification in the GHSG Protocols Compared to EuroNet-PHL-C1](image)

In contrast to the protocols of the GHSG, elevated ESR, large mediastinal mass and spread of disease (number of involved lymph node areas) were not taken into account for treatment stratification into TGs within the EuroNet-PHL-C1 protocol. We therefore investigated whether these factors had been prognostic in EuroNet-PHL-C1.

An assessment of risk factors across all TGs has revealed that elevated ESR (> 30mm/hr) and bulk (> 200ml) define a higher risk sub-group within former TG-1 only:

- ESR: It has been documented that the upper normal value of ESR increases with age (Miller et al., 1983). In the adult setting, “ESR ≥ 50 mm/h” or “ESR ≥ 30 mm/h and B-symptoms” are used for stratification. ESR ≥ 30 mm/h will be used in the paediatric
setting, since ESR ≥ 50 mm/h is rare in stage I/IIA. ESR ≥ 30 mm/h has been found to be prognostic in our data and identifies a subgroup within former TG-1 only at higher risk.

- **Bulk:** Classical mediastinal bulk captured as a proportion of the thoracic aperture was available in less than 50% of EuroNet-PHL-C1 patients. Volumetric assessment is the routine tumour volume assessment in the DAL/GPOH-HD trials (Mauz-Körholz et al., 2010) and has been determined in the EuroNet-PHL-C1 trial in more than 2000 patients. A contiguous tumour volume larger than 200 ml, corresponding to an approximation of a sphere of 7.4 cm in diameter defines a higher risk group within former TG-1.

In the second interim analysis of EuroNet-PHL-C1 a higher risk group in TG-1 was found using ESR ≥ 30 mm/h and bulk ≥ 200 ml. Enumeration of involved lymph node areas did not yield additional prognostic information. These results were confirmed in the fourth interim analysis (November 2013; Fig. 6). The higher risk group in TG-1 is defined as “ESR ≥ 30” or bulk ≥ 200 ml.

![Figure 6: TG-1 Risk Group Based on Elevated ESR and a Maximum Volume of Larger than 200 ml – Data of the Fourth Interim Analysis](image)

**Figure 6:** TG-1 Risk Group Based on Elevated ESR and a Maximum Volume of Larger than 200 ml – Data of the Fourth Interim Analysis

Former TG-1 patients with ESR > 30 or bulk > 200ml will be treated in the C2 trial in TL-2.

Additional prognostic factors to refine former TG-2 and TG-3 are not significant:
In the second interim analysis, we attempted to define a higher risk group in TG-2 similar to the criteria used in TG-1 (according to GHSG criteria) proposing a higher risk group in IIB with bulk or IIIA with bulk or with high ESR. However these preliminary results were not confirmed in the fourth interim analysis (November 2013), the differences were not significant. Thus, a change in treatment level assignment for TG-2 patients would not be justified.

In addition, a high risk group in TG-3 could not be identified (data not shown). At 36 months the EFS for all TG-3 patients was 86.1 (CI 83.5 – 88.8) and for stage IVB patients 80.4% (CI 75.2-85.9%).

Proposed TL risk grouping for the EuroNet-PHL-C2 trial:

Instead of the three traditional treatment groups (TGs) in EuroNet-PHL-C2 three treatment levels (TLs) are defined:

TL-1 = former TG-1 without risk factors

TL-2 = former TG-1 with risk factors and former TG-2

TL-3 = former TG-3

TL allocation now becomes more comparable to treatment stratification in adult study groups (Fig. 7).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Stage (Ann Arbor)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I, IIA</td>
</tr>
<tr>
<td>No risk factor</td>
<td>TL-1</td>
</tr>
<tr>
<td>ESR ≥ 30 mm/h</td>
<td></td>
</tr>
<tr>
<td>Bulk ≥ 200 ml</td>
<td></td>
</tr>
<tr>
<td>E-lesions</td>
<td></td>
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</tbody>
</table>

Figure 7: Treatment Stratification According to Treatment Levels (TLs) in EuroNet-PHL-C2

5.4.2 Changes in FDG-PET Response Assessment

The Deauville scale for visual assessment of PET response (Le Roux et al., 2011) uses the liver and the mediastinal blood pool for internal reference; i.e. residual signals of involved sites are
compared to signals of the mediastinal blood pool and the liver in five ordinal categories. This is currently regarded as the standard approach for assessing PET response in lymphoma (Barrington et al., 2010). Therefore, in EuroNet-PHL-C2 the PET response assessment will switch from the older IHP criteria used in EuroNet-PHL-C1 to the Deauville scores.

An ERA FDG-PET scan shall detect complete metabolic remission after 2 cycles of OEPA in all patients. There is growing consensus that Deauville 1 - 3 is consistent with complete metabolic response [Menton workshop 2012, Meignan 2013].

The EuroNet PHL-C2 trial will apply these consensus criteria at the ERA FDG-PET with Deauville scores 1, 2 and 3 considered negative and scores 4 and 5 considered positive.

While the Deauville score has provided a very useful model for response assessment there are limitations of visual PET assessment and with the ordinal scale. Visual assessments can be influenced by optical illusions (see Fig. 8) and differences in the readers’ perception. In addition, PET-response may be described as a continuum rather than by ordinal categories. Responses at the borderline between Deauville scores 2-3 or 3-4 are particularly difficult to assign with certainty. To address the recognised difficulties of visual interpretation and the limitations of the ordinal scale the EuroNet PHL-C2 trial formally integrates a newly developed semi-quantitative PET assessment method to aid and compliment the Deauville score determination at staging and response assessment.

Figure 8: Illustration of Optical Illusion Caused by Background Variation
Optical illusions can be eliminated by semi-automatic quantification of the residual PET signal transforming the ordinal Deauville scale to a continuous scale.

The semi-quantitative method of PET response (qPET) will detect the peak PET-signals (SUV) in residual lymphoma and average PET-signals of the liver. These signals are measured with standardised volumes of interest (VOI) in the residual lymphoma and liver. The final qPET-value is the quotient of these measurements.

Quantification in the residual lymphoma involves visual identification of the FDG avid residua and a software assisted program applies a fixed volume of interest in the hottest voxels. An average SUV value is determined. Quantification in the liver calculates the average liver uptake within a fixed volume (Fig. 9 and 10) (Hasenclever and Kurch et al., 2014).

**Figure 9: Quantification of Average Liver Uptake in a Volume of Interest of 30ml**

**Figure 10: Quantification of Residual Up-take in Lymphoma**
Deauville scores and qPET-values were determined in 898 pediatric HL patients after 2 OEPA cycles in the EuroNet-PHL-C1 trial. Deauville categories correspond to thresholds on the qPET scale: Categories 3, 4, 5 correspond to qPET values of 0.95, 1.3 and 2.0, respectively (Figure 11).

**Figure 11:** Density and Cumulative Distribution Functions of qPET Signals by Visual Deauville Categories

qPET thresholds discriminating between Deauville categories with approximately symmetric discrepancies are indicated. qPET=0.95 (dotted line), qPET=1.3 (solid line), qPET=2.0 (dashed line) discriminate between Deauville categories 2 and 3, 3 and 4 and 4 and 5 respectively.

The distribution of qPET values is unimodal with a peak representing normal metabolic responses and a tail of abnormal responses. In the C1 patient cohort the peak is at 0.95
coinciding with the borderline between Deauville 2 and 3. The qPET thresholds of 1.3 or 2 select abnormal metabolic responses with high sensitivity and specificity. This has been determined by mixture models (Hasenclever and Kurch et al., 2014).

**Figure 12: Histogram of qPET Signals**

*The dotted line indicates the mode at 0.95 (corresponding to uptake above mediastinal blood pool), the solid line a threshold at 1.3 (corresponding to uptake above liver) and the dashed line at 2 (corresponding to uptake markedly above liver).*

EFS rates support our working hypothesis that qPET < 1.3 is consistent with an adequate response to 2 OEPA (Fig. 13). The cut-off value 1.3 was derived from the histogram (Fig. 12) prior to analysing EFS results.
Figure 13: Event-Free Survival by qPET ≥ 1.3 in the Fourth Interim Analysis of EuroNet-PHL-C1

All patients with qPET ≥ 1.3 received radiotherapy. Only about half of the patients with qPET < 1.3 received radiotherapy. Outcome in patients with qPET < 1.3 with or without radiotherapy was superimposable.

The threshold for a positive ERA FDG-PET is 1.3 which corresponds to the borderline between Deauville 3 and 4. Patients with a positive ERA PET and in TL-2 and TL-3 will also have a late response assessment (LRA) PET scan.

The LRA PET shall detect minimal residual tumour. The threshold for a positive PET scan at the end of all chemotherapy is lower than at ERA. Therefore, LRA PET-positivity is captured at Deauville 3+ in contrast to Deauville 4+ at ERA. In the experimental DECPDADAC-21 arm patients will receive no further therapy, if LRA PET is negative. This approach is similar to the successful strategy pursued in the GHSG HD15 trial which applied local RT to end of treatment residual PET positive sites only (Engert et al., 2012).

In summary: response assessment in EuroNet-PHL-C2 will be based on Deauville scores determined with the help of qPET measurements. Visual Deauville scores will be documented prior to qPET measurements. Discrepancy rates will be estimated. Outcome in discrepant cases will be explored.
5.4.3 Intensification of Consolidation Chemotherapy with DECOPDAC-21

Intensification of consolidation chemotherapy will be investigated to further improve the treatment results and to compensate for a significant reduction of radiotherapy. The new intensified consolidation chemotherapy DECOPDAC-21 has been designed deriving evidence from other study groups.

An intensive chemotherapy approach has been applied in other HL trial settings in children and adults. Kelly et al. (2011) showed feasibility of 6 to 8 BEACOPPesc cycles in 99 advanced stage paediatric HL patients. The 5-year EFS was 94%, overall survival was 97% and only 2/99 patients presented with secondary leukaemia. The GHSG showed excellent results in adult advanced stage HL patients using BEACOPPesc (Diehl et al. 2003; Engert et al., 2012). Currently, best results are achieved with 6 x BEACOPPesc and RT only to LRA PET-positive sites > 2.5 cm (Engert et al., 2012). The 5-year PFS in these patients is 92.6%. Within this study 739 patients with persistent residual lesions were evaluated by LRA PET. At 48 months after treatment LRA PET-positive (Deauville ≥ 3) patients had a PFS of 86% whereas LRA PET-negative patients achieved 92.6% (Engert et al., 2012). Application of RT to LRA PET positive residua after intensive chemotherapy achieves excellent outcomes, which we will seek to replicate with our DECOPDAC-21 arm.

We will not use BEACOPPesc because there are major concerns regarding the toxicity of the BEACOPPesc regimen preventing its widespread use. These include procarbazine-associated gonadotoxicity, the bleomycin-associated pulmonary toxicity and the increased risk of secondary leukaemia.

The DECOPDAC-21 regimen (Tab.1) has been designed to have similar effectiveness as the BEACOPPesc regimen and is an intensification of the standard COPDAC-28 regimen by increasing the dose of cyclophosphamide (CY) by 25%, adding doxorubicin and etoposide. As it is a 21 day cycle the prednisone/prednisolone application is restricted to days 1 to 8.

DECOPDAC-21 has some similarities to the BEACOPPesc regimen but with important modifications addressing these toxicity concerns:

- substitution of procarbazine by dacarbazine (DTIC)
- omission of bleomycin
- reduction of the doxorubicin (DOX) dose from 35 to 25 mg/m² per cycle resulting in cumulative doses of 210 mg/m² in TL-2 and 260 mg/m² in TL-3 for OEPA-DECOPDAC-21.
• reduction of etoposide (ETO) from 600 to 300 mg/m² per cycle resulting in a cumulative dose of 1850 mg/m² (TL-2) or 2450 mg/m² (TL-3) for OEPA-DECOPDAC-21 which is still less than in 6 x BEACOPPesc

• reduction of the prednisone/prednisolone (PRED) dose from 600 mg/m²/cycle to 320 mg/m²/cycle by restricting prednisone/prednisolone application to cycle days 1 to 8. Reduction of prednisone/prednisolone may be important to prevent osteonecrosis in HL patients (Fossa et al., 2012).

Table 1: DECOPDAC-21 Drug Doses

DECOPDAC-21 is a 21-day cycle:

- DTIC 250 mg/m² d1-3
- CY 625 mg/m² d1+2
- ETO 100 mg/m² d1-3
- DOX 25 mg/m² d1
- VCR 1.5 mg/m² (cap at 2mg) d1+8
- PRED 40 mg/m² d1-8

According to the effective dose model (Hasenclever et al., 2001), a tool for ranking HL chemotherapies by efficacy and predicting study results (Carde, 2005) the combination of 2 x OEPA and 4 x DECOPDAC-21 has an effective dose of 27.3 which is comparable to that of 6 x BEACOPPesc (28.9). In this model, 2 x OEPA and 4 x COPDAC-28 have a calculated effective dose of 23.1. As DECOPDAC-21 is expected to be more intensive than COPDAC-28 inferior efficacy of the experimental regime is very unlikely.

Since BEACOPPesc has been successfully used in children (Kelly et al. 2011) and DECOPDAC-21 is an attenuation of BEACOPPesc no feasibility study with DECOPDAC-21 is deemed necessary. Nevertheless, a safety analysis will be performed after 50 DECOPDAC-21 cycles.
5.5 Justification of Study Questions

Patients will be treated in three different sub-studies:

- patients in TL-1
- ERA PET-negative patients in TL-2 and TL-3
- ERA PET-positive patients in TL-2 and TL-3

5.5.1 Patients in TL-1

Patients in TL-1 will be treated with two cycles of induction OEPA chemotherapy.

ERA PET-negative patients will receive one consolidation COPDAC-28 cycle.

ERA PET-positive patients will receive standard involved node radiotherapy (Fig. 14).

In the fourth interim analysis of EuroNet-PHL-C1 an analysis of low-risk TG-1 ( = the TL-1 subgroup) was done. TL-1 ERA PET-positive patients after 2 OEPA who received radiotherapy had an excellent outcome with 3-yr EFS 98.3% (95%-CI: 0.95 -1.0) while TL-1 ERA PET-negative patients without radiotherapy had 3-yr EFS of 88.4% (95%-CI: 0.83-0.94).

In TL-1 patients with a positive FDG PET scan at ERA additional chemotherapy is not justified as the outcome of TL-1 plus RT in the C1 trial was a 3-yr EFS of 98.3%

In the TL-1 patients with a negative PET scan in C1 omission of RT resulted in a reduction of the EFS. In addition, radiotherapy indication in EuroNet-PHL-C2 TL-1 patients will be further restricted by shifting the ERA PET threshold from Deauville 3+ to 4+. To compensate for the EFS reduction in the TL-1 group with omission of RT we will add one consolidation COPDAC-28 cycle in the ERA PET negative group. Two cycles of OEPA plus one cycle of COPDAC-28 are more intensive than 2 x ABVD. Acute toxicity is higher but reversible. The addition of one COPDAC-28 cycle will not change the risk-benefit analysis since COPDAC is extremely well tolerated and the additional cumulative drug doses are considered not to cause long-term side effects. The aim of this strategy is to confirm EFS rates consistent with a target of 90% or better which is comparable to the 5-year PFS rates are 91.6% in adult early stage HL treated with 2 x ABVD + 20 Gy involved node irradiation (Engert et al., 2010). The major advantage for most children and adolescents being treated in TL-1 is the avoidance of radiotherapy and our view is that a small reduction in EFS is an acceptable outcome since the benefits are considered to outweigh the risks. Notably, relapse after TL-1 treatment is highly salvageable. The avoidance of late morbidity and mortality associated with RT is expected to improve long-term results by eliminating the risk of radiotherapy-associated second cancers and late cardiovascular mortality.
5.5.2 Patients in TL-2 and TL-3

All patients in TL-2 or TL-3 will receive 2 x OEPA and respectively two or four cycles of consolidation chemotherapy (Figure 15). All TL-2 and TL-3 patients will be randomised between consolidation COPDAC-28 and DECOPDAC-21.

The standard arm consolidation chemotherapy is COPDAC-28 which is equally effective, but less gonadotoxic than COPP in GPOH-HD-2002 and EuroNet-PHL-C1.

The single chemotherapy randomisation is performed as soon as the TL-assignment is confirmed by central review. The time-point for randomisation has been chosen in the interests of patients so that there is no delay in delivering consolidation treatment. Other time-points, such as ERA, have been considered and rejected as unacceptable because of the issue of delay in consolidation. The ERA assessment is performed after two cycles of OEPA and the consolidation chemotherapy should start as soon as the ERA PET scan is done.

**Two randomised sub-studies arise based on the ERA result (Fig. 15).**

- In patients with adequate response at ERA a randomised chemotherapy comparison
In patients with inadequate response at ERA a randomised chemotherapy-radiotherapy comparison

**Figure 15:** Study Design in TL-2 and TL-3

### 5.5.2.1 Patients in TL-2 and TL-3 with adequate response

In TL-2 and TL-3 patients with adequate response at ERA there will be an unconfounded comparison of different chemotherapies (OEPA + COPDAC-28 versus OEPA + DECOPDAC-21).

**TL-2:** will comprise patients of the former TG-2 and high-risk patients of TG-1 (I and IIA with bulk or ESR >= 30 mm/h) who are expected to have similar results as TG-2 patients (~90%).

The TG-2 group in EuroNet-PHL-C1 achieved a 3-year EFS of 89% with RT and 91% without RT. A historical comparison of these outcomes with the GPOH-HD2002 study, in which all patients were irradiated, and achieved an EFS of 92% shows that omission of radiotherapy in 50% of patients in TG-2 in the C1 trial has resulted in only a small increase in relapses.
In EuroNet-PHL-C2 the rate of radiotherapy indication will be further reduced because the threshold for a positive ERA PET has been raised from Deauville 3+ to 4+. A 3-year EFS rate of about 87-88% will be expected in TL-2 patients treated with the standard COPDAC-28 chemotherapy.

Other trials have achieved good results in intermediate risk HL. The GHSG HD14 trial applied two BEACOPPesc and two ABVD plus 30Gy radiotherapy in all intermediate stage patients and achieved a 5-year FFTF (Freedom from Treatment Failure) rate of 94.8% (OS 97%) which is better than expected in the COPDAC-28 standard arm. However the justification for our standard arm is the major advantage for most children and adolescents in being treated in TL-2 without radiotherapy hence eliminating the risk for radiotherapy-associated second cancer and cardiovascular risks.

Moderate intensification of chemotherapy in the experimental arm with DECOPDAC-21 is intended to improve EFS rates in TL-2 patients without RT compared to standard COPDAC-28.

**TL-3:** This is identical to the previous TG-3 in the EuroNet-PHL-C1 trial. The TG-3 group in the C1 trial achieved a 3-year EFS rate of 86% (CI 83 – 90.7) with RT and 87% (CI 74.8 – 89) without RT. In EuroNet-PHL-C2 the rate of radiotherapy indication will decrease further in TL-3 patients by shifting the ERA PET-threshold from Deauville 3+ to 4+. A 3-year EFS rate of about 80-85% will be expected in TL-3 patients treated with the standard COPDAC-28 chemotherapy. This reduction in the EFS rate is expected to be due to the reduction in the number of irradiated patients. Nevertheless, the long-term benefit associated with the omission of RT and the prognosis of TG-3 patients at first relapse which remains favourable (Schellong et al., 2005) make TL-3 standard therapy acceptable.

Intensification with DECOPDAC-21 is intended to improve EFS rates in TL-3 patients without RT compared to standard COPDAC-28.

### 5.5.2.2 Patients in TL-2 and TL-3 with inadequate response

Approximately 25% of the patients overall in TL-2 and TL-3 will be ERA PET-positive.

TL-2 and TL-3 patients who are PET positive at ERA are scheduled for a late response assessment PET scan (Figure 15).

TL-2 and TL-3 patients randomised to COPDAC-28 with positive ERA PET:
These patients will receive standard radiotherapy with 20 Gy to all initially involved nodes and the LRA PET is used to define the boost indication with an additional 10 Gy boost to LRA PET-positive residuals.

**TL-2 and TL-3 patients randomised to DECOPDAC-21 with a positive ERA PET:**

These patients will receive radiotherapy with 30 Gy restricted to LRA PET-positive residuals only. No Radiotherapy is given to LRA PET-negative patients in the DECOPDAC-21 arm.

The radiotherapy strategy in the intensified DECOPDAC-21 arm is similar to the standard approach in the HD15 trial (Engert et al., 2012). In HD-15, patients with positive late response PET received radiotherapy to PET-positive residual sites only and achieved about 86% 4-year PFS.

We expect 5-year EFS rates in the order of 84% in the standard (COPDAC-28) arm for TL-2 and TL-3 patients. This expectation is in the range of the HD15 results.

We anticipate that DECOPDAC-21 and radiotherapy restricted to LRA PET-positive residuals may result in marginally improved treatment results for TL-3 ERA PET-positive patients.

Our objective for the TL-3 patients is to obtain comparable results while avoiding radiotherapy or significantly reducing the number and size of sites being irradiated using DECOPDAC-21 and LRA-based RT so reducing the risk of radiotherapy-induced SST in these patients.

### 5.6 Risk Benefit Analysis of DECOPDAC-21

DECOPDAC-21 is an intensification of COPDAC-28. Compared with the standard COPDAC-28 the new DECOPDAC-21 has increased dose of cyclophosphamide from 1000 to 1250 mg/m² (25%), and doxorubicin 25mg/m² and etoposide 300mg/m² are added in each of the 2-4 cycles. The DECOPDAC-21 recycles at 21 day intervals compared with 28 day cycles for the standard COPDAC-28. While DECOPDAC-21 is clearly more intensive than standard COPDAC-28 it may also be considered as a derivation of the BEACOPP regimen which has been proven to be very effective. The concerns with BEACOPPesc relate to toxicity and hence the DECOPDAC regimen was designed to maximise effectiveness and address the concerns regarding BEACOPP toxicity.

A particular concern is the relatively high secondary AML (sAML) rates of 2-4% that have been observed with eight cycles of escalated BEACOPP [Engert 2009]. Recently, however a low rate of sAML (< 1%) has been reported for 6 x BEACOPPesc. The most recent analysis of the
GHSG showed a sAML risk of 1.7% vs 0.7% in patients receiving 4 or more vs less than 4 courses of BEACOPPesc [Eichenauer 2014]. However, the patients with sAML were significantly older than those without (43 vs 34 yrs). These data are encouraging because within this protocol only young people will be included and the OEPA-DECOPDAC-21 combination even in the TL3 group has similar cumulative doses of Etoposide compared to 4 BEACOPPesc and lower cumulative doses of than 6 BEACOPPesc.

As patients are treated with multi-drug regimen it is difficult to disentangle the individual drug effects. Cyclophosphamide is reported to be less leukaemogenic than mechlorethamine [vanLeeuwen 1994]. The same may [vanLeeuwen 1994] or may not [Boisin 1995] be true for procarbazine. It is difficult to assess the leukaemogenicity of procarbazine since mechlorethamine and procarbazine were often used in combination. Cyclophosphamide and procarbazine are part of BEACOPP, but procarbazine has been eliminated from COPDAC-28 and DECOPDAC-21.

The second class of cytotoxic drugs that may be associated with an increased risk of sAML are topoisomerase II inhibitors, such as anthracyclines like doxorubicin and epipodophyllotoxins like etoposide (LeDeley et al., 2003). Etoposide has been associated with a high sAML risk in ALL studies of the 1990s [Pui et al., 1991]. However, in ALL treatment a weekly or twice weekly schedule was used which induced pronounced haematotoxicity. Etoposide-associated sAML risk is lower if etoposide is administered over 3 to 5 consecutive days and repeated after two or more weeks (Hijiya et al., 2009). A prospective meta-analysis of twelve COG studies on various cancers treated with such regimens failed to demonstrate a cumulative dose effect of etoposide (Smith et al., 1999). High cumulative doses of 5g/m² etoposide combined with 9.6g/m² cyclophosphamide, 90g/m² iphosphamide and 375mg/m² doxorubicin showed no increased sAML rate in paediatric Ewing sarcoma (Bhatia et al., 2007).

Acute and chronic haematopoietic damage is reported to increase sAML risk (Radford et al., 1990; vanLeeuwen et al., 1994) as well as the use of growth factors (Hijiya et al., 2009).

Thus, the leukaemogenicity of chemotherapy regimens is not necessarily determined by the cumulative dose, but rather by the schedule, the drug combination and the degree of regimen-induced haematotoxicity. DECOPDAC-21 and BEACOPP include etoposide on cycle days 1 to 3 within 21-day cycles. Therefore, these can be considered lower risk schedules. In contrast to BEACOPP, DECOPDAC-21 does not include G-CSF.

A detailed analysis of the risk of secondary AML with the DECOPDAC-21 regimen is considered in Appendix VIII but our conclusion is that it is very unlikely that DECOPDAC-21 will significantly increase the sAML risk.
The benefits of the intensified DECOPDAC-21 chemotherapy in EuroNet-PHL-C2 are the potential improvement in EFS over COPDAC-28 in the ERA PET negative patients who are treated with chemotherapy only.

The benefit for the ERA PET positive patients who will receive DECOPDAC-21 are that the RT indication is based on the LRA PET. Consequently, some patients will avoid RT altogether if they are LRA PET negative and for those that remain PET positive at LRA the RT field size and number of sites will be reduced since only to LRA PET positive residua will be irradiated.

The potential benefits of DECOPDAC-21 to ERA PET negative and ERA PET positive patients outweigh the potential small increase in sAML.
6 AIMS, OBJECTIVES AND OUTCOME MEASURES

6.1 Aims
To reduce the indication for radiotherapy (RT) in newly diagnosed patients with classical Hodgkin lymphoma without compromising cure rates. To investigate a chemotherapy intensification randomisation in intermediate and advanced classical Hodgkin lymphoma (HL) to compensate for reduction in RT.

6.2 Primary Objectives

6.2.1 Randomised
To increase event-free survival in ERA PET-negative intermediate and advanced stage patients (TL-2 and TL-3) without radiotherapy by using intensified consolidation chemotherapy (DECOPDAC-21). With a sample size of 1345 patients we will have 84% power to detect an increase in 5-year EFS rates from 88% to 93% at a two-sided significance level of $\alpha = 5\%$.

To demonstrate in ERA PET-positive TL-2 and TL-3 patients that the combination of intensified consolidation chemotherapy (DECOPDAC-21) plus late response assessment (LRA) PET-based radiotherapy is comparable to the standard consolidation chemotherapy (COPDAC-28) plus standard involved node radiotherapy. For the expected 424 patients the log hazard ratio (lhr) as a measure of treatment difference will be estimated with an expected standard error of 0.26. An 80%- and 95%-confidence bound will be provided. As we have limited power the experimental arm will be considered comparable to the standard if the lhr point estimate is less than 0.26, i.e. about 4% in EFS rates, away from equality.

6.2.2 Non-randomised
To further reduce the radiotherapy indication in early stage patients by increasing the threshold for a positive FDG PET scan at early response assessment (ERA) to Deauville 4+ while still preserving a 5 year EFs estimate at a target of 90% or above.
6.3 Secondary Objectives


Comparison of the LRA PET-positivity rates in ERA PET-positive patients after consolidation chemotherapy with COPDAC-28 or DECOPDAC-21, respectively.

6.4 Tertiary Objectives

Description of quality endpoints (treatment delivery and trial logistics).

6.5 Outcome Measures

6.5.1 Primary Efficacy Endpoint:

Event-free survival (EFS) defined as time from start of treatment until the first of the following events:

- progression/relapse of disease
- secondary malignancy
- death from any cause.

6.5.2 SecondaryEndpoints:

- **Efficacy**: overall survival (OS), progression-free survival (PFS)
- **Safety**: CTC (common toxicity criteria) grading during any individual treatment element including assessment of osteonecrosis
- **Quality**: Time from day of PET imaging until decision on response category at ERA or LRA, respectively. Time from last day of chemotherapy to first day of radiotherapy in patients with radiotherapy indication. Time from last dose of prednisone/prednisolone in OEPA to start of the first consolidation cycle. Duration of chemotherapy. Chemotherapy dose actually administered divided by scheduled total dose for each drug. Discontinuation or substitution rate for each drug. Time from FDG-Injection to start of PET acquisition. Proportion of patients with enhanced FDG-uptake in brown fat under use of beta-blockers. Average liver FDG-uptake at staging, ERA and LRA (reproducibility). Applied FDG-dose in relation to the EANM paediatric dosage card recommendation. Applied radiation dose in low dose (PET-)CT (tube current, tube
voltage and rotation time). Duration of radiotherapy, radiotherapy discontinuation rate. Delivery of radiotherapy according to protocol guidelines (see radiotherapy manual).
7 TRIAL DESIGN

The EuroNet-PHL-C2 trial is a multinational, multicentre, randomized controlled trial. At least 200 trial sites are expected to take part, enrolling at least 2200 patients. According to past experience these patients will be distributed among the treatment level TL-1, TL-2 and TL-3 in a ratio of approximately 20:40:40.

For patients in TL-1 the trial is designed as a quality control treatment study in a stable patient population addressing consistency of 5-year EFS/PFS rate estimates with a target rate of 90% although the indication for radiotherapy will be reduced compared to EuroNet-PHL-C1.

Patients in intermediate (TL-2) and advanced stage (TL-3) will be randomised between standard COPDAC-28 and intensified DECOPDAC-21 consolidation chemotherapy. To avoid delayed consolidation, randomisation has to be performed before ERA and as soon as the TL-assignment is confirmed by central review. Therefore two randomised sub-studies arise:

- In patients with adequate response at ERA not receiving radiotherapy a randomised controlled chemotherapy comparison between COPDAC-28 and DECOPDAC-21 concerning efficacy is carried out. Acute toxicity will be an important secondary endpoint.
- In patients with inadequate response at ERA a randomised controlled comparison of combined modality chemotherapy-radiotherapy treatment strategies concerning efficacy will be performed.

7.1 Summary of Changes in EuroNet-PHL-C2 Compared to EuroNet-PHL-C1

- The term “treatment group” will be replaced by “treatment level” (TL-1, TL-2 and TL-3).
- The single change in risk group allocation is for former TG1 patients with risk factors, so called TG-1 ‘high-risk’ patients who will be treated in TL-2.
- TL-1 patients who are ERA PET negative after 2 OEPA are consolidated with one cycle of COPDAC-28.
- PET response will be assessed in EuroNet-PHL-C2 using the five point Deauville scores determined by visual analysis and aided by semi-automatic quantitative PET measurements.
- The threshold for negative PET at early response assessment (ERA) shifts from the previously used Deauville 3 to Deauville 4 score, thereby increasing the number of patients without indication for RT.
• Evaluation of an intensified consolidation regimen DECOPDAC-21 in TL-2 and TL-3 patients.

• In TL-2 and TL-3 patients, combination of DECOPDAC-21 with radiotherapy to LRA PET-positive sites in ERA PET-positive patients.
Notably, threshold for negative PET at LRA will be different from that at ERA.

7.2 Treatment and Duration of Trial Arms

All patients start their treatment with two cycles of OEPA followed by early response assessment (ERA) including FDG-PET. All patients with a negative ERA PET scan after 2 OEPA do not receive radiotherapy.

Patients in TL-1 with a negative ERA PET scan are consolidated with one additional cycle of COPDAC-28.

Patients in TL-2 and TL-3 will be randomised between COPDAC-28 (standard chemotherapy) or DECOPDAC-21 (intensified chemotherapy). They receive two (TL-2) or four (TL-3) cycles of consolidation chemotherapy.

In case of inadequate response at ERA:
• Patients in TL-1 receive involved node radiotherapy (20 Gy) after 2 OEPA.
• Patients in TL-2 and TL-3 randomised to COPDAC-28 will receive standard involved node radiotherapy (RT; 20 Gy). A 10 Gy boost will be delivered to LRA PET-positive sites.
• Patients in TL-2 and -3 randomised to DECOPDAC-21 will receive radiotherapy (30 Gy) to LRA PET-positive sites only.

The treatment duration varies according to treatment level and the patient’s response (Table 2).

Table 2: Treatment Duration

<table>
<thead>
<tr>
<th>Treatment Level</th>
<th>Scheduled treatment duration (according to response)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TL-1</td>
<td>12 – 14 weeks</td>
</tr>
<tr>
<td>TL-2 DECOPDAC-21 arm</td>
<td>14 – 18 weeks</td>
</tr>
<tr>
<td>TL-2 COPDAC-28 arm</td>
<td>16 – 20 weeks</td>
</tr>
<tr>
<td>TL-3 DECOPDAC-21 arm</td>
<td>20 – 24 weeks</td>
</tr>
<tr>
<td>TL-3 COPDAC-28 arm</td>
<td>24 – 28 weeks</td>
</tr>
</tbody>
</table>
8 ELIGIBILITY

8.1 Inclusion Criteria

EuroNet-PHL-C2 is open to all patients with

- histologically confirmed primary diagnosis of classical Hodgkin’s lymphoma
- patients under 18 years of age on the date of written informed consent (In specialised Teenage and Young Adult units in Australia, France, Italy, New Zealand and UK patients under 25 years of age can also be enrolled.). Lower age limits will be country specific according to national laws or formal insurance requirements that may preclude very young patients.
- written informed consent of the patient and/or the patient’s parents or guardian according to national laws
- negative pregnancy test within 2 weeks prior to starting treatment for female patients with childbearing potential.

8.2 Exclusion Criteria

Patients with one or more of the following criterion are excluded:

- prior chemotherapy or radiotherapy for other malignancies
- pre-treatment of Hodgkin’s lymphoma (except for steroid pre-phase to a maximum of 7-10 days for emergency treatment of a large mediastinal tumour)
- diagnosis of lymphocyte-predominant Hodgkin’s lymphoma
- other (simultaneous) malignancies
- contraindication or known hypersensitivity to study drugs
- severe concomitant diseases (e.g. immune deficiency syndrome)
- known HIV-positivity
- residence outside the participating countries where long term follow-up cannot be guaranteed
- pregnancy and/or lactation
- patients who are sexually active and are unwilling to use adequate contraception during therapy and for one month after last trial treatment
• current or recent (within 30 days prior to date of written informed consent) treatment with another investigational drug or participation in another interventional clinical trial

8.3 Justification for the Inclusion of Vulnerable Populations

The trial addresses questions in paediatric Hodgkin lymphoma. Therefore, trial subjects will be children or adolescents under 18 years of age. These individuals may not be able to provide consent for trial participation according to country specific regulations. Before trial entry written informed consent of the child's/adolescent’s parent/guardian is mandatory. The willingness (assent) of the child/adolescent for trial participation will be taken into account. The child/adolescent will be informed about the trial appropriate to his/her age using age-specific patient information.

8.4 Participation in More than One Clinical Trial

If the patient is currently participating in any other interventional clinical trial the patient cannot be included in EuroNet-PHL-C2. Signing the informed consent form, the patient and/or the patient's parents or guardian confirm that he/she is not participating in any other interventional clinical trial simultaneously.

8.5 Inclusion of Dependent Individuals

Since EuroNet-PHL-C2 represents the standard of care for children and adolescents with HL all eligible patients will be included.

8.6 Rationale for Gender Distribution

All eligible patients (and his/her parents/guardian) will be asked for informed consent for trial participation irrespective of gender. Therefore, the gender distribution will reflect the underlying gender distribution in paediatric Hodgkin’s lymphoma.
9 INVESTIGATIONAL PRODUCT

9.1 Trial Drugs

The drug products used in this trial are defined by active substances only and have a marketing authorization in the EU. The drugs are sourced from the EU market and are used in the trial without modification. These drugs have been used in paediatric oncology for many years. The packaging and labelling is carried out for local use only as per article 9.2. of the Directive 2005/28/EC (GCP Directive).

The information on trial drugs is listed in the Appendix IX.

9.2 Compliance

No additional drug account is necessary in this trial. Administration of trial medication will be documented in the patient files and CRF. All drugs, except prednisone/prednisolone are given intravenously. Patients will document time and date of prednisone/prednisolone intake in a patient diary.

9.3 Replacement of Trial Medication

In case of severe vincristine neuropathy, vinblastine (6 mg/m², capping dose 10 mg) may be substituted.

In case of drug allergies or other severe side effects please contact the co-ordinating study chairperson at the EuroNet-PHL central study office Halle (until the end of October 2015) or Giessen (from November 2015), respectively (contact data: please see ch. 1.1) or contact the responsible national chairperson.
10 SCREENING AND INFORMED CONSENT

10.1 Screening and Pre-Treatment Mandatory Investigations

The following assessments and procedures should be performed prior to start of treatment (for further details see Appendix III).

- **Biopsy and confirmation of diagnosis:** The histo-pathological diagnosis is based on biopsy of lymph nodes or other primarily involved organs before trial entry. Biopsies should be excision or tru-cut biopsies where adequate diagnostic material is obtained. Fine needle aspiration biopsies are not appropriate. National – Central Pathology review is mandatory. In case of CD20+ positivity in early stages (I and IIA without bulky mediastinum), treatment should not be started until the diagnosis of classic Hodgkin’s lymphoma versus lymphocyte predominant HL is reference pathology confirmed. Patients with LP-HL are ineligible for this study but qualify for the EuroNet-PHL-LP1 study.

- Full medical history and physical examination including height, weight and body surface

- **Erythrocyte sedimentation rate (ESR; 1 hour) is mandatory for appropriate treatment level allocation.**

- **Imaging:**
  - Whole-body PET-CT with i.v. contrast or
  - Whole body PET-MRI with i.v. contrast or
  - Whole body PET scan plus chest CT and CT or MRI of neck, abdomen and pelvis

- In case of PET-positive skeletal lesions:
  - Additional acquisition of the legs at the PET-CT examination
  - Bone scan: **Only** in case of PET-positive skeletal lesions not assessable by CT

- Assessment of B-symptoms

- Full blood counts, Biochemistry, Liver Function Tests, Creatinine, Coagulation Screen

- ECG and Echocardiography (mandatory); EEG (optional)

- HIV serology

- Pregnancy test for all female patients of child bearing age. This must be performed within 2 weeks prior to starting treatment

- Chest-X-ray (optional)

- Ultrasonography of spleen and liver (mandatory)
• Semen cryopreservation before treatment should be offered to post-pubertal male patients
• At centres with IRB/ethical approvals ovarian cortical tissue harvesting (or egg cryopreservation after hormone stimulation in post menarchal females) may be offered to patients who are likely to receive pelvis radiation.

10.2 Informed Consent

It is the responsibility of the principle investigator (or delegate if this duty has been delegated to a suitably qualified person) to obtain written informed consent for each patient prior to start of treatment. Investigators or the authorised personnel must ensure that they adequately explain the aim, trial treatment anticipated benefits and potential hazards of taking part in the trial to the patient and/or parent (legal guardian) as appropriate. In addition, patient/parent (legal guardian) are asked for informed consent to participate in country specific research projects, if applicable. Informed consent on randomisation in TL-2 and TL-3 patients has to be obtained before the randomisation procedure. The investigator should point out that the patient is completely free to refuse participation and if participation is agreed the patient can withdraw from the trial or trial related projects at any time. If patient/parent (legal guardian) refuse randomisation the patient will be treated in the standard arm (COPDAC-28). The patient/parent (legal guardian) should be given ample time to read each Information Sheet and to discuss the participation with others outside of the site research team. The patient/parent (legal guardian) must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the patient/parent (legal guardian) to refuse to participate in the trial without giving a reason must be respected.

The investigator and the patient/parent (legal guardian) must date and sign the approved informed consent form before entering the trial. Informed consent must be obtained before start of chemotherapy. Screening procedures follow good patient care and may have been performed before informed consent for the trial. However, screening results can be used for the trial. Both guardians (parents)/all legal representatives have to sign the informed consent. However, if one guardian/parent is not available the signing parent may declare on oath to act in consent with the other. If only one parent is the legal representative this parent shall declare on oath that he/she is the only legal representative of the minor.

Under the EU directive on clinical trials (2001/20/EC), parents/legal guardians should give consent on behalf of patients defined as minors by the directive. This is generally considered to be anyone under the age of 18. However, the 2008 guidelines on best practice in paediatric trials recognize that in some countries the age of majority is 16, and in such cases, patients
should give their own consent. The same guidelines also recognize the concept of ‘assent’, whereby minors capable of understanding the implications of partaking in a trial should be asked to confirm the consent given on their behalf. It is also important to note that where a minor expresses an 'explicit' wish to refuse participation or withdraw from a trial, despite consent being given on his/her behalf, the directive requires the investigator to consider this.

A copy of the Informed Consent Form should be given to the patient/parent (legal guardian), a copy should be filed in the hospital notes and the original placed in the Investigator Site File.

The informed consent of the patient/parent (legal guardian) must refer specifically to the assessment and processing of data on the patients' health. The patient/parent (legal guardian) have to be informed on the data collection and the use of personal data, especially the health-related data.

Trial sites associated with the EuroNet-PHL trial centre in Halle or Giessen, respectively for the provision of central review (or for Austria trial sites associated with the EuroNet-PHL study office in Vienna) should ensure that patient/parent (legal guardian) are informed about the central review staging and response assessment including transfer of images and PET data sets via secured internet lines and storage of these documents on a central server in Stockholm, Sweden. In addition, patients should be informed that in case radiotherapy will be required, radiotherapy planning documentation is reviewed by an expert team for quality control. For this purpose, all medical experts involved in central review need access to all of the required medical files and images.

The central review provides a second medical opinion for trial patients. To guarantee correct patient identification full names are required by the central review panel and this should be stated on the Informed Consent Form. However, in accordance with the Data Protection Plan (version 2012-1-27) of the central review process all trial related data are documented and archived in the central database with pseudoanonymised patient identifiers.

If the use of full names is forbidden by country specific laws or if patient/parent (legal guardian) refuse to give consent to use full names, the principal investigator at the local site is responsible to ensure pseudoanonymisation of all images and documents involved in the central review process.

In Germany only, patient/parent (legal guardian) are asked to give consent to transfer of personal and health related data to the

- German Childhood Cancer Registry in Mainz (PD Dr. Kaatsch),
- Registry for Radiogenic Long-term Sequelae (Prof. Dr. Willich)
10.3 Long-term Follow-up

At inclusion, the patient/parent (legal guardian) will be asked for their consent to be directly contacted by the national chairperson or the respective country-specific institution for long-term follow-up.
11 TRIAL ENTRY

11.1 Registration

After informed consent has been obtained, the local trial site will complete and fax patient registration forms (PR-1 and PR-2), to the respective trial office/data centre for patient registration (for details on trial procedures see Appendix VI).

The following data are required for registration:

- date of written informed consent
- (provisional) date of treatment start
- date and location of staging PET acquisition
- ESR value (If the ESR value is missing, the lowest treatment level of the patient will be TL-2)

Additional information asked at registration are:

- Participation in country specific biological side projects (blood and serum collected)
- Participation in country specific psycho-social scientific side projects
- Report to German childhood cancer registry (for patients in Germany only)

Confirmation of the registration including the patient identifier (Pat-ID) will be faxed by the respective data centre (e. g. ZKS Leipzig) to the investigator at latest on the next working day.

11.2 Randomisation

After a patient has been assigned to TL-2 or TL-3 (by the Central Review boards) and consented to randomisation the local trial site will send the randomisation request form via fax or secured e-mail to the appropriate study office (ZKS Leipzig//Birmingham). Randomisation result will be faxed by the respective data centre to the investigator at latest on the next working day including a checklist regarding trial related procedures and timelines. This should be within 4 to 6 weeks after start of treatment at the latest (for details on trial procedures see Appendix VI).

The randomisation request form should also be submitted for registered patients who refuse randomisation to document the refusal. The patients that refuse randomisation will receive consolidation treatment with standard COPDAC-28.
12 TREATMENT DETAILS

The EuroNet-PHL group pursues a quality assurance strategy by real time central review of staging and response assessment. Decisions on stage, treatment level and response are made by the Central Review Board according to a defined assessment algorithm depending on cooperation with the local sites. Central review is provided by the EuroNet-PHL trial centre in Halle/Giessen/Leipzig (Austria: trial office in Vienna). Details on central review organisation are given in Appendix IV. Important time lines for continuation of treatment are described in detail in Appendix VI. For details on rare oncological emergencies please see Appendix V.

12.1 Assessment of Involvement

12.1.1 Assessment of Lymphatic Involvement

12.1.1.1 Lymph node involvement

- If the largest diameter of a lymph node or a lymph node conglomerate is smaller than 1 cm the region is considered not involved – independent of the PET result. Small tumour lesions do not impair therapy results according to previous experience.

- If a lymph node or a lymph node conglomerate has a diameter of 1.0 – 2.0 cm the region is considered involved only if it is FDG-PET positive.

- If the largest diameter of a lymph node or a lymph node conglomerate exceeds 2.0 cm the region is considered involved – independent of the PET result.

12.1.1.2 Definition of bulk

Bulk is present if the volume of the largest contiguous lymph node mass is ≥ 200 ml. In the mediastinum the total volume of the initial tumour mass in the upper, middle and lower mediastinum and both hila and both supradiaphragmatic recessus is considered contiguous for bulk assessment due to the complex anatomic structure.

Volumes will be measured using the three largest perpendicular diameters on multiplanar reconstruction mode in CT/MRI (Bulk volume calculation = A x B x C/2 = > 200 ml)

12.1.1.3 Assessment of Waldeyer’s ring

Involvement is defined by clinical assessment preferably by an ENT physician.

Biopsy is not recommended.

(At ERA reassessment of Waldeyer’s ring is not used for definition of response groups.)
12.1.1.4 Spleen involvement

Spleen involvement is assumed if

- focal PET positive lesions that are confirmed by CT or MRI or ultrasound

  or

- tumour suspicious multiple small focal changes in the spleen structure are detected by ultrasound – irrespective of the FDG-PET result.

Exclusive splenic involvement without other lymphatic disease is classified as stage I.

12.1.2 Assessment of E-lesions

An E-lesion is a contiguous infiltration of a lymph node mass into extra-lymphatic structures or organs (e.g. lung, bone).

12.1.2.1 Involvement of the pleura

Involvement of the pleura is assumed if

- an adjacent nodal lesion infiltrates the pleura or chest wall AND

- the infiltrate and/or the adjacent nodal lesion is PET positive

Pleural effusion is not considered to be an E-lesion.

12.1.2.2 Pericardial involvement

Pericardial involvement is assumed if

- an adjacent nodal lesion infiltrates the pericardium AND

- the infiltrate and/or the adjacent nodal lesion is PET positive

Pericardial effusion is not considered to be an E-lesion.

12.1.3 Organ Involvement

Disseminated organ involvement always implies stage IV.

12.1.3.1 Lung involvement

Disseminated lung involvement is assumed if

- there are more than two small foci between 2 mm and 10 mm within the whole lung

  or

- there is at least one intrapulmonary focus of a diameter ≥ 10 mm
If all lesions are exclusively in one lung, then only this particular lung is considered as involved. However, even if there is just one additional smaller focus found within the other lung, then both lungs are considered involved.

12.1.3.2 Liver involvement
Liver involvement is assumed if at least one focal PET positive lesion is confirmed by CT or MRI or ultrasound.

12.1.3.3 Skeletal involvement
- Bone marrow involvement is assumed, if
  - More than two PET-positive lesions are found in skeleton, irrespective of positivity in CT or MRI
- Bone involvement is assumed, if
  - the PET-positive skeletal lesion shows tumour-typical correlation in CT or increased uptake in bone scan if CT is not assessable

Note Bone Marrow Biopsy – is no longer a mandatory investigation as bone marrow involvement is defined by the FDG PET scan.
12.2 Stage Classification

Stage classification is performed according to Cotswolds revision of the Ann Arbor staging system.

12.2.1 Independent Lymph Node Regions

**Independent lymph node regions are:**

- **Waldeyer’s ring** (left and right)
- **cervical (left and right) with sub-regions relevant for irradiation:**
  - upper neck: above hyoid bone
  - lower neck: below hyoid bone above lower margin of cricoid cartilage
- **supraclavicular (left and right)** (below lower margin of cricoid cartilage above fossa jugularis)
- **infraclaviular (left and right)**: (subpectoral on the thoracic wall)
- **axillar (left and right)**
- **pulmonary hilum (left and right)**: bronchopulmonary lymph nodes
- **mediastinum with sub-regions relevant for irradiation:**
  - upper mediastinum: fossa jugularis to carina, including paratracheal and paraoesophageal lymph nodes, preaortic lymph nodes and lymph nodes in the aorto-pulmonary window
  - middle mediastinum (lymph nodes at the level of the carina): tracheobronchial lymph nodes, broncho-pulmonary lymph nodes (lung hili and lymph nodes adjacent to base of the heart) and subcarinal lymph nodes
  - lower mediastinum: lymph nodes clearly below carina to upper edge of the diaphragm along the oesophagus, the lower descending thoracic aorta and spine
- **supradiaphragmatic recessus** (below upper edge of the diaphragm but still above diaphragm)
- **spleen**
- **splenic hilum**
- **porta hepatis**
- **mesenteric**: mesentery or mesocolon
- **paraaortic**: upper (above the renal hilum), lower (at or below the renal hilum)
- **iliac (left and right)**: below aortic bifurcation to inguinal ligament
- **inguinal (left and right)**: below inguinal ligament

### 12.2.2 Stage Classification of Hodgkin lymphoma

Stages of Hodgkin's lymphoma according to the Cotswolds revision of the Ann Arbor staging system

I  Involvement of a single independent lymph node region or lymph node structure

II Involvement of two or more lymph node regions on the same side of the diaphragm

III Involvement of lymph node regions or lymph node structures on both sides of the diaphragm

IV Involvement of extra-nodal sites beyond “E”-sites

### 12.2.3 Additional Stage Definitions

- **A** No B symptoms
- **B** At least one of the following systemic symptoms
  - a. Unexplained weight loss of more than 10% within the last 6 months
  - b. Unexplained persisting or recurrent temperature above 38 °C
  - c. Drenching night sweats
- **E** Involvement of a single extra-nodal site contiguous to known nodal site

### 12.3 Treatment Levels

Patients are assigned to treatment levels (TL) according to stage, bulk and ESR values (see Fig. 16).

Treatment levels are defined as follows:
### Treatment Overview

#### 12.4.1 Treatment Level 1 (TL-1)

All patients receive two cycles of OEPA.

Patients in TL-1 with a negative PET scan at ERA have an adequate response (AR) and receive one cycle of COPDAC-28. The third chemotherapy cycle (COPDAC-28) starts as soon as possible after confirmation of the negative PET result. Preferably, consolidation COPDAC-28 should start within one week after ERA, within three weeks latest.

Patients in TL-1 with a positive PET scan at ERA have an inadequate response (IR) and will receive involved node radiotherapy to all initially involved sites (see section 12.7. and radiotherapy manual). Radiotherapy should start as soon as possible after receipt of the reference radiotherapy plan (see Appendix VI).

Follow-up visits start six weeks after completion of therapy (details see Appendix VII).
12.4.2 Treatment Level 2 and 3 (TL-2 and TL-3)

All patients receive two cycles of OEPA, followed by two (TL-2) or four (TL-3) cycles of COPDAC-28 or DECOPDAC-21 consolidation treatment according to the respective randomisation result.

Patients in TL-2 and TL-3 with a negative PET scan at ERA (AR) receive no radiotherapy.

Patients with a positive PET scan at ERA (IR) will receive either COPDAC-28 chemotherapy and standard involved node radiotherapy to all initially involved sites and a boost to LRA PET-positive residuals or intensified DECOPDAC-21 chemotherapy and radiotherapy to LRA PET-positive sites with morphologic residuals (see section 12.7. and radiotherapy manual) only. Radiotherapy should start as soon as possible after receipt of the reference radiotherapy plan (see Appendix VI).

Follow-up visits start six weeks after completion of therapy (see Appendix VII).

12.5 Response Assessment

12.5.1 Early Response Assessment

The ERA PET scan (Im-2) is performed 14-17 days (i.e. day 29 – 32 of the second OEPA) after the last dose of prednisone/prednisolone in OEPA cycle 2. Note: Prednisone/prednisolone must not be tapered (Stop on day 15 of OEPA). Important time lines for continuation of treatment and sending ERA PET scan and images to the central review Board are described in detail in Appendix VI.

For all sites with visibly enhanced FDG-uptake the visual Deauville score will be determined and documented. Afterwards the qPET-value is determined (for details see PET Manual).

The decision on radiotherapy indication at ERA will be based on the Deauville score aided by the qPET-value (note: the qPET value is decisive).

The response is ERA PET-positive if at least one site corresponds to Deauville 4+ which is equivalent to a is qPET-value ≥ 1.3. Otherwise the response will be ERA qPET-negative.

In contrast to EuroNet-PHL-C1, the morphological response is assessed in the initially largest reference volume only. Bulk is present if the largest reference volume exceeds 200 ml. Poor Bulk Response is defined as volume reduction of less than 50% of the initial volume.
If no tumour progression is detected, response groups are defined based on Deauville score aided by the qPET-value and by bulk response.

**Inadequate response (IR):**

- ERA PET at Deauville ≥ 4 which is equivalent to qPET ≥ 1.3 and/or
- Poor bulk response (< 50% volume reduction) and/or
- At least one nodal site with largest diameter of ≥ 2 cm and non-assessable qPET-value due to brown fatty tissue.

**Adequate response (AR):**

- No IR criterion fulfilled

**Patients with AR do not receive radiotherapy.**

### 12.5.2 Late Response Assessment

PET at LRA (Im 3) will be performed 14 – 17 days after the last dose of prednisone/prednisolone in the second (TL-2) or fourth (TL-3) COPDAC-28 (i.e. LRA at day 29 - 32 of the last COPDAC-28) or DECOPDAC-21 cycle (i.e. LRA at day 22 – 25 of the last DECOPDAC-21). Prednisone/prednisolone must not be tapered. Important time lines for continuation of treatment and sending LRA PET scan and images to the central review Board are described in detail in *Appendix VI.*

For late response assessment only sites with morphologic residuals ≥ 1 cm are considered. A site is LRA PET-positive if the Deauville 3+ which is equivalent to qPET value is ≥ 0.95.

All LRA qPET-positive sites must be identified.

Patients in TL-2 or TL-3 randomised to COPDAC-28 receive 10Gy boost irradiation to LRA qPET-positive sites (Radiotherapy field is based on pre-treatment sites.).

Patients in TL-2 or TL-3 randomised to DECOPDAC-21 receive radiotherapy to LRA qPET-positive sites only (Radiotherapy field is restricted to LRA PET positive residua only.).

### 12.5.3 Progression or Relapse

Progression or relapse is suspected if

- at least one initially involved mass increases by more than 25% compared to the best previous response or
• new lymphatic or extra-lymphatic lesions occur
• B-symptoms (re)occur which cannot be explained otherwise.

Biopsy of enlarging or new lesions is mandatory to confirm progression or relapse.

Reference pathology including subtyping and immunochemistry should be documented on the reference pathology form within two months (for details see Appendix IV.3).

The date of the biopsy defines the time point of disease recurrence. Disease recurrence is defined as

• **Primary Progression**, if it occurs on or within three months after end of treatment
• **Early Relapse**, if it occurs > 3 to 12 months after end of treatment
• **Late Relapse**, if it occurs > 12 months after end of treatment

### 12.6 Chemotherapy Plans

The first cycle of OEPA starts immediately after completion of staging.

Chemotherapy administration guidelines:

• Physical examination
• ALAT, ASAT, GGT, bilirubin, creatinine
• Pregnancy test

• Blood counts including differential blood count (preferably on day 0, 8, 11, 17 and 21 of each cycle of chemotherapy). These values will be documented to describe the haematotoxicity profile and to investigate the prognostic value of WBC and neutrophil nadir.

• ECG, echocardiography
• Pulmonary function test are carried out if appropriate

Chemotherapy continues on **d29** (OEPA, COPDAC-28) or **d22** (DECOPDAC-21) if the following criteria are fulfilled:

• No on-going infections
• WBC > 2,000/mm³
• ANC > 500/mm³
• Platelets > 80,000/mm³

If treatment delay of more than one week is expected, please contact the trial centre in Halle. Expected adverse reactions of the drugs used in OEPA, COPDAC-28 or DECOPDAC-21 are
listed below. Chemotherapy cycles should only be interrupted in case of severe infections or other severe complications. Treatment should not be interrupted for cytopenia during the cycle. Patients may receive hydration with 2.5-3 l/m² per day of glucose-saline or normal saline solution concomitantly to chemotherapy for the first cycle of OEPA to prevent tumour lysis syndrome.

12.6.1 OEPA

The first OEPA cycle starts after informed consent is obtained and the patient is registered (Appendix VI). The OEPA regimen is shown in Tab. 3. Between day 16 and 28 no treatment is administered, the following cycle starts on day 29.

<table>
<thead>
<tr>
<th>Tab 3: OEPA Scheme</th>
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<tbody>
<tr>
<td><strong>Day</strong></td>
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<tr>
<td>Prednisone/Prednisolone</td>
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<tr>
<td>60 mg/m²/day p.o. divided into 3 doses</td>
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<td>day 1 – 15</td>
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<tr>
<td>Vincristine</td>
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<td>1.5 mg/m² i.v., capping dose 2 mg</td>
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<tr>
<td>day 1 + 8 + 15</td>
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<tr>
<td>Doxorubicin</td>
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<td>40 mg/m² per 1-6 hour infusion</td>
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<td>day 1 + 15</td>
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<tr>
<td>Etoposide/Etopophos</td>
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<tr>
<td>125 mg/m² Etoposide (NB: 142 mg Etoposide phosphate equals 125 mg etoposide): 2hrs infusion time</td>
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<td>day 1 – 5</td>
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12.6.2 COPDAC-28 (28-day cycle)

The first COPDAC-28 cycle start as soon as the ERA PET scan is done, ideally on the day of the ERA PET (Appendix VI). The COPDAC-28 regimen is shown in Table 4. Between day 16 and 28 no treatment is administered, the following COPDAC-28 cycle starts on day 29.

To minimise urinary tract toxicity the uroprotector Mesna (i.v. Bolus of 150 mg/m² and additional 500 mg/m² as 24 hour continuous infusion, days 1 and 8) may be applied along with
cyclophosphamide applications (iv hydration is not mandatory if equivalent fluid volume is drunk orally).

Dacarbazine is highly emetogenic. Prophylactic antiemetics should be administered according to local policy. Nausea and vomiting should be treated according to established local practice.

Table 4: COPDAC-28 Scheme

<table>
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<td>40 mg/m²/day p.o. divided into 3 doses (capping dose 80 mg/day)</td>
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<td>day 1 – 15</td>
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<td>250 mg/m² per 15 – 30 min. infusion</td>
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<td>1.5 mg/m² i.v. capping dose 2 mg</td>
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<td>500 mg/m², per 60 min. infusion</td>
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<td>optional concomitant intravenous hydration with glucose/saline solution at a rate of 3 l/m² over 24 hours</td>
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</table>

12.6.3 DECOPDAC-21 (21-day cycle)

The first DECOPDAC-21 cycle starts as soon as the ERA PET is done, ideally on the day of the ERA PET (Appendix VI). The DECOPDAC-21 regimen is shown in Tab. 5. Between day 9 and 21 no treatment is administered, the following cycle starts on day 22.

Dacarbazine is highly emetogenic. Prophylactic antiemetics should be administered according to local policy. Nausea and vomiting should be treated according to established local practice.
The uroprotector Mesna (i.v. Bolus of 300 mg/m² and additional 625 mg/m² per 24 hour continuous infusion; day 1 and day 2) may be administered along with each cyclophosphamide application to minimise toxicity to the urinary tract (iv hydration is not mandatory if equivalent fluid volume is drunk orally).

Prophylactic use of G-CSF is not recommended. G-CSF 5 µg/Kg BW may be given subcutaneously from day 9 to day 15 in individual patients if severe infection or significant treatment delay have occurred.

Since the anthracycline dose increases over 200mg/m² please perform an echocardiography before starting on the cycle. If cardiac function is impaired please contact the national chairperson or the trial office in Halle for advice.

Table 5: DECOPDAC-21 Scheme

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
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<tbody>
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<td>Prednisone/Prednisolone</td>
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<td>40 mg/m²/day p.o. divided into 3 doses, day 1 – 8, no capping dose prescribed</td>
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<td>Dacarbazine</td>
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<td>250 mg/m² per 15 – 30 min. infusion</td>
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<td>Vincristine</td>
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<td>1.5 mg/m² i.v. capping dose 2 mg</td>
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<td>Cyclophosphamide</td>
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<td>625 mg/m², 60-min. infusion</td>
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<td>optional: concomitant intravenous hydration with glucose/saline solution at a rate of 3 l/m² over 24 hours</td>
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<td>100 mg/m²/day Etoposide infusion over 2 hrs</td>
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<td>NB: 113,6mg Etoposide phosphate equals 100 mg Etoposide</td>
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<td>Doxorubicin</td>
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<td>25 mg/m² per 1-6 hour infusion</td>
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</table>
12.6.4 Dose and Treatment Modifications

Since the chemotherapy regimens are generally well tolerated no provisions for dose modifications are given. Haematotoxicity of CTC grade 4 is a common finding during the OEPA regimen. Treatment delays should be avoided, any deviation from the protocol specification has to be documented in the patient files and on the respective CRF-pages. In case of drug-specific toxicity (examples: doxorubicin-related impaired cardiac function, severe neuropathy during or after vincristine) or other unexpected severe adverse events must be reported on the respective SAE reporting/toxicity forms. The following modifications in case of complications are recommended:

Vincristine

- **Seizures**: Hold 1 dose, then reinstitute.
- **Severe foot drop, paresis or ileus**: Hold dose(s); institute aggressive regimen to treat constipation (except enemas if neutropenic), if present. When symptoms abate, resume at 1mg/m²; escalate to full dose as tolerated.
- **Jaw pain**: Treat with analgesics; do not modify vincristine dose.

Hyperbilirubinemia: Check LFTs only if patient jaundiced.

- Withhold if total bilirubin > 50 μmol/L. Administer 50% of dose if total bilirubin 25 - 50 μmol/L.
- Do not alter dose for abnormal transaminases.

Steroids

- **Hypertension**: Steroid should not be reduced. Sodium restriction and antihypertensives may be employed in an effort to control hypertension.
- **Malignant Hypertension**: Reduce dose by 33%. Sodium restriction and antihypertensive drugs may also be utilized.
- **Hyperglycemia**: Steroids should not be reduced if the patient develops clinical signs of diabetes. Rather, insulin therapy should be employed to control the blood glucose level such that symptoms and signs are minimal.
- **Pancreatitis**: Do not modify dose.
- **Psychosis**: Administer half dosage of steroid.
• **Suspected steroid-induced myopathy:** Measure CPK with isoenzymes, consider EMG studies.

• **Avascular necrosis:** Contact national chairperson or trial office in Halle if AVN occurs.

• **Varicella Zoster:** Discuss with trial office in Halle or the national chairperson in case of active infection. They should not be withheld during incubation period following exposure to varicella.

### Doxorubicin

#### Hyperbilirubinemia

- If total bilirubin $>120$ μmol/L omit dose
- If $>90$ μmol/L but $\leq 120$ μmol/L give 25% of dose
- If $>50$ μmol/L but $\leq 90$ μmol/L give 50% of dose
- If $\leq 50$ μmol/L give full dose
- Check LFTs only if patient is jaundiced. Do not alter dose for abnormal transaminases.

#### Dose adaptation due to cardiotoxicity

- If temporary deterioration of myocardial function occurs, e.g. decrease in fractional shortening to $<29\%$, or a decrease of 10% or more relative to previous tests, and if this is confirmed by a repeat echocardiogram, omit doxorubicin in the next course and discuss alternatives with the trial office in Halle or the national chairperson.
- If persistent deterioration of myocardial function occurs, e.g. persistent decrease in fractional shortening by an absolute value of 10 percentile points from previous tests or a persistent fractional shortening $<29\%$, 40% LVEF, avoid further doxorubicin and discuss alternatives with the trial office in Halle or the national chairperson.

### Cyclophosphamide

- **Gross haematuria:** Hydrate at 125 ml/m²/hr for 24 hours after dose and use mesna infused alongside hydration fluid according to local established practice.
- **Acute fluid retention:** Treat with furosemide.
In case of other complications, the trial office in Halle should be consulted to discuss therapeutic alternatives.

12.6.5 Adverse Effects of Chemotherapy

Common adverse effects of chemotherapy are nausea, vomiting, weight loss and alopecia. Late effects of chemotherapy may be risk of secondary malignancies, infertility, premature menopause or cardiovascular damage.

Additional information on adverse effects of the investigational drugs are listed in Appendix IX.

Etoposide

Common adverse effects of Etoposide are allergic reactions, mucositis, peripheral neuropathy, CNS toxicity, myelotoxicity.

Dacarbazine (DTIC)

Dacarbazine is highly emetogenic. Diarrhoea, influenza-like symptoms, allergic skin reactions, fever, photosensitization, local vein irritation as well as flush symptoms may occur during or after drug infusion. Myelotoxicity is generally low. Rarely liver, kidney and CNS toxicities (apathy, seizures) occur. A mutagenic, carcinogenic and teratogenic effect of DTIC has been demonstrated in animal studies. During the GPOH-HD 2002 trial one patient died of rhabdomyolysis after DTIC.

Vincristine (VCR)

Common adverse effects of Vincristine are peripheral neuropathy, constipation; rarely syndrome of inappropriate ADH secretion (= SIAD). In case of severe peripheral neuropathy, especially in motor disturbances or paralysis of limbs replacement of vincristine by vinblastine at a dose of 6 mg/m² (capping dose 10 mg) is recommended.

Cyclophosphamide

Common adverse effects of cyclophosphamide are myelotoxicity, increased risk for infections, haemorrhagic cystitis. The risk for haemorrhagic cystitis following cyclophosphamide is dose-dependent. Therefore, in DECOPDAC-21 uroprotection with Mesna (Tab. 5) is prescribed.

Doxorubicin

Adriamycin (doxorubicin) even at low cumulative doses can lead to permanent myocardial damage. However, the extent of long-term cardiac risks is unknown. Therefore, before start of treatment the cardiac function has to be examined by echocardiography and documented. In
case of initial damage of the heart function a therapeutic alternative should be discussed with the trial centre in Halle.

**Prednisone/prednisolone**

Prednisone/prednisolone treatment is associated with a risk of osteonecrosis (avascular necrosis) which is well described in patients being treated for acute leukaemia. In rare cases joint replacement may be required. In addition, the prednisone/prednisolone therapy may lead to reversible retention of water, weight gain, increased risk of infection and psychosis/mental disorders. The prednisone/prednisolone dose in COPDAC-28 is capped at 80mg per day.

12.6.6 Supportive Treatment

**Antibacterial prophylaxis**

All patients should receive co-trimoxazole (trimethoprim/sulphamethoxazole) for PCP prophylaxis during chemo- and radiotherapy and up to three months after end of chemo-radiotherapy or according to local standard practice. **PCP prophylaxis is mandatory.**

At WBC below 1000/mm³, patients may receive oral colistin sulphate or other oral non-absorbable antibiotics according to local standard practice.

**Antifungal prophylaxis**

During chemotherapy and radiotherapy patients may receive antifungal prophylaxis according to local practice. This is not mandatory. Oral anti-fungals in the ‘azole’ group (flu-, itra-, voriconazoles should not be administered within 48 hours before or after Vincristine due to drug interactions).

**Prevention of GvH reaction/infection through blood transfusions**

Transfusions of packed red cells or platelets should be leukocyte-depleted and **irradiated** with 30 Gy.

**Supportive care**

In the UK, PICC/Portacath/Hickman line insertion prior to treatment is recommended to avoid extravasation particularly of doxorubicin. In the presence of large mediastinal mass and/or venous compression delay in placement of the central line until the second cycle of chemotherapy may reduce the risk of CVC related thrombosis.
12.7 Radiotherapy

For patients in all treatment levels (TL-1, TL-2 and TL-3), the decision on radiotherapy is based on early response assessment after 2 cycles of OEPA. Patients with adequate response (AR, see section 10.3.1) will not receive radiotherapy.

A detailed description of the principles of radiotherapy, radiation planning and technical requirements and the organs at risk is provided in the Radiotherapy Manual.

A short overview of important definitions is provided within this protocol:

12.7.1 Target Volumes

For details on target volume definitions like gross tumour volume (GTV), clinical tumour volume (CTV) and planning target volume (PTV) please refer to the Radiotherapy Manual.

Principles of radiotherapy application are described below.

The term modified involved field radiotherapy (mIFRT) was used to describe the RT field volume in EuroNet-PHL-C1, the GPOH-HD-2002 GPOH-HD-95 and DAL-HD-90 trial. In this study the term “involved node radiotherapy” (INRT) will replace the expression “modified involved field radiotherapy” (mIFRT), since 3D target definition will be based on involved lymph nodes. The resulting volume is not expected to differ significantly from the previously defined modified involved field technique.

12.7.1.1 ERA PET-positive patients in TL-1 or in TL-2 and TL-3 in the COPDAC-28 arm

The target volume definition in patients in TL-1 and in patients in TL-2 and TL-3 treated in the COPDAC-28 arm will be based on initial nodal and extra-nodal involvement, as presented on the staging PET-CT scans at the time of diagnosis.

In TL-2 and TL-3 patients late response assessment (LRA-PET) will be performed after end of chemotherapy to determine the need for boost. If residual lymph nodes > 1 cm are still PET-positive at LRA-PET, 10 Gy boost will be administered to any of these lesions.

Note: E-lesions and initially involved organs will only require radiotherapy if they are still positive at ERA-PET assessment. The morphological residual PET-positive lesion at ERA will be contoured as target volume plus a security margin. Total lung, pericardium and liver irradiation will be avoided if possible. Maximal tolerated dose for the organ must be taken into account (see radiotherapy manual for details).
12.7.1.2 ERA PET-positive patients in TL-2 and TL-3 in the DECOPDAC-21 arm

The target volume definition for patients in TL-2 and TL-3 in the DECOPDAC-21 arm will be restricted only to any LRA PET-positive lymph node > 1cm at the end of all chemotherapy. If more than one lesion is LRA PET-positive they should be delineated as one target wherever feasible to avoid multiple small fields (patchwork irradiation).

E-lesions and organ involvement will only require radiotherapy if these lesions are LRA PET-positive at the end of chemotherapy. The target volume for E-lesions will be the morphological residual PET-positive lesion seen on the LRA-PET plus a security margin depending on the site. Total lung, pericardial and liver irradiation will be avoided wherever possible.

12.7.2 Timing of Radiotherapy

The timelines for radiotherapy application are provided in Appendix VI.

In patients with inadequate response at ERA radiotherapy should start as soon as possible after receipt of the reference radiotherapy plan. In TL-1 patients ERA-PET and in TL-2 and TL-3 patients LRA-PET is time critical for RT planning. Radiotherapy should start ideally within two weeks after response assessment. Delays of more than four weeks must be avoided.

In case of both supra- and infra-diaphragmatic tumour involvement, radiotherapy may be performed sequentially depending on the radiation volume (small supra- and infra-diaphragmatic volumes can be irradiated at the same time). If the volumes are treated separately, the gap between the first and second series should not be longer than one week.

12.7.3 Organs at Risk (OAR)

Radiosensitivity of normal tissues varies with age. Radiation effects are more significant in young children than in older children or adults. Soft tissue, bones, thyroid gland, lung, spinal cord, heart, large vessels, breasts, kidney, liver and gonads are regarded as organs at risk. Relevant organs at risk must be delineated on the treatment planning scan.

Bony structures within and adjacent to the PTV should be delineated in young children. Dose constraints for whole kidneys (12 Gy), whole lung (15 Gy), whole liver (15 Gy), testis (< 1 Gy) and ovary (< 5 Gy) must be taken into account and the dose to normal structures should be kept as low as reasonably achievable. Further details are described in the Radiotherapy Manual.
12.7.4 Radiotherapy Planning and Radiotherapy Doses

Details of the organisation of radiotherapy planning as well as the recommended radiotherapy techniques are described in the Radiotherapy Manual.

Radiotherapy should be given daily (five days per week). Treatment interruptions must be kept to a minimum.

For patients in TL-1 and in TL-2 and TL-3 in the COPDAC-28 arm, the standard radiotherapy dose consists of **19.8 Gy in 11 fractions** (1.8 Gy per fraction). If required in TL-2 and TL-3 patients, the boost dose is 10 Gy in 5 fractions (2 Gy per fraction) for LRA PET positive residuals. In all patients in the COPDAC-28 arm, E-lesions should be treated to **19.8 Gy in 11 fractions**, or the appropriate tolerance dose to the OAR.

For patients in TL-2 and TL-3 in the DECPDAC-21 arm with positive LRA-PET, the prescribed dose is **30 Gy in 15 fractions** (2 Gy per fraction). In patients in the DECPDAC-21 arm positive E-lesions at LRA-PET require **30 Gy in 15 fractions** (2 Gy per fraction) or the appropriate tolerance dose to the OAR.

If whole lung irradiation (unilateral and bilateral) is prescribed, the dose should not exceed 12 Gy if both lungs are involved and 15 Gy for unilateral involvement. The fraction size should not exceed 1 to 1.2 Gy.

12.7.5 Technical Requirements

The following equipment is required:

- Computed tomography for treatment planning
- 3D Treatment Planning System integrating 3D sectional imaging, DVH
- Linear accelerators with photon energies of 4 - 6 (- 10) MV and high energy electrons
- Multi-leaf collimators and/or conformal blocks for individual shielding
- LINAC on-board verification system (EPIDs, CBCT, ExacTrac system)
- Positioning equipment like mask systems and vacuum cushions.

12.7.6 Adverse Effects of Radiotherapy

**Adverse effects**

Adverse effects like nausea, mucositis, erythema, hair loss, dry mouth, diarrhoea, leucocytopenia, and thrombocytopenia occurring during radiotherapy with less than 20 Gy are rare and mostly temporary. The nature and severity of adverse effects will also depend on the site irradiated, field size, and the chemotherapy received. Most acute side effects can be treated symptomatically and are self-limiting.
**Late effects**

Radiosensitivity of normal tissues varies with age. Radiation effects are more pronounced in young age (0-6 years) and pre-pubertal children compared to young adults, but most children with Hodgkin lymphoma are over age 6. Late effects reflect the location and field size and dose of radiotherapy as well as the type of chemotherapy received, e.g. doxorubicin. Radiation-induced changes in organs and tissues may develop after long latency periods and may not become clinically evident until puberty or adulthood. Secondary malignancies (e.g. increased risk of breast and thyroid cancer) may increase after 20 to 30 years, and these, together with cardiac late effects, remain a major cause of mortality in long-term survivors.

The documentation of long-term side effects will continue in the RISK Study in Germany or in the relevant different national databases.

**12.7.7 Ovariopexy**

Whenever iliac nodal sites have to be irradiated in girls lateral movement of the adjacent ovary should be considered.

Ovariopexy is particularly recommended if both ovaries are expected to receive a dose of more than 5 Gy potentially leading to significant long-term ovarian impairment. This can usually be avoided when using opposed fields with 20 Gy, and if the ovary is more than 2 cm distant from the adjacent field (shield) border.

**When performing ovariopexy sutures should be marked with clips!** After consultation with the radiotherapist surgery should be carried out immediately before infra-diaphragmatic irradiation.

**12.7.8 Radiotherapy Quality Assessment**

Quality control is an essential component of radiotherapy planning and treatment. Therefore, data from all patients receiving radiotherapy will be reviewed and analysed centrally in Halle, Vienna and Lyon. Therefore, CT 3D treatment plans with structure sets (defined GTV, CTV, PTV and OAR) and isodose distributions plus DVHs will be transferred from the local oncology centre directly onto the Hermes server in Sweden or is sent on a CD to the trial centre in Halle, where it will be uploaded to the central server in Sweden. Portal images should also be submitted. This transfer should occur **as soon as radiotherapy is completed**. For details see Radiotherapy manual.

Data from all patients will be evaluated by the reference radio-oncologists in Halle, Vienna, and Lyon. In case of divergent interpretation of quality parameters, the data will be re-evaluated at
an online conference. All trial sites of EuroNet-PHL-C2 will receive feedback on the most important protocol deviations and recommendations to avoid these, via six-monthly reports from the RT quality control teams. Prof. Karin Dieckmann, Vienna, chairperson of the EuroNet-PHL-RT subcommittee is responsible for the reports.

12.8 Patient Withdrawal

The reasons for withdrawal from EuroNet-PHL-C2 should be recorded in the patient’s medical notes and on the CRF. Reasons for withdrawal may include, but are not limited to:

- Patient was not eligible for the trial
- The patient withdraws consent to further trial treatment
- Unacceptable toxicity
- Disease progression whilst on treatment

The decision should be discussed with the respective national chairperson and/or the co-ordinating chairperson. The patient will remain within the trial and followed according to protocol unless the patient/guardian withdraws informed consent for data collection.

12.8.1 Violation of Eligibility Criteria

If violation of eligibility criteria is detected after registration/randomisation the patient may not be withdrawn from the trial. The investigator has to report the violation to the co-ordinating chairperson who decides on appropriate actions after consultation with the responsible biometrician.

If the reference pathologist does not confirm the diagnosis of Hodgkin’s lymphoma, the patient is still documented and followed within the trial. Patient’s physician together with the patient/parents or guardian decides on further therapy.

12.8.2 Withdrawal of Consent

Patient/parent (legal guardian) may withdraw their consent to participate at any time of the trial without affecting his/her subsequent medical treatment or relationship to the treating physician. The patient/parent (legal guardian) will be informed that data already stored will be used further

- to assess effects of the investigational medicinal products
- to guarantee that the interests of the patient are not impaired
- to comply with the regulatory requirements.
Date of enrolment and date of withdrawal (if available) have to be documented. No further CRFs must be completed.

12.8.3 Termination of Trial Treatment

Trial treatment may be terminated due to disease progression or unacceptable toxicity. Follow-up within EuroNet-PHL-C2 continues unless consent to data collection is withdrawn. Patient’s physician together with the patient/parents or guardian decides on further therapy. The co-ordinating chairperson and/or the national chairperson may be consulted for advice.

12.9 Lost to Follow-up

If a patient has not attended to follow-up clinic for more than two years, every effort should be made to contact the patient or the patient’s general practitioner (if consented) by the national chairperson or the corresponding national cancer registry or similar institutions in order to complete study follow-up.

To reduce the number of loss of follow-up patients the local investigator should contact the respective general practitioner or the respective adult clinic for patients above 18 years of age.

12.10 Plan for Further Treatment

After end of treatment patient will enter follow-up (see Appendix VII for details). Relapsed patients may be treated according to the relapse recommendations of the EuroNet-PHL-C1 or an updated version. The co-ordinating chairperson and/or the national chairperson may be consulted for advice. However, follow-up of these patients will continue.
13 ADVERSE EVENT REPORTING

13.1 Adverse Event Definitions and Reporting is Detailed in Appendix II.

13.2 Adverse Events (AE)

Adverse events (see Appendix II for definition) will be documented on the chemotherapy and radiotherapy toxicity forms. These forms must be completed at the end of each cycle. Only the highest grade of toxicity per CTCAE term in each chemotherapy cycle will be documented. This seems reasonable because of the well-known safety profiles of the chemotherapeutics used in the trial.

If adverse events occur that are not explicitly named in case report forms, these events have to be named and classified using the severity levels mentioned in Appendix II.

The observation period for adverse events begins at start of treatment and is restricted to events occurring within 3 months after the end of the trial treatment.

13.3 Serious Adverse Events (SAE)

Investigators should document AEs that meet the definition of an SAE (see Appendix II for definition) and are not excluded from the reporting process as described in section 13.4 (below) immediately (within 24 hours) after the event becomes known on a SAE Form.

The investigator must report every serious adverse event to the following address:

**ZKS Leipzig - KKS/Pharmacovigilance**
Universität Leipzig
Zentrum für Klinische Studien Leipzig – KKS
Härtelstr. 16-18, 04107 Leipzig
Telefon: +49/341/97-16129
E-mail: pharmacovigilance@zks.uni-leipzig.de

Fax: +49 341 9716278

If more information about the SAE becomes available later, it must also be reported to the ZKS Leipzig - KKS (pharmacovigilance) immediately. The initial and the follow-up reports have to be correlated using the patient’s ID.

The investigator shall supply the ZKS Leipzig - KKS (pharmacovigilance), the representative of the sponsor, the national chairperson and the Ethics Committee(s) with any additionally information requested.
In all reports personal data have to be pseudoanonymised using the patient’s ID.

The representative of the Sponsor or authorised staff at central study office is responsible for medical evaluation of the SAE. Details of the sponsor’s documentation and reporting obligations will be specified in a trial-specific pharmacovigilance plan.

**13.4 Events That Do Not Require Expedited Reporting**

Patients receiving chemotherapy may require admission to hospital for appropriate medical intervention following development of some of the more severe known side effects of treatment (see below). **For this reason the following SAEs do not require expedited (immediate) reporting by site and are not regarded as unexpected for the purpose of this trial. These events should be reported on the chemotherapy toxicity forms.**

**Events exclusively related to tumour progression are not stated as SAE.**

The chemotherapy regimens OEPA, COPDAC-28, DECOPDAC-21 or radiotherapy are known to be associated with acute adverse reactions. The following are examples:

- Changes in laboratory parameters (haemoglobin, WBC, neutrophils, platelets, creatinine, bilirubin, liver enzymes)
- Mucositis
- Fever
  - Suspected or proven viral, bacterial, fungal or protozoal Infection
- Stomatitis/pharyngitis
- Upper respiratory tract infection, pneumonia or gastroenteritis during therapy
- Vomiting
- Diarrhoea
- Constipation
- Cellulitis around the line or other sites
- Line infection
- Mite infestations
- Allergic reactions
- Sensory neuropathy
- Motor neuropathy
o Bone pain, leg pain
o Dysphagia (pharyngeal and oesophageal)
o Salivary gland toxicity
o Pain caused by radiation
o Skin toxicity

These expected adverse reactions have to be reported immediately (within 24 h) at latest on the next working day after the event becomes known on the SAE pages only if they

- result in death
- are life-threatening
- result in persistent or significant disability/incapacity

13.5 Monitoring Preganncies for Potential Serious Adverse Events

It is important to monitor the outcome of pregnancies of patients in order to provide SAE data on congenital anomalies or birth defects. In the event that a patient or their partner becomes pregnant during the SAE reporting period please complete a form “Pregnancy report for trial subject” and report to the ZKS-Leipzig, the representative of the Sponsor and the national chairperson as soon as possible.

ZKS Leipzig/Pharmacovigilance
Universität Leipzig
Zentrum für Klinische Studien Leipzig – KKS
HärTELstr. 16-18, 04107 Leipzig
Telefon: +49/341/97-16129
Fax: +49/341/97-16278
E-mail: pharmacovigilance@zks.uni-leipzig.de

Severe side effects and complications during a pregnancy as well as congenital birth defects have to be reported on the form “Serious Adverse Event” according to the report procedures described above.

The outcome of a pregnancy has to be reported on the form “Outcome of pregnancy report for trial subject” including information on a spontaneous or voluntary abortion, details on the birth process, the presence or absence of congenital malformations and birth defects, maternal or foetal complications and the potential relationship to the trial drug.
Collecting data on the outcome of a pregnancy is only permitted if the trial subject or their partner gives permission in writing beforehand.

The local principal investigators are responsible for implementing country specific regulations on frequency of pregnancy testing in trial subjects during treatment.
14 BIOMETRY

14.1 Biometrical Aspects of the Trial Design

EuroNet-PHL-C2 implements a comprehensive treatment strategy for all first line classical Hodgkin lymphoma (cHL) patients under the age of 18. EuroNet-PHL-C2 is the 9th study generation from a series of treatment-optimisation studies starting in the late 70s.

EuroNet-PHL-C2 will de facto coincide with standard patient-centred care for children and adolescents in most of the participating countries. In Germany, cross-checking with the children cancer registry showed that > 95% of all patients up to the age of 15 were treated within the predecessor study EuroNet-PHL-C1.

EuroNet-PHL-C2 promotes treatment quality by organising real-time central review of all images both for staging and response assessment. Most patients will be covered by the central review in Halle. Austrian patients are served in Vienna.

Most patients with classical Hodgkin lymphoma can achieve long term remissions with full intensive chemotherapy and radiotherapy. The therapeutic challenge is to avoid over-treatment and in particular reduce the risk of long term sequelae. The overall strategy is to tailor the amount of treatment to the individual patient.

EuroNet-PHL-C2 therefore consists of a bundle of three sub-studies stratifying patients by initial disease burden (Treatment level assigned at staging) and response to treatment (Response groups determined in early response assessment after 2 cycles of OEPA). All patients start out with two cycles of OEPA after which treatment delineation according to treatment level and early response sets in.

14.1.1 EuroNet-PHL-C2 Sub-Study in TL-1

Patients in TL-1 (i.e. early stages without bulk, or B symptoms and ESR < 30) are treated with two cycles of OEPA. A minority of 5-10% will present with an inadequate response at ERA; these patients will receive standard involve field radiotherapy without further chemotherapy. The majority of patients with an adequate response at ERA will be consolidated by one cycle of COPDAC-28 and will not receive radiotherapy.

Based on early results of EuroNet-PHL-C1, patients in TL-1 are expected to have a 5-year event free survival rate of 90% or better with this emerging standard treatment.

Such an outcome would be deemed a satisfactory trade-off between the conflicting aims of achieving a high cure rate with first line treatment and avoiding over-treatment and serious late side effects. Relapses in these patients have an excellent outcome with second line treatment.
EuroNet-PHL-C2 in TL-1 is an open single arm study with the aim to monitor results with this treatment recommendation estimating 5-year EFS rates and to confirm that EFS rates are consistent with a target of 90% or even better both for the whole group and for the subgroup without radiotherapy.

Having an absolute rate as primary endpoint is meaningful since the study population will not be a convenience sample, but be nearly population-based i.e. representative of patients in Europe meeting the inclusion criteria.

14.1.2 EuroNet-PHL-C2 Sub-Study in TL-2 and TL-3 with Adequate Response

All patients in TL-2 or TL-3 receive two respectively four cycles of consolidation chemotherapy. They will be randomised between COPDAC-28 and DECOPDAC-21 and stratified into two sub-studies according to the ERA response.

Standard consolidation chemotherapy is COPDAC-28 which emerged as equally effective to but less gonadotoxic than COPP in GPOH-HD-2002 and EuroNet-PHL-C1.

The new DECOPDAC regimen essentially adds Doxorubicin and Etoposide to COPDAC and may be understood as a less toxic variant of the BEACOPP regimen which showed excellent result in both paediatric and adult setting.

No radiotherapy is given to TL-2 and TL-3 patients with adequate response at ERA after 2 x OEPA.

The sub-study in TL-2 and TL-3 patients with adequate response is an open randomised parallel group chemotherapy comparing trial intending to show that more intense consolidation therapy with DECOPDAC-21 improves EFS as compared to COPDAC-28.

14.1.3 EuroNet-PHL-C2 Sub-Study in TL-2 and TL-3 with Inadequate Response

Two different radiotherapy strategies are combined with COPDAC-28 respectively DECOPDAC-21 in TL-2 and TL-3 patients with inadequate response at ERA after 2 OEPA. Radiotherapies depend on a late response assessment (LRA) after end of chemotherapy:

After COPDAC-28, standard radiotherapy 20 Gy to all initially involved sites is given with an additional 10 Gy boost to residua still PET-positive at LRA.

After DECOPDAC-21, radiotherapy with 30 Gy will be restricted to residua that are still PET-positive at LRA. Radiotherapy is omitted if no such sites persist at LRA. Excellent results with a similar strategy have been reported with BEACOPP in the adult setting.
The sub-study in TL-2 and TL-3 patients with inadequate response is an open randomised parallel group trial comparing different chemotherapies combined with different radiotherapy strategies.

This comparison is clearly confounded, but so is the clinical question to be answered: COPDAC-28 followed by involved node radiotherapy is considered the standard arm. Combining COPDAC-28 with radiotherapy to LRA-positive residua only is considered too risky in terms of relapse. Combining intensive DECOPDAC-21 chemotherapy with full involved node radiotherapy is deemed too toxic and contrary to the objective of reducing use of radiotherapy in order to avoid late toxicity. A factorial design thus is out of the question.

In TL-2 and TL-3 patients with inadequate response at ERA it is intended to show that more intense consolidation therapy with DECOPDAC-21 combined with radiotherapy restricted to late problem sites has comparable or better EFS as compared to COPDAC-28 plus standard involved node radiotherapy which implies rather large radiotherapy volumes.

14.2 Recruitment Targets and Study Duration

This is a large European study. The study will start in the country of the sponsor (Germany). Recruitment in Germany is limited to five years for insurance reasons. As delays in opening countries are difficult to avoid, overall accrual will end after 6 years.

In year four and five, the accrual rate in EuroNet-PHL-C1 was about 40 patients per month. Envisaging delays in opening countries and trial sites we expect 15 patients per month in the first year when the trials starts in Germany, 30 in year two, 40 in year three to five and 25 in the sixth year (when accrual in Germany is stopped for insurance reasons). This assumes that opening the trial in the different countries may be moderately quicker than in EuroNet-PHL-C1 in which several countries joined after significant delay. This should be possible now because of established cooperation structures. Thus there is an accrual potential of N = 2280 (see Fig. 17).
This is a pragmatic trial. We will recruit as many patients as possible within the study duration of six years. Power calculation will be based on an overall sample size of \( N = 2200 \). This recruitment target is feasible. EuroNet-PHL-C1 accrued \( N = 2112 \) evaluable patients in 6 years.

### 14.2.1 Expected Sample Sizes in the Sub-studies

Assuming a total sample size of \( N = 2200 \), the samples sizes in the three sub-studies can be projected:

<table>
<thead>
<tr>
<th>Sub-study</th>
<th>Sample Size</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>TL-1</td>
<td>431</td>
<td>20%</td>
</tr>
<tr>
<td>TL-2+3 ERA negative</td>
<td>1345</td>
<td>61%</td>
</tr>
<tr>
<td>TL-2+3 ERA positive</td>
<td>424</td>
<td>19%</td>
</tr>
<tr>
<td><strong>TOTAL N=</strong></td>
<td><strong>2200</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

Table 6: Expected Sample Sizes in Sub-Studies

These projections are based on the proportions of the treatment levels and the respective conditional distributions of qPET aided Deauville scores observed in EuroNet-PHL-C1.
14.2.2 Expected Information Flow

Baseline Event-free-Survival Curve

EFS curves in Hodgkin’s lymphoma typically follow the proportional hazard model. For modelling the information flow of EuroNet-PHL-C2 we use the following baseline EFS-curve based on prior experience in EuroNet-PHL-C1 and GPOH-HD-2002. In order to perform model simulations, the 5 year EFS rate can be adjusted to specific levels applying the proportional hazard model.

![Assumed Time to Event curve](image)

**Figure 18: Baseline Event-Free-Survival Curve**

Assuming the expected sample sizes in Table 6 and the overall recruitment (Figure 17) and the Baseline EFS curve (Fig. 18) we can simulate the expected number of events in all three sub-studies (see Fig. 19).

From these projections it becomes clear that interim analyses become meaningful only after 3-4 years.
Figure 19: Projected Information Flows for the Three Sub-Studies
14.2.3 Measures to Prevent Bias

Patients are registered before start of OEPA. Patients in TL-2 or TL-3 will be randomised as soon as stage and treatment level assignment is confirmed.

Randomisation of patients between COPDAC-28 and DECPDAC-21 is performed centrally with a modified minimisation procedure with stochastic component according to Pocock (1983) in a 1:1 proportion.

Randomisation will be balanced according to the following criteria:

- TL (TL-2 versus TL-3)
- Countries
- Trial site

The clinical stratification factors have priority in the given order.

Independent from randomisation patients will be stratified by ERA response such that two twin sub-studies result.

Although clearly desirable, it is not feasible to stratify randomisation on the ERA result for logistic reasons. Waiting for ERA result after central review would trigger unacceptable delays (2-3 weeks) between OEPA and start of consolidation therapy which would be hazardous for patients.

**Impossibility to stratify on ERA response group is unlikely to constitute a relevant source of bias.** Nuclear physicians assessing early response use a semi-automated method. Randomisation and central review are independent processes. Participants of the central review will be unaware of the result of randomisation. In addition, progressive disease during OEPA is rare (< 1%).

14.3 End Points

14.3.1 Primary Efficacy Endpoint

Primary endpoint is event free survival (EFS):

\[
\text{EFS} = \text{Time from start of treatment until the first of the following events:}
\]

- progression/relapse of disease
- diagnosis of a secondary malignancy
- death of any cause
14.3.2 Secondary Efficacy Endpoints

- Overall survival (OS)
  
  \[ OS = \text{Time from start of treatment until death of any cause} \]

- Progression free survival (PFS):
  
  \[ PFS = \text{Time from start of treatment until the first of the following events:} \]
  - progression/relapse of disease
  - death of any cause

14.3.3 Safety Endpoints

- Acute toxicity will be documented using CTC criteria
- SAE rates

14.3.4 Quality Endpoints

We will describe and closely monitor the following quality endpoints concerning study logistics and treatment delivery:

**Response assessment logistics**

- Time from day of PET imaging until decision on response category in ERA and LRA
- Time from last day of chemotherapy to first day of radiotherapy in patients with radiotherapy indication
- Time from last dose of prednisone/prednisolone in OEPA to start of the first consolidation cycle

**FDG-PET/CT imaging**

- Time from FDG-Injection to start of PET acquisition (recommended 60 ± 10 min)
- Proportion of patients with enhanced FDG uptake in brown fat (no, moderate or strong) by use of beta blockers
- Average liver FDG-uptake at staging, ERA and LRA (reproducibility)
- Applied FDG dose in relation to the EANM paediatric dosage card recommendation
- Applied radiation dose in low dose (PET/CT (Tube current, Tube voltage and rotation time)
Chemotherapy delivery

- Duration of chemotherapy (Time from start of treatment until date of the last drug application)
- Total dose given divided by initially planned total dose for each drug
- Discontinuation (or substitution) rate for each drug

Radiotherapy

- Time to Radiotherapy (Time from last chemotherapy dose until start of radiotherapy)
- Duration of radiotherapy (Time from start of treatment until date of last fraction)
- Discontinuation rate
- Delivery of RT (dose and fields) according to protocol regulations

14.4 Statistical Description of the Trial Hypothesis

14.4.1 Statistical Objective in Sub-Study TL-1

In this single arm sub-study, the 5 year EFS rate will be estimated with a two-sided 95% confidence interval with an expected half width in the order of 3%. We believe we have an adequate standard treatment with satisfactory results in TL-1 and want to monitor the outcome using it.

We expect about \( N = 431 \) patients in this sub-study (cf. table 10). Assuming five year EFS rates of 85%, 90%, 95% the expected half width of the 95% confidence interval is ± 3.5%, 3.0%, 2.5% respectively.

If observed EFS rates are consistent with an EFS of 90% or better, i.e. if the confidence interval contains EFS rates ≥ 90% we will conclude that treatment strategy works acceptably. Assuming a true EFS rate of 90% we will have more than 80% power to exclude 85% from a two sided 95% confidence interval.

If the lower bound of the 95% confidence limit is above 90% we will conclude that the treatment strategy has 5 year EFS rates above 90% and works satisfactorily.
14.4.2 Statistical Objective in Sub-Study TL-2 and TL-3 with Adequate Early Response

In this open randomised parallel group chemotherapy comparison trial we want to show that intense DECOPDAC-21 consolidation therapy improves EFS as compared to standard COPDAC-28 after induction chemotherapy with two OEPA.

A relevant improvement would be an increase in 5 year EFS rates from 88% to 93%. This corresponds to a log hazard ratio (lhr) of 0.566 (coded such that a positive log hazard ratio favours the experimental arm).

We will test the null-hypothesis $H_0$: lhr = 0 versus $H_A$: lhr ≠ 0 basing samples size calculation on the specific alternative hypothesis $H^*_A$: lhr = 0.566 using the Wald-test of the coefficient of the treatment indicator and the proportional hazard model including TL as further covariate. A two-sided 95% confidence interval for lhr will be provided.

We expect about N = 1345 patients in this sub-study (cf. table 10) i.e. about 672 per arm.

With a sample size of N = 1345 we will have 84% power to reject the null-hypothesis at a two-sided significance level of $\alpha = 5\%$.

14.4.3 Statistical Objective in Sub-Study TL-2 and TL-3 with Inadequate Early Response

In TL-2 and TL-3 patients with inadequate response at ERA we want to show that more intense consolidation therapy with DECOPDAC-21 combined with radiotherapy restricted to late PET positive sites only has comparable or better EFS as compared to COPDAC-28 plus standard involved field radiotherapy. If this is the case, we would choose the experimental arm as a new standard in order to avoid late toxicity caused by large radiotherapy field volumes.

The power of this sub-study is limited by the number of available patients in Europe. We take pragmatic account of this limitation in our statistical objectives.

As a measure of treatment difference we estimate the log hazard ratio (lhr) and provide 80% (and 95%) lower confidence limits. Secondarily this difference (and its confidence limit) will be represented as a difference in 5-year EFS rates to facilitate interpretation.

The log hazard ratio (coded such that a positive log hazard ratio favours the experimental arm) will be estimated within a proportional hazard model with TL as a further covariate.

We expect about N = 424 patients in this sub-study (cf. table 10) i.e. about 212 per arm. We expect at least 60 events (conservatively assuming no treatment difference and EFS rate in the standard arm of 85%).

The lhr-estimate is approximately normally distributed. The standard error can be calculated from the number of observed events and will thus be less than sqrt (4/60) < 0.26.
An lhr of 0.26 corresponds to a EFS rate difference of about 4% with expected EFS rate in the standard arm in the order of 85%.

Given our power limitations, we will call outcome of the experimental arm comparable to that of the standard arm if the lhr point estimate is less than 0.26 away from equality; i.e. about 4% in EFS rates.

If this is the case the lower 80% confidence bound for the lhr will be above 0.26 - 0.832*0.26 > 0.47 which corresponds to a rate difference of less than 6.5% in EFS rates with expected overall EFS rates in the order of 82-85%. So we would be reasonably confident that there is no marked reduction in efficacy.

Assuming equality of EFS in both arms (lhr = 0) and a standard error of .26 we have at least 84% power to show that arms are comparable in the sense defined above. Indeed, we expect the experimental arm to be slightly superior (2% in EFS rates).

14.5 Statistical Methods

14.5.1 Analysis Population

The analysis is based on the intention to treat principle.

The Full Analysis Set (FAS) for the overall study consists of all registered patients who started OEPA and were assigned a treatment level.

Patients assigned to TL-1 form the FAS for sub-study 1.

Patients assigned to TL-2 or TL-3 who were randomised and have adequate response at ERA form the FAS for sub-study 2.

Patients assigned to TL-2 or TL-3 who were randomised and show an inadequate response at ERA (but no early progression) form the FAS for sub-study 3.

If a relevant number of patients switched randomisation arms an additional “as-treated” analysis would be performed.

Analysis sets for the description of acute toxicities comprise all patients that started on the therapy block in question.

14.5.2 Planned Methods for Analysis

Time-to-event endpoints are described with the Kaplan-Meier estimator, and 5-year survival rates are stated with 95% confidence interval. Regression analyses are performed with the proportional hazard model.
Log hazard ratios between treatment arms will be estimated within the proportional hazard model with TL as covariate.

Qualitative variables are described by frequency tables (with 95% confidence interval where relevant) and compared using contingency tables (Chi²-test if relevant).

Metric variables are described by adequate measures of location (average, median) and of spread (standard deviation, inter-quartile range). Histograms or box-plots are used for graphic representation. For comparisons adequately chosen difference measures with 95% confidence interval can be estimated and t-test or Mann-Whitney-U-test can be used respectively.

The following lists are compiled:

- Registered, but excluded patients
- Arm switches/major protocol deviations
- Patients with SAEs
- Patients with treatment failure
- Deceased patients with cause of death

A detailed analysis plan is developed on the occasion of the first interim analysis.

14.5.3 Planned Subgroup Analyses

In TL-1 we will look at results by ERA response. In particular 5-year EFS rates will be estimated in the subgroup of patients with adequate response (treated with 2 OEPA-, 1 COEPAC-28 without radiotherapy) in a secondary analysis.

In sub-study 2 and 3, subgroup analyses by treatment level (TL-2 versus TL-3) and detailed treatment level (by TL-2a (former TG-1 high risk) vs. TL-2b (former TG-2) vs. TL-3 will be performed.

In sub-study 1 and 2, sub-group analyses by ERA qPET aided Deauville score (1-2 versus 3) will be performed.

14.6 Interim Analyses and Stopping Rules

Descriptive data analyses will be performed annually checking data integrity, monitoring study performance quality endpoints as well as describing treatment related toxicities for the annual safety report.
The clinical board of EuroNet-PHL will decide on adequate measures in response to potential findings. The DMC may be consulted for independent guidance if there is a potential change in the risk-benefit analysis or lack of consensus in the clinical board.

Interim analyses on efficacy will be performed annually starting in year three after the start of accrual when a meaningful number of patients will be on study for more than one year (compare Figure 15).

14.6.1 Interim Analyses in TL-1

The evolving EFS curves will be tested against an EFS reference curve adjusted to a target 5-year EFS of 90% based on the known hazard function in Hodgkin’s lymphoma (one sample test assuming reference curve and proportional hazards). These tests are performed on the 0.1% significance level, the final analysis will thus remain unaffected (Peto-sequential testing scheme).

In non irradiated patients we will compare patients qPET aided Deauville score 1-2 and 3 i.e. with ERA qPET signal < 0.95 with those with 0.95 - 1.3. Should relapses markedly accumulate in the 0.95 - 1.3 group the DMC will be consulted.

14.6.2 Interim Analyses in TL-2 and TL-3

All efficacy analyses on randomised treatment differences will follow the Peto-sequential strategy, i.e. early significance will only be claimed in case of a p-value of less than 0.001. With this approach, the final analysis remains unaffected by multiple testing considerations.

In general, these interim analyses are not formal stopping rules, but alarm trigger. If the criteria are met, the DMC must be consulted. Then the clinical board of EuroNet-PHL will decide on adequate measures.

In addition, in TL-2 and TL-3 with adequate response, we will compare patients ERA qPET aided Deauville score 1-2 versus 3.

14.6.3 DECOPDAC-21 Safety Analysis

After 50 cycles of DECOPDAC-21 have been documented toxicity will be described and related with the toxicity profile of COPDAC-28. A respective safety report will be reviewed by the clinical board and presented to the Data Monitoring and Safety Committee.
14.7 Final Analysis

The final evaluation concerning EFS is performed as soon as at least 80% of patients have more than five years of follow-up.
15 CONCOMITANT SCIENTIFIC PROJECTS

Scientific side projects to the trial will be organised by the national groups in accordance with national regulations for individual patient's data protection. Collection of tumour tissue and blood samples will be handled accordingly. Separate country-specific protocols and respective informed consent forms will be developed and submitted to the relevant Ethics Committees together with this protocol. All scientific side projects have to follow the publication policy of the EuroNet-PHL group (see chapter 22) and must not infringe the main study questions.
16 TRIAL ORGANISATIONAL STRUCTURE

16.1 Sponsor

This trial is sponsored by the Justus Liebig University of Giessen.

16.2 Coordinating Centre

This trial is being conducted under the auspices of the Justus Liebig University of Giessen, Division of Pediatric Hematology and Oncology in cooperation with the Zentrum für Klinische Studien Leipzig – KKS, University of Leipzig.

16.3 Trial Related Committees

16.3.1 General Assembly of EuroNet-PHL

The general assembly of EuroNet-PHL consists of the chairpersons of the participating national study groups, the responsible biometrician, the study secretary and further consulting experts. The general assembly of EuroNet-PHL meets annually.

The general assembly of EuroNet-PHL is responsible for organising the trial in the participating countries. The general assembly will meet at least once a year or more often if required.

16.3.2 Clinical Board of EuroNet-PHL

The Clinical Board (CB) consists of seven voting members: The study chairpersons of Germany (Dieter Körholz), UK (Hamish Wallace), France (Judith Landman-Parker) and Poland (Walentyna Balwierz) as permanent members and two chairpersons from other participating countries (Jonas Karlen and Michaela Cepelova) and the responsible biometrician (Dirk Hasenclever).

Non-voting members are the study secretary (Christine Mauz-Körholz), experts for associated medical disciplines (Regine Kluge, Karin Dieckmann) and one further expert from UK (Stephen Daw) and one from France (Thierry Leblanc).

The CB will decide on all aspects relevant for the trial. All members of the CB are involved in writing the trial protocol. The study secretary will report the decisions of the CB to the general assembly of EuroNet-PHL. The CB will meet at least once a year one day in advance to the annual meeting of the general assembly or more often if required. The CB will meet either in person or by teleconference.
16.3.3 Committees of National Study Groups

The committees of the national study groups are responsible for endorsing and implementing EuroNet–PHL approved protocols in their respective countries.

16.3.4 Data Monitoring Committee

The Data Monitoring Committee (DMC) consists of independent medical and biometrical experts (Members are listed in Appendix I).

The DMC receives confidential information on the progress of the study at annual intervals and has the following tasks:

- assessment of the trial progress and its scientific integrity
- assessment of safety aspects
- advice on serious adverse events
- assessment of interim analysis results and stopping rules.

The DMC will advise the Clinical Board referring to conduct, modification or early termination of the trial. The DMC recommendations will be discussed and approved by the Clinical Board.
17 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

17.1 GCP-Statement

All persons participating in the conduct of the trial (sponsor, authorised representative of the sponsor, investigators, etc.) commit themselves to observe the Declaration of Helsinki (Version Fortaleza, Brazil 2013), as well as all pertinent national laws and the ICH guidelines for Good Clinical Practice (GCP) issued in June 1996 and CPMP/ICH/135/95 from September 1997, taking into account the Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001.

17.2 Sponsorship

The Justus Liebig University of Giessen is sponsor of the international clinical trial EuroNet-PHL-C2 in the legal sense as defined by the Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001. The sponsor transfers his duties for every participating country to an authorised institution (as nominated by the national study group and/or the national study chairperson) by written agreement.

The authorised institution will fulfil the transferred duties for the sponsor and warrants the compliance with all the statutory provisions relevant for the sponsor. The authorised institution is responsible for pointing out to the sponsor country specific duties required by respective national regulations that were not included in the written agreement and has to support the sponsor in fulfilling these additional duties.

Beginning with the date of the agreement the authorised institution will annually draw up a written report (a check list will be provided) on the progress of the clinical trial in the respective country, the fulfilment of the transferred duties and the compliance with legal requirements. In addition the authorised institution will on demand provide all documents (if applicable as copy) necessary for the Trial Master File of the sponsor.

The sponsor reserves the right to audit the authorised institution to control adherence to all legal requirements.

17.3 Request for Authorisation by the Competent Authorities

The representative of the sponsor is responsible for the request of authorisation to the competent authority in Germany, taking into account the German laws. Furthermore, representative of the sponsor will provide all authorised institutions of the participating countries with all documents necessary for request of authorisation according to German law.
The authorised institutions of the participating countries are responsible for provision of all further documents required by national law and for requesting authorisation by their competent authority, taking into account the national laws.

### 17.4 Application for National Ethical Approvals

The representative of the sponsor is responsible for the application for an Ethics Committee opinion in Germany, taking into account the German laws. Furthermore, the representative of the sponsor will provide all authorised institutions of the participating countries with all documents required for application for ethical approval according to German law.

The authorised institutions of the participating countries are responsible for provision of all further documents required for application for ethical approval in their country, taking into account the national laws.

### 17.5 Notification of the Local Authorities (Germany)

Prior to enrolment of the first patient in the trial, the sponsor, his or her legal representatives, all contractors and all investigators are responsible for notifying the respective regulatory authorities of their participation in the trial under provision of national laws. The same applies for amendments, premature termination of trial arms or of the whole trial and the regular trial termination. The sponsor takes over the notification for all investigators in Germany as contracted.

### 17.6 Protocol Amendments and Their Notification

Substantial amendments to the protocol need approval by the Clinical Board of EuroNet-PHL.

Furthermore, any protocol amendments prepared by the EuroNet-PHL group, which are likely to have an impact on the safety of the trial subjects or to change the interpretation of the scientific documents in support of the conduct of the trial, or which are otherwise significant, require an authorisation of the Competent Authorities of the participating countries, as well as approval of the concerned Ethics Committees.

The representative of the sponsor is responsible for the request of amendment authorisation to the Competent Authority in Germany as well as for application for an Ethics Committee opinion in Germany, taking into account the German laws. Furthermore, the representative of the sponsor will provide all authorised institutions of the participating countries with all documents for request of amendment authorisation respectively for application for an Ethics Committee opinion and an approval of the Competent Authority according to German law.
The authorised institutions of the participating countries are responsible for provision of all further documents required by national law and for requesting amendment authorisation by the Competent Authority and application for ethical approval in the respective country.

17.7 Declaration of the End of Trial

The representative of the sponsor is responsible for providing all documents required for the notification of the regular or premature termination of the trial. The representative of the sponsor is responsible for notification of the end of trial to the Competent Authority and the Ethics Committee concerned in Germany, according to German laws.

The authorised institutions of the participating countries are responsible for notification of the end of trial to the Competent Authority and the Ethics Committee concerned in the respective country, taking into account the national laws.

17.8 Insurance

In Germany, patients are insured by the insurance company Gerling Industrie Versicherung AG (Am Schönenkamp 45, 40599 Düsseldorf, Tel 0049 221 7482 5404). The number of the certificate of insurance is 48 15757572. A copy of the certificate of insurance and the insurance conditions will be filed in the investigator site file. Copies of both documents should be handed over to the patients and/or their parents or guardian.

The authorised institutions of all other participating countries are responsible for the provision of insurance or indemnity to cover the liability of the investigator and the sponsor in the respective country (if required by national law), as required by the Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 and the corresponding national laws.

17.9 Initial Submission

17.9.1 Submission to the Ethics Committee and Competent Authority in the Country of the Sponsor (Germany)

Prior to submitting the trial related documents to the leading (and involved) Ethics Committee(s) and the responsible federal authority, the representative of the sponsor must enter the trial into the European database for clinical trials (EudraCT).

Afterwards, the protocol and all other associated documents according to GCP-V § 7 will be submitted to the leading Ethics Committee for approval. Parallel to the submission to the leading Ethics Committee (EC), each participating EC is informed of the submission and also
receives a copy of the documents including those of the trial sites, which they have to approve. At the same time the study documents will be submitted to the responsible federal authority (BfArM) according to the requirements of GCP-V § 7.

The trial can start only after obtaining a positive review by the leading EC and approval from the responsible federal authority. The written approval of the EC must be filed in the trial master file (TMF). Additionally, every participating site must receive a copy of these documents to be filed in the investigator site file (ISF).

17.9.2 Submission to the Ethics Committee and Competent Authorities in Participating Countries

After receiving trial related documents including the EudraCT number the authorised institutions of the respective countries will submit relevant documents to Ethics Committees and Competent Authorities according to national requirements for approval.

The trial can start only after obtaining a positive review by the Ethics Committee in charge and approval from the national Competent Authorities. The written approval of the EC and the national authorities must be filed in the trial master file (TMF).
18 DATA HANDLING AND RECORD KEEPING

18.1 Case Report Forms (CRFs)

The CRFs will be provided by the ZKS Leipzig – KKS. The Sponsor or its authorised representative (trial offices/data centres) will retain the originals of all CRF pages for data entry according to GCP while the investigator will retain a copy of all completed CRF pages.

CRFs should always be completed with a black ballpoint pen. Pens or pencils cannot be used. Attention has to be paid to a clear, legible script, preferably block letters. Mistakes in completion of CRFs are cancelled with a single stroke and correction is written above or next to it. All corrections have to be clearly signed and dated. The use of correction fluid is not permitted. Data fields that cannot be completed due to missing information have to be annotated. The forms have to be completed in a timely fashion and finally checked, signed and dated by the investigator or authorised staff (see also Appendix VI).

The signatures serve to attest that the information contained in the CRF is true and has not been falsified. In case of a major correction or missing data, the reason for it shall also be given.

The investigator must assure completion, review and approval of all CRF-pages. At all times the principal investigator has final responsibility for the accuracy and authenticity of all clinical and laboratory data entered in the CRFs. Even if there are no changes from a previous examination the questions which are repeated in each section of the case report forms should be answered completely.

The completed original case report forms are sent to the trial offices at the scheduled time points (see also Appendix VI).

Source data is regarded as:

- all data contained in the patient’s medical record
- all data provided by the reference pathology
- all data provided by the Central Review (in countries were a centralized staging and response assessment procedure is installed)

Further information on data collection and CRFs is given in specific Handling Guidelines, which are provided in the investigator site file.

18.2 Data Management

Data management will be performed by the designated EuroNet PHL-C2 trial offices according to standard working instructions provided by the ZKS Leipzig.
General data management features include:

- Preparation of CRF
- Preparation and shipment of investigator site files for all EuroNet-PHL trial sites according to national requirements
- Opening sites for recruitment (in cooperation with the respective national chairperson)
- Support for all trial sites regarding logistics and administrative issues
- Opening of trial sites according to national requirements
- Data entry: All data (except data from UK/IRL) will be entered by the data centre at ZKS Leipzig.
- Collection of paper CRFs including reminder-campaigns automatically generated from the database in cooperation with data centre at ZKS Leipzig

Oracle Forms® will be used for creation of the study database and the study management tools building on the experience of the Euro-Net-PHL-C1 trial. The database and the study management tools will be validated according to the SOPs of the ZKS Leipzig prior to data capture.

Database and study management features include:

- Data entry mechanism with clearing by data managers
- An audit trail of all changes in the trial database will be recorded automatically. This includes reasons why changes were made.
- Real time registration of incoming paper CRFs
- Generation of reminders concerning overdue CRFs based on the course of the patient
- Randomisation
- Provision of individualized checklists proposing optimal dates for trial procedures to the trial sites
- Query management system including automatic discrepancy checks and checks on missing data
- Standard reports
- Database of all institutions and persons associated with the trial concerning their tasks within the trial and their contact data
Once the trial database has been declared complete and accurate, the database will be locked. Thereafter, any changes to the database are only possible by joint written agreement between the coordinating investigator, the biometrician and the data manager.

The national trial offices and all national chairpersons can be linked via internet to the common database at the ZKS Leipzig on demand (read-only access to country-specific data only). The communication will be realised using a standard web protocol (https), in most cases no configuration of firewalls will be necessary. No local installation is required. Use of database will be described within detailed handling guidelines and will be provided by ZKS Leipzig (incl. email/telephone support, if applicable).

18.3 Archiving

The archiving of all study relevant documents at the trial site, at the regional trial offices and at the institution of the coordinating investigator will be performed according to the requirements of ICH-GCP, the Commission directive 2005/28/EC of 8 April 2005, and the pertinent national laws.

In countries were a central staging and response assessment procedure is installed, all CT/MRI/PET images sent to the trial office in Giessen/Halle/Leipzig will be archived electronically on the Hermes server using the Paediatric Hodgkin Network (see Data protection plan version 2012-1-27).

All relevant trial documentation (Trial Master File), the electronically stored data, the original CRFs and the final report will be stored for at least 10 years by the sponsor after the trial's completion.

At the investigating sites, the investigators' files, patient identification lists, signed written consent forms, copies of all CRFs and the patients' files will be stored for at least 10 years after the trial's completion. If local rules or other legal requirements require longer periods of archiving, then these are to be met.
19 QUALITY MANAGEMENT

19.1 Site Set-up and Initiation

The principal investigators have to be board-certified in paediatric haematology/oncology.

Requirements for trial sites:

- Access to intensive care unit
- Access to diagnostic facilities: CT, MRI, FDG-PET or FDG-PET/CT or FDG-PET/MRI
- Access to radiotherapy facilities

In addition, in Germany the GPOH and national law require¹:

- 24h on-call service in paediatric haematology/oncology
- At least one investigator and one deputy investigator board-certified in paediatric haematology/oncology per trial site, investigator qualification according to ICH Guideline E6 and relevant national laws by appropriate training courses
- The investigator of each trial site is responsible for appointment and authorisation of adequate qualified staff members and for prompt documentation of the staff delegation log.

Additionally, the involved ethics committees will assess the qualification criteria required by ICH-GCP and the pertinent national laws before start of the trial.

The co-ordinating chairperson on behalf of the sponsor is responsible for setting up written agreements with every trial site in Germany as well as with the respective national chairpersons of the participating countries and their respective institutions.

The national study chairpersons on behalf of their respective institutions (authorised by the sponsor) are responsible for the selection of qualified investigators and trial sites in their countries and for setting up written agreements with every trial site involved in the respective country.

Before start of the trial, the national study chairpersons/trial offices will organise the initiation of their local trial sites.

¹ Germany: Detailed definition of qualification of investigator, deputy and other trial staff incl. description of composition of the trial team will be made in separate documents necessary for application at ethics committee. The qualification of the investigator and the study group at every site will be evaluated prior to the start of the study.
19.2 Premature Closure of a Trial Site

Premature closure of a trial site has to be considered if:

- it does not meet the technical requirements of the protocol,
- the conduct of the study is not compliant with the protocol,
- data quality does not meet required standards or
- data reporting is insufficient.

The national chairperson of the respective country will decide on the premature closure of a trial site after consultation with the clinical board of EuroNet-PHL.

Investigators and trial sites deciding not to take part in the trial any longer have to inform the co-ordinating chairperson and the respective national chairperson immediately. The decision should be well founded.

Details on further treatment and follow-up of patients already on study have to be discussed with the representative of the Sponsor.

19.3 Direct Access to Source Data

According to ICH-GCP and to the applicable European laws, the principal investigator must permit all authorised third parties access to the trial site and insight into the medical records of the trial subjects (source data). This permission includes the clinical trial monitors, auditors and other authorised employees of the sponsor, as well as members of the competent authorities. All these persons are sworn to secrecy.

19.4 Monitoring

Monitoring is mandatory for all participating study groups. Monitoring procedures will be country specific and as agreed by the Sponsor and the individual regional offices. General principles for monitoring will be outlined in the Monitoring Manuals for those regional offices.

Like in the EuroNet-PHL C1 trial, extensive central and biometrical monitoring procedures will be combined with on-site monitoring visits in order to achieve high protocol compliance and data quality, as well as to ensure patients’ safety and rights.

A risk-based monitoring strategy will be implemented, using the risk-based approach proposed by the ADAMON project group [Brosteanu et al., 2009]. According to ADAMON risk analysis,
EuroNet-PHL-C2 belongs to the intermediate risk category. Treatment delivery parameters, toxicities, timing of imaging, follow-up information and informed consent documents comprise risk-bearing trial aspects which have to be monitored.

The first monitoring visit at a site will be scheduled after the inclusion of the site’s first two patients to check protocol compliance and to prevent further systematic errors due to misunderstandings. All trial sites will be visited on a regular basis. The frequency of monitoring visits will depend on the trial site’s recruitment rate and on whether problems have been detected during previous on-site visits or by central monitoring.

Prior to every scheduled on-site visit, the monitor will receive summaries of the site’s patient data already documented in the database, and if applicable with data indicating possible protocol deviations or inconsistencies. During the visits, the monitor will

- check informed consent forms of all patients enrolled (if not monitored centrally)
- perform targeted source data verification for patients with possible deviations
- perform source data verification of the key data (selected baseline parameters, therapy delivery, toxicities, serious adverse events, follow-up) in a random sample of at least 20% of the site’s patients
- discuss open queries raised by data management or drug safety personnel
- check essential parts of the investigator site file (see Monitoring Manual).

Staging, early and late response assessment are not subject to on-site monitoring. The Central Review will document these items based on original imaging and medical records.

19.5 Audits

To keep the conduct of the study in accordance with ICH-GCP and the national laws, the sponsor or his legal representatives reserve the right to audit selected trial sites and also national authorised institutions. The auditor will be independent from the staff involved in the proceedings of the clinical trial.

The national authorised institutions and the investigators agree to give the auditors access to all relevant documents for review as contracted.

19.6 Inspections

According to the pertinent European legislation, the competent authorities may perform inspections of the trial sites at any time during or after completion of the trial.
19.7 Termination of the Trial or Individual Trial Arms

In case of the following situations, a premature termination of the trial or of trial arms has to be considered:

- Serious adverse drug reactions or other circumstances leading to substantial changes in risk-benefit considerations
- Unacceptable toxicity (e.g. cumulative occurrence of treatment related deaths)
- Insufficient efficacy
- Superiority of one treatment arm
- New insights from other trials
- Insufficient recruitment rate
- Unsustainable trial organisation

The Data Monitoring Committee will monitor the study conduct and the safety aspects of the trial on a regular basis, and will give recommendations to the Clinical Board of EuroNet-PHL whether to stop the trial or to change the trial protocol. The Clinical Board of EuroNet-PHL will then decide on the actions to be taken.

The trial is subject to German drug law. Therefore, the trial can be suspended or terminated by the responsible federal authority (Bundesinstitut für Arzneimittel und Medizinprodukte – BfArM) or the responsible Ethics Committee. Even if the trial or individual arms are terminated, the patients already enrolled will still be followed-up according to the protocol.

19.8 Contraception

Due to the mutagenic and teratogenic effects of chemo-/radiotherapy, pregnancy in female patients or fathering children in male patients is not recommended during and for up to one year after the end of treatment. The local investigator should advise on adequate contraception methods individually. Any pregnancy event of patients on trial or their partners should be reported to the trial office.
20 END OF TRIAL DEFINITION

The EuroNet-PHL-C2 study is planned to recruit patients for a total of 6 years (only five years in Germany due to insurance regulations). The trial will start in Germany as soon as possible after grant approval by the "Deutsche Krebshilfe" and approval by the Ethics Committee and the Competent Authority. Overall accrual of 6 years allows for delays in trial opening in other countries.

All patients will be followed-up for 5 years. After the individual study end (i.e. at 5 years after study entry), the patients will be enrolled in an observational protocol to assess long-term sequelae. This registry is not part of this trial.

The EuroNet-PHL-C2 trial will terminate with the 5-year follow-up (last visit) of the last patient enrolled.
21 CONFIDENTIALITY AND DATA PROTECTION

Within this trial personal data of the trial subjects and data regarding the therapy and the course of disease will be collected.

In the interests of patient safety to guarantee correct patient identification when providing complex physicians second opinions during the central review process patients and their parents or guardian are expected to give consent to provide full patient name and address on the Informed Consent Forms so that this information may be used and stored in the trial offices in accordance with the data protection plan, version 2012-1-27. If national laws forbid the use of full names or if the patient/guardian or representative do not consent to the use of full names, all images must be pseudoanonymised before sending. The treating physician is responsible for pseudoanonymisation. All members of the Central Review Panel and their authorised assistants who will have access to the patients’ full name maintain patient confidentiality and operate in adherence to data protection. Documentation of the central review results in the trial database are only performed in a pseudoanonymised fashion.

The investigators are obliged to keep all study data and information confidential and to use those data only in context with the persons involved in the trial conduct. Study material or information generated in this trial must not be made available to third parties, except for official representatives of the sponsor or regulatory authorities.

Only pseudoanonymised data will be processed in the ZKS Leipzig - KKS, according to the written safety concept of this institution and the data protection plan version 2012-1-27. Access to the data will be strictly limited to authorised persons. Extensive back-up procedures are installed to prevent loss of data. All legal requirements concerning data protection and confidentiality will be respected. All authorised persons are sworn to secrecy.

The trial database is completely backed up every day. By applying a hierarchic role-based access method unauthorised access to patient data is excluded as far as possible. Anonymity of data in the scope of statistical analysis is ensured.

21.1 Confirmation of Data Protection

Access to the data is strictly limited to authorised persons. Data are protected against unauthorised access.
21.2 Declaration Regarding the Pseudoanonymised Transfer of Personal Data

The sponsor certifies herewith that the transfer of pseudoanonymised personal data will take place according to the requirements of ICH Guideline E6 Chapter 5.5.5. Moreover, the sponsor certifies that persons who do not permit the transfer of data will not be admitted to the trial.
22 ADMINISTRATIVE AGREEMENTS

22.1 Adherence to the Protocol

After a patient has been enrolled, it is the investigator's duty to make any reasonable effort to avoid protocol deviations or violations in order to uphold the scientific integrity of this study.

In rare exceptional cases, investigators should consult with their national chairperson or the coordinating chairperson whether a protocol divergence may be indicated.

**Protocol deviations** are minor quantitative departures from procedures specified in the protocol that may be required in practice due to medical or logistic reasons. Examples are

- dose modifications or substitution of single drugs in response to toxicity
- moderate delays in treatment delivery for medical or logistic reasons
- Performing FDG-PET imaging less than 14 days after the last dose of prednisone/prednisolone.

Such protocol deviations (and the **reasons** therefore) should be indicated on the respective CRF.

Quality endpoints have been defined (section 12.3.4.) to describe and closely monitor such protocol deviations in order to ensure an overall high standard of protocol adherence.

**Protocol violations** are major qualitative deviations from procedures specified in the protocol. Protocol violations must be reported via protocol-violation-form (PPV) to the ZKS-Leipzig unless they can be documented adequately on a regular CRF-page (see Handling Guideline PPV).

All protocol violations will be listed and discussed between the representative of the Sponsor and the biometrician prior to statistical analysis.

22.2 Protocol Amendments

In order to ensure comparable conditions during all stages of the trial and in the interests of valid statistical analysis, the investigators, the representative of the Sponsor or any other person involved in the trial conduct may not alter the study conditions agreed upon and set out in this protocol.

Amendments may be made only in exceptional cases and by mutual agreement within the clinical board of EuroNet-PHL. Any amendment and the reasons therefore must be set out in writing, and signed by all parties concerned. The amendment then becomes part of the study protocol, and has to be filed in the Trial Master File (TMF).
The clinical board of EuroNet-PHL also decides when such protocol changes become effective. If protocol changes are profound, i.e. if they are modifications of a therapy arm, changes to inclusion or exclusion criteria, accrual duration or closure of a therapy arm or the whole study the opinion of the DMC should first be obtained.

Amendments which might have an impact on the well-being of the trial subject (major amendments) such as the use of additional invasive diagnostic procedures require an additional approval by the Ethics Committees (EC) and by the competent authorities concerned as well as the respective insurance companies. In addition, a further informed consent form has to be signed by all trial subjects already enrolled in the trial who might be affected by the amendment. Minor changes will only be submitted to the Ethics Committees and the competent authorities in a written form.

The clinical board may implement a change to the protocol to eliminate an immediate hazard(s) to trial subjects without prior EC approval. As soon as possible, the implemented change, the reason for it, the proposed protocol amendment(s) will be submitted to respective EC and competent authorities for agreement.
23 FUNDING

The Deutsche Krebshilfe agreed to fund this protocol in Germany. The national chairpersons have to apply at appropriate institutions in their countries for funding of additional study cost in the respective countries.
24 PUBLICATION POLICY

 Participating centres may if they wish publish their own cases but agree to allow the clinical board of EuroNet-PHL exclusive rights to publish the major results of the EuroNet-PHL-C2 study (primary, secondary and tertiary study questions as detailed in the protocol) in part or in total.

 All such publications will acknowledge the contribution of the participating clinicians. Authorship of such publications, including abstracts, will represent members of the clinical board, the national chairpersons, members of the central review panel and other persons who made a major contribution to the design of the trial, the preparation of the data, its analysis or the writing of the manuscript. Every author should have participated sufficiently to take public responsibility for the content. It is the responsibility of the clinical board of EuroNet-PHL to determine and agree the composition of manuscript writing committees.

 Additional specific publications from the contributing medical disciplines as well as biological side projects (e.g. reference facilities, quality assurance) are welcome as long as they do not preclude the publication of major study results. Authorship of such publications, including abstracts, will represent those persons who made a major contribution to the preparation of the data, its analysis or the writing of the manuscript.

 All publications (abstracts or manuscripts) require prior written approval of the members of the clinical board.
25 REFERENCE LIST


10. Declaration of Helsinki: Guiding Physicians in Biomedical Research Involving Human Subjects. Adopted by the 18th World Medical Assembly, Helsinki (Finland), June 1964. Last amendment by the 64th General Assembly, Fortaleza (Brazil) 2013.


Recommended for Adoption at Step 4 of the ICH Process on 27 May 1994.

www.ifpma.org/ich5e.html#Safety


26 PROTOCOL AGREEMENT

Herewith I declare that I have read and understood the present protocol and agree to honour each part of it. I will ensure that all the patients enrolled in the trial by my site will be treated, observed and documented in accordance with this protocol. I will ensure that all persons assisting with the study under my supervision are adequately informed about the protocol, the investigational products and their duties.

Date: _____________________________

Signature of Principal Investigator: _____________________________

Affiliation/address (stamp): _____________________________

_________________________
_________________________
_________________________
_________________________
27 APPENDICES

APPENDIX I: MEMBERS OF THE DMC

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Prof. Dr. John Radford,
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University of Manchester
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Tel. 0161 446 3094
Fax 0161 446 3092
APPENDIX II – DEFINITION OF ADVERSE EVENTS

II.1. Adverse Event

Any untoward medical occurrence in a patient or clinical trial subject administered a pharmaceutical or medical product, which does not necessarily have a causal relationship to this treatment. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings for example), symptom, or disease temporarily associated with the use of a medicinal (investigational) or medical product, whether or not related to the investigational medicinal product. Adverse events encompass illness, signs of illness including pathological laboratory findings and symptoms that initiate during the trial or previous conditions that become worse.

II.2. Serious Adverse Event

Any untoward medical occurrence or effect that at any dose:

- results in death unrelated to original cancer
- is life-threatening*
- requires in-patient hospitalisation** or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- Or is otherwise considered medically significant by the investigator***

* Life-threatening in the definition of an SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus hospitalisation for protocol treatment (e.g. line insertion, blood transfusion) elective procedures (unless brought forward because of worsening symptoms) or for social reason (e.g. respite care) are not regarded as an SAE. In-patient hospitalisation or prolongation of existing hospitalisation due to adverse reactions explicitly covered on the toxicity forms need not be reported as an SAE.

***Medical judgment should be exercised in deciding an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or
hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

II.3. Adverse Event Classification and Reporting

II.3.1. Severity

The severity of adverse events will be assessed according to the CTC criteria. A copy of the CTCAE version 4.0 can be downloaded from http://ctep.cancer.gov/reporting/ctc.html.

Adverse events that are not explicitly listed in the CTC criteria are assessed by the following 5-point system. Assessment of severity is performed according to CTCAE V4.0:

<table>
<thead>
<tr>
<th>Mild Adverse Event</th>
<th>Moderate Adverse Event</th>
<th>Severe Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>asymptomatic or mild symptoms;</td>
<td>minimal, local or noninvasive intervention indicated;</td>
<td>medically significant but not immediately life-threatening;</td>
</tr>
<tr>
<td>clinical or diagnostic observations only;</td>
<td>limiting age-appropriate instrumental ADL*2.</td>
<td>hospitalisation or prolongation of hospitalisation indicated;</td>
</tr>
<tr>
<td>intervention not indicated.</td>
<td></td>
<td>disabling;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>limiting self care ADL**</td>
</tr>
</tbody>
</table>

**Life-threatening Adverse Event**

- Life-threatening consequences;
- urgent intervention indicated

---

2 Activities of Daily Living (ADL):

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
II.3.2. Causal Relationship

The investigator must judge whether or not in his opinion the adverse event was caused by the investigational product according to the classification given below (Venulet and Ham, 1996):

- Reasonable possibility
- No reasonable possibility

Relationship to study drug administration will be determined by the investigator responding yes or no to this question: Is there a reasonable possibility that the AE is associated with the study drug?

Each adverse event has to be reported, even if the investigator feels that it is not related to the administration of study drugs.

II.3.3. Expected/Unexpected

An unexpected AE is an AE, the nature or severity of which is not consistent with the applicable product information (SmPC) available in the ISF.

The distinction expected/unexpected only depends on whether the untoward reactions have been previously described.

II.3.4. Outcome

The outcome of an AE has to be classified as follows:

- recovered/resolved
- recovering
- not recovered/not resolved
- recovered/resolved with sequelae
- fatal*
- unknown

* A subject's death per se is not an event, but an outcome. The event which resulted in the subject's death must be fully documented and reported, for all cases where the death occurs up to four weeks after end of therapy, and irrespective of whether considered treatment-related or not.
II.4. Suspected Unexpected Serious Adverse Drug Reactions (SUSAR)

II.4.1. Definition

Suspected unexpected serious adverse drug reactions (SUSARs) are side effects (probably or definitely connected with the administration of the investigational product), the nature or severity of which are inconsistent with the information available about the product. Information about the trial product contained in the SmPC (Summary of medicinal Product Characteristics) should be used to verify if the adverse reaction has been previously described.

II.4.2. Evaluation and Reporting

Information for the Sponsor

After medical evaluation and discussion with the representative of the Sponsor the ZKS Leipzig – KKS submits all information available about a SUSAR immediately, at latest within 15 days after the event becomes known to the leading Ethics Committee, the competent authorities, the investigators of Germany and the national chairpersons concerned. In case of death or immediate danger to life caused by a SUSAR the competent authorities, the leading ethics committees, the investigators of Germany and the national chairpersons concerned must be informed within 7 days after the event becomes known to the sponsor. Additional information has to be given within further 8 days.

The involved national chairpersons are responsible for informing the Ethics Committee(s) as well as the investigators in the respective country about the occurrence of a SUSAR. The reporting procedure has to comply with the national legislation. Where applicable, the national chairperson will also have responsibility for informing their Competent Authority about the occurrence of a SUSAR.

Details of the sponsor’s documentation and reporting obligations will be specified in a trial-specific pharmacovigilance plan.

Information for the Investigator

The local principal investigator passes down all relevant information concerning the SUSAR to all participating trial investigators at his/her trial centre.
II.5. Periodic Reports

II.5.1. Periodic Safety Update Report (PSUR, according to AMG)

The representative of the Sponsor together with the project manager at the ZKS Leipzig - KKS and the responsible biometrician will produce (annually or on request) a safety report (Annual Safety Report, ASR).

The representative of the Sponsor will submit the report about the safety of the trial medication to the leading Ethics Committee and the respective federal authority in Germany as well as to the national chairpersons, who are responsible to disseminate the ASR to their respective authorities and Ethics Committees.

The key reporting date is the date of the first authorisation of the clinical trial by the federal authorities. All data obtained up to this date (each year) will be included in the ASR. Beginning with the key date, there is a time limit of 60 days for the preparation and submission of the ASR.

II.5.2. Periodic SUSAR Reports for Ethics Committees

Upon request of the Ethics Committees a periodic SUSAR listing accompanied by a brief report of the sponsor highlighting the main points of concern will be created. These periodic reports only include SUSARs reported within the period covered by the report. The reporting will be organised by the ZKS.

II.5.3. Other Safety Relevant Issues

Other safety issues also qualify for expedited reporting where they might materially alter the current risk-benefit assessment of an investigational medicinal product or would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial, for instance:

New events related to the conduct of a trial or the development of an IMP likely to affect the safety of subjects, such as:

- a serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial,
- a significant hazard to the subject population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease,
- a major safety finding from a newly completed animal study (such as carcinogenicity),
- a temporary halt of a trial for safety reasons if the trial is conducted with the same investigational medicinal products in another country by the same sponsor
- recommendations of the DMC, if any, where relevant for the safety of subjects.

The representative of the Sponsor, together with the clinical board of EuroNet-PHL and the DMC if appropriate, will decide if the number of events or qualitative changes in the expected SARs comprises a safety issue and must be reported.

II.6. Therapeutic Procedures

AEs requiring therapy must be treated with recognized standards of medical care to protect the health and well-being of the subject. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment of an emergency situation.

The action taken by the investigator must be documented on the SAE forms according to the following classification:

<table>
<thead>
<tr>
<th>a) in general</th>
<th>b) on the investigational product</th>
</tr>
</thead>
<tbody>
<tr>
<td>the action taken has to be documented by the investigator in the appropriate section of the CRF and/or by additional documents</td>
<td>• drug withdrawn</td>
</tr>
<tr>
<td></td>
<td>• dose reduced</td>
</tr>
<tr>
<td></td>
<td>• dose increased</td>
</tr>
<tr>
<td></td>
<td>• dose not changed</td>
</tr>
<tr>
<td></td>
<td>• unknown</td>
</tr>
<tr>
<td></td>
<td>• not applicable</td>
</tr>
</tbody>
</table>
APPENDIX III SCREENING PROCEDURES

III.1. Histopathology

Pathology central review is mandatory and will be organised by each participating country on a national level (details see Pathology Manual). HL subtyping including diagnosis of Grey Zone Lymphoma should be coded according to the 2008 WHO classification. The required immunochemistry results will be documented on the reference pathology form. The local investigator is responsible for sending the reference pathology form to the respective regional trial office within three months after registration. Thereafter, this form will be subject to query management by the central database.

At relapse diagnosis, reference pathology results should be submitted to the respective regional study office.

III.2. Full Clinical History and Physical Examination

- History or clinical symptoms of paraneoplastic phenomena
- Assessment of B-symptoms
- History of prior treatment

III.3. Laboratory Analyses at Staging

III.3.1. Mandatory

- ESR
- CRP (for correlation with ESR)
- Serum albumin
- Complete blood count (Hb, WBC, platelets, lymphocytes, neutrophils)
- TSH, fT4

III.3.2. Recommended

- Fibrinogen
- Ferritin
o ALAT (GPT), ASAT (GOT), GGT, bilirubin
o Sodium, potassium, calcium, phosphorous
o LDH, AP
o Creatinine
o Protein electrophoresis (gamma-globulin and alpha-2 globulin)
  o INR, PTT
  o Immunoglobulin A, G and M
  o Baseline virology including serology examinations for antibodies against VZV, EBV, CMV, HSV, HIV, toxoplasmosis, hepatitis A, B, C (HCV-PCR).

### III.4. Recommended Imaging Options

For technical details of PET-MRI, PET-CT and conventional cross-sectional imaging see Imaging Manual.

**A)** Whole-body PET-MRI with i.v. contrast

Acquisition from skull base to mid thighs and respiratory triggering for chest and abdomen is recommended.

For detection of lung involvement an additional chest CT of diagnostic quality in end-inspiration is required at staging (Im1) if chest-CT was not performed within two to three weeks prior to diagnosis of HL.

In patients with lung involvement the chest CT as described above has to be repeated at ERA (Im2) and LRA (Im3), if applicable.

At Im1 liver and spleen ultrasonography is required.

At Im1 an additional bone scintigraphy is required for suspected skeletal involvement, if no corresponding CT is performed in the respective region of a PET-positive lesion.

**B)** Whole-body PET-CT (low dose) with i.v. contrast

Acquisition from skull base to mid thighs.

For detection of lung involvement an additional chest CT of diagnostic quality in end-inspiration is required at staging (Im1) if chest-CT was not performed within two to three weeks prior to diagnosis of HL.
In patients with lung involvement the chest CT as described above has to be repeated at ERA (Im2) and LRA (Im3), if applicable.

At Im1 liver and spleen ultrasonography is required.

No bone scintigraphy is required.

C) Only if imaging options A) and B) are not available:

PET-CT (low dose) without contrast (not recommended!) or PET only

Acquisition of PET from skull base to mid thighs is required at Im1 and Im2 and for ERA PET-positive patients at Im3.

For detection of lung involvement an additional chest CT of diagnostic quality in end-inspiration is required at staging (Im1) if chest-CT was not performed within two to three weeks prior to diagnosis of HL.

In patients with lung involvement the chest CT as described above has to be repeated at ERA (Im2) and LRA (Im3), if applicable.

At Im1 MRI with i.v. contrast (CT in diagnostic quality, if MRI is not available) of neck, abdomen and pelvis is required.

At Im2 and Im3 MRIs have to be repeated for initially involved regions only.

At Im1 liver and spleen ultrasonography is required.

At Im1 an additional bone scintigraphy is required for suspected skeletal involvement, if no corresponding CT is performed in the respective region of a PET-positive lesion.
APPENDIX IV REFERENCE EVALUATION

After patient registration the central trial office will be notified by the ZKS-Leipzig via Email about the Pat-ID, trial site ID, the scheduled date of PET, local PET centre and name of the local investigator for all patients registered in a country associated with Central Review in Giessen/Halle (all countries except Austria).

Immediately after patient registration, local sites will send patients’ staging images as well as image reports to the central trial office in (please note: Austrian site send to study office Vienna).

All images for staging and response assessment will undergo real-time central review in Giessen/Halle/Leipzig (or Vienna for Austria only).

IV.1. Central Staging and Response Assessment

IV.1.1. Determination of Reference Stage

The Central Review Board will define the reference stage and subsequent assignment to treatment level for all patients during their weekly tumour conferences at the central trial office in Giessen/Halle/Leipzig (resp. Vienna for Austria). The following information and material is required for the central staging and response assessment, and has to be provided by the local investigator:

- Results of clinical examination (including ENT findings)
- Results of ultrasound
- Results, images (preferably via the central server (Hermes Med. Sol. Sweden) of all CT/MRI examinations and FDG-PET data sets
- Information on the biopsy site
- ESR prior to start of treatment

IV.1.2. Organisation of Central Review

IV.1.2.1. Preparations before Tumour Conference

The participating trial sites will send the written results and electronic data sets on CD in DICOM format or – preferably via the central Hermes server to the trial office in Giessen (Vienna for Austria) including an English (or German) summary of the written results. Data sent on CD in DICOM will be uploaded to the central Hermes server by the trial office in Giessen (for CT, MRI) or Leipzig (PET).
The trial coordinator/study physician at the (central) study office will check the documents for completeness. In case of incompleteness, the local investigator will receive a reminder telephone call or an Email. As soon as all required documents are available the patient will be scheduled for the next tumour conference.

Prior to the tumour conference the reference radiologist and the reference nuclear medicine physician will evaluate the submitted image data sets.

**IV.1.2.2. Central Review**

The participants of the central review board are the coordinating chairperson, the trial coordinator/study physician, the reference radiologist, the reference nuclear medicine physician and the reference radio-oncologist or their respective deputies.

During the central review,

- the clinical findings and the ultrasound results will be presented by the trial coordinator/study physician.
- The reference radiologist will present the results based on his CT/MRI evaluation, including the volume of the largest lymph node mass.
- The reference nuclear medicine physician will present the PET results.
- Finally the reference stage will be determined by the coordinating chairperson or his deputy.

For ERA and LRA, the reference nuclear medicine physician will present the PET-positive tumour residuals. For all initially involved regions the visual Deauville score and the semi-quantitative qPET-values will be documented. The reference radiologist will present the volume response of the bulky sites.

**IV.1.2.3. Notification of Central Review Results**

The result of the central review including stage and treatment level or ERA/LRA PET results will be documented on the central review staging/response assessment CRF. Subsequently, these CRF pages will be signed by the coordinating chairperson and sent to the investigators by fax or secured e-mail within two working days. In TL-1 patients, the reference nuclear physicians will inform the (central) trial office about the ERA PET-results within two days after receipt of the PET data sets from the local sites. The (central) trial office will notify the respective local investigators immediately. Thereby, delayed start of the COPDAC-28 cycle in patients with AR will be kept at a minimum.
IV.2. Reference Radiotherapy Planning

The most time critical visits during the trial are the ERA for all TL-1 patients and the LRA for all TL-2 and TL-3 patients. Thus, any information about the LRA investigations must be provided to the Central Review Panel as soon as possible.

At ERA, the Central Review Panel will decide on late response assessment (LRA) in TL-2 and TL-3 as well as on radiotherapy in TL-1 or TL-2 and TL-3 patients treated in the COPDAC-28 arm.

For ERA PET-positive patients in TL-1 and those in TL-2 and TL-3 randomised into the COPDAC-28 arm the reference radio-oncologist will provide a RT plan, which will be sent to the local investigator along with the ERA results. For patients in TL-2 and TL-3 the decision on boost will be fixed at LRA by the review panel. If sites will require boost RT, the reference radio-oncologist will provide an amended RT plan. The revised RT plan will be sent along with the LRA results to the local investigator.

For ERA PET-positive patients randomised to the DECOPDAC-21 arm the indication for radiotherapy will be decided at LRA. If indicated, the reference radio-oncologist will provide a RT plan, which will be sent to the local investigator along with the LRA results. The local investigator should then immediately inform the local radio-oncologist.

Within four weeks after completion of radiotherapy, radiotherapy planning and delivery documentation should be sent to the EuroNet-PHL radiotherapy Quality Control Panel for evaluation (if consented). The panel will deliver a quality control report biannually to all radio-oncologists and national chairpersons involved describing major protocol deviations. A real time reference review of radiotherapy planning documents is unfeasible since time lag between end of chemotherapy and start of radiotherapy is critical.

IV.2.1. Documentation of Radiogenic Late Effects (Germany only)

Due to national legislation, radio-oncologists in Germany are obliged to perform annual follow-up of irradiated patients concerning the development of late effects for a 5-year follow-up period. A registry for radiogenic late effects (chairperson: Prof. Dr. Willich, Universitätsklinik Münster) will collect this data. At LRA, the study office in Halle will notify the late effects registry of all patients with radiotherapy indication in Germany. The registry for radiogenic late effects will then contact the local investigator to receive the required information.
IV.3. Reference Pathology

In countries where there is already an established and successful system for Reference Pathology that has been functioning in a manner acceptable to the Sponsor - then this system will continue.

The local investigator is responsible for requesting pathology review for all patients enrolled onto EuroNet-PHL-C2, since reference pathology results are an important prerequisite for trial participation. This applies for all tumour specimens defining the initial diagnosis and for biopsies in case of suspected relapse. The local investigator specifies:

- Patient’s name
- Date of birth
- EuroNet-PHL-C2 Pat-ID

on the CRF “Reference Pathology” and sends it to the local pathologist.

The local pathologist will request reference pathology assessment at one of the reference pathology centres (see list above) by forwarding paraffin blocks and formalin fixed material and the pre-filled CRF-page. The reference pathologist will complete and sign the reference pathology CRF and send it to the local pathologist together with the standard reference pathology report. The local pathologist will forward a copy of the report and the CRF to the local investigator.

The local investigator (or authorized staff) will blacken the patient’s name and all identifying information on the form, will enter and confirm the Pat-ID on the form and send the pseudoanonymised original CRF to the ZKS Leipzig – KKS (or the respective regional trial offices, e. g. CRCTU Birmingham). A copy should be kept in the patient's records.

If the diagnosis of Hodgkin’s lymphoma is not confirmed, the respective reference pathologist must inform the local investigator immediately.

The reference pathology CRF should be submitted within 3 months after patient registration.
APPENDIX V EMERGENCIES

V.1. Large Mediastinal Tumour

For patients with large mediastinal tumour, the level of respiratory insufficiency should be determined.

- **level 0**: No respiratory insufficiency. No restriction of trachea or bronchi visible in X-ray and/or chest CT. No venous congestion.
- **level 1**: Clinically no signs of respiratory insufficiency but radiological restriction of trachea or bronchi.
- **level 2**: Stridor and/or upper venous congestion (headache as a first sign among others).
- **level 3**: Orthopnoea

Lymph node biopsy under local anaesthesia or a mini-thoracotomy in general anaesthesia can be performed only in patients up to level 1. Before surgery it should be discussed with the anaesthetist that the patient may need prolonged mechanical ventilation for 1 – 2 days until the tumour has shrunk during treatment. In all other patients a pre-phase with prednisone/prednisolone 30 – 60 mg/m² (5 – 10 days) should be initiated before biopsy.

A therapeutic pleural puncture with drainage should be performed under local anaesthesia in case of respiratory insufficiency caused by a large pleural effusion.

V.2. Tumour Lysis Syndrome

In the rare case of tumour lysis syndrome (in patients with hyperuricaemia or patients with bulky disease) the following is recommended:

- Hyperhydration with 3000 ml fluid/m² (up to 5000 ml/m²; cap at 7000 ml) per day.
- For forced diuresis, the infusion may contain 10 mg furosemide/1000 ml. Every 6 hours fluid balance should be calculated and if needed furosemide should be added.
- The initial infusion should not contain potassium (addition of potassium only in patients with hypokalaemia within short-term electrolyte checks).
- Urine alkalinisation is not recommended as increasing the pH will reduce the solubility of phosphate.
- All patients with tumour lysis syndrome should receive allopurinol for prophylaxis. In case of hyperuricaemia Rasburicase (Fasturtec® or a comparable drug) may be considered.

**APPENDIX VI TRIAL PROCEDURES**

**VI.1. Brief Summary of Important Time Lines for Trial Sites**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Time line</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Registration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Start of treatment</strong></td>
<td>Immediately after completion of screening and informed consent</td>
<td>patient registration start of OEPA chemotherapy</td>
</tr>
<tr>
<td><strong>Initial staging and TL assignment</strong></td>
<td>Until day 7 after start of treatment (latest by day 15 of the second OEPA cycle)</td>
<td>sending of documents, completed CRF-pages with screening data and images of the initial staging to the central trial office in Halle (until the end of October 2015) / Giessen (from November 2015) (if consented; Austrian sites send to Vienna) Confirmation of TL assignment Central Review Board</td>
</tr>
<tr>
<td><strong>Randomisation in TL-2 and TL-3</strong></td>
<td>Immediately after confirmation of TL assignment</td>
<td>Randomisation request form (R) faxed to the appropriate EuroNet-PHL trial office. Randomisation result returned on the next working day via fax or secured Email.</td>
</tr>
</tbody>
</table>

Local investigator

Respective trial office/data centre (e.g. ZKS Leipzig)
<table>
<thead>
<tr>
<th><strong>Documentation of OEPA</strong></th>
<th>Within four weeks after completion of OEPA regimen</th>
<th>Sending of completed chemotherapy and chemotherapy-toxicity CRF to the appropriate regional trial office.</th>
<th>Local investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confirmation of dates for ERA PET</strong></td>
<td>At the start of the second OEPA</td>
<td>confirmation of ERA PET dates</td>
<td>Local investigator and local PET centre</td>
</tr>
<tr>
<td><strong>Early response assessment</strong></td>
<td>Day 29-32 after start of second OEPA (= day 14 -17 after last dose of prednisone/prednisolone)</td>
<td>ERA PET-acquisition</td>
<td>local PET centre</td>
</tr>
</tbody>
</table>
| **Central review of ERA – time critical in TL-1** | **TL1:** day 35 after start of second OEPA at latest  
**TL-2 and TL-3:** within three weeks after ERA | Sending of ERA documents and images to the central trial office in Halle (until the end of October 2015) / Giessen (from November 2015) (Austrian sites send to Vienna) | Local investigator |
<p>|  |  | Provision of ERA-assessment data (incl. decision on RT yes/no) | Central Review Board |
| <strong>Continuation of treatment in ERA PET-negative TL1 patients</strong> | One week after ERA (delays of more than three weeks after ERA must be avoided) | Start of COPDAC-28 | Local investigator |
| <strong>Continuation of treatment in TL1 in ERA PET-positive patients</strong> | Two weeks after ERA (delays of more than four weeks after ERA must be avoided) | Start of RT | Local investigator |
| <strong>Continuation of treatment in TL-</strong> | On the day of ERA PET | Start of COPDAC-28 or DECOPDAC-21 | Local investigator |</p>
<table>
<thead>
<tr>
<th>2 and TL-3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Documentation</strong></td>
</tr>
<tr>
<td>Within four weeks after completion of COPDAC-28 or DECOPDAC-21</td>
</tr>
<tr>
<td><strong>Confirmation of dates for LRA PET</strong></td>
</tr>
<tr>
<td>At the start of second (TL-2) or fourth (TL-3) COPDAC-28 or DECOPDAC-21</td>
</tr>
<tr>
<td><strong>Late response assessment in ERA PET-positive TL-2 and TL-3 patients</strong></td>
</tr>
<tr>
<td>LRA PET at day 29-32 after start of COPDAC-28 or day 22-25 after start of DECOPDAC-21 of the second (TL-2) or fourth (TL-3) consolidation cycles</td>
</tr>
<tr>
<td><strong>Central review of LRA – time critical</strong></td>
</tr>
<tr>
<td>latest by day 35 after start of COPDAC-28 or day 28 after start of DECOPDAC-21 of second (TL-2) or fourth (TL-3) consolidation cycle</td>
</tr>
<tr>
<td>Sending of LRA documents and images to the central trial office in Halle (until the end of October 2015) / Giessen (from November 2015) (Austrian sites send to Vienna)</td>
</tr>
<tr>
<td>Provision of LRA-assessment data (incl. Reference RT plan, if appl.)</td>
</tr>
<tr>
<td><strong>Radiotherapy in ERA PET-positive patients in TL-2 or TL-3</strong></td>
</tr>
<tr>
<td>Ideally within two weeks (latest four weeks) after LRA</td>
</tr>
<tr>
<td><strong>Local investigator and local Radiotherapist</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------------------------</td>
</tr>
<tr>
<td>Follow-up</td>
</tr>
<tr>
<td>Documentation of radiotherapy, if appropriate</td>
</tr>
<tr>
<td>Documentation of Follow-up</td>
</tr>
<tr>
<td>Documentation of certain events</td>
</tr>
</tbody>
</table>
APPENDIX VII FOLLOW-UP

Follow-up Recommendations

<table>
<thead>
<tr>
<th>Diagnostics</th>
<th>1 year</th>
<th>2. + 3. Year</th>
<th>4. + 5. year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete clinical examination and follow-up</td>
<td>6 weeks and 3, 6, 9 and 12 months after end of treatment</td>
<td>Every four months</td>
<td>Every six months</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>6 months and 9 months after end of treatment</td>
<td>Every four months</td>
<td></td>
</tr>
<tr>
<td>Ultrasound neck, abdomen and pelvis</td>
<td>6 and 9 months after end of treatment</td>
<td>Every four months</td>
<td>Every six months</td>
</tr>
<tr>
<td>Chest CT in patients with initial lung involvement</td>
<td>3 months and 12 months after end of treatment*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI of all initially involved regions</td>
<td>3 months and 12 months after end of treatment*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung function testing; Echocardiography</td>
<td>3 months</td>
<td>Once every two years</td>
<td>Once every two years</td>
</tr>
<tr>
<td>T4, TSH, ultrasound of thyroid</td>
<td>Once a year</td>
<td>Once a year</td>
<td>Once a year</td>
</tr>
</tbody>
</table>

*Images are sent to central review only in case of suspected relapse

Note: Routine FDG-PET for follow-up is not recommended.

Additional cross sectional images are performed in case of suspected relapse.

Some countries may consider it appropriate to perform fewer investigations as part of their follow-up procedures.
APPENDIX VIII REGRESSION MODEL ON sAML RISK

In order to assess the potential sAML risk with DECOPDAC-21, data on sAML in advanced stage HL from all BEACOPP trials of the GHSG in adults and the paediatric DAL-, GPOH-, and EuroNet-PHL-trials were integrated into a regression model.

Estimated cumulative sAML incidence curves are not available in most publications. Therefore the sAML risk was quantified by the observed primary sAML rate. Relapse treatment is known to be highly leukaemogenic [Scholz 2011]. The cumulative doses of the cytostatic drugs discussed above were abstracted in mg/m².

Table 7: Data from Adult HL Studies HD9


ETOP = Etoposide; CY = Cyclophosphamide, PROC = Procarbazine, DOX = Doxorubicin

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Study</th>
<th>ETOP</th>
<th>CY</th>
<th>PROC</th>
<th>DOX</th>
<th>N</th>
<th>sAML medobs</th>
<th>rate%</th>
<th>Lower</th>
<th>Upper</th>
<th>Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4 COPP-ABVD</td>
<td>HD9</td>
<td>0</td>
<td>5200</td>
<td>5600</td>
<td>200</td>
<td>261</td>
<td>1</td>
<td>122</td>
<td>0.22</td>
<td>0.02</td>
</tr>
<tr>
<td>2</td>
<td>6 BEACOPPesc</td>
<td>HD15</td>
<td>3600</td>
<td>7200</td>
<td>4200</td>
<td>210</td>
<td>711</td>
<td>2</td>
<td>48</td>
<td>0.24</td>
<td>0.05</td>
</tr>
<tr>
<td>3</td>
<td>8 BEACOPPbase14</td>
<td>HD15</td>
<td>2400</td>
<td>5200</td>
<td>5600</td>
<td>200</td>
<td>710</td>
<td>8</td>
<td>48</td>
<td>1.00</td>
<td>0.52</td>
</tr>
<tr>
<td>4</td>
<td>4 esc+4base</td>
<td>HD12</td>
<td>3600</td>
<td>7400</td>
<td>5600</td>
<td>240</td>
<td>787</td>
<td>10</td>
<td>78</td>
<td>1.25</td>
<td>0.65</td>
</tr>
<tr>
<td>5</td>
<td>8 BEACOPPbase-21</td>
<td>HD9</td>
<td>2400</td>
<td>5200</td>
<td>5600</td>
<td>200</td>
<td>469</td>
<td>7</td>
<td>111</td>
<td>1.45</td>
<td>0.66</td>
</tr>
<tr>
<td>6</td>
<td>8 BEACOPPesc</td>
<td>HD12</td>
<td>4800</td>
<td>9600</td>
<td>5600</td>
<td>280</td>
<td>787</td>
<td>12</td>
<td>78</td>
<td>1.51</td>
<td>0.83</td>
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<tr>
<td>7</td>
<td>8 BEACOPPesc</td>
<td>HD15</td>
<td>4800</td>
<td>9600</td>
<td>5600</td>
<td>280</td>
<td>705</td>
<td>19</td>
<td>48</td>
<td>2.68</td>
<td>1.68</td>
</tr>
<tr>
<td>8</td>
<td>8 BEACOPPesc</td>
<td>HD9</td>
<td>4800</td>
<td>9600</td>
<td>5600</td>
<td>280</td>
<td>466</td>
<td>14</td>
<td>107</td>
<td>2.98</td>
<td>1.72</td>
</tr>
<tr>
<td>9</td>
<td>2OEPA-4COPDAC-28</td>
<td>C1</td>
<td>1250</td>
<td>4000</td>
<td></td>
<td>0</td>
<td>290</td>
<td>1</td>
<td>20</td>
<td>0.20</td>
<td>0.02</td>
</tr>
<tr>
<td>10</td>
<td>2OPPA-4(6)COPP</td>
<td>DAL</td>
<td>0</td>
<td>4000</td>
<td>9000</td>
<td>160</td>
<td>197</td>
<td>2</td>
<td>101</td>
<td>0.85</td>
<td>0.18</td>
</tr>
<tr>
<td>11</td>
<td>2OEPA-4COPDAC-28</td>
<td>HD2002</td>
<td>1250</td>
<td>4000</td>
<td></td>
<td>0</td>
<td>120</td>
<td>0</td>
<td>58</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>12</td>
<td>2OPPA-4COPP HD2002</td>
<td>0</td>
<td>4000</td>
<td>9000</td>
<td>160</td>
<td>119</td>
<td>1</td>
<td>58</td>
<td>0.49</td>
<td>0.04</td>
<td>5.28</td>
</tr>
</tbody>
</table>

Assuming that the sAML risk is not caused by a single drug but rather by the overall treatment burden in CY, PROC, DOX and ETO eight BEACOPP escalated is the most leukaemogenic
regimen in the table. Therefore the cumulative doses used in eight BEACOPP escalated define the maximum of treatment burden: Burden = CY/9600+PROC/5600+DOX/280+ETO/4800.

Figure 20:  Relationship Between Treatment Burden and Risk of sAML

The logit transforms of the observed sAML rates with 95% confidence intervals are plotted versus the burden on the log scale. A linear regression line (weighted for differing precision of sAML rate estimates due to varying patient numbers) is shown. The slope is significantly different from zero (p = 0.0054) indicating that sAML risk increases with the treatment burden.
Figure 21:  Relationship Between Treatment Burden and Risk of sAML

The back-transform of the regression line (Fig. 19) to the original scales is shown. Black bullets correspond to adult studies, green bullets to paediatric ones. The pink bullet represents the current adult standard therapy of six BEACOPP (HD15). The blue bullet is the prediction for 2 OEPA plus 4 DECOPDAC-21.

Six BEACOPP from HD15 is coloured pink. It looks like an outlier, but would also be consistent with the hypothesis that risk of sAML is not only related to the treatment burden, but increases with pronounced haematotoxicity. BEACOPP has pronounced haematotoxicity particularly in cycles 7 and 8. Thus, the low observed leukaemogenicity of six BEACOPP in HD15 may be realistic (Fig. 21).

The blue bullet designates the estimated sAML risk for 2 OEPA plus 4 DECOPDAC-21 on the regression curve. It is in the lower range of sAML risk - within the range observed in paediatric trials (green bullets). The overall low sAML rate reported for the DAL/GPOH trials [Schellong 1997] concerns all stages of HL; only about 1/3 of the reported cases were indeed advanced stage HL in which the sAML risk is concentrated.
Therefore it is reasonable to expect that the introduction of DECOPDAC-21 will not lead to an increase in sAML risk compared to previous DAL/GPOH/EuroNet-PHL trials.
APPENDIX IX DRUG DESCRIPTIONS

CYCLOPHOSPHAMIDE

SECTION 1

Alternative Names
- Cyclophospham
- Endoxana \textsuperscript{TM}
- Cytoxan \textsuperscript{TM}

Mechanism of Action
Oxazaphosphorine alkylating agent. Cyclophosphamide is a prodrug which undergoes biotransformation primarily by hepatic P450 mixed function oxidases to 4-hydroxycyclophosphamide. This metabolite decomposes spontaneously to produce the bifunctional alkylating species phosphoramid mustard. Bi-functional alkylating agents are thought to exert their cytotoxicity by forming intra-strand and inter-strand DNA cross-links at the N7 position of guanine residues. The generation of phosphoramid mustard is accompanied by the production of the metabolite acrolein which is thought to be partially responsible for the dose-limiting urotoxic effects of the drug. Co-administration of the uroprotectactant agent mesna (Sodium mercaptoethane sulphonate) can help prevent urotoxicity.

Considerations prior to Administration
- Concurrent acute urinary-tract infection.
- Urothelial damage following previous cytotoxic chemotherapy or pelvic irradiation.
- Full Blood Count
- Renal function
- Liver function

Adverse Effects

Common
- Dose related nausea and vomiting
- Alopecia
- Chemical or haemorrhagic cystitis if administered without mesna or with inadequate hydration and micturition.

Occasional
- SIADH

Rare
Cardiotoxicity presenting as congestive cardiac failure, pericardial effusion and pericardial tamponade. Possible association with previous anthracycline therapy or mediastinal irradiation.
SECTION 2

Recommended Routes
Intravenous

Administration
By slow bolus into established IV line or by intravenous infusion over 1 hour.
By IV infusion in Glucose 5%, Sodium chloride 0.9% or Glucose/saline.

Dose/schedule
In order to prevent urothelial toxicity, hydration and mesna are required, particularly with higher daily doses of the drug.

Hydration and Mesna
The manufacturers recommend concurrent mesna administration at daily doses of cyclophosphamide in excess of 10 mg/kg. In paediatric clinical practice, mesna is not required until higher daily, or higher cumulative doses per course are exceeded, providing adequate hydration and micturition can be maintained.

Daily cyclophosphamide doses < 10mg/kg (< 300 mg/m²)
No mesna required, maintain fluid intake, encourage frequent micturition.

Daily or total course cyclophosphamide dose 300 mg/m² to 1 g/m²
No mesna required. Intravenous hydration with glucose/saline solution at a rate of 3 l/m²/24 hours commencing with the first cyclophosphamide dose and continuing for at least six hours after last cyclophosphamide dose.

Daily or total course cyclophosphamide dose > 1 g/m²
Intravenous hydration with glucose/saline solution containing mesna at 120% (mg/mg) of the prescribed daily cyclophosphamide dose. Infuse this solution at a rate of 3 l/m²/24 hours, commencing 3 hours before the first cyclophosphamide dose and continuing for a minimum of 12 hours after completion of the last cyclophosphamide infusion.

Interactions
Possible with previous or current exposure to hepatic enzyme inducing agents including phenytoin².
Concurrent dexamethasone treatment may increase cyclophosphamide metabolism²
Concurrent allopurinol administration may decrease cyclophosphamide metabolism²
SECTION 3

Dilution Specification
Cyclophosphamide is reconstituted with Water for Injections BP to produce a final concentration of 20 mg/ml. At this concentration, absorptive losses onto glass, PVC and polypropylene are thought to be negligible.\(^3,4\)

Compatible with glucose 5%, Sodium chloride 0.9% and glucose/saline solutions

Stability
Cyclophosphamide appears to be chemically stable when stored at 4\(\degree\)C. A large body of information exists on stability and compatibility’s of cyclophosphamide in solution.\(^3,4\)

Pharmacokinetics
The pharmacokinetics of cyclophosphamide are complex, and since the anti-tumour activity of the oxazaphosphorines rests with their metabolites, little information can be gained from the pharmacokinetics of the parent drug. In children, the plasma half-life of cyclophosphamide ranges from 2.15 to 8.15 hours. Urinary excretion of cyclophosphamide and its metabolites is largely complete within 24 hours of administration\(^1\). Plasma half-life, apparent volume of distribution and total body clearance increase with increasing dose. Daily administration of cyclophosphamide over 2-4 days results in auto-induction of metabolism but this cannot be demonstrated with repeated 3-weekly courses of the drug.\(^2\)

Pharmacodynamics
The role of individual metabolites in producing tumour responses is still not clear. In children, there is significant inter-patient variation in metabolism and pharmacokinetics\(^1,2\), but the clinical consequences of these variations remain unknown. No correlation between either total plasma alkylating activity or individual metabolite plasma AUC's and tumour response has been demonstrated.

References
1. Pharmacokinetics and metabolism of cyclophosphamide in paediatric patients.
2. Cyclophosphamide metabolism in Children.
DACARBAZINE

SECTION 1

Alternative Names
5-(3,3-dimethyl-1-trazeno)imidazole-4-carboxamide. (DTIC)

Mechanism of Action
- Purine analogue, inhibits purine synthesis
- Atypical alkylator
- Methylates nucleic acids
- Requires metabolic activation

Considerations prior to Administration
Dose modification required in hepatic or renal abnormality

Adverse Effects

Early

Common
- Myelosuppression
- GI upset (nausea and vomiting most common)

Occasional:
- Flu like syndrome

Rare
- Alopecia
- Cutaneous hypersensitivity
- Hepatotoxicity
- Hepatic vein thrombosis

Late

Common
None

Occasional
- Photosensitivity

Rare
- Carcinogenic
- Teratogenic

SECTION 2

Recommended Route
Intravenous

Caution
Protect from light

Administration
Intravenous bolus or infusion
Intra arterial

Dose/Schedule

Interactions
Half life increases when corynebacterium parvum immunotherapy used
Interleukin-2 has been reported to increase the clearance of Dacarbazine².

Overdose
No recommendations

SECTION 3

Dilution Specification and Stability
Dilute 100mg or 200 mg vials in 9.9 or 19.7 ml sterile water respectively
May be diluted in up to 250 ml of dextrose 5% or sodium chloride 0.9%.

Pharmacokinetics
With conventional doses (2.65-6.85 mg/kg) the terminal half-life of DTIC is 41 min, with a volume of distribution of 0.6 l/kg and clearance of 0.9 l/kg/h³.
Half-life values of 0.2 and 2.0 hr have been reported following intravenous infusion of high dose (850-1980 mg/m²) DTIC, with a volume of distribution of 0.4 l/kg. Clearance was 0.6 l/kg/h, with 11 to 63% of the dose recovered unchanged in the urine¹.
Oral absorption is slow and incomplete\textsuperscript{4}. 

\textbf{Pharmacodynamics}  
There are no data available, but activity may depend upon metabolism\textsuperscript{5}.

\textbf{References}  
\begin{enumerate}
\item Buesa JM and Urrechaga E: Clinical pharmacokinetics of high dose DTIC. Cancer Chemotherapy and Pharmacology, 1991, 28, 475-479.
\item Breithaupt H. et al. Pharmacokinetics of dacarbazine (DTIC) and its metabolite 5-aminoimidazole-4-carboxamide (AIC) following different dose schedules. Cancer Chemotherapy and Pharmacology, 1982, 9, 103-109.
\item Loo TL et al. Mechanism of action and pharmacology studies with DTIC (NSC-45388). Cancer Treatment Reports, 1976, 60, 149-152.
\item Trissel LA Handbook of Injectable Drugs 8\textsuperscript{th} Edition ASHP Bethesda, Maryland , USA
\end{enumerate}
DOXORUBICIN

SECTION ONE

Alternative Names
Adriamycin hydrochloride,
14- hydroxydaunorubicin
3- Hydroxyacetyldaunorubicin

Mechanism of Action
Doxorubicin is an anthracycline antibiotic active in all phases of the cell cycle with maximal activity in S phase. It has several modes of action including intercalation to DNA double helix, topoisomerase II mediated DNA damage, production of oxygen-free radicals which cause damage to DNA and cell membranes, and complex formation with iron or copper via the hydroquinone moieties. Iron doxorubicin complexes may contribute to cardiotoxicity by toxic free radical generation.

Considerations prior to Administration
Well established robust venous access. A central venous catheter or indwelling vascular access port is recommended for prolonged infusions to reduce the risk of extravasation.

Full blood count
Liver function tests
Cardiac function
Creatinine, urea, electrolytes

Adverse Effects

Common
- Nausea and Vomiting
- Myelosuppression
- Alopecia
- Mucositis
- Red urine
- Diarrhoea
- Severe tissue damage if extravasated

Occasional
- Increased bilirubin
- Cardiomyopathy

Rare
- Hepatocellular necrosis
- Hyperpigmentation of skin, mucous membranes, nails
- Anaphylaxis, chills, fever
- Renal damage
- Drowsiness
- Conjunctivitis

SECTION TWO

Recommended Routes
Intravenous

CAUTION
A baseline echocardiogram must be done prior to treatment. This should be repeated prior to alternate courses of doxorubicin up to a total cumulative dose of 300mg/m², and before each course thereafter. If the left ventricular shortening fraction (SF) is < 29% to 30% (depending on precise echocardiographic methodology), temporary withdrawal of doxorubicin therapy should be considered. If subsequent testing shows an improvement in SF consider reintroducing doxorubicin. A fall in SF by an absolute value of > 10 percentile units, or a rate of fall of > 2 to 3 percentile units per 100mg/m², despite an SF > 29% to 30%, may also represent significant deterioration. If the patients hepatic function is significantly impaired, doxorubicin dosage reduction should be considered.

Dose/Schedule
Due to the vesicant properties of doxorubicin it is strongly recommended that doxorubicin is given through a central venous line. For ease of administration, to reduce cardiotoxicity, and allow haematological recovery the following schedule is recommended: administration of doxorubicin as a 6 hour infusion (in dextrose 5% or sodium chloride 0.9%)

Interactions
Doxorubicin may interact with the following:
- ICRF-187(Dexrazon)- reduce cardiotoxicity
- Cardiac irradiation - increased cardiac damage
- Actinomycin, mithramycin- cardiomyopathy
- Mercaptopurine- increased hepatotoxicity
- Mitomycin-increased incidence of late congestive heart failure
- Barbiturates - increased doxorubicin elimination\textsuperscript{2,13}
- Verapamil- increased doxorubicin serum levels, reversal of doxorubicin resistance, reduced absorption of verapamil\textsuperscript{2,13}
- Propranolol- increased cardiotoxicity\textsuperscript{2,13}
- Tamoxifen- reduced doxorubicin clearance, modulation of doxorubicin resistance \textsuperscript{2,13}
- Cyclosporin- increased doxorubicin serum levels and myelotoxicity, modulation of doxorubicin resistance \textsuperscript{2,13}
- Carbamazepine, phenytoin, sodium valproate- altered anticonvulsant serum levels \textsuperscript{13}
- Warfarin- increased warfarin effect \textsuperscript{2,13}
- Cimetidine, ranitidine- increased doxorubicin toxicity \textsuperscript{2}
  - Interferon alfa-altered doxorubicin disposition, doxorubicin dose reduction \textsuperscript{2}
  - Paclitaxel-increased toxicity of doxorubicin, if administered after paclitaxel \textsuperscript{32}
- Cyclophosphamide - increases AUC and reduces clearance of parent drug and active metabolite \textsuperscript{38}

The clinical relevance of many of these interactions is unclear.

**Overdose**

Doxorubicin overdosage can prove fatal. Manifestations of overdose may include acute myocardial degeneration, severe myelosuppression and delayed cardiac failure. There is no specific antidote. Symptomatic supportive measures should be implemented \textsuperscript{7,8}.

**SECTION THREE**

**Dilution Specification**

**Preparation**

Doxorubicin supplied in:-

(i) Vials containing 10mg and 50mg freeze dried powder. Reconstitute with water for injection or sodium chloride 0.9% injection adding 5ml to the 10mg vial and 25ml to the 50mg vial to give a 2mg/ml solution \textsuperscript{7,8}.

(ii) Vials containing 10mg and 50mg as a 2mg/ml solution in sodium chloride 0.9% \textsuperscript{14}.

**Dilution**

Doxorubicin is compatible with sodium chloride 0.9% and dextrose 5% \textsuperscript{7,8,14}.

**Stability**

A large body of information is available on the stability of doxorubicin in solution \textsuperscript{15}.

Doxorubicin is compatible with polypropylene \textsuperscript{15,16}, polyvinyl chloride (PVC) \textsuperscript{15,16}, glass \textsuperscript{17}, ethylene vinylacetate (EVA) \textsuperscript{18} and polyisoprene \textsuperscript{19} containers. Solutions should be protected...
from light during storage and administration unless the solution is freshly prepared and the concentration is greater than or equal to 0.5mg/ml. In addition, doxorubicin appears to be chemically stable in polypropylene, PVC, or EVA containers for at least 7 days, when refrigerated or stored at room temperature, protected from light, and diluted in the following:

- Sodium chloride 0.9% at concentrations of 0.1mg/ml to 2mg/ml
- Dextrose 5% at concentrations of 0.1mg/ml to 1.25mg/ml
- Adsorptive losses which may be pronounced at low concentrations can be prevented by storage in polypropylene or when doxorubicin is used at concentrations of at least 0.5mg/ml. In addition, at least a 7 day expiry can be given to doxorubicin reconstituted with water for injection to a concentration of 2mg/ml, stored in polypropylene syringes at 4°C.

**Pharmacokinetics**

The pharmacokinetics of doxorubicin in paediatric patients have been characterised in children, but the large number of protocols and different disease types make it difficult to produce representative summaries. Volume of distribution varies from 20-28 l/kg (approx. 609 l/m²). Anthracyclines are ionised and have low lipid solubility and so do not easily cross the blood-brain barrier. Doxorubicin is metabolised to doxorubicinol, an active metabolite which may occur at higher concentrations than parent drug in plasma. Excretion of drug and metabolites is via further metabolism and/or biliary excretion, with only 5 to 15% excreted by the kidney. Elimination is triphasic, with no effect of age on clearance when normalised for surface area. Terminal half-life is 14 to 50 hours, with clearance varying from 267 to 1443 ml/min/m². Relatively little difference in pharmacokinetics has been observed in infants, but there was a trend to lower systemic clearance than in older children (790 vs. 1500 ml/min/m², p=0.07). Dosage adjustment has been recommended in patients with impaired hepatic function, although this has not been validated in paediatric patients.

**Pharmacodynamics**

Although some data exists regarding the influence of plasma concentrations on the therapeutic and toxic effects of doxorubicin, little of this has been obtained in paediatric patients.

**Additional Information**

A number of ways to reduce cardiotoxicity have been suggested but the use of an alternative dosage schedule of weekly rather than 3 weekly, prolonged infusion schedules, adjuvant cardioprotective agents (e.g. ICRF-187) or the administration of doxorubicin in a liposome formulation, whilst increasingly advocated are not yet of proven utility. The dose/schedule in this document is recommended as a reasonable compromise. Due to the risk of cardiac abnormalities developing many years after doxorubicin therapy, long term cardiac follow up is recommended.
References


4. Bu'Lock, FA. (1995). Anthracyclines and the heart. Primary Cardiology. 21(9), 5-17


7. Pharmacia & Upjohn: Data Sheet Doxorubicin Rapid Dissolution

8. Faulding Pharmaceuticals Ltd (David Bull Laboratories): Data Sheet Doxorubicin hydrochloride


ETOPOSIDE

SECTION ONE

Alternative Names
- VP16
- VEPESID

Mechanisms of Action:
Acts by inhibition of Topoisomerase II which results in DNA strand breakage

Considerations prior to Administration
- FBC
- Renal function
- Liver function

Adverse Effects

Common
- Alopecia
- Myelosuppression

Occasional
- Nausea/vomiting

Rare
- Anaphylactic reactions
- Fever
- Hypotensive reactions
- Headache
- Pruritus
- Pigmentation
- Mucositis
- Second tumours

SECTION TWO

Recommended Routes

1) Intravenous

Administration
- Ampoules 100mg in 5ml
- Dilute to a concentration of 0.4mg/ml in 0.9% Sodium Chloride Injection, give as an IV infusion over 1 to 4 hours. One hour infusion is recommended in order to avoid problems with “line time” during complex chemotherapy regimens.
• Data sheet recommends administration over at least 30 minutes, to avoid hypotensive reaction.\(^3\)
• Due to potential solubility problems care should be taken when mixing with other agents\(^2\).

**Dose/Schedule**

Daily administration has greater anti-tumour efficacy than an equivalent dose given over 24 hours with comparable toxicity + AUC e.g. 100mg/m\(^2\)/day for 5 days versus 500mg/m\(^2\) over 24 hours\(^5,6\), although this is the subject of some debate\(^7\).

Drug is undetectable (< 0.2microgram/ml) in plasma by 48 hours post administration in the majority of patients (important for protocols with marrow reinfusion)\(^8\).

2) **Oral**

• Gelatin capsules 100mg and 50mg
• Injection can be used orally 20mg/ml (5ml amp)

**Administration**

• Short elimination \(t_{1/2}\) suggests twice daily dose
• Prolonged administration is possible but careful monitoring of haematological toxicity is necessary

**Interactions** (IV and Oral preparations)

• No major interactions with the possible exception of warfarin, where etoposide may displace protein bound warfarin or alter it's metabolism, leading to increased prothrombin times\(^1,9\)
• Cisplatin may reduce the clearance of etoposide\(^10\).
• For the related drug tenopiside and possibly for etoposide as well, co-administration of anticonvulsants (Phenytoin or Phenobarbitone) can also result in increase clearance\(^9\).

**Overdosage** (IV and Oral preparations)

• Full supportive measures, including the use of growth factors should be considered.
• Dialysis and haemofiltration are not effective as etoposide is highly plasma protein bound\(^11\).

**SECTION THREE**

**Dilution Specification & Stability**

**Intravenous**

• Manufacturers recommend diluting to 0.25mg/ml, **however a dilution of 0.4mg/ml is stable at room temperature for 96 hours (may precipitate if refrigerated).**
• Only licensed in UK for administration in Normal Saline.
• Poor water solubility therefore formulated in polyethylene glycol solubilising agent which dissolves plastics.
• Use nylon filters + PVC bags or glass bottles
Oral
- IV preparation is stable for 28 days in glass vials.

Pharmacokinetics:
Intravenous

- Medium (range) clearance 26 (14-54) ml/min/m^2, \( t_{1/2b} \) 132 (87-673) mins \(^{8,12,13}\).
- AUC - 3.9 (1.8 - 7.3)mg/ml.min/100mg/m^2.
- Children tend to have shorter elimination half life than adults, possibly because of better renal function and hence higher renal clearance. Clearance can be increased in hypoalbuminaemic patients leading to a reduced AUC. However, since this is associated with a reduction in protein binding, haematologic toxicity may be greater in such patients\(^{14}\).
- Clearance is independent of age\(^{8,15}\) and dose\(^{6} \) (90 - 250mg/m^2) but is more variable at doses > 100mg/m^2 and therapeutic drug monitoring may be indicated.

Oral
- Absorption of capsules differs from IV preparation taken orally\(^{9}\).
- Approximate equivalence ratios:

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Ratio</th>
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</thead>
<tbody>
<tr>
<td>IV: Oral capsules</td>
<td>1:2</td>
</tr>
<tr>
<td>IV: Oral injection</td>
<td>1:1.4</td>
</tr>
<tr>
<td>Oral capsules: Oral injections</td>
<td>1:0.7</td>
</tr>
</tbody>
</table>

- Larger oral doses over 200mg/m^2 are less effectively absorbed than lower doses.
- Medium bioavailability is 48% at dose > 300mg, but 86% at a dose of 100mg. This suggests a saturable step in oral absorption\(^{16}\).
- Oral bioavailability varies, with big inter and intra patient variability\(^{17,18}\).
- Bioavailability is not affected by food.

Pharmacodynamics:
Correlation’s between AUC and/or steady state levels and haematological toxicity has been seen in adult patients\(^{19}\). There is a closer pharmacodynamic relationship with unbound rather than with total concentrations of etoposide in plasma\(^{20,21}\).

REFERENCES
2. Vepesid pharmaceuticals ref KF/KD/0005K Jan 1993
   Bristol Myers Squibb Technical Services
3. Data Sheet Compendium 1995-96 ABPI Data Pharm Publications Ltd


VINBLASTINE

SECTION ONE

Alternative Names:
- Velbe

Mechanisms of Action
Tubulin binding agent producing mitotic arrest.

Considerations prior to Administration
Ensure good, robust, venous access
Hepatic function.

Adverse Effects

Common
- Abdominal pain
- Constipation
- Leucopenia

Occasional
- Peripheral neuropathy (mild)
- Thrombocytopenia and Anaemia

Rare
- Nausea and vomiting
- Alopecia
- Paralytic ileus

SECTION TWO

Recommended Routes
By bolus injection or into the tubing of a fast running intravenous infusion.
Hydration not required.
CAUTION
Vinblastine is a highly vesicant drug, and great care must be taken to avoid extravasation.

Dose/Schedule
Concentration for administration 1 mg/ml.
Recommended dose: 6mg/m² no more frequently than every 7 days.
Maximum dose: 10mg.

Interactions
Nil known

SECTION THREE

Pharmacokinetics:
There are no published data on the clinical pharmacokinetics of vinblastine in children. In adults, vinblastine plasma clearance is greater than that of vincristine, possibly explaining the need to administer higher doses of vinblastine\(^1\). In adults, vinblastine pharmacokinetics are variable and elimination is due to metabolism, urinary and faecal excretion\(^1\). Daily administration in adults can lead to vinblastine accumulation\(^2\). Vinblastine pharmacokinetics may be non-linear and dependent upon hepatic function\(^3\). A dose reduction has been recommended for patients with a raised serum bilirubin\(^4\).

Pharmacodynamics
Unconfirmed studies in adults suggest that patients treated with continuous infusion vinblastine are more likely to develop leucopenia if plasma levels exceed 1ng/ml\(^5\) and that reduced clearance may also be associated with an improved response rate in breast cancer\(^6\).

References
1       Anticancer Res 1992 12:1699-1716
        Pharmacology, bio-analysis and pharmacokinetics of the vinca alkaloids and semi-
        synthetic derivatives (Review)
        O van Tellingen et al
2       Anticancer Research 1992 12:655-660
        Increasing peak levels of vinblastine given in repeated divided doses
        SJ-P van Belle et al
3       Clin Pharmacol Ther 1987 41:61-67
        Intertpatient and intrapatient variability in vinblastine pharmacokinetics
        MJ Ratain et al
4       Cancer Chemotherapy: Principles and Practice, Chapter 10 pp253-275, 1990, JB
        Lippincott, Philadelphia , RA Bender et al (BA Chabner and JM Collins, eds.)
5  Cancer Res 1986 46:4827-4830
   Phase I and pharmacological study of vinblastine by prolonged continuous infusion
   MJ Ratain and NJ Vogelzang

6  Cancer Res 1983 43:1405-1408
   Clinical pharmacokinetics of vinblastine by continuous intravenous infusion
   K Lu et al
VINCRISTINE

SECTION ONE

Alternative Names
- Oncovin

Mechanisms of Action
Tubulin binding agent producing mitotic arrest.

Considerations prior to Administration
- Well established, robust, venous access.
- Hepatic function.
- Neurotoxicity
- Avoid administration at the same time as intrathecal methotrexate.

Adverse Effects

Common
- Alopecia
- Abdominal pain - cramps
- Pain in jaw, bones and joints
- Constipation

Occasional
- Peripheral neuropathy (loss of deep tendon reflexes)
- Autonomic neuropathy (paralytic ileus, urinary retention)

Rare
- Leucopenia, Thrombocytopenia, Anaemia
- Nausea and vomiting
- Raised LFTs (mild and transient)
- Convulsions
- Diplopia and Photophobia

Toxicity related to individual and cumulative dose of Vincristine

SECTION TWO

Recommended Routes
By bolus injection or into the tubing of a fast-running intravenous infusion.
Hydration not required.

CAUTION
Vincristine is a highly vesicant drug, and great care must be taken to avoid extravasation.
DO NOT GIVE INTRATHECALLY

Dose/Schedule
- Variable
- Dose reduction may be necessary if toxicity unacceptable
- The need to limit the total vincristine dose per administration to 2mg is not supported by clinical experience in adults.¹

Interactions
Vincristine plasma clearance can be reduced by nifedipine², cimetidine³ or ranitidine³, and increased by phenobarbitone³. The clinical relevance of these interactions in not clear.

Overdose
Plasmapheresis and phenobarbitone have been reported to be of value in cases of systemic vincristine overdose⁴,⁵.

SECTION THREE

Dilution Specification
- Dextrose 5%, Sodium Chloride 0.9%
- Undiluted at 1 mg/ml but at this concentration there would be increased toxicity with extravasation, therefore can be administered at lower concentrations, e.g. 0.2 mg/ml.

Stability
- Solution 1 mg/ml - 2 years in vial at 2 to 8 °C
- Lyophilised powder - 3 years at 2 to 8 °C. Chemically stable for 30 days after reconstitution when stored at 2 - 8 °C.

Pharmacokinetics
Vincristine is eliminated by hepatic metabolism and biliary excretion⁶. Clearance is variable and may be age dependent.³,⁷

Mean (±SD) pharmacokinetic parameters:³,⁷

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance</td>
<td>431±238, 482±342</td>
<td>ml/min/m²</td>
</tr>
<tr>
<td>t½b</td>
<td>1122±1128, 823±390</td>
<td>min</td>
</tr>
<tr>
<td>AUC</td>
<td>3.2±1.8, 2.9±2.1</td>
<td>mg/ml.min per 1.4mg/m²</td>
</tr>
</tbody>
</table>

In adults, but not children, vincristine neurotoxicity has been related to AUC³,⁸. Also in adults, impaired liver function has been related to reduced clearance and predisposition to...
neurotoxicity\(^9\). A dose reduction has been recommended for patients with a raised serum bilirubin\(^10\).

**References**

   Reappraisal of some dosage adjustment guidelines.
   A Sulkes and JM Collins

2. Cancer 1989 64:1805-1811
   Pharmacokinetics of vincristine in cancer patients treated with nifedipine
   L Fedeli et al

   Pharmacokinetics of vincristine in children and adolescents with acute lymphocytic leukaemia
   WR Crom et al

   Favorable outcome after plasmapheresis for vincristine overdose
   JY Pierga et al

   Vincristine overdose: Experience with 3 patients
   Kosmidis et al

   Pharmacology, bio-analysis and pharmacokinetics of the vinca alkaloids and semi-synthetic derivatives (Review)
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   Vincristine disposition in children with acute lymphoblastic leukaemia
   SSN de Graff et al

   Can severe vincristine neurotoxicity be prevented?
   ZR Desai et al

   The pharmacokinetics of vincristine in man
   HW van den Berg et al

    RA Bender et al (BA Chabner and JM Collins, eds.)