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Intergroup Study (EORTC 20101-23101)

(EudraCT number 2011-005473-22)
(NCT01652261)

Very early FDG-PET/CT-response adapted therapy for advanced stage Hodgkin Lymphoma (H11), a randomized phase III non-inferiority study of the EORTC Lymphoma Group and the Polish Lymphoma Research Group.

Coordinating Groups: **EORTC Lymphoma Group**
EORTC Imaging Group

Collaborative Groups: **Polish Lymphoma Research Group**

Study Coordinator: **Martin Hutchings**
Study Co-coordinators: **Berthe Aleman**
Gustaaf van Imhoff

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Warning:

This is an Intergroup study coordinated by the EORTC. The present protocol is written according to the EORTC template and is fully applicable to all **collaborative groups** (with the exception of EORTC specific chapters or other collaborative group(s) specific appendix and unless otherwise specified).

The chapter 18 is fully applicable to **EORTC investigators** only.

Corresponding items and contact addresses for non EORTC investigators are provided in their **Group specific appendix** that supersedes the contents of chapter 18 (unless otherwise specified).

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Protocol 20101-23101

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Protocol summary

Title of the Study	Very early FDG-PET/CT-response adapted therapy for advanced stage Hodgkin Lymphoma (H11), a randomized phase III non-inferiority study of the EORTC Lymphoma Group and the Polish Lymphoma Research Group.
Objective(s)	The main objective of the trial is to show that ABVD-based response-adapted therapy for advanced-stage Hodgkin lymphoma, with treatment intensification (BEACOPP) in case of a positive FDG-PET after one cycle of ABVD, has non-inferior efficacy compared with the intensive BEACOPP regimen. Secondary objectives include the assessment of the prognostic value of PET after one cycle of BEACOPPesc; of the predictive and prognostic value of serum TARC levels as tumor marker; of treatment related toxicities with a focus on second malignancies, pulmonary toxicities and cardiotoxicity during therapy and during (long term) follow up.
Methodology	This is an open-label, randomized, multicenter phase III non inferiority trial.
Number of patients Number planned (Statistical design)	570 per-protocol patients, i.e. eligible and who start their allocated treatment (285 in each treatment arm). In order to account for the randomization of patients who are not eligible or who do not start their allocated treatment, approximately 600 patients will need to be randomized. The primary trial objective is to test the null hypothesis (H0) of inferiority in terms of freedom from treatment failure (FFTF) of the experimental arm as compared to the reference arm. The null and alternative hypotheses are stated as follows: H0: Hazard ratio of experimental versus standard = 1.87 H1: Hazard ratio of experimental versus standard = 1.00 The null hypothesis corresponds to a 10% difference in FFTF at 5 years, from 87% to 77%. The study sample size is determined to provide 80% power of rejecting the null hypothesis in the alternative of no difference between the two arms, using a log-rank test at the 1-sided 2.5% significance level. This test requires that 80 events be observed at the time of the final statistical analysis. It is estimated that if 570 eligible patients who start their allocated treatment are randomized in the study in a total of 6.2 years, the 80 events should be observed approximately 3.3 years after the entry of the last randomized patient in the study, under H1. Patients will be centrally randomized. A minimization algorithm with a random element will be used for treatment allocation stratifying by institution, stage (III vs. IV), gender and age (<45 vs. ≥45).

Number analyzed	The primary analysis of efficacy is conducted on the per-protocol population, thus 570 patients will be analyzed.
Diagnosis and main criteria for inclusion	* Previously untreated, histologically proven classical Hodgkin lymphoma * Clinical stages III/IV (Ann Arbor, see Appendix F) * Age 18-60 * WHO performance 0-2 (see Appendix C) * FDG-PET/CT scan prospectively planned after one cycle of chemotherapy in all patients * Adequate organ function: ♦ Heart: New York Heart Association (NYHA) functional classification ≤ II (EF ≥ 50% or FS ≥ 25%) No symptomatic coronary heart disease (stable angina pectoris is allowed), No severe uncontrolled hypertension. ♦ Liver: Total Bilirubin ≤ 2 x ULN, alanine aminotransferase (ALT, SGPT) ≤ 3 x ULN, aspartate aminotransferase (AST, SGOT) ≤ 3 x ULN (exception: elevated values due to HL liver involvement). ♦ Kidney: creatinine clearance ≥ 60 ml/min (measured or calculated according to the method of Cockcroft), uric acid, calcium (all <ULN). ♦ Hematological: Hemoglobin ≥ 10 g/dl, Leukocyte concentration ≥ 3.0 x 109/L absolute neutrophil count ≥ 1.5 x 109/L, platelets ≥ 75 x 109 /L. (exception: reduced values related to HL (e.g. BM infiltration, splenomegaly)) Patients with a buffer range from the normal values of +/- 10% for hematology and +/- 10% for biochemistry are acceptable. * Patients of childbearing/reproductive potential should use adequate birth control measures during the whole duration of study treatment. ♦ **Female subjects of childbearing potential** (defined as any female subject unless she meets at least one of the following criteria: Age ≥50 years and naturally amenorrheic for ≥ 1 year {amenorrhea following cancer therapy does not rule out childbearing potential}, premature ovarian failure confirmed by a specialist gynecologist, previous bilateral salpingo-oophorectomy or hysterectomy, XY genotype, Turner syndrome or uterine agenesis.) must: ♦ Agree to have a medically supervised pregnancy test with a minimum sensitivity of 25 mIU/ml not more than 3 days before the start of study medication. This requirement also applies to women of childbearing potential who practice complete and continued abstinence

	♦ **Male subjects must:** ♦ Agree to use condoms throughout study drug therapy, during any dose interruption and for one week after cessation of study therapy if their partner is of childbearing potential and has no contraception. ♦ Agree not to donate semen during study drug therapy and for one week after end of study drug therapy. * Written informed consent according to ICH/EU Good Clinical Practice, and national/local regulations * No pregnancy or breast feeding * No specific contraindications to BEACOPPesc therapy, so therefore: ♦ No poorly controlled diabetes mellitus ♦ No known HIV infection ♦ No chronic active hepatitis B and/or hepatitis C * No concomitant or previous malignancies with the exception of basal cell skin tumors, adequately treated carcinoma in situ of the cervix and any cancer that has been in complete remission for > 5 years * No psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before randomization in the trial. **Important note:** All eligibility criteria must be adhered to, in case of deviation discussion with Headquarters and study coordinator is mandatory. All indicated timelines and absolute values requested by the eligibility criteria must be adhered to. However, a maximum of +/- 10% of the reference value for laboratory parameters and a maximum of +/- 2 days for timelines may be acceptable. Discussion with EORTC Headquarters and study coordinator is encouraged.
Treatment	All patients will have a baseline FDG-PET/CT and diagnostic quality CT scan prior to randomization. All patients will be randomized between: **1. An experimental arm** (very early PET-response adapted), where all patients are initially treated with a single cycle of ABVD, followed by Very early FDG-PET/CT and if negative patients continue on ABVD therapy to a total of six cycles. Very early FDG-PET/CT-positive patients receive 3 cycles of BEACOPPesc followed by another 3 cycles of BEACOPPesc. Mid-treatment evaluation is performed after 4 cycles. In case of treatment failure (less than PR), the patient goes off protocol treatment. **2. A standard arm,** where patients are treated with four cycles of BEACOPPesc followed by 2 cycles of BEACOPPesc. Very early PET/CT is performed after one cycle, but with no therapeutic consequences. Mid-treatment evaluation is performed after four cycles. In case of treatment failure (less than PR), the patient goes off protocol treatment.

	Only patients with residual PET positive disease after chemotherapy will receive radiotherapy (36 Gy/18 fractions to the FDG-PET/CT positive residual mass (es)).
Duration of treatment	**ABVD** ♦ Doxorubicin 25 mg/ m^2 i.v. day 1 and 15 ♦ Bleomycin 10 IU/ m^2 i.v./i.m. day 1 and 15 ♦ Vinblastine 6 mg/ m^2 i.v. day 1 and 15 ♦ Dacarbazine 375 mg/ m^2 i.v. day 1 and 15 (next cycle day 29) **BEACOPP ESCALATED** ♦ Cyclophosphamide* 1250 mg/ m^2 i.v. day 1 ♦ Doxorubicin 35 mg/ m^2 i.v. day 1 ♦ Vincristine 1.4 mg/ m^2 i.v.(max.2mg) day 8 ♦ Bleomycin 10 IU/ m^2 i.v./i.m. day 8 ♦ Etoposide** 200 mg/ m^2 i.v. day 1 to 3 ♦ Procarbazine 100 mg/ m^2 orally day 1 to 7 ♦ Prednisone 40 mg/ m^2 orally day 1 to 14 ♦ Pneumocystis jiroveci prophylaxis with Sulfamethoxazole/Trimethoprim (Cotrimoxazole) ♦ Ciprofloxacin or levofloxazin 500 mg (or similar quinolon antibiotic) per day on day 6 to 12 ♦ G-CSF *** day 4 – recovery leukocytes >$1.0x10^9$/l (next cycle on day 22) *Cyclophosphamide to be given plus Uromitexan (Mesna i.v., on hours 0, 4 and 8 (20% of cyclophosphamide dose, last dose may be given orally) to prevent hemorrhagic cystitis. The patient should also drink 2.5 l of fluid on this treatment day **113 mg Etoposide phosphate is equivalent to 100 mg Etoposide. *** The G-CSF should be given from day 4, until leukocytes recovery (3 days with leukocytes greater than 1.0 x 10^9/l after passing through nadir), or as pegylated G-CSF on day 4.

Criteria for evaluation	
Efficacy	Primary endpoint Freedom from treatment failure (FFTF) will be measured from the date of randomization to the date of first occurrence of any of the following events: ♦ Progression during treatment, or SD after 4 cycles of chemotherapy as defined by International Harmonization Project response criteria (IHP) (according to Cheson, 2007 criteria). ♦ Lack of complete remission at the end of protocol treatment, as defined by the IHP criteria (according to Cheson, 2007); i.e. patients will be considered as failure only if active disease is confirmed by either a biopsy, or a repeated positive PET/CT scan 2-3 months after the previous scan. ♦ Relapse ♦ Death from any cause Patients free of these events are censored at the date of the most recent follow-up. Secondary endpoints include ♦ Response at the end of therapy ♦ Progression-free survival (PFS) ♦ Overall survival ♦ Serum TARC levels at baseline, during treatment and follow up; ♦ Frequency of acute toxicity and long-term toxicity in terms of second malignancies, cardiovascular and pulmonary events
Safety	Assessed according to CTCAE version 4.0

Statistical methods	Two analyses (and corresponding database locks) will be performed: ♦ the first one when the required number of events for the primary endpoint is reached (80 events), ♦ and a second one, after a median follow-up of 10 years, for a long-term evaluation of overall survival and toxicity. The primary analysis of all efficacy endpoints will be performed on the per-protocol population. Sensitivity analyses will be conducted on the intention-to-treat population. Freedom from treatment failure (primary endpoint) as well as overall survival and progression-free survival will be described using Kaplan-Meier curves. These endpoints will be compared between the randomized groups using the Cox's proportional hazards model adjusted for stage (III vs IV), gender and age (<45 vs. ≥45). Effects will be estimated using hazard ratios (HR) and the associated 95% confidence interval. With respect to the primary endpoint, non-inferiority of the experimental arm versus the reference arm will be declared if the upper bound of the 95% confidence interval of the treatment effect HR is below 1.87. The one-sided p-value for the test of the null hypothesis (H0) of inferiority will be provided. The complete response rate will be provided by randomized group with its 95% confidence interval. Safety analyses will be conducted on the set of patients who have started their allocated treatment. For each item of the CTCAE, the worst grade of acute toxicity observed throughout the treatment period will be presented in tables by treatment arm. Adverse events with onset after the end of treatment (follow-up) or with onset during treatment but with same or worse grade during follow-up will be categorized as late adverse events. Cumulative incidence of late adverse events will be analyzed by competing risk methods, with death as a competing risk. A separate analysis will be performed for the following endpoints: ♦ Second malignancies ♦ Cardiovascular disorders - Any CTCAE grade ≥3 ♦ Pulmonary disorders - Any CTCAE grade ≥3 ♦ Any CTCAE grade ≥3
Translational research	This trial will prospectively investigate the value of serum TARC levels for disease activity and prognosis after one and four cycles of chemotherapy and directly compare it to FDG-PET imaging. Also serum samples will be collected after treatment and during follow-up to investigate the value of serum TARC as a marker for disease recurrence. Secondly, other potential prognostic biomarkers will be analyzed on the tissue, serum and DNA samples in a validation and explorative setting

	A separate cardiac side study will be performed primarily to monitor cardiotoxicity during therapy and during (long term) follow up and secondarily to investigate the relationship between acute and late cardiotoxicity, to evaluate tool(s) to detect asymptomatic left ventricular dysfunction and to test how can we identify people at risk to develop late cardiac damage.

Trial organization

- This trial is an Intergroup Trial, jointly conducted by several national/international cancer clinical research groups in different countries of European Union.
- The EORTC is the Sponsor in all participating countries.
- The EORTC is the coordinating group in this trial and therefore centrally manages trial design and activation, attribution of duties and responsibilities between participating research groups, data collection and quality control of data, statistical analysis and publication.
- Each participating group locally manages the notification/submission of all necessary documents to the Competent Authorities and/or Ethics Committees and gets the confirmation of the review by IRB/IEC following the applicable national law.
- This protocol is to be followed by all participating groups. All chapters, except chapter 18, are fully applicable to all groups. Chapter 18 is specific to the EORTC participants. All particularities of participation of each individual group are included in the Group Specific Appendixes annexed at the end of the protocol.
- The patient information sheet and informed consent template is applicable for all participants.
- The participation to this trial is only possible through one of the participating clinical cancer research groups. For contacts and addresses please refer to the Group Specific Appendix of the group of your membership or of your national group (should you have any difficulty in identifying such a group, please contact the EORTC Headquarters).
- Investigators members of several groups participating to the trial should select one of these groups for the framework of this trial and to include all patients through this group. In some cases, because of the national legal framework the choice may be imposed. For EORTC members all patients will be accounted for the membership independently from the group they choose to participate through (see EORTC Policy 10).

This trial is an academic trial without any financial support from the industry.

1 Background and introduction

Hodgkin lymphoma (HL) is a relatively rare lymphoid B-cell malignancy, with an age-adjusted incidence of 1.0 per 100,000 individuals worldwide, occurring two to three times more frequently in developed countries (Ref. 1, Ref. 2). HL is seen in all age groups, but with a peak incidence in patients aged 15-35 years. Approximately 40% of patients have advanced disease at diagnosis, according to the revised Ann Arbor staging criteria (Ref. 3). Genetic and viral factors play a role in the HL etiology, but the pathogenesis of HL is largely unknown. During the last 45 years, HL has developed from an incurable disease to the most curable of all adult oncological diseases. The introduction of total lymphoid irradiation in the 1960's resulted in long-term survival and eventually cures for a large number of patients, including patients with advanced disease (Ref. 4). In the same era, remission rates of almost 50% were achieved using combination chemotherapy with mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) in the treatment of advanced HL (Ref. 5). Combined-modality treatment with combination chemotherapy and radiotherapy resulted in better survival than radiotherapy alone (Ref. 4). However, the large radiation fields resulted in severe late effects, including pulmonary disease, cardiac disease, and second cancer (Ref. 6). MOPP chemotherapy also caused serious late effects, including infertility and a high rate of secondary leukemia and myelodysplastic syndromes (Ref. 7). In the 1970's Bonadonna and colleagues introduced the ABVD chemotherapy regimen (adriamycin, bleomycin, vinblastine, and dacarbazine) (Ref. 8). This regimen resulted in better survival than MOPP and caused much less acute and late toxicity (Ref. 9, Ref. 10). Combined-modality therapy with a brief course of ABVD followed by radiotherapy to the initially involved disease sites became the gold standard treatment for patients with early stage HL, while six to eight cycles of ABVD, with or without consolidation radiotherapy, was widely accepted as the standard regimen for treatment of patients with advanced disease. Although ABVD causes a moderately increased risk of cardiac and pulmonary disease, it is a highly tolerable regimen, with no effect on fertility (of major importance in this young cohort of patients). ABVD can be safely given in an outpatient setting and also in developing countries (Ref. 11).

However, with the classical ABVD therapy, approximately 35% of advanced stage patients respond poorly to therapy or relapse later on, and 15-20% ultimately die of refractory or relapsed disease despite access to subsequent high-dose chemotherapy with autologous stem cell transplantation (HD+ASCT) (Ref. 12, Ref. 13). This has led to a search for more effective regimens for the treatment of advanced HL. In the late 1980's, the Stanford V regimen (doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone) was developed. This regimen had shown to lead to high long-term survival rates in a single-center phase II trial carried out by the Stanford group (Ref. 14, Ref. 15). An Italian cooperative study investigated two chemotherapy regimens; Stanford V and MOPPEBVCAB (mechlorethamine, vincristine, procarbazine, prednisone, epidoxorubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine), none of which were found superior to ABVD (Ref. 16). More recently, the results of a large, randomized intergroup study from the Eastern Cooperative Oncology Group (ECOG) and Cancer and Leukemia Group B (CALGB) showed equal efficacy and slightly higher toxicity of the Stanford V regimen compared with ABVD (Ref. 17). A UK multi-center study compared ABVD with two different multi-drug regimens: Alternating chlorambucil, vinblastine, procarbazine and prednisolone (ChlVPP) with prednisolone, doxorubicin, bleomycin, vincristine, and etoposide (PABIOE); or hybrid ChlVPP/EVA (etoposide, vincristine, and doxorubicin). Neither the alternating nor the hybrid regimen resulted in survival rates superior to those of ABVD (Ref. 18).

1.1 ABVD versus BEACOPPesc

The dose-intensive BEACOPP escalated regimen [bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPPesc)] was developed by the German Hodgkin Study Group (GHSG) (Ref. 19). The GHSG HD9 study showed that BEACOPPesc is superior to alternating cyclophosphamide, vincristine, procarbazine, and prednisone with ABVD (COPP/ABVD) in terms of both freedom from treatment failure (FFTF) and overall survival (OS) (Ref. 20). Follow-up data 10 years after study completion with a median follow-up of 112 months showed FFTF and OS rates 64% and 75% in the COPP/ABVD group versus 82% and 86% in the BEACOPPesc group (Ref. 21). Advanced-stage HL patients are risk-stratified according to the highly validated International Prognostic Score (IPS) which includes the seven unfavorable factors: Age > 45 years, male gender, albumin < 40 g/L, hemoglobin < 10.5 g/dL, stage IV disease, leukocytes > $15x10^9$/L, lymphocytes < $0.6x10^9$/L or < 8% of the white blood cell count (Ref. 22). The 10-year OS after COPP/ABVD and BEACOPPesc were approximately 76% versus 90% in the low-risk group (IPS score 0-2) and 62% versus 84% in the high-risk group (IPS core 3-7). Also of interest, this analysis of the mature data showed that the advantage of BEACOPPesc was particularly evident in the large group of patients with an intermediate prognosis (IPS score 2-3) (Ref. 21). However, the acute and late treatment related toxicity and mortality was significantly higher in the BEACOPPesc than in the COPP/ABVD arms, although there was no difference in treatment related death. The majority of patients become infertile after eight cycles of BEACOPPesc. In the HD9 trial the estimated 10-year cumulative incidence rate for AML/MDS was lower for patients receiving COPP/ABVD (0.4%) as compared to BEACOPPesc (3.2%; log-rank test: P= .030) (Ref. 21, Ref. 23). This led to the HD12 trial, where eight cycles of BEACOPPesc was compared to four cycles of BEACOPPesc followed by four cycles of the less dose-intensive BEACOPPbaseline regimen (4+4). Data from the HD12 trial clearly indicate non-inferiority of the 4+4 arm, but with no clear advantage in terms of toxicity, the GHSG has hitherto still considered eight cycles of BEACOPPesc their standard treatment for advanced HL (Ref. 24). However, recent results from the HD15 trial, presented at the Annual Meeting of the American Society of Hematology, have shown superiority of both safety and efficacy of 6 cycles BEACOPPesc over 8 cycles BEACOPPesc. For this reason, 6 x BEACOPPesc is now the GHSG standard treatment for advanced stage disease and to be considered the most effective therapy for this patient group. In the HD15 trial, 2182 patients were randomly assigned to receive either 8 x BEACOPPesc, 6 x BEACOPPesc, or 8 x BEACOPP14 (BEACOPP in baseline doses at 14-day intervals). After a median follow-up of 48 months, there were 53 deaths (7.5%) in the 8 BEACOPPesc group, 33 (4.6%) in the 6 BEACOPPesc group and 37 (5.2%) in the 8 BEACOPP14 group. The higher number of deaths in the 8 BEACOPPesc group mainly resulted from acute toxicity of chemotherapy (15 vs. 6 vs. 6) and second neoplasms (13 vs. 5 vs. 8). There were 72 second cancers including 29 secondary acute myeloid leukemias and myelodysplastic syndroms, 19 (2.7%) after 8 BEACOPPesc, 2 (0.3%) after 6 BEACOPPesc and 8 (1.1%) after 8 BEACOPP14. FFTF at 5 years was 84.4% in the 8 BEACOPPesc group, 89.3% in the 6 BEACOPPesc group, and 85.4% in the 8 BEACOPP14 group, respectively. Accounting for planned interim analyses, both 97.5 % repeated CIs for the hazard ratio excluded the non-inferiority margin. Overall survival at five years was 91.9%, 95.3%, and 94.5%, and was also significantly better with 6 BEACOPPesc compared to 8 BEACOPPesc. PFS results were similar to FFTF. So 6 x BEACOPPesc followed by *:* FDG-PET/CT-guided RT (see below) is the most effective therapy for advanced stage HL ever presented, and significantly less toxic compared to 8 x BEACOPPesc (Ref. 25).

While BEACOPPesc is the standard therapy for advanced HL in Germany and in some European institutions and groups, ABVD is still accepted as the gold standard in most countries. There are basically two different strategies for the treatment of advanced HL:

1) Start with ABVD and thereby achieve cure for the majority of patients with a relatively mild risk profile, but accept a relapse rate of 30-35% in a curable disease, and accept that the relapsing patients be subjected to the severe toxicity of high-dose salvage therapy. Roughly half of the relapsing patients will be cured with HD+ASCT (Ref. 26, Ref. 27, Ref. 28).

2) Start with BEACOPPesc in order to achieve cure for the highest possible number of patients with first-line therapy, accept the excess acute and late toxicity for the majority of patients, who would have been cured with a less intensive regimen.

Two Italian trials directly compare BEACOPPesc and ABVD in patients with advanced HL. The GISL (Gruppo Italiano Studio Linfomi) HD2000 study showed a significantly higher progression-free survival (PFS) with BEACOPPesc than with ABVD. After a median follow-up of 41 months, the five-year PFS and OS was 68% and 84%, respectively, for the 99 patients who received 6 cycles of ABVD versus 82% and 92%, respectively, for the 98 patients who received 4 cycles of BEACOPPesc followed by two cycles of BEACOPPbaseline. The difference in OS was not statistically significant (Ref. 29). The FM-GITIL-IIL (Fondazione Michelangelo, Gruppo Italiano Terapie Innovative nei Linfomi, Intergruppo Italiano dei Linfomi) study compared six to eight cycles of ABVD (166 patients) with BEACOPP 4+4 (155 patients) followed by a pre-planned HD-ASCT to poor responders. After a median follow-up of 61 months the 7-year rate of freedom from first progression was 85% in the BEACOPP group and 73% in the ABVD group ($P = 0.004$), and the 7-year rate of event-free survival was 78% and 71%, respectively ($P = 0.15$). The study was not powered to detect OS differences (89% versus 84%) (Ref. 30). There were five deaths due to treatment toxicity in the BEACOPP group versus one toxic death in the ABVD group (Ref. 31). The most recent toxicity data from our own EORTC/GELA 20012 advanced stage HL study, in which patients were randomized to either ABVD (8 cycles) or BEACOPP (4+4), confirm the high toxicity of BEACOPP treatment, with a 6-7 fold frequency of SAEs, life-threatening events and hospitalizations (unpublished data). The final efficacy analysis of this pivotal study is yet to be published. Until then, there is only indirect evidence of the OS benefit from BEACOPPesc. However, looking at the results from the HD9, GISL HD2000 and FM-GITIL-IIL studies together, and considering the available knowledge about the results of salvage second line therapy, the OS benefit of BEACOPP seems to be on the order of 7-8%, meaning that the number needed to treat with BEACOPPesc is approximately 15 in order to have one more surviving patient than with ABVD.

So while the efficacy of BEACOPPesc is proven beyond doubt, we cannot conclude that is the standard first line treatment in all patients with advanced stage HL. This would disregard the fact that the vast majority of patients cured by BEACOPPesc can also be cured by a more manageable and much less toxic regimen. On the other hand, the cure rates of ABVD are not satisfactory considering that HL is the most chemosensitive and curable of all cancers and affects predominantly young people. While ABVD and BEACOPPesc are the best available therapy combinations for HL, both regimens are still in search of their rightful positioning in the first-line strategy.

1.2 The role of radiotherapy in advanced stage HL

Not all advanced stage HL patients need radiotherapy, but despite a considerable number of trials it is not entirely clear in which patients radiotherapy can be avoided. In a previous study from our own group which included patients with advanced HL (EORTC 20884; 1989-2000), patients in complete remission (CR) after mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine (MOPP-ABV) were randomly assigned to receive either no further treatment or involved-field radiotherapy. Patients in partial remission (PR) were treated with involved-field radiotherapy. Patients in a CR after 6-8 cycles of MOPP-ABV hybrid chemotherapy did not benefit from the addition of involved-field radiotherapy. Patients in PR after chemotherapy, however, probably did benefit from radiotherapy since the event-free and overall survival rates of these patients treated with involved-field radiotherapy were comparable to the event-free and overall survival rates in patients in CR after chemotherapy. It is

important, however, to realize that in this study, FDG-PET/CT was not used for post-chemotherapy evaluation; the definition of CR was very strict and based on CT scans only (Ref. 32, Ref. 33).

In a GELA study, patients with stage IIIB/IV HL in CR after six cycles of chemotherapy were randomly assigned to receive either radiotherapy or two additional cycles of chemotherapy (H89 trial). Radiotherapy was shown not to be superior to the two cycles of consolidation chemotherapy in this study (Ref. 34, Ref. 35). These studies support the notion that radiotherapy can be omitted in advanced HL patients in CR after chemotherapy.

Since the EORTC 20884 and the GELA H89 studies were performed, the definition of a CR has changed, to include patients with a good treatment response who still have a residual, FDG-PET-negative mass after completion of therapy (Ref. 36). Such patients were previously considered in CRu (Complete Remission unconfirmed) or PR (Ref. 37). Brepoels and colleagues have validated the revised response criteria in an ABVD-treated cohort of HL patients, and showed that patients in CR according to the revised IHP criteria have a prognosis equally good as those in CR according to the old criteria (used in the EORTC 20884 trial) (Ref. 38). This is in line with a large number of studies, which have consistently shown a very high negative predictive value of post-chemotherapy FDG-PET in HL (Ref. 39, Ref. 40, Ref. 41, Ref. 42, Ref. 43).

The HD12 study from the GHSG (1999-2003; see also above) not only posed a chemotherapy question but was also performed to test whether consolidative radiotherapy (RT) in the region of initial bulky disease and of residual disease is necessary after effective chemotherapy. Patients with previously untreated HL, stage IIB (large mediastinal mass and/or extranodal lesions) or stage III-IV, were randomized according to a factorial design between: 8 x BEACOPPesc and RT, 8 x BEACOPPesc and no RT, 4 x BEACOPPesc + 4 x BEACOPPbaseline and RT, 4 x BEACOPPesc + 4 x BEACOPPbaseline and no RT. Patients randomized to the RT arms were to receive radiotherapy to the region of initial bulky disease (≥5 cm) and to residual disease (≥1.5 cm). Again, this was based on CT scans only, as FDG-PET was not a part of the study.

The recently published final analysis showed FFTF was inferior without radiotherapy (90.4% v 87%; difference,-3.4%; 95% CI, -6.6% to -0.1%), particularly in patients who had residual disease after chemotherapy (difference, -5.8%; 95% CI, -10.7% to -1.0%), but not in patients with bulk disease in complete response after chemotherapy (difference, -1.1%; 95% CI, -6.2% to 4%). There were no differences in OS when comparing the radiotherapy versus the non-radiotherapy arms. The authors concluded that their results do not support the omission of consolidation radiotherapy for patients with residual disease (Ref. 81). However, because of the irradiation of 10% of patients in the non-radiotherapy arms, equivalent effectiveness of a non-radiotherapy strategy could not be proven (Ref. 44).

In the UK LY09 study (a randomized comparison between three different chemotherapy regimens for advanced HL), 817 patients were included and 702 patients of whom achieved a satisfactory response with the vast majority a CR or CRu. The protocol gave advice on radiotherapy, but it was a local decision whether or not to give consolidation radiotherapy. Radiotherapy was given to 300 of the 702 patients. The long-term follow-up results showed a clear advantage for the patients who received radiotherapy, in terms of both PFS and OS. As the selection of patients for consolidation radiotherapy was not based on randomization, it is obviously not possible to exclude a selection bias in favor of the patients who received radiotherapy (Ref. 45).

An Italian study by Picardi and coworkers gave cause for some concern, as 160 patients with bulky HL and a negative FDG-PET after six cycles of VEBEP (vinblastine, etoposide, bleomycin, epirubicin, prednisone) were randomized to receive radiotherapy or no further treatment. At 18 months of follow-up, 14% of patients in the no radiotherapy arm had relapsed versus only 2.5% in the radiotherapy arm (Ref. 46).

In the GHSG HD15 study (see above), patients with advanced stage HL were randomized to three different BEACOPP regimens. After completion of chemotherapy, patients in PR with a persistent mass measuring 2.5 cm or more were assessed by FDG-PET. Only patients who were positive on centrally-reviewed FDG-PET scan received additional radiotherapy (RT) with 30 Gy. An interim analysis (median follow-up only 18 months) showed a very high negative predictive value for FDG-PET (94%; 95% confidence interval (CI), 91%-97%). At 12 months, progression free survival for FDG-PET-negative patients was 96% and 85% for those who were FDG-PET-positive (Ref. 47). FDG-PET scans performed after chemotherapy were centrally reviewed in 822 patients of whom 739 were in PR with residual mass ≥ 2.5 cm having no other exclusion criteria: 548 patients were FDG-PET-negative (74.2%) and 191 were FDG-PET-positive (25.8%). In the final analysis, after 48 months of median follow-up, PFS was comparable between patients in CR or those in FDG-PET-negative PR after chemotherapy with 4-year PFS rates of 92.6% and 92.1%, respectively. Only 11% of all patients in HD15 received additional RT as compared to 71% in the prior HD9 study. According to the HD15 results, consolidation radiotherapy can be omitted in BEACOPPesc treated patients with PET negative residual disease without increasing the risk for progression or early relapse compared with patients in CR (Ref. 25).

A recent study from the British Colombia Cancer Agency presented at the 2011 annual meeting of the American Society of Clinical Oncology analysed the results of a 5-year experience using post-chemotherapy PET/CT to select patients for consolidation radiotherapy. A total of 163 patients were included in the study, they were all treated with ABVD. Only patients with a PET-positive residual mass larger than 2 cm (19% of patients) were given radiotherapy. The vast majority of patients who were PET-negative and did therefore not receive radiotherapy had a 3-year PFS of 89% (Ref. 86).

Over the years different radiation doses have been used in HL treatment roughly varying from dose equivalents of 20 to 40 Gy in 2 Gy fractions. About two decades ago there was some debate about evidence for a radiation dose response relationship (Ref. 48, Ref. 49). Brincker et al. concluded, correctly we think, that there is no evidence for a dose response relationship above the dose of 32.5 Gy in case of radiation as a single modality treatment. Furthermore, there is some indication that the sensitivity to changes in dose per fraction is low. This allows the fraction size to be selected from considerations of the level of late treatment related morbidity (Ref. 49).

Nowadays radiation doses of 30 to 36 Gy in fractions of 2 Gy are common practice in patients with initial bulky disease and/or a partial response after chemotherapy (Ref. 32, Ref. 47, Ref. 50).

In conclusion, radiotherapy should not be given to patients in CR after adequate chemotherapy, whereas patients with a FDG-PET-positive residual mass may benefit from limited radiotherapy. Radiotherapy should be delivered only to residual lymphoma masses containing FDG-PET-positive areas after the end of chemotherapy.

1.3 Patient-tailored therapy

In order to minimise the harmful effects of therapy while optimising the efficacy, ideally treatment should be tailored to the individual patient's needs. Although a substantial number of HL patients failing first line treatment may still be cured by second line treatment, overall survival is markedly reduced among patients who do not respond to, or relapse after first line therapy. Patients who need highly intensive second-line treatment are at further increased risk of treatment-related illness and death (Ref. 23). Many experts believe that cure for HL depends on effective and rapid annihilation of suspected clonogenic HL stem cells responsible for generating and maintaining the Hodgkin and Reed-Sternberg (HRS) cells and their microenvironment (Ref. 51). The stem cells are thought to be more resistant to therapy than HRS cells and more likely to mutate into resistant clones. According to this hypothesis, chemo-resistance can develop early during first-line therapy. This is the theoretical background for the GHSG to develop their BEACOPPesc regimen, aiming at preventing of chemo-resistance by intensifying treatment right from the

start of treatment. But as described above, this strategy neglects the fact that a large majority of the patients can be cured by ABVD (Ref. 13) and thereby avoids the severe toxicities including secondary leukaemia and infertility. Ideally, patient-tailored therapeutic strategies could be based on precise pre-treatment prognostic stratification and predictive markers. But despite accurate staging and use of the prognostic markers such as the IPS, no tools can reliably identify those advanced stage patients who will be undertreated with first-line ABVD and thus be eligible for up-front BEACOPPesc (Ref. 52). Nevertheless, a relevant treatment adaptation is best performed as early as possible if we keep in mind the hypothesis of early chemo-resistance.

1.4 Prognostic value of early FDG-PET/CT

Positron emission tomography (PET) is a functional imaging modality based on measurements of events related to the decay of positron emitting radioactive nuclides. The most common isotopes used in PET tracer molecules are ^{15}O, ^{13}N, ^{11}C and ^{18}F (Ref. 53). PET tracers of relevance to oncology target glucose metabolism, hypoxia, blood flow, proliferation, amino acid transport, protein synthesis, DNA synthesis, apoptosis, and specific receptors. The glucose analogue 2-[^{18}F]fluoro-2-deoxyglucose (FDG), is the most widely used PET tracer and it is estimated that FDG-PET accounts for 90% of all clinical PET studies. Most state-of-the-art oncology and haematology facilities have access to FDG-PET/CT, which is considered part of the standard of care for staging and post-treatment evaluation of HL patients (Ref. 54).

FDG-PET has been shown to accurately predict PFS in advanced stage HL after only two cycles of ABVD chemotherapy, when ABVD treatment is completed according to the original treatment strategy (Ref. 55, Ref. 56, Ref. 57, Ref. 58). The PFS rate is 90-100% in patients FDG-PET-negative after two cycles of ABVD and very low, 10-20% among early FDG-PET-positive patients. The largest study to date of the prognostic value of early FDG-PET in ABVD treated advanced stage HL showed that the prognostic value of FDG- PET is independent of the IPS score (Ref. 59). In other words, patients who become FDG-PET-negative early during ABVD treatment have an excellent prognosis regardless of their IPS score, and patients who still have pathological FDG uptake after two therapy cycles have a very high risk of treatment failure, also regardless of the IPS. This independency of early interim FDG-PET from the IPS was confirmed in a recently published study by Cerci and colleagues (Ref. 60).

An international prospective study of 126 HL patients, who were FDG-PET/CT scanned at baseline and after both one and two cycles of chemotherapy, was concluded recently. Preliminary results from this study were presented at the International Conference on Malignant Lymphoma, Lugano in June 2011. The results showed that FDG-PET/CT was negative in 70% of patients after the first cycle (2-year PFS = 100%) and 30% were FDG-PET/CT positive (2-year PFS = 34%). After the second cycle, 85% of the patients were FDG-PET/CT negative (2-year PFS = 89%) and 15% were FDG-PET/CT positive (2-year PFS = 22%). All patients who were FDG-PET/CT negative after the first cycle stayed FDG-PET/CT - negative after the second cycle and entered a durable CR. So patients responding well to HL chemotherapy can be accurately identified by FDG-PET/CT after only one cycle of chemotherapy, and the negative predictive value is higher after one cycle than after two cycles (Ref. 61).

It is important to note that the prognostic value of early FDG-PET/CT (after 2 cycles of chemotherapy) has been shown in groups of patients where the full course of treatment has been completed, unaffected by the early FDG-PET/CT results. A positive very early FDG-PET /CT (after 1 cycles of chemotherapy) seems to be a clear sign of therapy resistance. A negative very early FDG-PET/CT is a sign of metabolic remission and a surrogate marker for treatment sensitivity and final response to the full treatment. A negative very early FDG-PET/CT does not mean the patient is cured. This should be kept in mind when considering treatment strategies where a negative very early FDG-PET/CT is used to guide de-escalation to a regimen less intensive than the regimen to which the very early FDG-PET/CT shows sensitivity.

1.5 Early FDG-PET-response adapted therapy - ongoing trials

Although we know that a very early positive FDG-PET can accurately predict the treatment response, we do not know if patients will benefit from very early treatment adaptation according to the results of very early FDG-PET. This is currently being investigated in a number of protocols:

In the United Kingdom and the Nordic countries, a randomized trial to assess Response Adapted Therapy using FDG-PET imaging in patients with advanced Hodgkin Lymphoma (RATHL) is currently being performed. In this trial all patients, regardless of IPS, receive two cycles of ABVD followed by a FDG-PET scan. If they are early FDG-PET-negative, they are randomized to four more cycles of ABVD versus four cycles of AVD (omission of Bleomycin). If early FDG-PET-positive, they receive four cycles of BEACOPPesc or the variant BEACOPP14. If a mid-treatment FDG-PET is again positive, patients are regarded as refractory and shifted to a salvage regimen. If the mid-treatment FDG-PET is negative, they receive another two cycles of BEACOPP. The main question in this trial is whether BEACOPPesc retains its survival benefit if given after two cycles of ABVD. This will not be clearly answered, since there is no control arm for the early FDG-PET-response adapted therapy question (Ref. 62).

Two Italian trials investigate FDG-PET-response adapted therapy in advanced stage HL. They both start out with two cycles of ABVD followed by a FDG-PET which determines the further course of treatment. In the first trial (GITIL HD0607), the FDG-PET-negative patients continue on standard ABVD therapy while FDG-PET-positive patients receive three cycles of BEACOPPesc. A repeat FDG-PET decides whether patients should continue with three cycles BEACOPPbaseline (FDG-PET negative patients) or go to high-dose chemotherapy with stem cell support or even non-myeloablative allogeneic bone marrow transplant (Ref. 63). The second trial, from the Italian Lymphoma Intergroup (IIL HD0801), takes the early FDG-PET-positive patients to a regimen containing four cycles of IGEV (ifosfamide, gemcitabine, vinorelbine and prednisolone) followed by HD chemotherapy with double autologous stem cell transplant (Ref. 64).

A trial led by the SWOG and the CALGB is being performed with a design very similar to the design of the GITIL (Ref. 65). The RATHL trial, both Italian trials and the US intergroup trial are non-randomized as far as the FDG-PET-response adapted therapy question is concerned. All these trials use the interim PET after two cycles. With the hypothesis of early chemoresistance in mind, the timing of treatment modification after two cycles could be too late.

In the current phase III GHSG HD18 trial, all patients, regardless of IPS, receive two cycles of BEACOPPesc followed by FDG-PET. Originally, patients with a negative FDG-PET were randomized to either the GHSG standard treatment (six additional cycles of BEACOPPesc) or only two additional cycles of BEACOPPesc. Patients with a positive FDG-PET will be randomized between standard treatment and addition of Rituximab to the following six cycles of BEACOPPesc (Ref. 66). The treatment protocol of HD18 was recently amended in the wake of the recent results of the HD15 trial. For the remainder of the trial, no patient will receive more than six cycles of BEACOPPesc. A concern for this study is data that suggest a lower prognostic value of early FDG-PET during BEACOPPesc therapy than during ABVD therapy (Ref. 67, Ref. 68). Also, with this strategy, all patients will still face the toxicity of BEACOPPesc.

The recently started AHL 2011 trial from the French GELA group (Groupe d'Etude des Lymphomes de l'Adulte) is also a randomized non-inferiority trial, using BEACOPPesc upfront. Patients in the standard arm will receive six cycles of BEACOPPesc, while patients in the experimental arm will have their treatment de-escalated to ABVD if PET-negative after two cycles of BEACOPPesc. This trial will markedly reduce the amount of BEACOPPesc therapy given to early PET-negative patients and investigate if these patients can be effectively cured despite de-escalation to ABVD (O Casasnovas, personal communication). The GELA trial is supported by the Israeli phase II experience of Avigdor and coworkers, who prospectively studied a small cohort of 45 patients with advanced HL and more than two

IPS risk factors. All patients were given BEACOPPesc upfront, and the treatment was de-escalated to four cycles of ABVD if a FDG-PET after two cycles of BEACOPPesc was negative. The results showed a four-year PFS rate of 87% in the early PET-negative group (31 patients).

In summary, there are trials investigating the value of escalating to BEACOPPesc in case of a positive FDG-PET after two cycles of ABVD. These trials will increase our understanding of FDG-PET-response adapted therapy, but since they are phase II studies with no comparator, any comparison with the current standard strategies will not be possible. Two randomized studies, one ongoing study (GHSG HD18) and one recently started study (GELA AHL2011) will attempt to show non-inferiority of abbreviating or de-escalating therapy in case of a negative FDG-PET after two cycles of BEACOPPesc. All patients in the experimental arms of these trials will still be subject to the toxicity of BEACOPPesc, although to a lower number of cycles than in the standard approach with eight treatment cycles.

1.6 Hypothesis of the trial

The current trial is based on the hypothesis that those patients with advanced HL who might be cured with ABVD chemotherapy can be selected very early on by a negative FDG-PET/CT scan after one cycle of ABVD, and that a switch to BEACOPPesc treatment for patients FDG-PET/CT positive after one ABVD cycle will be early enough to avoid compromising a possible superior effectivity of BEACOPPesc.

The hypothesis will be tested by a randomized comparison of two treatment strategies. In the experimental strategy arm of the trial patients will start with ABVD and after one cycle of ABVD continue with ABVD in case of a very early negative FDG-PET/CT scan or switch to BEACOPPesc in case of a very early positive FDG-PET/CT scan. In the standard strategy arm all patients will be treated with BEACOPPesc.

1.7 TARC translational research

In this trial, analysis of serial serum Thymus and Activation-Regulated Chemokine (TARC) levels is the main focus of translational research. TARC is specifically secreted by Hodgkin Reed Sternberg tumor cells in more than 90% of cases and can be used as a tumor cell specific marker for disease activity. Data from the University Medical Center Groningen have shown that serum levels correlate with tumor extensiveness and that plasma TARC during and after treatment correlate with clinical response (Ref. 82). Recent data showed that TARC levels after one cycle of chemotherapy could already predict final treatment response with high positive predictive value (Ref. 83). This trial will prospectively investigate the value of TARC levels for disease activity and prognosis after one and four cycles of chemotherapy and directly compare it to FDG-PET/CT imaging. Also serum samples will be collected after treatment and during follow-up to investigate the value of serum TARC as a marker for disease recurrence (see Chapter 10.1 on TARC and Biomarker Translational Research).

1.8 Cardiac Translational research

Both chemotherapy and radiotherapy for HL may cause early and late cardiovascular toxicity. Whereas cardiotoxicity following radiotherapy is usually observed from 5-10 years of follow-up and onwards anthracycline-related toxicity may be observed at different intervals after therapy.

Because of the extensive use of cardiotoxic therapy in the treatment of several malignancies (not only in lymphoma but also for instance in breast cancer) there is growing interest in possibilities to monitor myocardial damage from anti-cancer therapy, to guide initiation of cardio-protective therapy and to identify people at increased risk of cardiovascular toxicity. Cardiac biomarkers and genetic variability could be of great importance in cardiovascular risk prediction following anti-cancer therapy.

This trial will prospectively monitor cardiotoxicity during therapy and during (long term) follow up. We will try to investigate the relationship between acute and late cardiotoxicity, and to evaluate tool(s) to detect asymptomatic left ventricular dysfunction. Serum samples will be collected after treatment and during follow-up for this purpose (see chapter 10.2 Cardiac Translational study).

2 Objectives of the trial

2.1 General Objectives

2.1.1 Primary objective

- The main objective of the trial is to show that ABVD-based response-adapted therapy for advanced-stage Hodgkin lymphoma, with treatment intensification in case of a positive FDG-PET/CT after one cycle of ABVD, has non-inferior efficacy compared with the intensive BEACOPPesc regimen.

2.1.2 Secondary objectives

- To assess the prognostic value of FDG-PET/CT after 1 cycle of BEACOPPesc (standard arm).
- To assess the prognostic value of serum TARC levels as tumor marker.
- To monitor treatment related toxicities with a focus on second malignancies, pulmonary toxicities and cardiotoxicity during therapy and during (long term) follow up.

2.2 End-points

2.2.1 Primary end-point

- Freedom from treatment failure (FFTF) (definition see chapter 7)

2.2.2 Secondary end-points include

- Response at the end of therapy (chemotherapy and radiotherapy, whenever applicable);
- Progression-free survival (PFS) (definition see chapter 7);
- Overall survival (definition see chapter 7);
- Serum TARC levels at baseline, during treatment and follow up;
- Frequency of acute toxicity and long-term toxicity in terms of second malignancies, cardiovascular and pulmonary events.

3 Patient selection criteria

Selection criteria have to be checked within two weeks before randomization.

Previously untreated, histologically proven classical Hodgkin lymphoma

Clinical stages III/IV (Ann Arbor, see Appendix F)

Age 18-60

WHO performance 0-2 (see Appendix C)

FDG-PET/CT scan prospectively planned after one cycle of chemotherapy in all patients

Adequate organ function:

- Heart:
  - New York Heart Association (NYHA) functional classification ≤ II (EF ≥ 50% or FS ≥ 25%)
  - No symptomatic coronary heart disease (stable angina pectoris is allowed)
  - No severe uncontrolled hypertension
- Liver: Total Bilirubin ≤ 2 x ULN, alanine aminotransferase (ALT, SGPT) ≤ 3 x ULN, aspartate aminotransferase (AST, SGOT) ≤ 3 x ULN (exception: elevated values due to HL liver involvement)
- Kidney: creatinine clearance ≥ 60 ml/min (measured or calculated according to the method of Cockcroft), uric acid, calcium (all <ULN)
- Hematological: Hemoglobin ≥ 10 g/dl, Leukocyte concentration ≥ 3.0 x 109/L absolute neutrophil count ≥ 1.5 x 109/L, platelets ≥ 75 x 109 /L. (exception: reduced values related to HL (e.g. BM infiltration, splenomegaly))

Patients with a buffer range from the normal values of +/- 10% for hematology and +/- 10% for biochemistry are acceptable.

Patients of childbearing/reproductive potential should use adequate birth control measures during the whole duration of study treatment.

- Female subjects of childbearing potential (defined as any female subject unless she meets at least one of the following criteria: Age ≥50 years and naturally amenorrheic for ≥ 1 year {amenorrhea following cancer therapy does not rule out childbearing potential}, premature ovarian failure confirmed by a specialist gynecologist, previous bilateral salpingo-oophorectomy or hysterectomy, XY genotype, Turner syndrome or uterine agenesis.) must:
  - Agree to have a medically supervised pregnancy test with a minimum sensitivity of 25 mIU/ml not more than 3 days before the start of study medication. This requirement also applies to women of childbearing potential who practice complete and continued abstinence
- Male subjects must:
  - Agree to use condoms throughout study drug therapy, during any dose interruption and for one week after cessation of study therapy if their partner is of childbearing potential and has no contraception
  - Agree not to donate semen during study drug therapy and for one week after end of study drug therapy
- Written informed consent according to ICH/EU Good Clinical Practice, and national/local regulations

- No pregnancy or breast feeding
- No specific contraindications to BEACOPPesc therapy, so therefore:
  - No poorly controlled diabetes mellitus
  - No known HIV infection
  - No chronic active hepatitis B and/or hepatitis C
- No concomitant or previous malignancies with the exception of basal cell skin tumors, adequately treated carcinoma in situ of the cervix and any cancer that has been in complete remission for > 5 years
- No psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before randomization in the trial

Important note: All eligibility criteria must be adhered to, in case of deviation discussion with Headquarters and study coordinator is mandatory. All indicated timelines and absolute values requested by the eligibility criteria must be adhered to. However, a maximum of +/- 10% of the reference value for laboratory parameters and a maximum of +/- 2 days for timelines may be acceptable. Discussion with EORTC Headquarters and study coordinator is encouraged.

4 Trial Design

This is an open-label, randomized, multicenter phase III non inferiority trial.

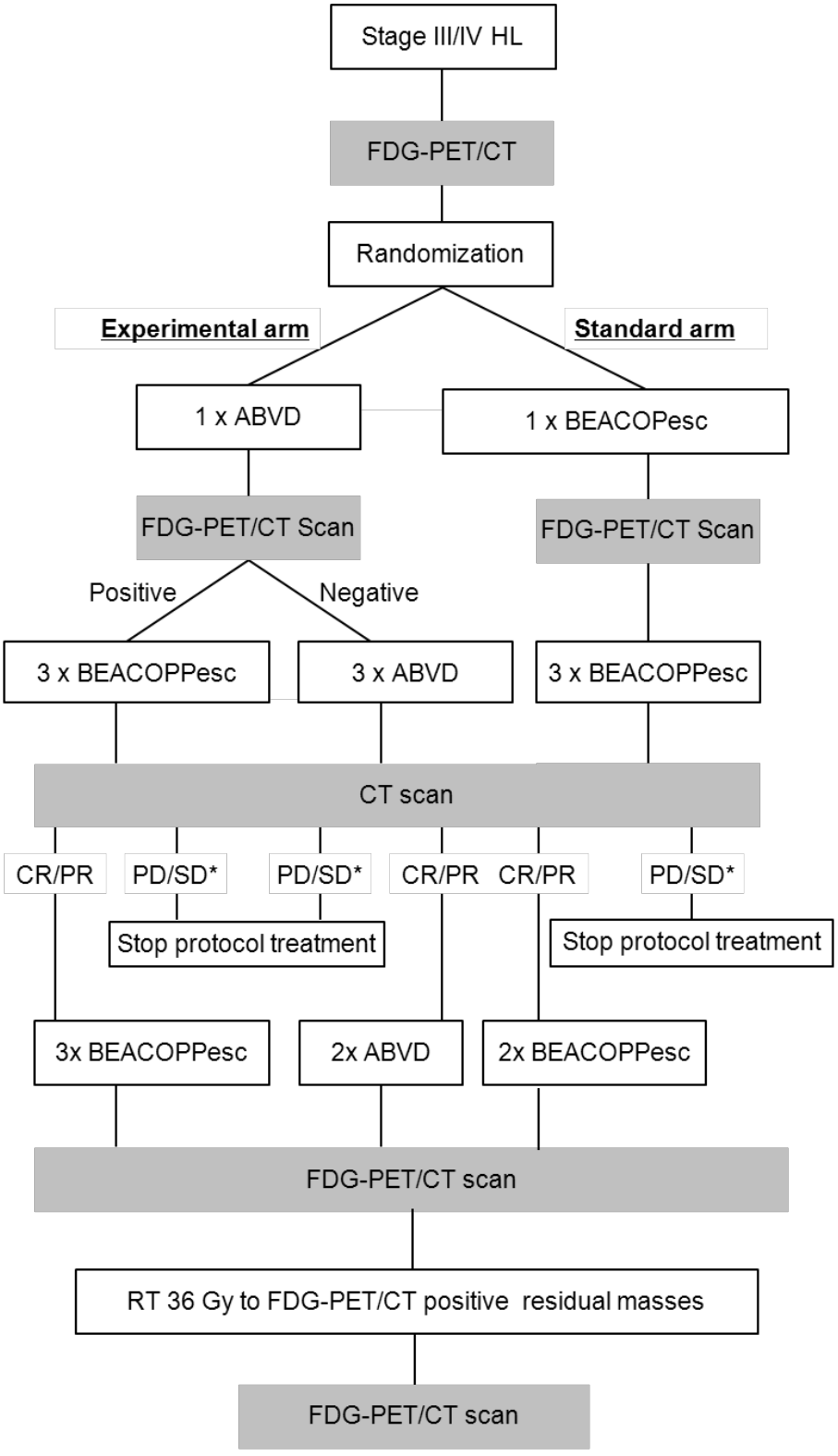
4.1 Chemotherapy

All patients will be randomized between:

1. An experimental arm (very early FDG-PET/CT-response adapted), where all patients are initially treated with a single cycle of ABVD. *Very early FDG- PET/CT-negative patients continue on ABVD therapy to a total of 6 cycles. Very early FDG-PET/CT-positive patients will receive a total of 6 cycles of BEACOPPesc. Mid-treatment evaluation is performed after 4 cycles of chemotherapy (4 cycles of ABVD for FDG-PET/CT negative patients; 1 cycle of ABVD and 3 cycles of BEACOPPesc for FDG-PET/CT positive patients). In case of treatment failure, the patient goes off protocol treatment.

2. A standard arm, where patients are treated with 6 cycles of BEACOPPesc. FDG-PET/CT is performed after 1 cycle, but with no therapeutic consequences. Mid-treatment evaluation is performed after 4 cycles: in case of treatment failure, the patient goes off protocol treatment.

* Note: A score of 4 or higher according to the Deauville criteria will be defined as PET positive.



* SD only if FDG-PET/CT positive after 4 cycles

4.2 Radiotherapy (on indication)

Patients with (a) FDG-PET/CT-positive residual lymphoma mass(es) after completion of chemotherapy will be irradiated to the residual mass(es) only according to specified guidelines. The decision will be based on local assessment of the scan. A dose of 36 Gy in 18 fractions, 5 fractions per week will be given to the whole residual mass and not just the FDG-PET/CT positive area in this residual mass. Modern imaging and radiation techniques will be used in order to minimize dose to normal tissues (especially the heart, lungs and breasts in young females). See chapter 5.4.

5 Therapeutic regimens, expected toxicity, dose modifications

5.1 Chemotherapy regimens

5.1.1 ABVD

- Doxorubicin 25 mg/m^2 i.v. day 1 and 15
- Bleomycin 10 IU/ m^2 i.v./i.m. day 1 and 15
- Vinblastine 6 mg/ m^2 i.v. day 1 and 15
- Dacarbazine 375 mg/ m^2 i.v. day 1 and 15

(next cycle day 29)

5.1.2 BEACOPPesc

- Cyclophosphamide* 1250 mg/ m^2 i.v. day 1
- Doxorubicin 35 mg/ m^2 i.v. day 1
- Vincristine 1.4 mg/ m^2 i.v.(max. 2 mg) day 8
- Bleomycin 10 IU/ m^2 i.v./i.m. day 8
- Etoposide** 200 mg/ m^2 i.v. day 1 to 3
- Procarbazine 100 mg/ m^2 orally day 1 to 7
- Prednisone 40 mg/ m^2 orally day 1 to 14
- Pneumocystis jiroveci prophylaxis with Sulfamethoxazole/Trimethoprim (Cotrimoxazole)
- Ciprofloxacin or levofloxazin 500 mg (or similar quinolon antibiotic) per day on day 6 to 12
- G-CSF *** day 4 – recovery leukocytes > 1.0 x 10^9/L

(next cycle on day 22)

*Cyclophosphamide to be given plus Uromitexan (Mesna i.v., on hours 0, 4 and 8 (20% of cyclophosphamide dose, last dose may be given orally) to prevent hemorrhagic cystitis. The patient should also drink 2.5 l of fluid on this treatment day.

**113 mg Etoposide phosphate is equivalent to 100 mg Etoposide.

*** The G-CSF should be given from day 4, until leukocytes recovery (3 days with leukocytes greater than 1.0 x 10^9/L after passing through nadir), or as pegylated G-CSF on day 4.

5.2 Expected toxicity

Toxicities will be assessed according to the CTCAE v 4.0 criteria (see Appendix D).

5.2.1 Acute toxicity

- Hematological toxicity (blood cell count) can be significant especially for patients who will receive BEACOPPesc. For these patients G-CSF is required to avoid vital complications. CTCAE grade 4 leukopenia and CTCAE grade 4 thrombocytopenia have been observed with BEACOPPesc. As the nadir may be expected near days 11-12 (mean duration 4 days), daily or every other day blood sampling should be done as soon as the CTCAE grade 4 hematological toxicity is observed and until improvement.
- Bleomycine interstitial pneumonitis has been frequently reported and requires the immediate stop of further bleomycine administration.
- Rarely, procarbazine allergy and intolerance has been reported.
- Nausea & vomiting due to cyclophosphamide, doxorubicin, dacarbazine and procarbazine may be significant.
- Total reversible alopecia occurs in most cases.
- Grade 3 or 4 acute cardiotoxicity is expected in approximately 1%.
- BEACOPPesc–related toxic deaths have been reported but do not exceed those observed with standard ABVD.

5.2.2 Late effects

- Pulmonary sequelae (pneumonitis due to bleomycin and or RT-induced) have been reported frequently.
- Cardiotoxicity is observed in 10% of the patients after a follow up of about 10 years. Cardiotoxicity often presents as electrocardiographic changes and arrhythmias, or as a cardiomyopathy leading to congestive heart failure. Anthracycline-associated cardiotoxicity is caused by direct damage to the cardiomyocyte. Several risk factors for anthracycline-associated cardiotoxicity have been identified. The occurrence of anthracycline-associated cardiotoxicity is strongly related to the cumulative dose (Ref. 93, Ref. 94).
- Gonadal toxicity may be irreversible in a significant number of cases.
- MDS & leukemia (related primarily to etoposide and procarbazine) have been reported infrequently but consistently. The risk is considered to be lower after ABVD than after BEACOPPesc.
- Early arteriosclerosis after RT to the mediastinum whether or not combined with chemotherapy is increasingly recognized as a treatment complication.

- Second solid tumors have been reported consistently. The risk of second solid tumors has been shown to be related to radiation dose and radiation volume.

5.3 Guidelines for dose modification

5.3.1 ABVD

Complete blood counts should be obtained before each intravenous drug administration, day 1 and day 15.

The treatment of the first cycle should be given at a 100% dosage regardless of blood cell counts (patient inclusion into the trial guarantees that patients are able to receive the first cycle at full dosage). Unless a life-threatening CTCAE grade 4 toxicity including infection occurs before day 15, full doses of ABVD will also be given at day 15 of the first cycle. If a life-threatening CTCAE grade 4 toxicity has occurred, treatment should be postponed for a maximum of two weeks and schedule at full dose. When life-threatening CTCAE grade 4 toxicity persists or only decreases to grade 3 beyond two weeks, treatment is stopped and patient goes off protocol treatment.

Subsequent ABVD cycles:

It is of utmost importance that treatments are continued punctually and at full dosage, provided that, after the blood values have reached the nadir:

- Total leukocyte count is > 2.5 x 10^9/L
- Total thrombocyte count is > 80 x 10^9/L.
- Isolated neutropenia should not in itself result in treatment delays or dose reductions (Ref. 69, Ref. 70).

When full dose cannot be given on day 1 or 15 of subsequent cycles, therapy is postponed and blood values should be tested again after 3, 7, 10 and 14 days.

As soon as the critical values (see above) are reached, treatment is resumed. If after the second week of postponement blood cell counts did not recover to at least the threshold for giving 100% dose, a 25% dose reduction of Adriamycin, Vinblastin and Dacarbazin is recommended.

If life-threatening CTCAE grade 4 toxicity including infection persists, chemotherapy shall be stopped and this will be considered a treatment failure.

G-CSF may be considered according to the local guidelines of each participating center or country.

CAUTION:

Do not give hematopoietic growth factors concomitantly with cytotoxic drugs, even if they are not myelosuppressive (Bleomycin), as severe toxicity may ensue.

5.3.2 Escalated BEACOPP

For patients in the standard arm, the first cycle of BEACOPPesc should begin at the 100% dosage level. For patients in the experimental arm, the first cycle of BEACOPPesc after a previous ABVD cycle should also preferably begin at the 100% dosage level. The start will take place on day 29 counting from day 1 of the first cycle of ABVD.

Treatment is always to be continued punctually and at full dosage, provided that, after the blood values have reached the nadir, the following conditions are fulfilled:

- Leukocytes ≥ 2.5 x 10^9/L
- Neutrophilic granulocytes ≥ 1.5 x 10^9/L

- Thrombocytes $\geq 80 \times 10^9$/L

If the critical values are not reached on the planned day of treatment continuation, therapy is postponed and blood values should be tested again after 3, 7, 10 and 14 days. As soon as the critical values (see above) are reached, treatment is resumed according to the strategies described below.

Bleomycin and vincristine are administered on day 8, even if leukopenia is observed. If non-hematological events occur (fever, infection or signs of infection, etc.), the application of bleomycin and vincristine on day 8 is omitted without substitution. When the patient has recovered (Grade I toxicity), treatment is continued with the next cycle.

If serious unexpected non-hematological side-effects occur with CTCAE grade 3 or grade 4, treatment should not be continued until the patient has fully recovered.

Therapy cycles should be postponed by no more than two weeks. When after two weeks postponement blood cell counts or serious side effects have not recovered, BEACOPPesc cannot be delivered and the patient must go off protocol treatment.

DE-ESCALATION SCHEME:

Dose reduction for BEACOPPesc follows a predefined de-escalation scheme, which is based upon the occurrence of toxic events in the previous cycles. Any reduced dose level, once reached, represents a maximum above which later cycles do not rise.

The following are regarded as toxic events:

- Leukopenia CTCAE grade 4 for more than 4 days (leukocytes $< 1 \times 10^9$/L);
- Thrombopenia CTCAE grade 4 on one or more days (thrombocytes $< 25 \times 10^9$/L);
- Infection CTCAE grade 4;
- Other toxicity CTCAE grade 4, e.g. mucositis;
- Postponement of treatment for more than 2 weeks due to inadequate recovery of blood values.

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

If a toxic event occurs in 2 successive cycles, the administration is reduced to the baseline dose.

Further possible reductions follow the dose reduction scheme for BEACOPPbaseline. No reduction is made for a treatment postponement of up to 2 weeks.

DOSE LEVELS FOR ESCALATED BEACOPP

Treatment begins at full dose. The following levels are to be used for dose reductions, as necessary.

BEACOPPesc

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

Level 3

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

Level 2

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

Level 1

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

BEACOPPbaseline

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

5.3.3 Non haematological toxicity (both ABVD and BEACOPPesc)

- In case of heart failure whether or not responsive to treatment (cardiac left ventricular function CTCAE grade ≥ 3), doxorubicin should be stopped. In this case, the patient should go off protocol treatment and be treated at the discretion of the investigator. Any further treatment will no longer be considered as protocol treatment.
- In case of gross hematuria (CTCAE grade ≥ 3) with clots requiring catheterization or instrumentation or transfusion, cyclophosphamide (BEACOPPesc schedule only) should be stopped. In this case, the patient should go off protocol treatment and be treated at the discretion of the investigator. Any further treatment will no longer be considered as protocol treatment.
- In case of interstitial pneumonitis (CTCAE grade ≥ 2) bleomycin should be stopped without substitution. However, treatment without bleomycin is still considered as protocol treatment.
- In case of neuropathy (CTCAE grade ≥ 3) and/or constipation (CTCAE grade ≥ 3), vincristine has to be replaced by vinblastine 4 mg/m^2. If after this replacement, the neuropathy and/or constipation persist, vinblastine has to be stopped without any replacement. However, treatment without vincristine or without vinblastine is still considered as protocol treatment.

A chest X-ray or HR-CT and a lung function test should be arranged at the slightest suspicion of bleomycin-induced pneumonitis or pulmonary fibrosis. The following possible risk factors are recognized:

Elderly patient,

Cumulative bleomycin dose > 300-400 mg,

Mediastinal irradiation,

Administration of extra oxygen,

Renal insufficiency,

Additional administration of other pulmonary toxic substances

Since there are no histological or clinical findings that are pathognomonic for bleomycin-induced pneumonitis, the diagnosis must be made on the basis of clinical, radiological and/or histological findings after excluding other differential diagnoses. A considerable fall in vital capacity (25 % of baseline) can be interpreted as a sign of toxicity. In this case, it is imperative that no further bleomycin is administered. Later resumption of bleomycin administration is justified only if the suspicion of bleomycin-induced toxicity has proved unfounded.

5.4 Radiotherapy

5.4.1 General

Patients with one or more FDG-PET/CT-positive residual lymphoma masses after completion of chemotherapy will be irradiated. Radiotherapy to a dose of 36 Gy/18 fractions should be delivered only to residual lymphoma masses containing FDG-PET/CT-positive areas after the end of chemotherapy. FDG-PET/CT will be scored according to the following 5-point scale (Deauville criteria):

(1) No uptake

(2) Uptake ≤ mediastinum

(3) Uptake > mediastinum but ≤ liver

(4) Uptake moderately more than liver uptake, at any site

(5) Markedly increased uptake at any site

Score 3 and higher will be considered FDG-PET/CT positive*.

Bulky disease at presentation is not in itself an indication for radiotherapy. Irradiation of a residual mass without (a) FDG-PET/CT positive area(s) is not indicated.

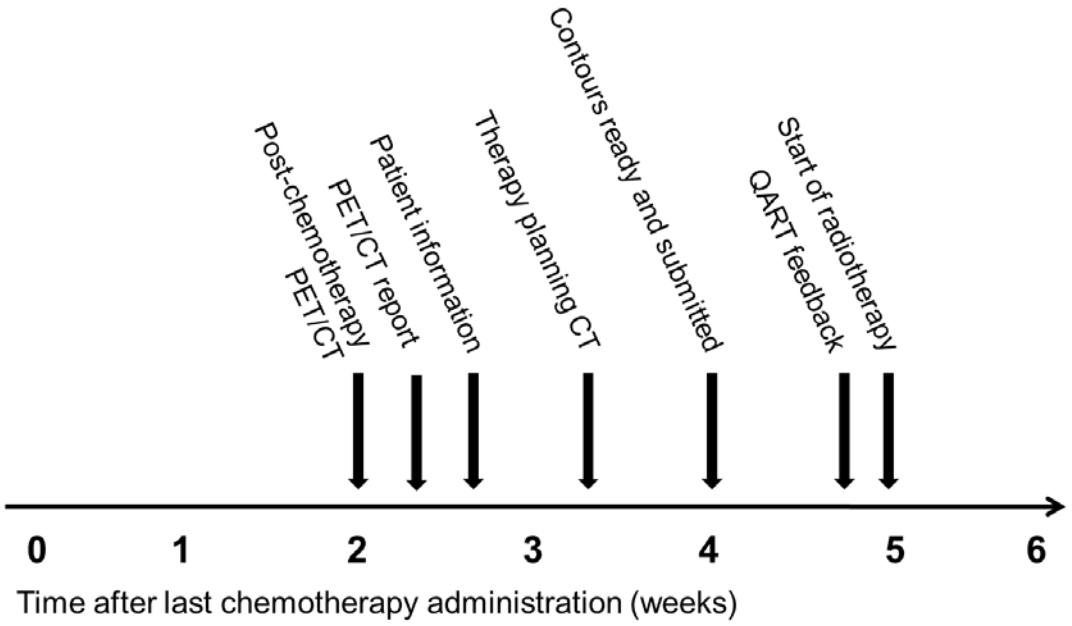
The FDG-PET/CT scan should be performed 2 weeks after the last administration of chemotherapy (i.e. in case of BEACOPPesc around day 21 of the last cycle and in case of ABVD around day 28 of the last cycle).

Central and prospective quality assurance of radiotherapy (QART) will be performed for all patients that will be irradiated (see section 16.4).

Radiotherapy should be started preferably 5-6 weeks after the last chemotherapy administration and no later than 3 months after the last chemotherapy administration.

Before the start of radiotherapy there should be adequate bone marrow recovery i.e. leukocytes ≥ 2 x 10^9/L, and thrombocytes ≥ 80 x 10^9/L.

* Note: A score of 4 or higher is the cut-off switch from ABVD to BEACOPesc in the experimental arm.



5.4.2 Facility and Equipment

Institutions must comply with the Quality Assurance of Radiotherapy requirements and procedures described in detail in the Quality Assurance in Radiotherapy chapter.

Megavoltage equipment with nominal photon energies ≥ 6MV and with three-dimensional conformal Radiotherapy (3D-CRT) or Intensity Modulated Radiotherapy (IMRT) capabilities is required.

5.4.3 Patient position and data acquisition

Patient position:

- When the residual mass is located in the neck, an immobilization mask should be used. The treatment planning CT-scan should be performed using this mask. The use of immobilization devices, including vacuum mattresses, for other target volumes is allowed.
- If a mask is not applicable, reference crosses are marked on the patient using tattoos or any validated skin mark system.
- If possible, the patient position should be similar for the treatment planning CT and the post-chemotherapy evaluation FDG-PET/CT. The arms should preferably be positioned as they were in the post-chemotherapy FDG-PET/CT scan, enabling image fusion. In the case of mediastinal or axillary irradiation, the position should also take into account possible avoidance of OAR including heart and breasts (in young women), for which e.g. a table wedge or a bra might be used.

Data acquisition:

- A planning CT scan will be performed in supine position, preferably using a knee and leg support. An immobilization mask is used on indication.
- The planning CT scan should include the residual mass after chemotherapy with generous margins. The organs at risk that are expected to be in the treated radiation volume have to be scanned completely. The use of i.v. contrast is strongly recommended (except in case of only pulmonary residual abnormalities).

- Slice thickness preferably ≤ 3mm but no more than 5mm.

Fusion of planning CT-scan and post chemotherapy FDG-PET/CT scan is recommended. However, in case of possible differences in positioning, these fusion images must be used with caution. If the post-chemotherapy evaluation FDG-PET/CT is made in treatment position and fulfills all criteria for a planning CT-scan as mentioned above, then this can be used instead of a supplementary CT scan for planning purposes.

5.4.4 Volume definition

The definition of volumes will be in accordance with ICRU Reports #50, #62 and #83 (Ref. 72, Ref. 73, Ref. 74).

Delineation on the therapy planning CT-scan of all FDG-PET/CT positive areas, all CTVs and specified organs at risk is mandatory. It is allowed to use a 4D CT-scan for the delineation of moving organ lesions.

5.4.4.1 Target volume definitions and delineation guidelines

GENERAL:

GTV is considered to be equal to CTV.

Contouring should be done on a planning CT matched with a FDG-PET/CT scan.

CTV = residual mass(es) containing FDG-PET/CT-positive areas after completion of chemotherapy (independent of the size of the residual mass).

PTV margins are described below. Local setup protocols should be taken into account when defining the PTV margins.

NB. Residual abnormalities without FDG-PET/CT-positive areas should NOT be irradiated.

NODAL AREAS:

CTV = residual lymphoma masses containing FDG-PET/CT-positive areas after completion of chemotherapy.

PTV = CTV + margin of 5-15 mm, depending on the location of the mass and the local imaging protocol. Generally in the head and neck area a margin of 5 mm is sufficient if an immobilization mask is used. In the mediastinum a margin of 10-15 mm in lateral and anteroposterior direction and 12-15 mm in craniocaudal direction should be used depending on the breathing movement.

SPLEEN:

CTV = residual abnormality in the spleen as defined on FDG-PET/CT scan after completion of chemotherapy.

PTV = CTV + a margin of 12-20 mm, depending on the breathing movement.

ORGAN INVOLVEMENT:

CTV = the pathological mass containing FDG-PET/CT-positive areas visible after completion of chemotherapy only.

PTV = CTV + a margin of 12-20 mm, depending on the location and thereby the possible movement.

Lung:

CTV = FDG-PET/CT-positive area in the lung after chemotherapy + surrounding residual abnormalities.

PTV = CTV + margin of 12-20 mm depending on the breathing movement.

The contouring should be carried out using the lung window setting of the CT-scan.

Liver:

CTV = area of residual abnormality after chemotherapy containing FDG-PET/CT-positive areas.

PTV = CTV + margin of 12-15 mm depending on the breathing movement.

The contouring should be carried out on a contrast enhanced planning CT-scan, using the liver/abdomen window setting.

Bone lesion:

CTV = FDG-PET/CT positive area + all surrounding abnormalities of the originally involved bone. In case of a lesion in the vertebral body the whole vertebral body should be included.

PTV = CTV + margin of 10-15 mm depending on the location and thereby the possible movement.

The contouring should be carried out on a planning CT-scan using the bone window setting.

5.4.4.2 Organs at risk

Since the HL patient population is generally young and relatively low doses of radiation are used, the normal tissue constraints generally defined for patients with solid tumors should not be applied.

Radiation exposure of the normal tissues depends on the site that will be irradiated. Only the heart, lungs, breasts (in females <40 years old at treatment), kidneys and liver will be contoured and only if they are situated within the region to be irradiated.

LUNGS

Both the right and left lungs should be contoured as one structure (or as 2 structures and added for DVH calculation). Contouring should be carried out using pulmonary window. All inflated lung should be contoured. In case of pulmonary involvement, PTV should be excluded from the OAR delineation. The use of automatic contouring software is allowed.

THE HEART

The cranial limit of the heart will include the infundibulum of the right ventricle, the right atrium, the right atrium auricle and exclude the pulmonary trunk, the ascending aorta and the superior vena cava. The lowest external contour of the heart to be drawn will be the caudal border of the myocardium (Ref. 71).

BREASTS

The left and right breast (glandular tissue only) should be contoured separately in all women <40 years old at treatment.

KIDNEYS

Both the right and left kidneys should be contoured separately. The use of automatic contouring software is allowed.

LIVER

The whole liver should be contoured.

5.4.5 Dose

The prescribed dose will be 36 Gy in 18 fractions, 5 fractions per week over 3.5 weeks. The overall treatment time should be maximally 28 calendar days (but preferably no more than 25 days). The prescription dose is to be specified and reported at the ICRU reference point as defined in ICRU Reports #50, #62 and #83 (Ref. 72, Ref. 73, Ref. 74).

5.4.6 Treatment planning

3D-CRT or IMRT should be applied, with Volumetric Modulated Arc Therapy (VMAT) and Tomotherapy to be considered as IMRT techniques. The choice of the technique will be left to the discretion of the treating physician taking into account the available facilities and the exposure of organs at risk. The use of parallel opposed fields is allowed. The use of more advanced techniques, like inspiration breath hold technique, is allowed. Treatment will be planned using inhomogeneity corrections.

5.4.6.1 Dose prescription to PTV

The 95% isodose curve of the prescribed dose should encompass at least 95% of the PTV.

The required dose homogeneity within the PTV must be from -5% to +7%.

5.4.6.2 Dose constraints to organs at risk

In order to avoid late toxicity, the dose to the described organs at risk should be as low as reasonably achievable without compromising the dose to the PTV.

Lungs: mean lung dose should be < 15 Gy and V20 preferably ≤ 30%.

Heart: mean heart dose should be kept as low as possible, preferably below 20 Gy and V30 ≤ 50%

Breast: currently there is evidence for a dose-response relationship between radiation dose and the risk of breast cancer in women below the age of 40 years. The effect of irradiated volume is however unclear. The breast cancer risk should be weighed against the risks of pulmonary and cardiac toxicity. It is currently not possible to describe a general dose constraint in terms of max (or mean) breast dose. In case of treatment of women, especially below the age of 25 years, the breast tissue should receive the lowest possible dose.

Kidneys: At least 2/3 of the volume of one normally functioning kidney should receive < 18 Gy.

Liver: Mean liver dose < 30 Gy, V30 ≤ 50%.

5.4.6.3 Dose recording

PTV:

- The reported doses for the PTV shall include the prescription dose, the maximum point dose and the % target volume receiving <95% and >107%

Organs at risk:

Hot spots outside the PTV should be recorded.

- For each organ at risk the following dose and volume data should be recorded:
  - Lungs: mean lung dose and V5, V20, V36
  - Heart: mean heart dose, V5, V20, V30 and V36
  - Kidney: separately for each kidney: mean kidney dose and V18

- Breast: separately for each breast: mean breast dose, V5, V20, V36
- Liver: mean liver dose, V30

5.4.7 Treatment verification and accuracy

Daily patient set-up shall be performed using laser alignment to reference marks on the skin of the patient.

The minimum requirement for treatment verification is an off-line set-up correction protocol that requires imaging at least once per week. It is strongly advised to adhere to the adapted "shrinking action level" (SAL) or extended “no action level” (eNAL) off-line protocols as described in the literature (Ref. 75, Ref. 76).

Local treatment verification protocols may be acceptable provided they are accepted by the QART team before the start of participation to the trial.

5.4.8 Complications of Radiotherapy

Any observations regarding radiation reactions will be recorded according to Criteria for Adverse Events version 4.0 (CTCAE) (see Appendix D).

5.4.8.1 Acute toxicity

Radiation toxicity

Most frequently expected acute toxicity (highly depending on the area irradiated):

- Dysphagia
- Nausea
- Abdominal discomfort and other lower GI symptoms
- Bone marrow toxicity
- Radiation pneumonitis

5.4.8.2 Late toxicity

Both chemotherapy and radiotherapy may lead to late toxicity (Ref. 77, Ref. 78, Ref. 79, Ref. 80).

Most relevant RT-related late toxicities:

- Second malignancies
- Cardiovascular diseases (coronary heart disease, valvular disease, heart failure, conduction abnormalities)
- Hypothyroidism (in case of RT of the neck)
- Muscular atrophy
- Pulmonary fibrosis
- Functional asplenia (in case of RT of the spleen).

Risks of second malignancies and cardiovascular diseases have been shown to be dose and volume related.

5.4.9 Treatment interruptions / modifications

Radiotherapy treatment interruptions are expected to be necessary only very rarely. Treatment breaks should be kept as short as possible. Lowering the daily dose per fraction is not allowed.

In case the radiation volume is considered to be too large for one radiation course (for instance in case of extensive residual disease in mediastinum and abdomen), the application of more than one sequential course is allowed, however with the shortest interval possible and respecting the above mentioned criterion for start of radiotherapy.

5.5 Reasons for stopping protocol treatment

- Ineligibility (Ineligible patients will go off the protocol treatment; however treatment continuation/stop or change will be according to the treating physician)
- Normal completion of protocol treatment
- No FDG-PET/CT scan performed after one cycle of ABVD. This is considered to be a major protocol violation
- Toxicity (related to study treatment)
- Progression/Relapse/death due to PD
- Patient's decision not related to toxicity
- Death not due to malignant disease or toxicity
- Start of a new anti-cancer treatment
- Other malignancy

Note: Follow up data for patients are still to be provided in the follow up visits.

6 Clinical evaluation, laboratory tests and follow-up

6.1 Before treatment start

All the following examinations, tests or imaging studies are mandatory before the start of treatment unless otherwise stated.

- Confirmed local histology excluding lymphocyte predominant sub-type
- History: B-symptoms, WHO performance status (see Appendix C), cardiopulmonary complaints, hypertension, diabetes mellitus, menstrual status, and smoking history
- Physical examination including height, body weight
- Blood tests: ESR, hemoglobin, platelets, leukocyte count including neutrophils and lymphocytes
- Serum chemistry: total bilirubin, creatinine, alkaline phosphatase, ALAT, ASAT, LDH, serum albumin
- Hormonal tests: Thyroid function (T4, TSH), fertility tests (FSH, LH, 17-beta-oestradiol, progesterone, testosterone). In males spermogram (optional), and if indicated sperm preservation
- Serum sample for TARC measurement (to be stored at -20°C in the participating center. See chapter 10)
- Blood sample for DNA isolation (to be sent to central lab within 24h. See chapter 10)

- Samples for Cardiac study (please refer to summary table and chapter 10)
- 12 lead ECG
- Imaging: chest X-ray (PA and lateral)
- Imaging: A baseline FDG-PET/CT scan less than 2 weeks before treatment start
- Imaging: diagnostic quality CT-scan (neck, chest and abdomen)
- Toxicity studies: pulmonary function tests and cardiac ejection fraction (EF > 50 %)
- Adverse events assessment according to the CTCAE v.4.0 (see Appendix D for reference)

6.2 During treatment

6.2.1 At each cycle

- Adverse events assessment according to CTCAE v.4.0 after each cycle, before starting the next cycle (see Appendix D)
- Body weight
- Blood tests: hemoglobin, platelets, leukocyte count including neutrophils and lymphocytes:
  - Day 1 and 15 for ABVD
  - Day 1, 8 and 11 (and dependent of the results on day 11 additionally on consecutive days) for BEACOPPesc
- Serum chemistry: total bilirubin, creatinine, alkaline phosphatase, ALAT, ASAT, LDH and (serum albumin; if clinically indicated)
- Samples for Cardiac study (please refer to summary table and chapter 10)

6.2.2 After 1 cycle of chemotherapy: major evaluation point

In addition to the examinations mentioned in section 6.2.1

- Serum sample for TARC measurement (to be stored at -20°C in the participating center. See chapter 10)
- Imaging: FDG-PET/CT scan after completion of the first cycle of chemotherapy. For more information, please see the Imaging Guidelines for this trial.

6.2.3 After 4 cycles of chemotherapy

In addition to the examinations mentioned in section 6.2.1

- Serum sample for TARC measurement (to be stored at -20°C in the participating center. See chapter 10)
- Imaging: Diagnostic quality CT scan of the neck, thorax, abdomen and pelvis, after completion of the fourth cycle of chemotherapy. Additional FDG-PET/CT is needed in case of stable disease on the diagnostic quality CT scan.
- Imaging: chest X-ray (PA and lateral)
- Samples for Cardiac study (please refer to summary table and chapter 10)

6.2.4 After completion of chemotherapy

Evaluation should be performed 2-4 weeks after completion of chemotherapy.

- History: WHO performance status, cardiopulmonary complaints
- Blood tests: hemoglobin, platelets, leukocyte count including neutrophils and lymphocytes
- Serum chemistry (total bilirubin, creatinine, alkaline phosphatase, ALAT, ASAT, LDH, serum albumin,) if clinically indicated
- Serum sample for TARC measurement (to be stored at -20°C in the participating center. See chapter 10)
- Samples for Cardiac study (please refer to summary table and chapter 10)
- Adverse events assessment according to the CTCAE v.4.0 (see Appendix D)
- Imaging: FDG -PET/CT scan.

  Note: the FDG-PET/CT scan should be performed 2 weeks after the last administration of chemotherapy (i.e. in case of BEACOPPesc around day 21 of the last cycle and in case of ABVD around day 28 of the last cycle). The restaging evaluations are mandatory and required to determine whether radiotherapy is indicated (i.e. in case of FDG-PET/CT positive residual masses at the end of chemotherapy) and in case radiotherapy is indicated for adequate definition of the radiation target volumes. Guidelines for FDG-PET/CT scan are provided in the Imaging Guidelines of this trial.
- Toxicity studies: pulmonary function tests and cardiac ejection fraction

6.2.5 After completion of radiotherapy (in case radiotherapy was given)

Evaluation should be performed 6 weeks after completion of radiotherapy.

- History: WHO performance status, cardiopulmonary complaints
- Blood tests: hemoglobin, platelets, leukocyte count including neutrophils and lymphocytes
- Serum chemistry (total bilirubin, creatinine, alkaline phosphatase, ALAT, ASAT, LDH, serum albumin) if clinically indicated
- Serum sample for TARC measurement (to be stored at -20°C in the participating center. See chapter 10)
- Samples for Cardiac study (please refer to summary table and chapter 10)
- Adverse events assessment according to the CTCAE v.4.0 (see Appendix D)
- Imaging: FDG -PET/CT scan.
- Toxicity studies: pulmonary function tests and cardiac ejection fraction

6.3 After the end of treatment (Follow-up)

After completion of final response evaluation, patients will be closely monitored for relapse/progression or toxicity of treatment according to the following schedule.

6.3.1 Timing of follow-up visits

Timing of follow-up visits after last administration of protocol therapy (final response evaluation has already taken place)

- During the first and second year: every 3 months
- During the third, fourth and fifth years every 6 months
- Beyond the fifth year yearly
- Beyond the 10^{th} year once every two years

6.3.2 Investigations at follow-up after the end of treatment

6.3.2.1 At every follow up visit (up to 5 years)

- History, B-symptoms, physical examination and blood test according to local practice
- WHO performance status
- Incidences of cardiopulmonary disease, second malignancy
- Serum sample for TARC measurement at disease recurrence (if applicable) or after treatment (during the first 2 years) (to be stored at -20°C in the participating center. See chapter 10)
- Samples for Cardiac study (please refer to summary table and chapter 10)

6.3.2.2 After 3, 6, 12, 18 and 24 months and 3, 4 and 5 years

In addition to the examinations mentioned in section 6.3.2.1

- Imaging: CT scan neck, chest and abdomen
- In males, spermogram after 3 years (optional)

6.3.2.3 Annually until 5 years

- Adverse events assessment according to the CTCAE v.4.0 (see Appendix D for reference)

6.3.2.4 After 1, 3 and 5 years

In addition to the examinations mentioned in section 6.3.2.1

- Hormonal tests: Thyroid function (T4, TSH), fertility tests (FSH, LH, 17-beta-oestradiol, progesterone, testosterone)
- Toxicity studies: pulmonary function tests and cardiac ejection fraction

6.3.2.5 After five years / life long

Patients are followed annually and after 10 years once every two years unless the patient is at increased risks of radiation associated breast cancer (see below).

- History, B-symptoms, physical examination, blood tests, regular hormonal function tests and regular mammograms according to local practice
- WHO performance status
- Toxicity studies: Pulmonary function tests and cardiac ejection fraction evaluation after 10, 15 and 20 years
- Samples for Cardiac study (please refer to summary table and chapter 10)
- Incidences of cardiopulmonary disease, second malignancy
- Adverse events assessment according to the CTCAE v4.0 (see Appendix D for reference)

6.4 Summary table

	baseline	at each cycle	after 1 cycle	after 4 cycles	after completion CT	after completion RT	3 & 6 month FU	9 months FU	12 months FU	15, 18 & 21 months FU	24 months FU	36 months FU	48 months FU	60 months FU	at each FU (>5 years)	10, 15 & 20 year FU
B-symptoms and history[a]	x						x	x	x	x	x	x	x	x	x	
Cardiopulmonary complaints	x	x	x*	x*	x	x	x*	x*	x*	x*	x*	x*	x*	x*	x*	
AE assessment	x	x			x	x			x		x	x	x	x	x	
WHO performance	x				x	x	x	x	x	x	x	x	x	x	x	
Height	x															
Body weight	x	x	x*	x*	x*	x*	x*	x*	x*	x*	x*	x*	x*	x*	x*	
Hematology[b]	x	x[c]			x	x	x	x	x	x	x	x	x	x	x	
Serum chemistry[d]	x	On indication and according to local policy														
Hormonal tests[e]	x								x			x		x	x	
Chest X-ray	x				x											
Diagnostic CT-scan[f]	x			x	x	x	x		x	x[μ]	x	x	x	x		
FDG-PET/CT scan	x		x		x[g]	x										
ECG	x				x*	x*			x*			x*		x*		x*
Cardiac ejection fraction**	x				x	x			x			x		x		x
Pulmonary function tests	x				x	x			x			x		x		x
Spermogram (optional)	x											x				

	baseline	at each cycle	after 1 cycle	after 4 cycles	after completion CT	after completion RT	3 & 6 month FU	9 months FU	12 months FU	15, 18 & 21 months FU	24 months FU	36 months FU	48 months FU	60 months FU	at each FU (>5 years)	10, 15 & 20 year FU
Mammography (optional)															x	
Second malignancy							x	x	x	x	x	x	x	x	x	x
TARC study																
Diagnostic biopsy sample(s)	x															
DNA blood Sample	x‡															
TARC Serum Samples***	x		x	x	x	x	x	x	x	x	x					
Cardiac side study																
Cardiac medication	x		x	x	x	x	x	x	x	x	x	x	x	x	x	
Blood pressure	x		x	x	x	x	x	x	x	x	x	x	x	x	x	
DNA blood Sample	x‡															
BNP/NTproBNP	x	x			x	x	x	x	x	x	x	x	x	x	x	
Hs Troponin T	x	x			x	x	x†									
Lipid profile	x								x			x		x		x
MUGA scan**	x				x	x			x			x		x		x
Echocardiography**	x				x	x			x			x		x		x

FU intervals are defined after the end of protocol treatment

[a] Hypertension, diabetes mellitus, menstrual status, contraception and smoking. Investigators should make sure that patients are following adequate birth control measure during the whole duration of study treatment.

[b] Hematology: ESR (done in baseline), hemoglobin, platelets, leukocyte count including neutrophils and lymphocytes

[c] Day 1 and 15 for ABVD and day 1, 8 and 11 (and dependent of the results on day 11 additionally on consecutive days) for BEACOPPesc

[d] Serum Chemistry: Total bilirubin, creatinine, alkaline phosphatase, ALAT, ASAT, LDH, serum albumin (if clinically indicated)

[e] Hormonal tests: thyroid function (T4, TSH), fertility tests (FSH, LH, 17-beta-oestradiol, progesterone, testosterone)

[f] may be performed as part of the FDG-PET/CT scan

[g] two weeks after the last administration of chemotherapy

* For the cardiac side study only

** Ejection fraction will be measured for all patients using either MUGA or ultrasound. For those participating in the cardiac side study both MUGA and echocardiography will be performed.

[‡] DNA sample should be collected and sent to central lab within 24 hours (for more specification; please refer to translation guidelines). The same sample will be used for both the TARC and cardiac side study.

*** serum TARC samples to be drawn at diagnosis, before start of treatment, before 2nd chemotherapy course, before 5th course and during follow up visits. Serum to be kept in freezer (-80) at local site until shipment (see chapter 10)

[†] Only 3 months after end of treatment

[µ] Diagnostic CT-scan only at 18 months not necessary for 15 or 21 months

7 Criteria of evaluation

7.1 Freedom from treatment failure

Freedom from treatment failure will be measured from the date of randomization to the date of first occurrence of any of the following events:

- Progression during treatment or SD after 4 cycles of chemotherapy according to the IHP response criteria (requires a positive PET) (Ref. 36)
- Lack of complete remission at the end of protocol treatment, as defined by the IHP response criteria (Ref. 36); i.e. patients will be considered as failure only if active disease is confirmed by either a biopsy, or a repeated positive FDG-PET/CT scan 2-3 months after the previous scan
- Relapse
- Death from any cause

Patients free of these events are censored at the date of the most recent follow-up

7.2 Progression-free survival

Progression-free survival will be measured from the date of randomization to the date of first occurrence of any of the following events:

- Progression
- Relapse
- Death from any cause

Patients free of these events are censored at the date of the most recent follow-up.

7.3 Overall survival

Overall survival will be measured from the date of randomization to the date of death whatever the cause of death. Patients who are alive are censored at the date of the most recent follow-up.

7.4 Response criteria

7.4.1 Evaluation after 1 cycle of chemotherapy

Evaluation of FDG-PET/CT after 1 cycle of therapy is performed according to the 5-point scale of the Deauville criteria (Ref. 84, Ref. 85). A score of 1-3 is considered negative, a score of 4-5 is considered positive. According to these criteria, (^{18}F)FDG uptake in a lesion higher than the liver background uptake qualifies for a score of 4 or higher, provided this uptake is likely to represent disease activity. A new focus of increased uptake in a previously uninvolved area is considered unlikely to represent disease, if other involved sites respond well to the treatment.

Deauville criteria for interim PET/CT interpretation (Ref. 85)	
Score	PET/CT scan result
1	No uptake above background
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately increased compared to the liver at any site
5	Uptake markedly increased compared to the liver at any site
x	New areas of uptake unlikely to be related to lymphoma

7.4.2 Evaluation after 4 cycle of chemotherapy

Evaluation after 4 cycles is performed according to the IHP response criteria for malignant lymphoma (Ref. 36). The distinction between patients in CR and PR has no therapeutic consequence at this point, so only a diagnostic quality CT is mandatory. Additional PET or PET/CT is only needed in case of structural SD on CT, to determine whether the patient is to be considered a treatment failure and discontinue the trial. In the IHP response criteria, stable disease (SD) is defined as the following:

1. A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease.

2. Typically FDG-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET. A positive PET according to the IHP criteria corresponds to a Deauville score of 3 or higher (Ref. 84, Ref. 85).

7.4.3 Evaluation after completion of chemotherapy

After completion of chemotherapy, evaluation is performed with FDG-PET/CT according to the IHP response criteria for malignant lymphoma (Ref. 36). Patients with FDG-PET/CT positive residual masses (not considered to be in CR) should be referred for radiotherapy. A positive PET according to the IHP criteria corresponds to a Deauville score of 3 or higher (Ref. 84, Ref. 85).

7.4.4 Evaluation after completion of radiotherapy

After completion of radiotherapy, evaluation is performed with FDG-PET/CT according to the IHP response criteria for malignant lymphoma (Ref. 36). A positive PET according to the IHP criteria corresponds to a Deauville score of 3 or higher (Ref. 84, Ref. 85).

7.5 Central review of very early FDG-PET/CT

A Central Review (CR) will be organized for the FDG-PET/CT scans in this trial. Centers are requested to submit all scans, which will be collected during the course of the clinical trial. The CR will perform a central reading of all baselines and after one cycle FDG-PET/CT scans of all patients. The CR will be blinded to the treatment arm and the local review results.

The EORTC will track all scans of all patients received from the sites and will request/query missing/incomplete scans. Furthermore, if the scans arrive in unacceptable quality or in a non-acceptable format, the site will be informed to provide substitute scans.

FDG-PET/CT scans performed at baseline and after one cycle of chemotherapy will be centrally reviewed by an expert nuclear medicine core lab, and the treatment decisions will be made according to the results of the central FDG-PET/CT review.

In case of discrepancy between the central review and the local assessment, the central review will be used to guide treatment. However, the local investigator can contact the central reviewer through EORTC HQ for any clarification.

7.6 Evaluation of toxicity

7.6.1 Adverse events

All adverse events will be recorded during protocol therapy and during follow-up.

Only the worst grade per CTCAE category will be recorded per cycle; between end of chemotherapy and end of radiotherapy; yearly during the first 5 years after end of treatment.

The collection period will start from randomization.

7.6.2 General evaluation of side effects

This study will use the International Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, for adverse event reporting. A copy of the CTCAE can be accessed on the EORTC web site www.eortc.org\investigators-area\ctc

Hematological toxicity will be assessed on the basis of blood counts. The nadir count should be computed and graded according to the International CTCAE. The nadir in a given cycle is the lowest laboratory value in that cycle; the overall nadir for a patient is the lowest laboratory value during the treatment period.

Toxicities that are reported during treatment including those reported after completion of chemotherapy and after completion of radiotherapy (in case radiotherapy was given) will be regarded as acute toxicity. Toxicities that are reported after the end of treatment (follow-up) will be regarded as late toxicity.

Particular attention will be paid to the assessment of the following items that will be used for monitoring the late toxicity related to the protocol treatments (see section 8.2.5):

- Second malignancies;
- Cardiovascular disorders with CTCAE grade ≥ 3;
- Pulmonary disorders with CTCAE grade ≥ 3;
- Any CTCAE grade ≥ 3.

Planned safety analysis and tabulations are described in the statistics section.

7.6.3 Serious adverse events

Serious adverse events are defined by the Good Clinical Practice Guideline.

SERIOUS ADVERSE EVENTS SHOULD BE IMMEDIATELY REPORTED ACCORDING TO THE PROCEDURE DETAILED IN THIS PROTOCOL (see chapter 15 on Reporting of Serious Adverse Events).

7.6.4 Toxic deaths

Toxic death is defined as death due to toxicity (defined as adverse events at least with reasonable possibility related to study treatment). The cause of death must be reported as "toxicity".

The evaluation of toxic deaths is independent of the evaluation of response (patients can die from toxicity after a complete assessment of the response to therapy).

7.6.5 Evaluability for safety

All patients who have started the allocated treatment will be included in overall safety analyses.

For hematological events, the medical review team may decide that blood counts have not been performed and/or reported according to the protocol and are therefore inadequate for the evaluation of one/several hematological parameters in some patients.

Patients who have discontinued treatment because of toxicity will always be included in the toxicity analyses.

8 Statistical considerations

8.1 Statistical design

8.1.1 Sample size

The primary endpoint is freedom from treatment failure (FFTF): see chapter 7.1 for definition. The study is designed as an open-label randomized phase III non inferiority trial. The reference arm is the arm with 6 cycles of BEACOPPesc. The experimental arm is the arm where all patients are initially treated with a single cycle of ABVD. Very early FDG-PET/CT-negative patients continue on ABVD therapy to a total of 6 cycles. Very early FDG-PET/CT -positive patients receive a total of 6 BEACOPPesc chemotherapy cycles.

The primary trial objective is to test the null hypothesis (H0) of inferiority in terms of FFTF of the experimental arm as compared to the reference arm.

The null and alternative hypotheses are stated as follows:

H0: Hazard ratio of experimental versus standard = 1.87

H1: Hazard ratio of experimental versus standard = 1.00

The null hypothesis corresponds to a 10% difference in FFTF at 5 years, from 87% to 77%. 87% (95% CI: 83%-91%) is the estimated rate of freedom from treatment failure at 5 years in patients treated with increased-dose BEACOPP in the HD9 trial conducted by the German Hodgkin Study Group (Ref. 95).

The study sample size is determined to provide 80% power of rejecting the null hypothesis in the alternative of no difference between the two arms, using a log-rank test at the 1-sided 2.5% significance level. This test requires that 80 events be observed at the time of the final statistical analysis.

It is estimated that if 570 patients are randomized in the study in a total of 6.2 years (on the basis of 50 patients recruited the first year and 100 patients yearly for all subsequent years), the required 80 events should be observed approximately 3.3 years after the entry of the last randomized patient in the study, under H1. It is assumed that the events follow a piecewise exponential distribution with higher event rate

during years 1 and 2 and a very low event rate from year 2 onwards (survival rates in the reference arm are assumed to be 90% and 87% at 2 and 5 years respectively).

Because the primary analysis of the primary endpoint is conducted on the per-protocol population, these 570 patients will have to be eligible and start their allocated treatment (at least one dose of the study drug(s)). In order to account for the randomization of patients who are not eligible or who do not start their allocated treatment, approximately 600 patients will need to be randomized.

No interim analysis is planned.

8.1.2 Randomization and stratifications

Patients will be centrally randomized (for practical details, see chapter on registration / randomization procedure). A minimization algorithm with a random element (Ref. 78) will be used for treatment allocation stratifying by institution, stage (III vs. IV), gender and age (< 45 vs. ≥ 45).

8.2 Statistical analysis plan

Two analyses (and corresponding database locks) will be performed:

- the first one when the required number of events for the primary endpoint is reached (80 events),
- and a second one, after a median follow-up of 10 years, for a long-term evaluation of overall survival and toxicity.

8.2.1 Primary and secondary endpoints

The endpoints that will be used in the statistical analysis are defined in chapter 7.

The primary endpoint is freedom from treatment failure (FFTF). The secondary endpoints measuring treatment efficacy are overall survival (OS), progression-free survival (PFS) and response at the end of therapy. The secondary endpoints measuring treatment toxicity are acute and long-term toxicity.

8.2.2 Analysis populations

- Intention-to-treat population: All randomized patients will be analyzed in the arm they were allocated by randomization.
- Per protocol population: All patients who are eligible and have started their allocated treatment (at least one dose of the study drug(s))
- Safety population: All patients who have started their allocated treatment (at least one dose of the study drug(s))

A patient will be considered to be eligible if he/she did not have any deviation from the patient entry criteria listed in chapter 3 of the protocol. Potential eligibility problems will be assessed by the Clinical Research Physician at time of medical review.

8.2.3 Statistical methods

8.2.4 Efficacy

The primary analysis of all efficacy endpoints will be performed in the per-protocol population.

FFTF (primary endpoint) as well as OS and PFS will be described using Kaplan-Meier curves (Ref. 87) in the two treatment arms. Kaplan-Meier estimates of event-free rates at 3 years and 5 years will be provided; their associated 95% confidence interval will be calculated using the log-log transformation and the standard deviation of the Kaplan Meier estimate based on the Greenwood formula. The difference in event-free rates at 3 years and 5 years between the two arms will also be estimated with its 95% confidence interval.

The long term analysis of OS will provide survival estimates at 10 years.

All time-to-event endpoints will be compared between the randomized groups using the Cox's proportional hazards model (Ref. 88) adjusted for stage (III vs. IV), gender and age (< 45 vs. ≥ 45). Effects will be estimated using hazard ratios (HR) and the associated 95% confidence interval. Before fitting the Cox model, a substantial evidence for non-proportional treatment hazards in the form of a qualitative change over time will be explored (Ref. 89). If strong departure from the proportionality assumption is detected for a specific covariate, the model will be stratified for that variable instead of being adjusted for in the model, in order to relax the assumption of proportionality for that variable.

With respect to the primary endpoint, non-inferiority of the experimental arm versus the reference arm will be declared if the upper bound of the 95% confidence interval of the treatment effect HR is below 1.87. The one-sided p-value for the test of the null hypothesis (H0) of inferiority will be provided.

Response at the end of therapy will be tabulated, by randomized group; unevaluable patients will be included as an additional category. The complete response rate will be provided by randomized group with its 95% confidence interval.

8.2.5 Toxicity

The analysis of the toxicity endpoints will be performed in the safety population. No formal toxicity analyses with p values will be carried out.

Adverse events with onset during treatment including those reported after completion of chemotherapy and after completion of radiotherapy (in case radiotherapy was given) will be categorized as acute adverse events. For each patient and each item of the CTCAE, the worst grade of acute adverse events will be derived. The percentage of patients with a given grade of each adverse event will be presented by treatment arm.

Adverse events with onset after the end of treatment (follow-up) or with onset during treatment but with same or worse grade during follow-up will be categorized as late adverse events. The cumulative incidence of late adverse events will be analyzed in the safety population by competing risk methods, with death as a competing risk. Cumulative incidence curves will be displayed and cumulative event rates at 3 years and at 5 years will be documented with their 95% confidence interval. A separate analysis will be performed for the following endpoints:

- Second malignancies;
- Cardiovascular disorders - Any CTCAE grade ≥ 3;
- Pulmonary disorders - Any CTCAE grade ≥ 3;

- Any CTCAE grade ≥ 3.

The long term analysis of toxicity will provide estimates of event rates at 10 years.

8.2.6 Pre-planned sensitivity or exploratory analyses

A sensitivity analysis of all efficacy endpoints will be performed in the intention-to-treat population, using the same method of analysis.

The consistency of treatment arm comparisons will be assessed across subgroups of patients defined by the factors used for stratification of randomization: stage (III vs. IV), gender and age (< 45 vs. ≥ 45). A Cox model with treatment by factor interactions will be used and results will be illustrated by a Forest plot. Interaction tests will be performed at a 5% two-sided significance level.

8.2.7 Prognostic factor analyses

Kaplan-Meier curves for FFTF (primary endpoint), OS and PFS will be produced for the subgroups of patients FDG-PET/CT negative and positive after 1 cycle of BEACOPPesc and after 1 cycle of ABVD. Survival estimates will give insight on the prognosis of patients treated in each arm and according to the value of the very early FDG-PET. Kaplan-Meier curves will be constructed using landmark method (Ref. 90).

The prognostic value of FDG-PET/CT after 1 cycle of BEACOPPesc will be assessed formally in the reference arm (secondary study objective) Kaplan-Meier curves for FFTF (primary endpoint), OS and PFS will be produced for the subgroups of patients FDG-PET/CT negative and positive after 1 cycle of BEACOPPesc, with a landmark time of 22 days from the date of randomization, which corresponds to the timing of the FDG-PET/CT scan after the first cycle of BEACOPPesc. All efficacy endpoints will be compared between the two subgroups of patients using the Cox's proportional hazards model adjusted for stage (III vs. IV), gender and age (< 45 vs. ≥ 45). All tests will be performed at a 5% two-sided significance level. The fitted model will be evaluated for calibration and discrimination ability (Harrell's C-index). Bootstrap technique will be used to correct parameters for "optimism" and to assess the stability of the covariates (Ref. 135).

An additional analysis will be conducted in the standard and experimental arms pooled together. The statistical model will include an interaction term for FDG-PET/CT result after 1 cycle by treatment arm, in order to assess the predictive value of FDG-PET/CT after 1 cycle of chemotherapy.

8.2.8 Data recoding and display

Frequency tables will be tabulated (by treatment group or otherwise) for all categorical variables by the levels of the variables as they appear on the CRF (with %). Categories with a text field specification will be tabulated as categories and then supplemented by a listing with the following information for the patients fulfilling the condition for the specification (patient id, institution, treatment group, value of the item and text field contents).

Dates relating to events prior to entry will be presented as the delay in days (or weeks, months, or years) between the past event and the date of entry (date of randomization – date of past event + 1) and presented using the median and range. For example, on the randomization checklist, the date of last administration of prior treatment (or the date of first diagnosis of the cancer) will be presented as the time elapsed (in days, weeks, months or years, as appropriate) since the day of the last administration and the date of entry on study (date of randomization – last administration/diagnosis +1).

Other delays (e.g. re-treatment delays) are presented as continuous variables using the median and range.

Continuous variables for which a coding system exists (such as for laboratory data) will be recoded into categories (for adverse events, the grading scale specified in the protocol will be used). Whenever no specific scale exists, lab data will be categorized based on the normal range: for example, below the lower normal limit (when appropriate), within the normal range, above the upper normal limit (ULN) and the degree to which it is above the ULN (for example > 2.5 x ULN, > 5 x ULN, > 10 x ULN). For laboratory data, the nadir is generally displayed. The nadir in a given cycle is the lowest laboratory value in that cycle; the overall nadir for a patient is the lowest laboratory value among all cycles.

Other continuous variables (for example age, dose …) are presented using the median and range (minimum, maximum).

The dose intensity of each component of chemotherapy will be calculated on actual treatment duration (weeks) and actual treatment dose received (total dose received expressed in mg/m²).

As the last planned day of treatment is not the last day of the cycle, the total duration of the treatment will account for this by adding the appropriate number of days to complete the last cycle (e.g. if treatment is given on days 1-3 of a 21-day cycle, the total treatment duration in days is [date of last injection]-[date of first injection]+1+(21-3).

The dose intensity (expressed in mg/m² /week) is the ratio of the total dose received to the total treatment duration, for example, for a dose in mg/m² and duration in weeks:

$$DI_{observed}\ (mg/m^2/week) = \frac{Total\ dose\ (mg/m^2)}{Actual\ total\ treatment\ duration\ (weeks)}$$

The relative dose intensity is calculated as the ratio of the dose intensity as calculated above to the dose intensity indicated in the protocol, expressed in percent (%). The relative dose intensity will be presented using median and ranges, accompanied by a distribution into categories (e.g. ≤ 70%, > 70-90%, > 90-110%, > 110-120%, > 120%).

If appropriate, continuous data may also be presented in categories (for example, age may also be grouped in decades).

8.3 Interim analyses

Not applicable.

8.4 End of study

End of study occurs when all of the following criteria have been satisfied:

1. Thirty days after all patients have stopped protocol treatment

2. The trial is mature for the analysis of the primary endpoint as defined in the protocol

3. The database has been fully cleaned and frozen for this analysis

9 Data Monitoring

Safety data are reviewed within the EORTC Headquarters on a regular basis as part of the Medical Review process. Problems which are identified will be discussed with the Study Coordinators who will take appropriate measures. Safety information will also be included in trial status reports which serve as a basis of discussion during EORTC Group meetings. These reports will be made available to investigators participating in the study.

The EORTC Data Safety Monitoring Board (DSMB), a subcommittee of the EORTC Independent Data Monitoring Committee (IDMC), will review all safety problems identified by the EORTC Headquarters for which an advice is sought. This DSMB has early trials/drug development expertise and will provide a separate review process, having no access to outcome data. The EORTC DSMB will be primarily for phase I and non randomized phase II studies, but will also provide recommendations as an initial step in phase III trials to advise if the study should then go to the full IDMC.

The EORTC IDMC is charged with the interim review (planned or not planned) of randomized phase II and phase III studies. When interim analyses are carried out, the interim monitoring of efficacy and safety data is performed according to the Statistical Considerations chapter in this protocol and EORTC Policy 004 on “Independent Data Monitoring Committees and Interim Analyses”.

The results of the interim analyses are confidential and are discussed by the EORTC IDMC. The IDMC will subsequently recommend to the EORTC Group whether any changes should be made to the study.

No efficacy results will be presented at EORTC Group meetings or elsewhere before the trial is closed to recruitment and the data are mature for the analysis of the primary endpoint, unless recommended otherwise by the EORTC IDMC.

10 Translational research

This trial includes two translational research parts. The first part concerns TARC and the second concerns the cardiac translational study (Patients not participating in these studies can still be enrolled in the clinical study).

10.1 TARC translational research

10.1.1 Background

The Thymus and Activation-Regulated Chemokine (TARC) is present in tissue in approximately 90-95% of classical Hodgkin's Lymphoma (HL) patients, but is not in Nodular Lymphocyte Predominant Hodgkin's Lymphoma or other B cell derived lymphomas (Ref. 133). TARC is secreted by the HRS tumor cells in high levels and can be used as a tumor cell specific marker. It has been shown that serum levels at diagnosis correlate well with tumor extensiveness (Ref. 83; Ref. 82; Ref. 125).

Recent data from a study performed in the University Medical Center Groningen shows that final response to chemotherapy can already be predicted by plasma TARC levels after one cycle of chemotherapy. All non-responsive patients in this study had persistent high TARC levels whereas levels dropped to normal after one cycle of chemotherapy in all responsive patients. In fact, plasma TARC after one cycle or at mid-treatment showed a stronger positive predictive value for treatment failure than mid-treatment FDG-PET/CTimaging (Ref. 83). To exactly determine the prognostic value of TARC, TARC will be analyzed both on tissue samples and in serial serum samples in this trial (see summary table).

Secondly, other potential prognostic biomarkers will be analyzed on the tissue, serum and blood samples in a validation and explorative setting. Regarding the tissue markers, several markers related to the HRS cells and the micro-environment have been published. However, none of these markers have been clinically applied due to contradictory results or lack of proper validation studies (in uniformly treated cohorts of patients in controlled clinical settings). The most promising biomarkers include HLA class II, EBV and c-MET in tumor cells and CD68 in the reactive infiltrate (Ref. 126; Ref. 127; Ref. 128; Ref. 129). DNA analysis for HLA typing or a genome-wide association study (GWAS) approach may identify genetic determinants for treatment failure or other events (Ref. 130, Ref. 131, Ref. 132, Ref. 126). In serum, an explorative study regarding circulating miRNAs will be performed. Circulating miRNAs have shown both diagnostic and prognostic value in many other malignancies. Currently the UMCG is performing a pilot study on circulating miRNAs in HL.

10.1.2 Rationale

We showed that elevated serum TARC levels are strongly associated with disease activity. Based on the results of the study by Plattel et al. (Ref. 83), serum TARC holds potential as a tool to evaluate treatment response in a similar way as FDG-PET/CT imaging. If validated, future clinical trials might even study treatment allocation based on TARC levels. Furthermore, dynamics of serum TARC levels during follow-up will enable assessment of its value as a predictor for relapse. If TARC can be used for post-treatment evaluation during follow-up it may be feasible to reduce the use of post-treatment imaging studies. Besides the more tumor cell specific properties of this marker, other advantages of the use of serum TARC are the low costs and its non-invasive detection method.
The results of the other tissue and serum markers mentioned in the background might validate or reveal new potential biomarkers which can be used for future pre-treatment risk assessment or will offer additional information and further understanding of the pathophysiology of HL.

10.1.3 Objectives

10.1.3.1 Primary objective

- To determine the prognostic value of serum TARC measured after the first chemotherapy cycle (cycle 1) for the primary endpoint of the trial (FFTF)

10.1.3.2 Secondary objectives

- To determine the prognostic value of serum TARC measured after cycle 4 for the primary endpoint of the trial (FFTF)
- To determine the prognostic value of serum TARC measured after cycle 1 and 4 for response at the end of therapy
- To describe the dynamics of serum TARC values over time, including post-treatment follow-up in relation to possible disease recurrence
- To correlate the value of serum TARC measured at each time point (after cycle 1, after cycle 4 after completion of chemotherapy and after completion of radiotherapy) with simultaneously performed FDG-PET/CT and/or CT scan results
- To correlate pre-treatment TARC levels with IPS (International Prognostic Score) and Ann Arbor Stage

10.1.3.3 Tertiary aim

- To explore the clinical value of potential risk and prognostic biomarkers in diagnostic biopsy material, serum and DNA.

10.1.4 Patient samples and analysis

Diagnostic tissue samples will be obtained from the original pathology laboratories. DNA will be collected from blood at randomization. Serum samples will be collected in all study arms simultaneously with FDG-PET/CT and/or CT-imaging at diagnosis, after one chemotherapy cycle, after four chemotherapy cycles, after completion of chemotherapy, after radiotherapy (when given) and during the first two years of follow-up simultaneously with CT-imaging and at time of disease recurrence in between standard follow-up during the first two years after completion of treatment (if applicable, see summary table).

Sampling schedule for every included patient:

	Tissue sample	Blood sample for DNA	Serum sample
At diagnosis	x		
At randomization		x	x
After 1 cycle			x
After 4 cycles			x
Post chemotherapy			x
Post radiotherapy, if given			x
During the first two years of follow up (months 3, 6, 9, 12, 15, 18, 21 and 24)			x
At disease recurrence (if applicable) during or after treatment (during first 2 years)			x

10.1.5 Sample processing, storage and shipment

10.1.5.1 Tissue sample

From the diagnostic biopsy material, either 15 blank formalin fixed paraffin embedded tissue samples mounted on APES slides or a tissue block are requested. Detailed information on shipment is defined in the translational research guidelines.

10.1.5.2 DNA sample

For every patient participating in the TARC study, DNA will be isolated from whole blood lymphocytes. Detailed information on sample processing and shipment is defined in the translational research guidelines.

10.1.5.3 Serum

Serum will be collected from every patient participating in the TARC study at each time point as indicated in the sampling schedule. After blood draw, samples have to be transferred to the local laboratory in which serum will be isolated and stored until shipment according to the translational research guidelines.

10.1.5.4 TARC expression in tissue by IHC

Immunohistochemistry analysis will be performed by the UMCG. Tissue slides will be stained for TARC expression and for the other markers mentioned in the scientific background. Staining will be performed with well-defined commercially available primary detection antibodies and tissue slides will be pre-treated as described previously or according to the protocol provided by the manufacturer. CD30 staining will be performed to get a reliable estimate of the number of tumor cells. Slides will be scored for intensity and percentage of positive cells without prior knowledge of corresponding treatment results. DNA samples will be used for HLA typing and follow-up studies for the GWAS.

10.1.5.5 Serum samples

Serum samples will be analyzed for TARC levels by the UMCG after inclusion of all patients. TARC levels will be measured using a double antibody sandwich ELISA. All pre-treatment samples will be pre-diluted, to allow reliable measurement within the standard curve. Samples will be analyzed without prior knowledge of corresponding patient or treatment results.

Based on Plattel *et al.* (Ref. 83), the cut-off for elevated serum TARC levels is set to 1000 pg/mL.

10.1.6 Statistical considerations

10.1.6.1 Sample size and statistical power considerations

Power considerations are given for the first objective of this research, i.e. to determine the prognostic value of serum TARC measured after the first chemotherapy cycle (cycle 1) for the primary endpoint of the trial (FFTF).

The following table provides the assumptions underlying these analyses in terms of distribution of patients in the per-protocol population for the different strata determined by treatment arm, very early FDG-PET/CT and serum TARC level. The table also provides the expected FFTF rate at 5 years (under the alternative hypothesis of non-inferiority H1) in these strata.

At Randomization # patients (%)	Experimental arm 285 (100%)			Standard arm 285 (100%)		
At cycle 1						
PET % patients	Positive 30%		Negative 70%	Positive 30%		Negative 70%
TARC % patients	Positive 10%	Negative 20%	Negative 70%	Positive 10%	Negative 20%	Negative 70%
FFTF rate at 5 Years =	50%	65%	98%	50%	65%	98%

Because all patients in the standard arm receive the same protocol treatment, the evaluation of the prognostic value of serum TARC will be primarily performed in the standard arm.

All patients will be asked to take part in the TR project as part of the clinical trial. It is expected that all serial serum samples will be collected in at least two thirds of the patients and that this subpopulation will

be representative of the per-protocol population. This represents about 190 patients of the per-protocol population in the standard arm, of which 95% will be available for analysis (180 patients), as 5% of them will have tumors in which TARC is not expressed (Ref. 83).

Based on the hypotheses shown in the table above, FFTF rate at 5 years is expected to be 50% and 91% in patients with serum TARC after 1 cycle positive and negative respectively. This assumption is considered realistic based on Plattel *et al.* (Ref. 83). As for the primary endpoint analysis of the trial, it is assumed that the events follow a piecewise exponential distribution.

A total of 25 events are expected to be observed in the standard arm at the time of the final analysis of the primary endpoint of the trial. With this number of events, and based on the hypotheses above, the study will have 85% statistical power to reach the primary objective of the correlative study using a statistical test at a 5% two-sided significance level.

In this way, this biomarker evaluation study can be classified as having level IIB evidence, according to the criteria described by Simon *et al.* (Ref. 134).

10.1.6.2 Planned statistical analyses

The statistical analyses will be performed on the per-protocol population (see definition in section 8.2.2), restricted to the subset of patients with available serum TARC measurements.

Statistical tests will be performed at a 5% two-sided significance level. No adjustment for multiple analyses is planned.

Main baseline characteristics and outcomes of patients with and without samples for TARC assessment will be described for identification of possible selection biases.

The statistical methods to evaluate the primary and secondary objectives of this research are described in the next subsections.

Cox regression or logistic regression models will be adjusted for the factors used for stratification at randomization: stage (III vs. IV), gender and age (< 45 vs. ≥ 45). The fitted model will be evaluated for calibration and discrimination ability (Harrell's C-index). Bootstrap technique will be used to correct parameters for "optimism" and to assess the stability of the covariates (Ref. 135).

Because all patients in the standard arm receive the same protocol treatment, as mentioned above, each of the analyses will be primarily performed in the standard arm.

Additional analyses will be conducted in the standard and experimental arms pooled together. The statistical models will include a term for a TARC by treatment arm interaction, in order to assess the predictive value of TARC.

All graphical displays and descriptive statistics will be presented by treatment arm.

Exploratory analyses will be conducted to assess the relative prognostic effect of TARC and PET. A model including effects for both TARC and PET will be fitted. Because a large correlation between TARC and PET is anticipated, adjusted and unadjusted effects of TARC and PET are expected to differ markedly. The adjusted model will be compared to the models with TARC effect only (primary analysis) and with PET effect only (see section 8.2.7) in terms of calibration and discrimination. The aim of this investigation is to evaluate whether the prognosis of patients could be determined by TARC measurement instead of PET scan, thus gaining in cost effectiveness and burden for the patients. These analyses will use the central review of PET whenever available. These analyses will also be conducted primarily in the standard arm then in both arms pooled together.

10.1.6.2.1 Prognostic value of serum TARC measured after cycle 1 for the primary endpoint

Kaplan-Meier curves and estimated survival rates will be produced for patients with serum TARC positive versus negative, by treatment arm.

The prognostic value (positive versus negative) of serum TARC measured after the first chemotherapy cycle (cycle 1) for the primary endpoint of the trial (FFTF) will be evaluated using a Cox's proportional hazards model adjusted for stage (III vs. IV), gender and age (< 45 vs. ≥ 45).

The analysis will utilize landmark method (Ref. 90). The landmark time is determined as the time of serum sample collection after the first cycle of chemotherapy (22 and 29 days after the date of randomization for BEACOPPesc and ABVD respectively).

10.1.6.2.2 Prognostic value of serum TARC measured after cycle 4 for the primary endpoint

This analysis will be performed applying the methods used for the primary objective (see section 10.1.6.2.1 above). The landmark time will be adjusted to the timing of serum sample collection after 4 cycles of treatment.

10.1.6.2.3 Prognostic value of serum TARC measured after cycle 1 and 4 for response at the end of therapy

Serum TARC values (positive/negative) at cycle 1 and response at the end of therapy (CR/PR versus no response) will be cross-tabulated.

The prognostic value (positive versus negative) of serum TARC at cycle 1 for response will be evaluated using a logistic regression model.

The same analysis will be carried out for serum TARC values at cycle 4.

10.1.6.2.4 Serum TARC values over time

Serum TARC values as continuous variable (pg/ml) at each time point and change from baseline (pre-treatment) will be summarized descriptively. Graphical display will include box-plots over time.

Joint modeling of longitudinal and time-to-event data will be applied to explore the association between serum TARC values and risk of relapse.

10.1.6.2.5 Correlation between serum TARC values with FDG-PET/CT and/or CT scan results

Serum TARC values (positive/negative) and simultaneously performed FDG-PET/CT and/or CT scan results will be cross-tabulated at each time point:

- after cycle 1: serum TARC values versus PET result (positive/negative)
- after cycle 4, after completion of chemotherapy and after completion of radiotherapy: serum TARC values versus PET/CT or CT result (CR/PR/SD/PD)

Spearman rank correlation coefficients and their associated 95% confidence interval will be provided. Based on the study by Plattel et al (Ref. 83), a correlation coefficient between TARC and PET of the order of 0.5 is expected. The level of correlation is key for the interpretation of the prognostic effect of TARC and PET.

A similar analysis using serum TARC values as a continuous variable (pg/ml) will be performed. Graphical display will include a box-plot of serum TARC values versus FDG-PET/CT and/or CT scan results, at each time point.

10.1.6.2.6 Correlation between pre-treatment serum TARC levels with IPS and Ann Arbor Stage

Pre-treatment serum TARC values (positive/negative) will be cross-tabulated with IPS (< 3 versus ≥ 3). Spearman rank correlation coefficients and their associated 95% confidence interval will be provided. A similar analysis using pre-treatment serum TARC values as a continuous variable (pg/ml) will be performed. Graphical display will include a box-plot of pre-treatment serum TARC values versus IPS.

The same methods will be used to analyze the correlation between pre-treatment serum TARC levels with Ann Arbor Stage (III versus IV).

The aim of these analyses is to corroborate the findings of the study performed by Plattel *et al* (Ref. 83).

10.1.7 Laboratory in charge of analysis

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Departments of pathology and hematology

Responsible translational research persons:

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10.2 Cardiac Translational study

10.2.1 Background

Grade 3 or 4 acute cardiotoxicity is expected in approximately 1% of the patients and late cardiotoxicity in up to 10% of the patients after a follow up of about 10 years.

10.2.1.1 General aspects of chemo- and radiotherapy associated cardiotoxicity

Both chemotherapy and radiotherapy for HL may cause early and late cardiovascular toxicity. Whereas cardiotoxicity following radiotherapy is usually observed from 5-10 years of follow-up and onwards anthracycline-related toxicity may be observed at different intervals after therapy.

Radiation-associated heart disease in cancer survivors includes a wide spectrum of cardiac pathologies, such as coronary artery disease, myocardial dysfunction, valvular heart disease, pericardial disease, and electrical conduction abnormalities (Ref. 91, Ref. 92).

The most important cardiotoxic chemotherapeutic agents used in treatment for patients with HL are anthracyclines, especially doxorubicin and epirubicin. Anthracycline-related toxicity may be observed at different intervals after therapy. Cardiotoxicity often presents as electrocardiographic changes and arrhythmias, or as a cardiomyopathy leading to congestive heart failure. Anthracycline-associated cardiotoxicity is caused by direct damage to the cardiomyocyte. Several risk factors for anthracycline-associated cardiotoxicity have been identified. The occurrence of anthracycline-associated cardiotoxicity is strongly related to the cumulative dose (Ref. 93, Ref. 94). Doses less than 500 mg/ m^2 are usually well tolerated. The total dose of anthracyclines during first-line therapy for HL is relatively low compared with treatment regimens for breast cancer and pediatric malignancies. See table for anthracycline doses in H11 trial and for comparison some other schedules used to treat NHL (Cyclophosphamide, Doxorubicin (or Adriamycin), Vincristine (Oncovin) and Prednisolone=CHOP) and breast cancer patients (Adriamycin, Cyclophosphamide=AC).

Chemotherapy regimen	Treatment	Adriamycin dose per cycle on days	Total dose in mg/m^2
H11 trial			
6 BEACOPP esc (Ref. 95)	Standard arm H11	35 mg/m^2, day 1	210
6 ABVD (Ref. 8)	Experimental arm H11, PET negative after 1 ABVD	25mg/ m^2, day 1 and 8	300
1 ABVD+ 6 BEACOPP esc	Experimental arm H11, PET positive after 1 ABVD	25mg/ m^2, day 1 and 8 35 mg/ m^2, day 1	260
Other regimens HL, NHL breast cancer for comparison			
6 MOPP-ABV hybrid (Ref. 32, Ref. 96)	HL (H34 study)	35 mg/ m^2, day 8	210
6 CHOP (Ref. 96, Ref. 97)	Aggressive NHL	50 mg/ m^2, day 1	300
6 AC (Ref. 96, Ref. 98, Ref. 99)	Adjuvant therapy breast cancer	60 mg/ m^2, day 1	360
6 TAC (Ref. 100)	Adjuvant therapy breast cancer	50 mg/ m^2, day 1	300

Whether cardiotoxicity following chemotherapy and radiotherapy is additive or synergistic is still unclear. Several clinical studies showed that anthracycline-containing therapy may further increase the radiation related risk of congestive heart failure and valvular disorders by two to three-fold compared to radiotherapy alone (Ref. 92, Ref. 101) this effect may also be more than additive (Ref. 102).

A recent British study also showed that the increased risks for death from myocardial infarction may be related not only to supradiaphragmatic radiotherapy but also to anthracycline and vincristine treatment. The risk of death from myocardial infarction was increased for patients who did not receive supradiaphragmatic radiotherapy but had received vincristine with an SMR of 2.2 (95% CI=1.6 to 3.0) or anthracyclines with an SMR of 3.2 (95% CI = 1.9 to 5.2). Especially those who were treated with the ABVD regimen had an increased risk (SMR = 7.8, 95% CI = 1.6 to 22.7) (Ref. 103).

10.2.1.2 Management of chemotherapy-related cardiotoxicity

Currently there are no indications that anthracycline-associated congestive heart failure needs a specific approach. Treatment generally focuses on correcting underlying abnormalities such as increased afterload and decreased contractility and frequently includes treatment with angiotensin-converting enzyme (ACE) inhibitors and/or beta-blockers (Ref. 104). Present guidelines developed for treating patients with asymptomatic left ventricular dysfunction or heart failure (not specifically after cancer treatment) advise the use of beta-blockers, ACE-inhibitors in early stages of heart failure and diuretics and aldosteron blockers in later stages of heart failure (Ref. 105). There is an indication of a possible beneficial effect of ACE inhibitors in high risk patients showing troponin I release after cardiotoxic chemotherapy (Ref. 106).

10.2.1.3 Prevention of chemotherapy-related cardiotoxicity

Rather simple measures to prevent cardiotoxicity are the limitation of both cardiotoxic chemotherapy (especially anthracyclines), and radiation volume and – dose as much as possible.

Anthracyclines release free radicals that damage the cardiac myocytes, which are especially susceptible to free radical damage because of their highly oxidative metabolism and poor antioxidant defenses. The free-radical scavenging cardioprotectant, dexrazoxane has been shown to reduce anthracycline-associated myocardial injury in rats (Ref. 107) and in selected studies in humans (Ref. 108). More information is however needed before this agent can be introduced in clinical practice.

10.2.1.4 Cardiovascular risk prediction

Because of the extensive use of cardiotoxic therapy in the treatment of several malignancies (not only in lymphoma but also for instance in breast cancer) there is growing interest in possibilities to monitor myocardial damage from anti-cancer therapy, to guide initiation of cardioprotective therapy and to identify people at increased risk of cardiovascular toxicity. Cardiac biomarkers and genetic variability could be of great importance in cardiovascular risk prediction following anti-cancer therapy.

10.2.1.4.1 Ejection fraction measurement

Cardiac ejection fraction will be measured using a MUGA scan (Multi Gated Acquisition Scan).

10.2.1.4.2 Cardiac biomarkers

10.2.1.4.2.1 Troponins

Circulating cardiac troponin (cTn, which can be troponin I or troponin T) is a sensitive and specific biomarker for detection of myocardial injury. Although most commonly used to detect myonecrosis in the setting of ischemia, cTns are also elevated with other acute and chronic disease processes, including heart failure (Ref. 109).

Several studies suggest that troponin I elevations, soon after chemotherapy and after short-term follow-up, are associated with left ventricular dysfunction and cardiac events during follow-up (Ref. 110, Ref. 111). In the same studies, the absence of troponin I elevations could not exclude a transient left ventricular dysfunction during chemotherapy, but no left ventricular dysfunction was seen during follow up (Ref. 110, Ref. 111).

Troponin T and I have similar sensitivities and specificities for detecting myocardial injury, and both may be used according to the guidelines on non-ST-elevation myocardial infarction.

Only one (T or I) elevated troponin level above the established cutoff is required to establish the diagnosis of acute myocardial infarction, according to the American college of cardiology guidelines for Non–ST-Elevation Myocardial Infarction. The timing of troponin elevations after anthracyclines may differ; according to Cardinale et al (Ref. 110) the time until troponin I elevation > 0.04 ng/L occurred was within 36 hours after the end of chemotherapy infusion in 88% of patients. Since 2010 most labs use high sensitive troponin T (hsTnT), a more sensitive and more precise cTn measurement compared to the conventional TnT assay. HsTnT also enables measurement of abnormalities within 10 hours after an event.

Since a large between-method variation in troponin measurements has been shown (Ref. 112), troponin samples will be frozen and measurements will be performed in a central lab.

10.2.1.4.2.2 Natriuretic peptides

In addition to traditional imaging methods, serum biomarkers may also be useful in helping diagnose asymptomatic left ventricular dysfunction or heart failure. The serum biomarkers brain natriuretic peptide (BNP) and N-terminal fragment (NT-proBNP) are most commonly used. BNP is a natriuretic hormone, produced predominantly by the heart, and released into the circulation after it is cleaved from the C-terminal of its pro-hormone pro-BNP. The biologically inactive N-terminal fragment (NT-proBNP) that also results from the cleavage of pro-BNP, is released into the blood circulation along with BNP. In heart failure patients, elevation of both BNP and NT-proBNP levels is seen (Ref. 113). However, there are limitations to BNP or NT-proBNP measurements, since other diseases may also cause abnormal BNP levels and serum levels also depend on other factors like age. Information on the possible value of biomarkers in monitoring asymptomatic left ventricular dysfunction and early diagnosis of heart failure following cardiotoxic chemotherapy (Ref. 114, Ref. 115, Ref. 116, Ref. 117) and radiation exposure of the heart (Ref. 118) is still scarce and therefore more research is needed concerning these subjects.

10.2.1.4.2.3 Genetic profiling

The potential role of genetic variability in the pathogenesis of chronic cardiotoxicity, like congestive heart failure, remains to be elucidated. There is growing evidence in humans showing that genetic susceptibility may play an important role in the risk of anthracycline-associated cardiotoxicity (Ref. 119, Ref. 120, Ref. 121, Ref. 122).

Using a candidate gene approach in 170 cardiomyopathy cases after childhood cancer, an important role for single nucleotide polymorphisms (SNPs) in two candidate genes CBR1 and CBR3, involved in pharmacodynamics of anthracyclines was shown (Ref. 121). A SNP in the CBR3 gene predicted risk of cardiomyopathy in children exposed to low to moderate doses of anthracyclines (< 250 mg/m^2), while exposure to higher doses of anthracyclines (> 250 mg/m^2) was associated with an increased cardiomyopathy risk irrespective of CBR3 genotype. However, this same SNP was not associated with risk of cardiac events in another recent study (Ref. 122) possibly related to different cardiac endpoints in the two studies, or chance. In the latter study, a much broader candidate gene study of 2,977 SNPs in 220 key drug biotransformation genes was performed in a childhood cancer cohort with 78 cardiac events, resulting in significant associations with 9 SNPs; part of which were confirmed in a replication cohort. Verification of these associations is needed in much larger studies. Identification of the involved genes and their variants could help to develop safer individualized therapies. Genetic variants predisposing to congestive heart failure in general, apart from anthracyclines, may also contribute to cardiotoxicity in HL survivors.

10.2.2 Objectives

10.2.2.1 Primary objective

- To monitor cardiotoxicity during therapy and during (long term) follow up

10.2.2.2 Secondary objectives

- To investigate the relationship between acute and late cardiotoxicity
- To evaluate tool(s) to detect asymptomatic left ventricular dysfunction
  - Biomarkers (troponin, natriuretic peptides)
  - Ejection fraction
  - A combination of biomarkers and ejection fraction
- To test how can we identify people at risk to develop late cardiac damage
  - Biomarkers
  - Genetic profiling

10.2.3 Cardiac monitoring

All items concerning cardiac monitoring are summarized in the summary table. In addition to the measurements already described in the trial protocol the cardiac side study consists of measurements of troponin, genetic profiling and more extensive specific cardiac tests during follow up.

10.2.3.1 Before and during treatment

10.2.3.1.1 Specific cardiac measurements

ECG and echocardiography/MUGA Scan will be performed as a part of screening procedures (before treatment start); the results will be used in the analysis.

10.2.3.1.2 Laboratory tests

NT proBNP or BNP and serum sample for Hs troponinT before the start of chemotherapy, during chemotherapy, before every cycle and at end of treatment response evaluation. For detailed information see specific translational research guidelines

10.2.3.1.3 Genetic research

DNA blood sample: will be done before start of chemotherapy (will be used for genetic profiling). Normal genomic DNA will be extracted from blood samples before start of chemotherapy (will be used for genetic profiling- which may include genome sequencing). If the patient accepted to participate to both translational studies, only one sample will be withdrawn and no additional sample will be requested.

10.2.3.2 During follow up

10.2.3.2.1 Specific cardiac measurements

ECG (1, 3 and 5 years after the end of treatment and after 5 years, every 5 year).

Echocardiography (1, 3 and 5 years after the end of treatment and after 5 years, every 5 years).

Ejection fraction (MUGA scan; 1, 3 and 5 years after the end of treatment and after 5 years, every 5 years) – these measurements are part of the standard follow up and not restricted to those who participate in the cardiac side study.

10.2.3.2.2 Laboratory tests

NT proBNP or BNP and lipid profile (every follow up visit)
Hs troponin T: at first follow up visit 3 months after end of protocol treatment.

10.2.3.3 Possible therapeutic consequences of cardiac evaluation

Material for troponin measurements and genetic profiling will be collected during the trial, but measurements will not be performed immediately. Therefore the results will have no influence on the treatment of the patient.

Natriuretic peptides will be measured directly. In case of abnormal values of biomarkers a cardiologist should be consulted. Cut off values of (NT-pro) BNP are different for acute heart failure (NT-proBNP > 400 pg/ml; BNP > 100 pg/ml) and chronic heart failure (NT-proBNP > 125 pg/ml; BNP > 35 pg/ml).

In case of abnormal findings during cardiac ultrasound and/or a left ventricular ejection fraction of 45-49% a cardiologist should be consulted and in case of a left ventricular ejection fraction <45% the patient should be referred to a cardiologist for further examination.

Summary table of required investigations for the cardiac side study during treatment

Examination	Before treatment start	During treatment	End of treatment		Follow up		
		After every cycle	After end of CT	After end of RT	Year 1 and 2 (1/3 mnths)	Year 3-5 (1/6 mnths)	> 5 years (yearly)
History	x	x	x	x	x	x	x
Physical examination	x	x	x	x	x	x	x
ECG	x		x	x	x*	x*	x*
Ejection fraction	x		x	x	x*	x*	x*
Echocardiography	x				x*	x*	x*
Lipid profile	x				x*	x*	x*
BNP or proBNP	x	x	x	x	x	x	x
HsTroponinT	x	x	x	x	x**		
Sample for genetic profiling	x						

Items in italics indicate tests only for those participating in cardiac side study.

History: documentation of cardiac and/or pulmonary complaints, medication

Physical examination: measurement of length, weight, blood pressure

* ECG, echocardiography, ejection fraction and lipid profile: after 1, 3 and 5 years after the end of treatment and from 5 years every 5 year

** only at 3 months after the end of treatment

10.2.3.4 Sample processing, storage and shipment

Every participating center will have a contact person responsible for the laboratory processing and storage.

10.2.3.4.1 Serum samples for natriuretic peptides

NTproBNP or BNP measurements will be performed at the local hospital according to local protocol from every included patient at each time point as indicated in the sampling schedule.

10.2.3.4.2 Serum samples for troponin tests

Serum will be collected from every included patient at each time point as indicated in the sampling schedule. After blood draw, samples have to be transferred to the local laboratory in which serum will be isolated and stored -20°C until shipment according to the translational research guidelines.

10.2.3.4.3 DNA samples

For every patient participating in the cardiac side study, DNA will be isolated from whole blood lymphocytes. Detailed information on sample processing and shipment is defined in the translational research guidelines.

10.2.3.5 Statistical considerations

10.2.3.5.1 Planned sample size and statistical power considerations

All patients will be asked to take part in the cardiac project as part of the clinical trial. It is expected that these cardiac investigations will be performed in at least half of the patients of the per-protocol population, i.e. 285 patients.

As part of the primary objective of this research is the estimation of the rate of patients with (a) symptomatic heart failure. The precision of this estimate achieved with this number of patients is evaluated: with 285 patients, and assuming that the rate of patients with (a) symptomatic heart failure is 10.0%, the width of the 95% confidence interval for this rate will be +/- 3.5%.

10.2.3.5.2 Planned statistical analyses

The statistical analyses will be performed on the per-protocol population (see definition in section 8.2.2), restricted to the subset of patients with available cardio toxicity measurements.

Most analyses will be descriptive only and presented overall and for each arm separately. Parameters at each time point (and change from baseline, when applicable) will be estimated and presented with 95% confidence intervals, for each arm separately. Graphical display will include box-plots over time and individual profiles over time. When applicable, the correlation coefficient between two parameters and its 95% confidence interval will be computed.

Statistical tests will be performed at a 5% two-sided significance level. No adjustment for multiple analyses is planned.

Main baseline characteristics and outcomes of patients with and without cardio toxicity assessment will be described for identification of possible selection biases.

The classification of cardiotoxicity between acute and late will follow the same definition for acute and late adverse events specified in sections 7 and 8.

The statistical methods to evaluate the primary and secondary objectives of this research are described in the next subsections. In addition, subset analyses will be carried out to evaluate cardiotoxicity in patients who did/did not receive mediastinal RT.

Data concerning functional tests and biomarkers from this trial will have to be pooled with prospectively collected data from other trials. Furthermore, depending on the results of the genetic profiling possibilities for cross validation of these results using samples from other study groups will be evaluated.

10.2.3.5.2.1 Rate of (a) symptomatic heart failure

The primary objective is to monitor cardiotoxicity during therapy and during (long term) follow up. The primary endpoint will be (a)symptomatic heart failure defined as:

- as a reduction of the left ventricular ejection fraction (LVEF) from baseline of ≥5% to less than 50% with symptoms of heart failure (HF),
- or an asymptomatic reduction of the LVEF from baseline of ≥10% to less than 50%.

Classical symptoms of HF include shortness of breath, fatigue, fluid retention, and reduced exercise tolerance. The New York Heart Association (NYHA) functional classification categorizes HF according to the degree of effort required to elicit symptoms, from I (no limitation upon normal physical exertion) to IV (at rest) (see Appendix D).

The number and % of patients with (a) symptomatic heart failure will be tabulated at each time point. 95% confidence intervals for the rate of cardiotoxicity will be provided.

10.2.3.5.3 Rate of other cardiotoxic events

Additional cardiotoxicity events will be evaluated and include: myocardial infarction; cardiac ischaemia leading to an intervention and valvular replacement. The rate of these events will be estimated with their 95% confidence intervals.

10.2.3.5.3.1 Relationship between acute and late cardiotoxicity

- The number and % of patients with acute cardio toxicity and late cardio toxicity will be tabulated overall and at each time point. 95% confidence intervals for the rate of acute/late cardiotoxicity will be provided.
- The number of patients experiencing acute and late cardio toxicity will be cross-tabulated. Spearman rank correlation coefficient and its 95% confidence interval will be produced.

10.2.3.5.3.2 Tools to detect asymptomatic left ventricular dysfunction

- Biomarkers

The following biomarkers will be evaluated:

  - BNP or NTproBNP values, expressed in pg/ml. The following cut-off values will be used to categorize the values (low/high): BNP ≥ 35pg/l (Ref. 136) or NTproBNP ≥ 125pg/l (Ref. 123).
  - Troponin, expressed in µg/lm. The cut-off value to categorize the values (low/high) will be determined according to the selected central laboratory.

- Ejection fraction

Parameters of interest will be the following:

  - Left ventricular ejection fraction (LVEF, %) as measured using the MUGA scan
  - End-diastolic volume (EDV, ml), End-systolic volume (ESV, ml), Stroke volume (SV=EDV-ESV, ml), Left ventricular ejection fraction (LVEF, %) as measured by echocardiography
  - A cut-off value of 50% will be used to dichotomize LVEF values

The statistical analysis will consist of:

- Descriptive analysis of these parameters as continuous/categorical variables, over time. Graphical display will include box-plots and individual profiles over time. A repeated measures model will be fitted to assess the trend over time.
- The association between BNP or NTproBNP, Troponin and LVEF values will be assessed at each time point. Scatter plots of ejection fraction values (LVEF) versus each of the measured biomarkers (BNP or NTproBNP, Troponin) will be displayed to appreciate the nature of the relationship between these parameters at each time point. Spearman rank correlation coefficient and its 95% confidence interval will be produced. Changes in functional tests (EF) or biomarkers (HsTroponinT, NTproBNP or BNP) during treatment will be tested as early markers for late cardiotoxicity using logistic regression modeling.

10.2.3.5.3.3 Risk factors for developing late cardiotoxicity

Baseline LVEF, changes in lipid parameters during treatment and the cumulative doses of chemotherapy and radiotherapy during protocol treatment and as salvage treatment will be tested as possible risk factors for late cardiotoxicity using logistic regression modeling.

Lipid profile parameters will consist of total cholesterol, HDL, LDL and triglycerids, expressed in mmol/l. The values will be classified using the guidelines provided by Mayo Clinic and applicable to Canada and most Europe (http://www.mayoclinic.com/health/cholesterol-levels/CL00001) (Ref. 123):

Total cholesterol	Below 5.2 mmol/L	Desirable
	5.2-6.2 mmol/L	Borderline high
	Above 6.2 mmol/L	High
LDL cholesterol	Below 1.8 mmol/L	Ideal for people at very high risk of heart disease
	Below 2.6 mmol/L	Ideal for people at risk of heart disease
	2.6-3.3 mmol/L	Near ideal
	3.4-4.1 mmol/L	Borderline high
	4.1-4.9 mmol/L	High
	Above 4.9 mmol/L	Very high
HDL cholesterol	Below 1 mmol/L (men) Below 1.3 mmol/L (women)	Poor
	1.3-1.5 mmol/L	Better
	Above 1.5 mmol/L	Best
Triglycerides	Below 1.7 mmol/L	Desirable
	1.7-2.2 mmol/L	Borderline high
	2.3-5.6 mmol/L	High
	Above 5.6 mmol/L	Very high

10.2.4 Laboratory in charge of analysis

The Netherlands Cancer Institute (NKI-AVL, The Netherlands) and University Medical Center Groningen (UMCG, The Netherlands)

10.2.5 Research contact persons for cardiac side study

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10.3 Storage and shipment

Every participating center will have a contact person responsible for the laboratory processing and storage. Blood tubes for DNA will be sent directly to UMCG in special envelops, where DNA will be isolated to guarantee high DNA quality and appropriate storage. Tissue slides will be will be stored at the local participating hospital until shipment to a central location. All serum samples will be stored at the local participating hospital at -20°C until shipment. Storage and shipment of samples will be monitored by the EORTC, the UMCG and and the NKI-AVL using the EORTC tracking system. For detailed information see separate translational research guidelines.

10.4 Development of technical appendices

The translational projects will be the result of the work of collaborating institutions and EORTC HQ. Separate technical appendices will be jointly developed for each future translation research project. These appendices will be written before starting any analysis and will specify the analytical and methodological details and will precise data transfer procedures. Clinical and patient reported outcome data will be stored in the EORTC clinical database as well as biological investigational data evaluated at local sites. Biological investigational data evaluated at central laboratories will be stored at these collaborating laboratories and subsequently transferred to EORTC HQ. Data sharing will be performed according to existing Standard Operating Procedures.

10.5 General principles for human biological material (HBM) collection

Human biological material (HBM) collection involves the collection and storage of biological material, residual biological material or derivatives in compliance with ethical and technical requirements.

Biobanking refers to the chain of procedures that encompass the life cycle of the biological material, e.g. from collection, shipping to long term storage and use, and may also be subject to local regulation and/or national/international legislation.

In this study, biological material will be centralized and stored at NKI-AVL (EORTC certified biobank). From here, the biological material will be used or distributed to the other research laboratories involved in the translational research (TR) projects specified in this protocol or defined in the future. The biobank will perform the cardiac side study as stated in the protocol.

The following principles apply to storage of HBM:

The biobank will have a designated manager responsible for collection and will act as a communication point with the EORTC.

The collected HBM should be documented, i.e. the amount remaining and its location.

The Group's Scientific Steering Committee (SSC) will be responsible for TR project review and prioritization, including the consideration of newly proposed TR projects not specified in the protocol.

Final decisions on the use of HBM will be determined by a majority vote of the SSC. Additional expertise may be sought through advisory non-SSC members.

Access to HBM (see EORTC Biobanking Policy POL020): HBM may be used for another purpose for which it was originally collected, subject to meeting ethical principles/and is covered by informed consent/ethics approval. In the case of secondary use of HBM, (i.e. for new TR projects that are not specified in the clinical study protocol and that were not foreseen at the time of protocol writing) interested parties may apply for the use of HBM and will follow the next steps:

A short description of the new TR projects will be written and submitted to EORTC HQ for coordination with the SSC.

The SSC will prioritize the TR projects. Access procedures defined by the SSC will build on the following key points:

- Project prioritization
  - should be strongly based on scientific merit,
  - should consider the contribution of the different investigators to the trial and TR project,
  - will take into consideration if the applicant is an EORTC member or not (whilst maintaining the principle of access to the wider scientific community and commitments owed to study participants and ethical committees).
- Protection of confidentiality must be respected.

An EORTC HQ feasibility check, including recommendations for regulatory and ethical matters and other restrictions on the use of the HBM, will take place. If in the event the HBM collections are still retained at individual clinical sites, the TR project leader and the involved EORTC Group are responsible for collecting and providing information on availability of HBM for the feasibility assessment.

Prioritized TR projects will then be reviewed by the Translational Research Advisory Committee (TRAC).

Once SSC prioritization, the EORTC HQ feasibility assessment, and TRAC review are complete and when all applicable competent Ethics Committees approvals are in place and ethical principles are met, the TR project can be activated and HBM release and analysis can commence.

The EORTC Executive Committee will mediate any disagreements of opinion between TRAC, the EORTC HQ feasibility assessment, the SSC and the TR project leader(s), as needed.

11 Publication policy

All publications must comply with the terms specified in the EORTC Policy 009 “Release of Results and Publication Policy”, version 4.02 dated 19 March 2012.

The final publication of the main trial results will be written by the EORTC Study Coordinator on the basis of the final analysis performed at the EORTC Headquarters and published in a major scientific journal.

The final publication of associated translational research studies will be written by the Coordinator of the corresponding translational research study.

Authors of the manuscript(s) will include the Study Coordinators, the investigators who have included more than 5% of the eligible patients in the trial by order of number of patients included, the imaging central reviewer, the statistician and clinical research physician in charge of the trial at the EORTC Headquarters. For publication of results of reviews (for instance imaging and quality assurance of radiotherapy) and translational research results, co-authors will also include scientific collaborators who made substantial contribution to the research.

The title of all manuscripts will include “EORTC”, and all manuscripts will include an appropriate acknowledgment section, mentioning all investigators who have contributed to the trial, the EORTC Headquarters staff involved in the study, as well as supporting bodies (NCI, cancer leagues, supporting company).

Prior to submission, all publications (papers, abstracts, presentations) including data pertaining to patients from the present trial will be submitted for review to the EORTC Headquarters, to all co-authors, and to the Steering Committee of the Group.

The above rules are applicable to publications involving any individual patient registered/randomized in the trial.

12 Investigator authorization procedure

Investigators will be authorized to register and/or randomize patients in this trial only once they have returned the following documents to their Data Center (for the EORTC investigators see chapter 18: Administrative responsibilities, for non-EORTC investigators: see your group specific appendix):

- The updated signed and dated Curriculum Vitae of the Principal Investigator
- The (updated) list of the normal ranges, for their own institution signed and dated by the head of the laboratory. Please make sure normal ranges are provided also for those tests required by the protocol but not routinely done at the investigator's institution.
- A Confirmation of Interest Form and Study Agreement between EORTC and Principal Investigator, stating that the investigator will fully comply with the protocol. This must include an estimate of yearly accrual and a statement on any conflict of interest that may arise due to trial participation.

NB: A signed conflict of interest disclosure form will be required only if a possible conflict is declared on the Commitment Statement and Study Agreement.

- A copy of the favorable opinion of the local or national (whichever is applicable) ethics committee mentioning the documents that were reviewed (including the version numbers and version dates of all documents). A list of all members of the ethics committee is also requested.
- A copy of the translated and adapted (according to all national requirements) Patient Information / Informed Consent sheet. Version numbers and dates must be clearly stated on each page.
- The signature log-list of the staff members with a sample of each authorized signature and the indication of the level of delegations.
- The full name, address, phone numbers and e-mail address of the local pharmacist who will be responsible for the trial medication (for any trial where the drug will be provided).
- An accreditation, a certification, an established quality control / external quality assessment or another validation should be provided for the own laboratory.
- Imaging Guidelines "read and understood" acknowledgment signature page

The center specific applicable list of required documents will be included in the protocol activation package, with proper instructions as required by this protocol, your group and / or the applicable national law

The new investigator will be added to the "authorization list", and will be allowed to register/randomize patients in the trial as soon as

- All the above mentioned documents are available at their Data Center.
- All applicable national legal and regulatory requirements are fulfilled.

Patient registration/randomization from centers not (yet) included on the authorization list will not be accepted.

13 Patient randomization procedure

Patient randomization will only be accepted from authorized investigators (see chapter on “investigator authorization procedure").

A patient can only be randomized after verification of eligibility. Both the eligibility check and randomization must be done before the start of the protocol treatment.

An extensive list of questions to be answered during the randomization procedure is included in the registration checklist. This checklist should be completed by the responsible investigator before the patient is randomized.

STANDARD INFORMATION REQUESTED:

- EORTC institution number
- EORTC protocol number
- step number: 1
- name of the responsible investigator
- patient's code (*maximum 4 alphanumerics*)
- patient's birth date (*day/month/year*)

PROTOCOL SPECIFIC QUESTIONS:

- all eligibility criteria will be checked one by one
- date of written informed consent (*day/month/year*)
- participation to the TARC TR, the cardiac study and/or future research

At the end of the procedure, the treatment will be randomly allocated to the patient, as well as a **sequential patient identification number (“seqID”)**. The sequential identification number attributed to the patient at the end of the randomization procedure will allow the identification of the patients in the VISTA/Remote Data Capture system (VISTA/RDC) that will be used to complete the Case Report Forms.

All participants should randomize patients directly on the **EORTC online randomization system** (ORTA = online randomized trials access), accessible 24 hours a day, 7 days a week, through the internet. To access the interactive randomization program, the investigator needs a username and a password (which can be requested at www.eortc.be/random).

In case of problems, participants can phone the EORTC Headquarters from 9.00 am to 5.00 pm (Belgian local time) from Monday through Friday to randomize patients via the EORTC call center. Randomization via the phone is not available on Belgian holidays. A list of these holidays is available on the EORTC web site (www.eortc.be/random) and it is updated annually.

Through Internet:	www.eortc.be/random
In case of problems randomization by phone:	*+32 2 774 16 00*

14 Forms and procedures for collecting data

14.1 Case report forms and schedule for completion

Data will be reported on the **electronic CRFs specifically designed by the EORTC Headquarters for this study. Those CRFs will be used by all cooperative groups.** Forms should be electronically sent to the EORTC Headquarters through the VISTA/RDC (Remote Data Capture) system, with the exception of the SAE form which is a paper CRF.

SERIOUS ADVERSE EVENTS SHOULD BE IMMEDIATELY REPORTED ACCORDING TO THE PROCEDURE DETAILED IN THIS PROTOCOL (see chapter on Reporting of Serious Adverse Events).

A. Before the treatment starts

- The patient must be registered/randomized in the trial by INTERNET or in case of problems by phone.
- The electronic CRFs, to be completed for a patient, are available on the VISTA/RDC website one day after the registration/randomization on http://rdc.eortc.be/ or on http://www.eortc.org in the section for investigators. The SAE forms will be made available to the institution at the time the institution is authorized.

B. During/after treatment

The list of forms to be completed for this study and their submission schedule are available on the VISTA/RDC website and are also described in the "guidelines for completion of case report forms" that are provided to each participating investigator.

ALL Forms must be electronically approved and sent by the responsible investigator or one of his/her authorized staff members

14.2 Data flow

The forms must be completed electronically, with the exception of the paper forms (SAE forms), according to the schedule defined in the guidelines for completion of Case Report Forms.

The list of staff members authorized to enter data (with a sample of their signature) must be identified on the signature log and sent to the EORTC Headquarters by the responsible investigator before the start of the study. To enter the RDC system, the investigator or authorized staff member needs to use the same username and password that are used to access the interactive randomization program (ORTA).

In all cases, it remains the responsibility of the principal investigator to check whether data are entered in the database as soon as possible and that the electronic forms are filled out completely and correctly.

The EORTC Headquarters will perform extensive consistency checks on the received data and will issue queries in case of inconsistent data. The queries for the electronic forms will appear in the VISTA/RDC system and must be answered there directly.

The EORTC data manager will subsequently apply the corrections into the database.

When satellite institutions are involved, all contact is made exclusively with the primary institution, for purposes of data collection and all other study related issues.

If an investigator (or an authorized staff member) needs to modify a CRF after the form has been electronically sent to the EORTC Headquarters, he/she should create a request for data correction in the VISTA/RDC system.

15 Reporting of Serious Adverse Events

ICH GCP and the EU Directive 2001/20/EC require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.

15.1 Definitions

These definitions reflect the minimal regulatory obligations; specific protocol requirements might apply in addition.

AE: An **Adverse Event** is defined as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment”. An adverse event can therefore be any unfavorable and unintended signs (such as rash or enlarged liver), symptoms (such as nausea or chest pain), an abnormal laboratory finding (including results of blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment, whether or not considered related to the investigational medicinal product.

AR: An **Adverse reaction of an investigational medicinal product** is defined as “any noxious and unintended response to a medicinal product related to any dose administered”.

All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

UAR: An **Unexpected Adverse Reaction** is “any adverse reaction, the nature, or severity of which is not consistent with the applicable product information" (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for a marketed product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

Severity: The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe, or as described in CTC grades); the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as “serious,” which is based on patient/event outcome or action criteria usually associated with events that pose a threat to patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

SAE: A **Serious Adverse Event** is defined as any untoward medical occurrence or effect in a patient, whether or not considered related to the protocol treatment, that at any dose:

- results in death
- is life-threatening (i.e. an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or prolongation of existing patient hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect

- is a medically important event or reaction.

  Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

SAR: A **Serious Adverse Reaction** is defined as any SAE which is considered related to the protocol treatment.

SUSAR: Suspected Unexpected Serious Adverse Reaction.

SUSARs occurring in clinical investigations qualify for expedited reporting to the appropriate Regulatory Authorities within the following timeframes:

- Fatal or life-threatening SUSARs within 7 calendar days
- Non-fatal or non-life-threatening SUSARs within 15 calendar days

Inpatient hospitalization: a hospital stay equal to, or greater than, 24 hours.

Second primary malignancy is one unrelated to the treatment of a previous malignancy (and is NOT a metastasis from the previous malignancy).

Secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the previous malignancy.

15.2 Exceptions

The following situations do not need to be reported as SAEs:

- Elective hospitalization for pre-existing conditions that have not been exacerbated by trial treatment.
- A hospitalization which was planned before the patient consented for study participation and where admission did not take longer than anticipated.
- A hospitalization planned for protocol related treatment or protocol related procedure as per institutional standard timelines.
- Social and/or convenience admission to a hospital.
- Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an (S)AE .
- Situations where an untoward medical occurrence did not occur (palliative care, rehabilitation, overdose without occurrence of an adverse event).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

By EORTC convention, clinical events related to the primary cancer being studied or to the primary cancer progression are not to be reported as SAEs, even if they meet any of the seriousness criteria from the standard SAE definition, **unless** the event is more severe than expected and therefore the investigator considers that their clinical significance deserves reporting.

15.3 Severity assessment

The severity of all AEs (serious and non-serious) in this trial should be graded using CTCAE v4.0 www.eortc.org\investigators-area\ctc

15.4 Causality assessment

The investigator is obligated to assess the relationship between protocol treatment and the occurrence of each SAE following definitions in this table:

Relationship to the protocol treatment	**Description**
Reasonable possibility	There is a reasonable possibility that the protocol treatment caused the event
No reasonable possibility	There is no reasonable possibility that the protocol treatment caused the event

The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, medical history, concurrent conditions, concomitant therapy, other risk factors, and the temporal relationship of the event to the protocol treatment will be considered and investigated.

The decision will be recorded on the SAE form and if necessary the reason for the decision will also be recorded.

15.5 Expectedness assessment

The expectedness assessment is the responsibility of the sponsor of the study. The expectedness assessment for all drugs will be performed against the Summary of Products Characteristics

15.6 Reporting procedure for investigators

This procedure applies to all Serious Adverse Events (SAEs) occurring from the time a subject is registered until 30 days after last protocol treatment and to any SAE that occurs outside of the SAE detection period (after the 30-days period), if it is considered to have a reasonable possibility to be related to the investigational product or study participation.

Registration till 30 days after last protocol treatment:	All SAEs
From day 31 after last protocol treatment:	Only related SAEs

All reporting must be done by the principle investigator or authorized staff member (i.e. on the signature list) to confirm the accuracy of the report.

All SAE data must be collected on the study-specific SAE form.

All SAEs must be reported immediately and no later than 24 hours from the time the investigator or staff became aware of the event.

All SAE-related information needs to be provided in English.

All additional documents in local language must be accompanied by a translation in English, or the relevant information must be summarized in a follow-up SAE report form.

Investigators participating through **EORTC** must fax all SAE-related information to:

EORTC Pharmacovigilance Unit:

Fax No. +32 2 772 8027

Investigators participating through **non-EORTC groups** should consult their **group specific appendix** for further details on the reporting of Serious Adverse Events.

To enable the sponsor to comply with regulatory reporting requirements, all initial SAE reports should always include the following minimal information: an identifiable patient (SeqID), a suspect medicinal product if applicable, an identifiable reporting source, the description of the medical event and seriousness criteria, as well as the causality assessment by the investigator. Complete information requested on the SAE form of any reported serious adverse event must be returned within 7 calendar days of the initial report. If the completed form is not received within this deadline, the EORTC Pharmacovigilance unit will make a written request to the investigator.

Queries sent out by the EORTC Pharmacovigilance Unit need to be answered within 7 calendar days.

All forms need to be dated and signed by the principle investigator or any authorized staff member (i.e. on the signature list).

15.7 Reporting to investigators and competent authorities

The EORTC Pharmacovigilance Unit will forward all SAE reports within 24 hours of receipt to the appropriate persons within the EORTC Headquarters and the pharmacovigilance contact at the pharmaceutical company, if applicable.

All SUSARs will additionally be notified to all EORTC participating investigators, Ethics committees (of EORTC centers) and all central Data Managers of all Cooperating Groups.

The EORTC Pharmacovigilance Unit will take in charge the expedited reporting to *all* Competent Authorities and EVCTM, whenever applicable.

The EORTC Pharmacovigilance Unit will prepare the Annual Safety Report/ Development Safety Update Report and distribute it to the central Data Managers of all Cooperating Groups.

15.8 Pregnancy reporting

Pregnancy occurring during a patient's participation in this trial, although not considered an SAE, must be notified to the EORTC Pharmacovigilance Unit within the same timelines as an SAE (within 24 hours) on a Pregnancy Notification Form. The outcome of a pregnancy should be followed up carefully and any abnormal outcome of the mother or the child should be reported. This also applies to pregnancies following the administration of the investigational product to the father prior to sexual intercourse.

- Any pregnancy in a female subject or in a female partner of a male subject diagnosed during the treatment period or within 30 days after last study treatment administration must be reported to the EORTC Pharmacovigilance Unit
- This must be reported within 24 hours of first becoming aware of the event by fax, to the EORTC Pharmacovigilance Unit on a Pregnancy Notification Form
- If a Serious Adverse Event (SAE) occurs in conjunction with the pregnancy, please also complete an SAE form as explained in the SAE chapter

16 Quality assurance

16.1 Control of data consistency

Data forms will be entered in the database of the EORTC Headquarters by using the RDC system. Computerized and manual consistency checks will be performed on newly entered forms; queries will be issued in case of inconsistencies. Consistent forms will be validated by the Data Manager. Inconsistent forms will be kept "pending" until resolution of the inconsistencies.

16.2 On-site quality control

The EORTC Headquarters or delegates will perform on-site quality control visits.

The first visit in a participating site will be performed within 3 months after the first patient's randomization at this site. Frequency and number of subsequent visits will depend on site's accrual and quality observed during the first visit.

Overall, the frequency of site visits will be around one visit a year per recruiting site.

The aim of these site visits will be:

- to verify that the site facilities remain adequate for performing the trial
- to verify that the principal investigator and site staff involved in the trial are working in compliance with GCP and protocol requirements
- to assess the consistency of data reported on the case report forms with the source data
- to check that Serious Adverse Events have been properly reported and that follow-up information or queries are correctly fulfilled
- to assist the site in resolving any outstanding queries to control the drug accountability process

16.3 Audits

The EORTC Quality Assurance and Control Unit (QA&C) regularly conducts audits of institutions participating in EORTC protocols. These audits are performed to provide assurance that the rights, safety and wellbeing of subjects are properly protected, to assess compliance with the protocol, processes and agreements, ICH GCP standards and applicable regulatory requirements, and to assess the quality of data.

The investigator, by accepting to participate in this protocol, agrees that EORTC, any third party (e.g. a CRO) acting on behalf of the EORTC, or any domestic or foreign regulatory agency, may come at any time to audit or inspect their site and all subsites, if applicable.

This audit consists of interviews with the principal investigator and study team, review of documentation and practices, review of facilities, equipment and source data verification.

The investigator will grant direct access to paper and/or electronic documentation pertaining to the clinical study (e.g. CRFs, source documents such as hospital patient charts and investigator study files) to these authorized individuals. All site facilities related to the study conduct could be visited during an audit (e.g. pharmacy, laboratory, archives …). The investigator agrees to co-operate and provide assistance at reasonable times and places with respect to any auditing activity.

If applicable, the company(ies) supplying the study drug(s) may have access to anonymized data but will not have access to source documents.

If a regulatory authority inspection is announced, the investigator must inform the EORTC Headquarters QA&C Unit immediately (contact at: QualityAssuranceandControlUnit@eortc.be).

In this way EORTC can provide support in preparing and/or facilitating the inspection. EORTC representatives/delegates may also attend the inspection.

16.4 Central PET Review

FDG-PET/CT scan performed after one cycle of chemotherapy will be centrally reviewed by one of the expert nuclear medicine project core labs (Radboud University Nijmegen Medical Center and Rigshospitalet), and the treatment decisions will be made according to the results of the central FDG-PET/CT review.

The 20101 trial should follow the EORTC/GELA/IIL H10 trial for early stage HL, in which a similar real-time central FDG-PET/CT review has been functioning. Implementation and quality control of the FDG-PET/CT scans will be carried out according to EANM (European Association of Nuclear Medicine) and protocols for the standardization of imaging acquisition for monitoring tumor response to therapy. The EORTC imaging platform will be used for image review.

16.4.1 Scans submission, management, quality assurance and quality control

Without any exceptions, all FDG-PET/CT scans must be uploaded by the participating centers via the EORTC imaging platform. All diagnostic CT scans should be uploaded. Please refer to the imaging guidelines for more details.

16.4.2 Imaging QA/QC level description

All documents pertaining to the Imaging QA/QC procedures will be sent to the centers after receipt of the signed commitment form at the EORTC Headquarters.

The QA procedure consists of completing the following, which must be performed prior to site authorization:

- Imaging Guidelines “read and understood” acknowledgment signature page
- Dummy Run (DR)

During the trial, the following imaging QA/QC procedures must be performed:

- Full Prospective QC of all FDG-PET/CT scans
- Full Prospective Central Review of all the baseline and very early FDG-PET/CT scans

16.4.2.1 Imaging Guidelines “read and understood” acknowledgment page signature

This is the first page of the imaging guidelines. Every site participating in an EORTC study, must comply with the minimum requirements established as specified in the imaging guidelines. This first page of the imaging guidelines must be signed and returned to the EORTC HQ for every new version of the imaging guidelines. The page must be signed by the department head nuclear medicine physician. This is requested from all institutions in this study before activation to participate in it.

16.4.2.2 Dummy Run (DR)

Prior to enrolling patients to participate in this trial, the centers are required to submit a test scan, called dummy run to be reviewed by the EORTC imaging central review team who will verify image quality, consistency of acquisition/reconstruction parameters and imaging guidelines compliance. The dummy run will not be analyzed further. For more details on dummy run acquisition, reconstruction and submission please follow the imaging guidelines.

16.4.2.3 Prospective FDG-PET/CT scan QC

The QC will be performed prospectively, on an ongoing basis, and it is mandatory for this study where the therapy would be adapted based on FDG-PET/CT scan results.

16.5 Quality Assurance of Radiotherapy (QART)

16.5.1 QART Procedures

As soon as there is a patient with residual masses that will receive RT, sites should immediately contact the QART Office at EORTC at qart20101@eortc.be.

The Quality Assurance (QA) procedure consists of:

- Level I (Facility Questionnaire and External Reference Dosimetry Audit)
- Level II (Digital Data Integrity Quality Assurance)
- Level III & IV (prospective (target volume delineation) and retrospective (dose planning) Individual Case Review)
- Level V (Complex Dosimetry Check for all types of IMRT treatment)

Trial specific QART Guidelines will be sent to centers with the initiation package.

16.5.2 Patient-specific QART program

Central and prospective QART will be performed for all patients that will be irradiated (approximately 10% - 15% of all included patients). The main aim of the QA is to evaluate the delineation of target volumes prospectively and dose distributions retrospectively. In order to be able to check the target volumes we will also have to review at least pre- and post-chemotherapy imaging. We will use the Visualization and Organization of Data for Cancer Analysis (VODCA) and Imaging platforms to perform the QART. A panel of four to five experts from the participating centers and the EORTC Radiation Oncology Group will be identified to perform the reviews. Please see the trial specific QART guidelines which detail the QART levels, including the data required and the procedures for submission.

Feedback of the prospective individual case review will be provided within 3 business days of submission. Plans requiring modification must be resubmitted within 4 business days. Reviews of resubmissions will be provided within 3 business days.

Should the review result in a “major protocol deviation”, the site might be withdrawn from the authorization list and no longer be in the position to enter patients in the trial, until a resubmission results in an “acceptable – per protocol” review. The same rule will apply in case plans would not be submitted within the requested timelines.

17 Ethical considerations

17.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at http://www.ema.europa.eu/pdfs/human/ich/013595en.pdf).

The protocol must be approved by the competent ethics committee(s) as required by the applicable national legislation.

17.2 Subject identification

The name of the patient will neither be asked for nor recorded at the EORTC Headquarters. A sequential identification number will be automatically allocated to each patient registered in the trial. This number will identify the patient and will be included on all case report forms. In order to avoid identification errors, the patient's code (maximum of 4 alphanumerics) and date of birth will also be reported on the case report forms.

17.3 Informed consent

All patients will be informed about

- the aims of the study
- the possible adverse events
- the procedures and possible hazards to which the patient will be exposed
- the mechanism of treatment allocation
- strict confidentiality of any patient data
- medical records possibly being reviewed for trial purposes by authorized individuals other than their treating physician

The template of the patient's informed consent statement is given as a separate document dated and version controlled to this protocol.

An adapted translation of the PIS/PIC will be provided by EORTC Headquarters and it is the responsibility of the Coordinating investigators for this trial (sometimes called National Coordinators) to adapt it to national/local requirements where necessary.

The bold sections of the informed consent document must be reflected in any translation. The content of these bold sections can either be translated literally or translated in any way that best captures the information given.

The translated informed consent documents are to be submitted to ethics committees for approval. The competent ethics committee for each institution must approve the informed consent documents before the center can join the study. It is the responsibility of the competent ethics committee to ensure that the translated informed documents comply with ICH-GCP guidelines and all applicable national legislation.

It is emphasized in the patient information sheet that participation is voluntary and that the patient is free to refuse further participation in the protocol whenever he/she wants to. This will not have any impact on the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered and/or randomized at the EORTC Headquarters. The written informed consent form must be signed and personally dated by the patient or by the patient's legally acceptable representative.

All of the above must be done in accordance with the applicable national legislation and local regulatory requirements.

Chapter 18 pertains specifically to the participation of EORTC investigators. Participants from other organizations should consult the appendix that is specific to their group to determine if the content of this chapter is superseded by procedures specific to their group.

18 Administrative responsibilities

18.1 The study coordinator

Study coordinator:

Martin HUTCHINGS
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Phone: +45 2628 8720
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Study co-coordinators:

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Fax: +3150365960
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Study imaging central reviewer:

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Radboud University Nijmegen Medical Centre
Dept of Nuclear Medicine
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6500 HB Nijmegen
The Netherlands
Phone: +31 24 3614048
Fax: +31 24 3618935
E-mail: w.oyen@nucmed.umcn.nl

18.2 The EORTC Headquarters

The EORTC Headquarters will be responsible for writing the protocol and PIS/IC, reviewing the protocol, setting up the trial, collecting case report forms, controlling the quality of the reported data, organizing the medical review and generating reports and analyses in cooperation with the Study Coordinator. All methodological questions should be addressed to the EORTC Headquarters.

EORTC HEADQUARTERS

Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique
Fax: +32 2 7723545

Registration of patients:

http://www.eortc.be/random
Or
Phone (in case of problems): +32 2 774 16 00

18.3 The EORTC group

All questions concerning ongoing membership in the group should be addressed to the chairman and/or secretary of the group.

For new membership contact Membership Committee at membership@eortc.be

Lymphoma EORTC group

Chairman:

Richard W.M. Van Der Maazen
Dept of Radiotherapy
Radboud University Nijmegen Medical Center
P.O. Box 9101 - Geert Grooteplein 10
6500 HB Nijmegen
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Secretary:

Paul Meijnders
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ZNA MIDDELHEIM
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2020 Antwerpen
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Fax: +32 3 2810719
E-mail: paul.meijnders@zna.be

19 Trial sponsorship and financing

EORTC is the legal Sponsor for all EORTC participants.

The contact details of the EORTC are:

EORTC Headquarters
Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique
Phone: +32 2 7741611
Fax: +32 2 7723545
e-mail: eortc@eortc.be

20 Trial insurance

A clinical trial insurance has been taken out according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

Clinical trial insurance is only valid in centers authorized by the EORTC Headquarters. For details please refer to the chapter on investigator authorization.

Appendix A: References

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Ref. 8 Bonadonna G, Zucali R, Monfardini S, De Lena M, Uslenghi C. Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine, and imidazole carboxamide versus MOPP. Cancer 1975; 36(1):252-259.

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Appendix B: Abbreviations

3D-CRT	three-dimensional conformal Radiotherapy
ACE	angiotensin-converting enzyme
AE	Adverse Event
ALAT	Alanine transaminase
AML	Acute Myeloid Leukemia *or* Acute Myelogenous Leukemia
ASAT	Aspartate transaminase
ASCO	American Society of Clinical Oncology
BICR	Blinded Independent Central Review
BNP	Brain Natriuretic Peptide
CALGB	Cancer and Leukemia Group B
CI	confidence interval
CNS	Central Nervous System
CR	Complete Remission
CRF	Case Report Form
CRu	Complete Remission unconfirmed
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
cTn	cardiac Troponin
CTV	Clinical Tumor Volume
CV	Curriculum Vitae
DNA	Deoxyribose Nucleic Acid
DR	Dummy Run
DSMB	EORTC Data Safety Monitoring Board
DVH	Dose Volume Histogram
EANM	European Association of Nuclear Medicine
EARL	EANM Research Ltd
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme-Linked Imunosorbent Assay
eNAL	extended “no action level”
EORTC	European Organisation for Research and Treatment of Cancer
ESR	Erythrocyte Sedimentation Rate
FDG	Fluoro-2-deoxyglucose

FFTF	Freedom From Treatment Failure
FSH	Follicle Stimulating Hormone
FM-GITIL-IIL	Fondazione Michelangelo, Gruppo Italiano Terapie Innovative nei Linfomi, Intergruppo Italiano dei Linfomi
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GELA	Groupe d'Etude des Lymphomes de l'Adulte
GI	Gastrointestinal
GHSG	German Hodgkin Study Group
GISL	Gruppo Italiano Studio Linfomi
GTV	Gross Tumor Volume
GWAS	Genome-Wide Association Study
HL	Hodgkin's Lymphoma
HBM	Human Biological Material
HIV	Human Immunodeficiency Virus
HQ	Headquarters
HRS	Hodgkin and Reed-Sternberg
hsTnT	high sensitive Troponin T
IC	Informed Consent
ICH	International Conference on Harmonization
ICH/GCP	International Conference on Harmonisation /Good Clinical Practice
ICRU	International Commission on Radiation Units and Measurements
IDMC	EORTC Independent Data Monitoring Committee
IHP	International Harmonization Project response criteria
IMRT	Intensity Modulated Radiotherapy
IPS	International Prognostic Score
ITT	Intent to treat
i.v.	Intravenous
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
MDS	Myelodysplastic Syndrome
miRNA	microRNA
MRI	Magnetic Resonance Imaging
MUGA	Multi Gated Acquisition Scan
NHL	non-Hodgkin lymphoma

NT-proBNP	N-terminal fragment
OAR	Organ(s) At Risk
ORTA	Online Randomized Trials Access
OS	Overall Survival
PD	Progressive Dissease
PET	Positron emission tomography
PET-CT	Positron emission tomography-CT
PFS	Progression-Free Survival
PIS/IC	Patient Information Sheet/Informed Consent
PLRG	Polish Lymphoma Research Group
PR	Partial Remission
PTV	Planning Treatment Volume
QA	Quality Assurance
QART	Quality Assurance of Radiotherapy
QC	Quality Control
RDC	Remote Data Capture
RNA	Ribonucleic acid
RT	Radiotherapy
SAE	Serious Adverse Event
SAL	shrinking action level
SD	Stable Disease
SeqID	Sequential Identification
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWOG	American South West Oncology Group
TARC	Thymus and Activation-Regulated Chemokine
TR	Translational Research
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
VISTA	Visual Information System for Trial Analysis
VISTA RDC	Visual Information System for Trial Analysis Remote Data Capture
VMAT	Volumetric Modulated Arc Therapy
VODCA	Visualization and Organization of Data for Cancer Analysis
WHO	World Health Organization

WOCBP Women Of ChildBearing Potential

Appendix C: WHO performance status scale

Grade	Performance scale
0	Able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work.
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

Appendix D: New York Heart Association (NYHA) classification of heart failure

Class I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

(The Criteria Committee of the New York Heart Association: Diseases of the Heart and Blood Vessels; Nomenclature and Criteria for Diagnosis, 6th ed Boston, Little, Brown 1964).

Appendix E: Common Terminology Criteria for Adverse Events

In the present study, adverse events and/or adverse drug reactions will be recorded according to the

Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address: http://ctep.cancer.gov/reporting/ctc.html.

The EORTC Headquarters web site www.eortc.org\investigators-area\ctc provides a link to the appropriate CTC web site. This link will be updated if the CTC address is changed.

Appendix F: Ann Arbor Staging* - Cotswolds Recommendations **

ANATOMICAL STAGING CRITERIA

Lymph node involvement. (a) Clinical enlargement of a node when alternative pathology may reasonably be ruled out (suspicious nodes should always be biopsied if treatment decisions are based on their involvement); and (b) enlargement on plain radiograph, CT scan, or Iymphography.

Spleen involvement. Unequivocal palpable splenomegaly alone, or equivocal palpable splenomegaly with radiological confirmation of either enlargement or multiple focal defects which are neither cystic nor vascular (radiological enlargement alone is inadequate).

Liver involvement. Multiple focal defects which are neither cystic nor vascular noted with at least two imaging techniques. Clinical enlargement alone with or without abnormalities of liver function tests is not adequate.

Lung involvement. Radiological evidence of parenchymal involvement in the absence of other likely causes especially infection.

Bone involvement. History of pain or elevation of serum alkaline phosphatase, supported by plain X-ray changes or evidence from other imaging studies (isotope, CT scan or MRI).

CNS involvement. (a) A spinal extradural deposit may be diagnosed on the basis of the clinical history and findings supported by plain X-ray, myelography, CT scan and/or MRI ; and (b) intracranial involvement will rarely be diagnosed clinically at presentation. It should be considered on the basis of a space occupying lesion in the face of disease in additional extranodal sites.

CRITERIA FOR "B" SYMPTOMS

(a) Unexplained weight loss of more than 10% of the body weight during the 6 months before initial staging investigation;

(b) Unexplained, persistent, or recurrent fever with temperatures above 38°C during the previous month; and (c) Recurrent drenching night sweats during the previous months.

CRITERIA FOR BULK DISEASE

The bulk of palpable lymph nodes will be defined by the largest dimension (cm) of the single largest Iymph node or conglomerate node mass in each region of involvement. A node or nodal mass must be 10 cm or greater to be recorded as "bulky".

A mediastinal mass will be defined as "bulky" on a postero-anterior chest radiograph, when the maximum width is equal or greater than one-third of the internal transverse diameter of the thorax at the T5-T6 level. The chest radiography should be taken with maximal inspiration in the upright position at a source-skin distance of 2 m.

CRITERIA FOR EXTRANODAL SPREAD (E)

Involvement of extra lymphatic tissue on one side of the diaphragm by limited direct extension from an adjacent nodal site will be classified as extranodal extension (E) with the implicit expectation of a prognosis equivalent to that for treatment of nodal disease of the same anatomical extent. The E category may also include an apparently discrete single extranodal deposit consistent with extension from a regionally involved node. Multiple extranodal deposits will not be included. A single extralymphatic site as the only site of disease should be classified as IE.

STAGING NOTATION

Nodal disease (I-III)

STAGE I

Involvement of a single lymph node region (e.g. cervical, axillary, inguinal, mediastinal) or lymphoid structure as spleen, thymus and Waldeyer's ring.

STAGE II

Involvement of two or more lymph node regions or lymph node structures on the same side of the diaphragm. Hilar nodes should be considered to be "lateralized" and when involved on both sides, constitute stage II disease. The number of anatomical regions involved should be indicated by a subscript (e.g. II3). For the purpose of defining the number of anatomical regions, all nodal disease within the mediastinum is considered to be a single lymph node region. Hilar involvement constitutes an additional site of involvement.

STAGE III

Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm. This may be subdivided stage III1 or III2, stage III1 being described for patients with spleen or splenic, hilar, coeliac or portal node involvement and stage III2 for those with paraaortic, iliac or mesenteric node involvement.

BULKY DISEASE

The subscript "X" will be used if bulky disease is present. No subscripts will be used in the absence of bulk.

EXTRANODAL DISEASE

"E" subscript if limited extranodal extension as described above, is documented. More extensive extranodal disease will be designated stage IV.

Example

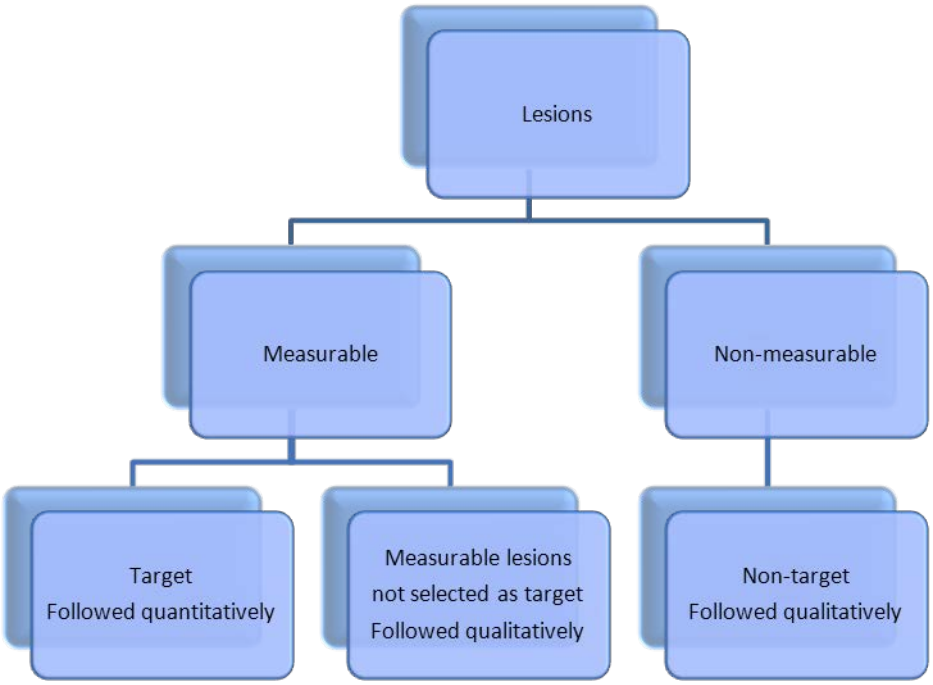
Asymptomatic clinically staged patient with bilateral neck and axillary nodes, bulky mediastinum, enlarged left hilar node and extension into chest wall: CSII6XEA.

* Carbone PP, Kaplan HS, Musshoff K, et al. Report of the committee on Hodgkin's disease staging classification. Cancer. Res. 31:1860-1861, 1971.

** Lister TA, Crowther D, Sutcliffe SB, et al. Staging for Hodgkin's disease. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J. Clin. Oncol. 7:1630-1636, 1989 (Erratum J. Clin. Oncol. 8:1602, 1990).

Appendix G: Response Criteria for Malignant Lymphoma

Baseline Lesion Burden (Flow Diagram):



1. What is a Measurable Lesion?

- Lesion which can be clearly measured in 2 perpendicular dimensions at baseline
- **Nodal lesions:** >15 mm in greatest transverse diameter (GTD) regardless of short axis (SA) measurement, or >10 mm in short axis, regardless of the GTD
- **Extra-nodal lesions:** ≥10 mm in the GTD
- **Nodules within the liver or spleen:** Must be ≥10 mm in two perpendicular Dimensions

2. Choosing Target Lesions:

- Select up to 6 lesions
- Larger lesions are preferred
- Lesions should be from disparate regions of the body if possible
- Include mediastinal and retroperitoneal lesions whenever these sites are involved (only if they are measurable lesions).
- Consider reproducibility

3. Non-Target Lesions:

- All other sites of disease present at baseline and not classified as target lesions will be classified as non-target lesions, including any measurable lesions that were not chosen as target lesions

  Examples:

  - PET positive non-measurable lesions
  - Measurable lesions beyond the maximum number of six
  - Bone lesions, irrespective of the modality used to assess them
  - Lymphangitis of the skin or lung
  - Splenomegaly and hepatomegaly (by CT)
  - Groups of lesions that are small and numerous
  - Pleural/pericardial effusions and/or ascites
  - Irradiated lesions
- Lesions found on physical examination, other than the spleen and liver, that are thought to be malignant (e.g. skin lesions) are non-target lesions
- Can combine multiple lesions in single organ as one entry e.g. “multiple right axillary lymph nodes”

4. Determining Response

- Assess the CT
  - Measure target lesions and calculate the sum of the products of diameters (SPD)
  - Visually assess non-target lesions
  - Search for new lesions
  - Combine these assessments into the overall CT-based response
- At end of treatment visit, assess PET and combine with CT for overall radiographic response, if appropriate
- Add clinical data (bone marrow, physical exam, b-symptoms) to arrive at overall response for the visit

a) Target Lesion Response

Complete **Remission (CR)**	♦ Nodes returned to normal (if GTD >15 mm before therapy, GTD now ≤15 mm; if GTD 11-15 and SA >10 mm before therapy, SA now ≤10 mm) ♦ All (non-nodal) target lesions completely resolved
Partial **Remission (PR)**	♦ SPD of target lesions decreased ≥50% from baseline ♦ Spleen and liver nodules regress by 50% in SPD or single lesion in GTD
Progressive Disease (PD) "if after PR or SD" or **Relapsed Disease (RD)** "if after CR"	♦ SPD increase ≥50% from nadir (smallest value seen during trial) ♦ in nodal target lesions overall ♦ or in any single nodal target lesion ♦ A node with SA <10 mm must grow ≥50% and to ≥15 x 15 mm or >15 mm GTD ♦ A node with SA >10 mm must increase ≥ 50% in GTD ♦ or in non-nodal target lesions overall (e.g. liver/spleen nodules selected as target lesions)
Stable Disease (SD)	♦ Not enough shrinkage for PR ♦ Not enough growth for PD
Unable to Evaluate (UE)	♦ One or more lesions cannot be seen ♦ This is most commonly caused by inadequate coverage

Special Circumstances:

Target lesion becomes "too small to measure"

- Non nodal lesion does not disappear, but decreases in size to <5 mm in two dimensions: assign measurements of 5 x 5 mm for the purpose of calculating the SPD
- If that lesion increases in size to >5 mm in any dimension afterwards, its actual size should be recorded

Target lesion splits into two or more smaller lesions:

- Shouldn't be reported as "new lesions"
- Measure each fragment, multiply diameters and add into SPD

Two lesions merge

- If both are target lesions, record the products of diameters for the merged lesion for lesion 1, and zero for lesion 2

b) Non-Target Lesion Response

Complete **Remission (CR)**	♦ All non-target lymph nodes returned to normal size ♦ All extra-nodal lesions have completely resolved ♦ Liver and spleen have returned to normal size (if enlarged at BL)
Stable Disease (SD)	Non-target lesions are still present, but not clearly increased in size
Progressive Disease (PD), if after PR or SD, **or Relapsed Disease (RD),** if after CR	♦ Unequivocal progression in any non-target lesion ♦ A node with SA <10 mm must grow ≥50% and to ≥15 x 15 mm or >15 mm GTD ♦ A node with SA >10 mm must increase ≥50% in GTD
Unable to Evaluate (UE)	One or more lesions cannot be seen

New Lesions

- ♦ Any new lesion which measures at least 15 mm in any axis
- ♦ Significant new effusions, ascites or other fluid collections, which are radiographically suggestive of malignancy
- ♦ New lesions automatically mean progression has occurred
- ♦ Be cautious in assessing possible new lesions. If uncertain, re-evaluate at next visit. If the new lesion is confirmed, progression is assigned to the visit when the new lesion was first visible.

"Unable to Evaluate" (UE) Lesion(s)

This category is reserved for target and non-target lesions that are deemed un-evaluable (UE) because:

1. Subsequent (post-baseline) imaging was not performed or did not include the lesion or
2. Lesion(s) could not be evaluated due to poor radiographic technique or poorly defined margins or
3. Lesion(s) identified at baseline were not assessable at a subsequent Time point

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"Use of Positron Emission Tomography for Response Assessment of Lymphoma: Consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma." Journal of Clinical Oncology, Volume 25, No 5, (February 10), 2007: pp. 571-578.