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EORTC protocol 1537-LYMG - COBRA

Very early FDG-PET-response adapted targeted therapy for advanced Hodgkin lymphoma: a single-arm phase II study

(EudraCT 2017- 000498-35)
(EU trial number 2023-508478-27)
(NCT03517137)

Study Coordinator: [redacted]

Study co-Coordinator [redacted]

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(Date)

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Investigator: (if applicable)

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Protocol summary

<table>
<tr><td>Title of the Study</td><td>Very early FDG-PET-response adapted targeted therapy for advanced Hodgkin lymphoma: a single-arm phase II study</td></tr>
<tr><td>Objective(s)</td><td>The main objective of this trial is to assess whether treatment adaptation based on a very early FDG-PET/CT results in improved efficacy while minimizing treatment toxicity in advanced stage Hodgkin Lymphoma (HL) patients treated with brentuximab vedotin containing regimens.</td></tr>
<tr><td>Methodology</td><td>Single arm, multicenter phase II study.</td></tr>
<tr><td>Number of patients
Number planned (Statistical design)
Number analyzed</td><td>A total of 150 patients will be registered in order to reach the target of 143 evaluable patients (taking into account ~5% patients not evaluable i.e., ineligible patients, patients who do not start the allocated treatment according to the result of the FDG-PET/CT after 1 cycle of BrAVD).</td></tr>
<tr><td>Diagnosis and main criteria for inclusion</td><td>Inclusion criteria
• Previously untreated, histologically proven classical Hodgkin lymphoma;
• Staged by PET with diagnostic-quality CT.
  • Clinical stages according to Lugano 2014 and based on FDG/PET CT:Stage IIB with large mediastinal mass > 1/3 max transverse diameter thorax and/or extranodal lesion(s) (GHSG)
  • Stage III - IV
• Participation in translational research is mandatory and therefore patient must consent to additional blood samples at multiple time points in the study. In addition, sufficient tissue must be available (15 blank formalin fixed paraffin embedded tissue samples mounted on APES slides or a tissue block).
• Age ≥18 and ≤60
• WHO performance status 0-2
• Patient demonstrates adequate organ function:
<table>
<tr><td>hemoglobin</td><td>≥ 8 g/dl (transfusions allowed) unless there is known HL marrow involvement</td></tr>
<tr><td>leukocyte concentration</td><td>≥ 3.0 x 10^9/L unless there is known HL marrow involvement</td></tr>
<tr><td>absolute neutrophil count</td><td>≥ 1.5 x 10^9/L unless there is known HL marrow involvement</td></tr>
<tr><td>platelets</td><td>≥ 75 x 10^9 /L unless there is known HL marrow involvement</td></tr>
<tr><td colspan="2">Exception to above requirements: reduced values related to HL (e.g., BM infiltration, splenomegaly)</td></tr>
</table>
</td></tr>
</table>

total Bilirubin	< 1.5 x ULN unless the elevation is known to be due to HL liver involvement or Gilbert Syndrome
alanine aminotransferase (ALT, SGPT)	< 3 x ULN unless the elevation is known to be due to HL liver involvement or Gilbert Syndrome
aspartate aminotransferase (AST, SGOT)	< 3 x ULN unless the elevation is known to be due to HL liver involvement or Gilbert Syndrome
Exception to above requirements: elevated values up to 5 times the ULN due to HL liver involvement or Gilbert Syndrome	
serum creatinine	< 2mg/dL
creatinine clearance	> 40ml/min measured or calculated according to the method of Cockcroft
calcium	< Upper Limit of Normal

- Women of childbearing potential (WOCBP) must have a negative serum pregnancy test within 72 hours prior to the first dose of study treatment.

Note: women of childbearing potential are defined as premenopausal females capable of becoming pregnant (i.e., females who have had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy). However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, antiestrogens, low body weight, ovarian suppression or other reasons.

- Patients of childbearing / reproductive potential should use two birth control methods, as defined by the investigator, from the time of signing the informed consent form, and throughout the entire study and for 6 months after the last dose of treatment. Two (2) of the following barrier methods in combination are allowed during the study. It is strongly recommended that at least one of these two methods be highly effective. A highly effective contraceptive method is one that has a failure rate of less than 1% and does not interfere with the proposed investigations.

Highly effective methods	**Other effective methods (barrier methods)**
Intra-uterine devices (IUD)	Latex condom
Hormonal (birth control pills/oral contraceptives, injectable contraceptives, contraceptive patches, or contraceptive implants)	Diaphragm with spermicide; Cervical cap; Sponge
If one of the highly effective methods cannot be used, using two other effective methods at the same time is required.	

	Birth control methods as directed above must be used unless patient completely avoid having heterosexual intercourse. Note: for sexual abstinence: occasional abstinence, the rhythm method and the withdrawal method are not acceptable methods of contraception. • Female subjects who are breast feeding should discontinue nursing prior to the first dose of study treatment and until 6 months after the last study treatment. • Absence of any medical, 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 registration in the trial • Before patient registration, written informed consent must be given according to ICH/GCP, and national/local regulations. **Exclusion criteria** • Known cerebral or meningeal disease (HL or any other etiology), including signs or symptoms of Progressive Multifocal Leukoencenphalopathy • Symptomatic neurologic disease compromising normal activities of daily living or requiring medications • Sensory or motor peripheral neuropathy greater than or equal to grade 2 according to CTCAE version 5.0 • Any of the following cardiovascular conditions or values: <u>within 6 months before registration:</u> • A left-ventricular ejection fraction <50% (at registration) • New York Heart Association (NYHA) Class III or IV heart failure. • Evidence of current uncontrolled cardiovascular conditions, including cardiac arrhythmias, congestive heart failure (CHF), angina, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities • symptomatic coronary heart disease (stable angina pectoris is allowed) • severe uncontrolled hypertension defined as blood pressure (BP) >150/100 mmHg despite optimal antihypertensive treatment <u>within 2 years before registration:</u> • Myocardial infarction • Patients with poorly controlled diabetes mellitus (HbA1c > 7.5 % or a fasting blood sugar > 200 mg/dL). • Any active systemic viral, bacterial, or fungal infection requiring systemic antibiotics within 2 weeks prior to registration. • Known HIV infection, chronic active hepatitis C, HBV positivity (HBsAg + patients; HBsAg -/HBcAb+/HBV DNA+ patients). *Note*: HBsAg-/HBV DNA – patients are eligible; patients who are seropositive due to vaccination are eligible

	• Concomitant or previous malignancies within the past 5 years with the exception of adequately treated carcinoma in situ of the cervix, nonmelanoma skin cancer. • Previous treatment with anti CD30 antibodies • Known hypersensitivity to any excipient contained in Brentuximab Vedotin formulation and other study drugs. • Concurrent anti-cancer treatment or use of any investigational agent(s) **Important note: All eligibility criteria must be adhered to, in case of deviation discussion with Headquarters and study coordinator is mandatory.**
Treatment Test product, dose and mode of administration PET1 based Treatment allocation Duration of treatment	BrAVD: one cycle of treatment is defined as 4 weeks and BrAVD will be administered intravenously on Days 1 and 15 of each cycle: Brentuximab vedotin 1.2 mg/kg iv day 1 and 15, Adriamycin 25 mg/m² iv day 1 and 15, Vinblastine 6mg/m² iv day 1 and 15, Dacarbazine 375 mg/m² iv day 1 and 15. BrECADD: one cycle of treatment is defined as 3 weeks and BrECADD will be administered intravenously On Days 1, 2, 3, 4 and 5 of each cycle. Brentuximab vedotin1.8 mg/kg iv day 1, Etoposide 150 mg/m² iv day 2 to 4, Cyclophosphamide 1250 mg/m² iv day 2, Adriamycin 40mg/m²iv day 2, Dacarbazine 250 mg/m² iv day 3 and 4, Dexamethasone 40 mg po day 2 to 5 All patients will receive 1 cycle of BrAVD followed by a PET/CT scan (PET1). Further treatment will be based on the PET1 results scored according to the Deauville 5-point score (DS) as follows: 1. If PET1-negative (DS: 1-3): patients will receive an additional 5 cycles of BrAVD 2. If PET1-positive (DS: 4-5): patients will switch treatment and receive 6 cycles of BrECADD Radiotherapy will be applied only to patients with residual PET positivity (Deauville 4 or 5) at the end of chemotherapy. Only sites of residual PET positive disease will be irradiated. Total duration of treatment: 1. for FDG-PET1 negative patients: approx. 24 wks of systemic therapy (6 x 4 weeks) 2. for FDG-PET1-positive patients: approx. 22 wks of systemic therapy (total: 1 x 4 + 6 x 3 weeks). For patients receiving consolidation radiotherapy treatment duration will be approximately 8-10 weeks longer.

<table>
<tr><td>Criteria for evaluation

Efficacy

Safety</td><td>Primary endpoint:

Modified progression-free survival rate at 2 years (2yr-mPFS for each patient), estimated from the Kaplan Meier curve of Modified PFS (mPFS). Modified PFS (mPFS) is defined as the time interval between the date of treatment start and the date of the first of:

• Progressive disease (PD)
• Start of new treatment for cHL when not in CR at the end of protocol treatment; in this case, the date of mPFS is the date of the FDG-PET/CT scan at the end of protocol treatment. Switching therapy prior to end of protocol treatment for reasons other than PD is not considered an event for mPFS. "End of protocol treatment" refers to completion of the planned protocol treatment with no more than 1 missed cycle, including radiotherapy on PET positive lesions if administered
• Death due to any cause

Patients without any of these events will be censored at the date of the last response assessment.

Secondary endpoints:

• FDG-PET result (positive/negative) after 1 cycle of BrAVD (central assessment).
• Response according to Lugano Criteria at end of protocol treatment i.e., both after chemotherapy as well as after radiotherapy (if administered), as defined by FDG-PET/CT
• Progression-free survival (where progression, relapse and death from any cause are considered events);
• Overall survival.
• Safety and tolerability
• Response according to RECIL 2017

Safety and tolerability

Safety will be assessed according to CTCAE Version 5.0</td></tr>
<tr><td>Statistical methods</td><td>Statistical design and sample size:

A'Hern design is used with one-sided type I error of 10% and 82% power for the following null and alternative hypotheses:

• H0: 2yr-mPFS=80%
• H1: 2yr-mPFS=87%.

Using the exact binomial distribution, the study needs to enroll 143 evaluable patients (exact type I error=9.8%, exact power=83.5%). Assuming a 5% proportion of patients not evaluable (i.e., ineligible patients, patients who do not start the allocated treatment according to the result of the FDG-PET/CT after 1 cycle of BrAVD), a total of 150 patients will be registered in order to obtain the required 143 evaluable patients.</td></tr>
</table>

	In order to avoid loss of statistical power for potential drop-outs during the 2 years of observation, the primary endpoint will be analyzed using time-to-event methods. With this approach, the statistical power to reject H0 under H1 is still 81.6% when the rate of drop-out at 2 years is 5%, compared to the test based on the exact binomial distribution where the statistical power drops to 75.8% (based on 10000 simulations, assuming mPFS and drop-outs follow an exponential distribution). **Patient populations**: • Intention-to-treat (ITT) population: All registered patients. • Evaluable population: All registered and eligible patients, who started the allocated treatment according to the result of the FDG-PET/CT after 1 cycle of BrAVD, as assessed by central review. • Radiotherapy population: All registered and eligible patients who started radiotherapy. • Safety population: All patients who have started BrAVD treatment (at least one dose of the study drug(s)) **Analysis of the primary endpoint**: The main analysis of the primary endpoint (2yr-mPFS) will be conducted on the evaluable population. The Kaplan-Meier curve of mPFS will be plotted; the estimated mPFS rate at 2 years will be obtained based on the Kaplan Meier method and its two-sided 80% confidence interval (CI) will be calculated using the log-log transformation and the standard deviation of the Kaplan Meier estimate based on the Greenwood formula. The study will be considered successful if the lower bound of the 80% CI is greater than the reference value of the null hypothesis 80%. The two-sided 95% confidence interval will also be provided, as additional information. Sensitivity analyses of the primary endpoint will be conducted: (1) in the ITT population (2) defining the primary endpoint as a binary endpoint for consistency with the A'Hern design.
Translational research	There are several translational research projects embedded in this study including tissue, serum, plasma and DNA based biomarker studies. These projects aim to find markers that are predictive for response or toxicity or markers that can be used for treatment response monitoring. Secondly, we aim to identify the role of circulating tumor DNA (ctDNA) as a predictive biomarker for treatment response and as a biomarker for minimal residual disease. Thymus and Activation Regulated Chemokine (TARC) is a serum-based biomarker that correlates with Hodgkin lymphoma tumor activity and can be used as a treatment response marker. The primary objective of the translational research is to assess the degree of correlation between serum TARC level after one cycle of BrAVD and FDG-PET results among patients with pre-treatment TARC elevation. It is possible that TARC can enhance or partially replace FDG-PET imaging in early treatment response monitoring. Other studies on TARC include correlating TARC during follow-up with disease recurrence, correlating TARC with both Deauville score and quantified FDG-PET

	parameters at different time points and correlation of TARC with clinical parameters and 2y-mPFS at different time-points. Other exploratory translation studies include correlation of sCD30 with treatment response and toxicity of Brentuximab-vedotin, correlation of tissue RNA expression profiles with treatment response and 2y-mPFS and correlation of immunohistochemistry markers with treatment response and 2y-mPFS.

1 Background and introduction

1.1 Introduction

Classical Hodgkin lymphoma (cHL) 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). It is characterized by the presence of rather few clonal cells, the so-called Hodgkin- or Reed-Sternberg cells (HRS), interacting with a rich inflammatory microenviroment. In 1994, the long-lasting debate on the cell of origin of the RS cells was settled, and the HRS cell was defined as a germinal center derived preapoptotic B cell, with multiple somatic mutations in the immunoglobulin genes (Ref. 3). HRS cells show an aberrant lack of expression of several mature B cell surface markers (CD19, CD20, surface immunoglobulin), and a high expression of CD30, a member of the TNF-receptor superfamily, normally expressed on activated T-cells.

cHL is seen in all age groups but with a peak incidence in patients aged 15-35 years. Genetic and viral factors play a role in the cHL etiology, but the pathogenesis of cHL is largely unknown. In around 30% of patients, the tumor cells present Epstein Barr virus (EBV) clonal genes and EBV related proteins, but still the precise role of EBV in the etiology of cHL is not known (Ref. 4). Just under half of all patients have advanced disease at diagnosis. This includes stages III and IV according to the Lugano classification, and some groups also include patients with stage IIB disease in the advanced category (Ref. 5).

1.2 Treatment of advanced Hodgkin lymphoma

During the last 45 years, from being an incurable disease, HL has become the most curable of all adult malignancies, thanks to the development of multiagent chemotherapy combined with radiotherapy. In most Western countries, 6(-8) cycles of ABVD (adriamicine, bleomycin, vinblastine, dacarbazine), first used in Italy in 1975, has been the standard for treatment of advanced HL for decades (Ref. 6, Ref. 7, Ref. 8). Although ABVD causes a moderately increased risk of cardiac and pulmonary toxicity (Ref. 8), it is a highly tolerable regimen, with little or no effect on fertility (of major importance) in this young cohort of patients (Ref. 9).

However, approximately 35% of advanced stage patients respond poorly to ABVD or relapse later on, and 15-20% ultimately die of refractory or relapsed disease, despite access to subsequent salvage treatment followed by high-dose chemotherapy with autologous stem cell transplantation (HD+ASCT) (Ref. 10). This has led to a search for more effective 1st line chemotherapy regimens for the treatment of advanced HL.

Based on statistical modelling, the German Hodgkin study group (GHSG) developed the more aggressive BEACOPP escalated scheme (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPPesc), and published the first results with this approach more than 15 years ago (Ref. 11, Ref. 12). Since then, results have consistently shown that in advanced stage HL long-term progression free survival (PFS) is superior for patients treated with BEACOPPesc (85-90%) when compared to ABVD (65-70%). This superior efficacy of BEACOPPesc translates into a modest OS benefit, the magnitude of which is debated, as all trials were powered for PFS and not for OS (Ref. 13, Ref. 14, Ref. 15, Ref. 16, Ref. 17). Also, this superior efficacy comes at the cost of significantly more serious acute toxicity (Ref. 16) and an increased risk of infertility (Ref. 18) and secondary malignancies, in particular treatment related acute myeloid leukemias and myelodysplastic syndromes (AML/MDS) (Ref. 19). The debate between those who prefer the less effective and less toxic approach, and those who prefer a more aggressive approach upfront is still unsettled and it appears that the choice of treatment between ABVD or BEACOPPesc in advanced HL is still in the eye of the beholder, eventually depending on the geography and preferences of the physicians and patients.

1.2.1 Radiotherapy

The role of radiotherapy in advanced HL patients has been extensively studied, but is still a matter of debate. In advanced disease classic HL, patients are frequently treated with chemotherapy alone (especially in the absence of bulky disease) and radiotherapy can be safely omitted in case a complete remission has been achieved (Ref. 21).

Radiotherapy should be delivered only to FDG-PET positive residual lymphoma masses after the end of chemotherapy (Ref. 20).

1.2.2 Patient tailored therapy

Ultimately, the goal in the management of Hodgkin Lymphoma is to tailor therapy to the individual patient's needs and to optimize the balance between efficacy of treatment and its toxicity. Although a substantial number of HL patients failing first line treatment may still be cured by second line treatment, OS is markedly reduced among patients who do not respond to, or relapse after first line therapy. Moreover, patients who need highly intensive second-line treatment are at further increased risk of treatment-related morbidity and death (Ref. 19).

1.2.3 Early PET-response adapted therapy

Over the last 10 years, a number of studies have shown a high prognostic value of an interim FDG-PET scan, performed early during chemotherapy for advanced HL. In patients treated with 6-8 cycles of ABVD, those who attain a negative FDG-PET scan after two ABVD cycles consistently reach long-term PFS rates over 90%, whereas those patients who remain interim FDG-PET positive have long-term PFS rates around 30% (Ref. 23, Ref. 24). More recently, a prospective international multicenter trial hypothesized that the negative predictive value would be even higher in patients responding rapidly enough to be FDG-PET negative after one cycle (Ref. 25). The trial included both early and advanced stages HL patients, who were scanned after one cycle (FDG-PET1) and after two cycles (FDG-PET2) of ABVD chemotherapy. In patients scanned at both time-points, this study showed that the negative predictive value of FDG-PET is higher after one cycle than after two cycles of chemotherapy, with more than 98% of FDG-PET1 negative patients alive and relapse-free after 2 years versus 90% of FDG-PET2 negative patients.

A number of trials investigate the value of early FDG-PET-response adapted therapy for both early and advanced HL. Some of these trials have recently been analyzed while others are still ongoing. The general aim of those trials is to reserve the more aggressive approach to those approximately 30% of advanced stage patients who really need it, in order to increase their chances of cure, while sparing the unnecessary toxicity for the 70% of patients for whom the vast majority will be cured with ABVD.

The latter approach has already been tested prospectively in the H10 study, a randomized trial by EORTC/LYSA/FIL for early-stage HL patients (Ref. 26). Patients with stage I/II HL were randomized between a standard treatment arm consisting of ABVD+ involved node radiotherapy (INRT) versus an experimental FDG-PET guided treatment arm. In the experimental arm, treatment was allocated based on results of the FDG-PET scan after 2 cycles of ABVD (FDG-PET2). Patients with FDG-PET2 positive scans in the experimental arm were switched to more intensive BEACOPPesc chemotherapy. FDG-PET2 positive patients in the standard arm continued with ABVD and INRT. The recently completed full analysis of this trial showed significantly better progression free survival for FDG-PET2 positive patients switched to BEACOPPesc compared to the FDG-PET2 positive patients in the standard arm who continued with ABVD (Ref. 26).

A number of studies have investigated similar PET-response therapy in advanced stage disease. The Italian GITIL HD0607 trial included 773 patients (stages IIB-IV and stage IIA with risk factors). All patients began treatment with 2 cycles of ABVD followed by FDG-PET. 151 patients (19.5%) were PET2 positive

and among the app 60% of PET2 positive patients evaluable for final response, 74% achieved CR after intensification with BEACOPPesc, following which 4-year FFS was 62% and 4-year OS 86%. For the entire cohort, 4-year FFS was 81% and 4-year OS 93% (Ref. 27).

The British-led RATHL included 1214 patients with stage IIB-IV (plus stage IIA with bulky disease and/or > 2 sites of involvement) disease who were likewise treated with 2 cycles of ABVD followed by FDG-PET. 172 Patients with a positive PET2 continued with BEACOPP-based treatment and achieved CR in 74% of cases. PET2 negative patients were randomized to either continued ABVD or AVD (omission of bleomycin). The omission of bleomycin from the ABVD regimen after negative findings on interim PET resulted in a lower incidence of pulmonary toxic effects than with continued ABVD but not significantly lower efficacy (primary endpoint: 3-year PFS 85.7% vs. 84.4% and 3-year OS 97.2% vs. 97.6% for the ABVD and the AVD arm, respectively). Of note, the results fall just short of the specified noninferiority margin (Ref. 28).

The Southwest Oncology Group (SWOG) S08016 study included 336 patients with stage III-IV disease and similarly performed FDG-PET after 2 cycles of ABVD which was given to all patients. 271 patients (82%) were PET2-negative and 60 (18%) were PET2-positive. Of 60 eligible PET2-positive patients, 49 switched to eBEACOPP as planned and 11 declined. Two-year OS was 98% (95% CI, 95% to 99%), and the 2-year PFS was 79% (95% CI, 74% to 83%). Two-year PFS for PET2-positive patients was 64% (Ref. 29).

Similarly, the Israeli H2 study and the Italian Intergruppo Italino dei linfomi (IIL) HD0801 studies have demonstrated a possible benefit of treatment escalation in patients who after 2 cycles of ABVD remain PET-positive (Ref. 30, Ref. 31).

1.3 Experimental treatment

Information of this section is based on brentuximab vedotin investigator's brochure (IB, Ref. 32) Edition 15 (26-October-2017) and in all subsequent appearances.

1.3.1 Antibody-Drug Conjugate Therapy and Brentuximab Vedotin

ADCs, which consist of cytotoxic agents or toxins chemically conjugated to a monoclonal antibody, potentially represent an advantage over traditional therapy because they are designed to deliver the cytotoxic agent to specific cells and their surroundings (i.e., CD30-expressing tumor cells or pathogenic leukocytes), thereby resulting in an improved balance between efficacy and safety (Ref. 33).

Brentuximab vedotin (BV) is a CD30-directed ADC consisting of 3 components: 1) the chimeric IgG1 antibody cAC10, specific for human CD30, 2) the microtubule-disrupting agent MMAE, and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10. The primary mechanism of BV is binding of the ADC to CD30-expressing cells, followed by internalization of the ADC-CD30 complex, and the release of MMAE via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic death of the cell (Ref. 34).

1.3.2 CD30 Antigen

CD30, a member of the tumor necrosis factor-receptor (TNF-R) superfamily, is a transmembrane glycoprotein receptor that is normally found on the surface of activated T-cells but has also been detected on a variety of cell types of hematopoietic origin, including other lymphocytes, myeloid-derived cells, megakaryocytes, and erythroid precursors. The CD30 antigen and/or its ligand (CD30 ligand, CD153) has a very low expression on normal cells but is present on malignant cells in a variety of cancers and on activated and potentially pathogenic T-cells and other leukocytes found in several inflammatory diseases. While the function of CD30 has not been clearly defined, CD30 has been implicated both in cell death and proliferation and in leukocyte differentiation and activation.

CD30 is expressed in HL, systemic ALCL, a type of non-Hodgkin lymphoma (NHL), and other types of NHL including cutaneous T-cell lymphoma (CTCL), peripheral T-cell lymphoma, diffuse large B-cell lymphoma and some follicular lymphomas (Ref. 35).

The limited normal tissue expression profile of CD30 and its apoptosis inducing characteristics make it an optimal target for immunotherapy.

1.3.3 Clinical Data

A pivotal phase 2 study evaluating the efficacy and safety of brentuximab vedotin as a single agent was conducted in patients with relapsed or refractory Hodgkin lymphoma (HL). In this study (Ref. 36), 75% of patients had an objective response (complete or partial remission) with median duration of approximately 11 months (Ref. 37). One-third of patients achieved a complete remission (CR) and in those patients achieving a CR the median duration of response was not reached at latest follow-up, with an estimated 5-year PFS of 52% (Ref. 38). Treatment-emergent adverse events (AEs) occurring in $\geq$20% of patients with HL and systemic ALCL in the phase 2 studies were peripheral sensory neuropathy (45%), fatigue (43%), nausea (41%), diarrhea (34%), pyrexia (31%), upper respiratory tract infection (31%), neutropenia (21%), and vomiting (20%). These events were primarily Grade 1 or 2, with the exception of neutropenia, for which Grade 3 and Grade 4 events were reported for 13% and 7% of patients, respectively. Similar patterns and incidences of AEs were generally observed for HL and ALCL patients (Ref. 39, Ref. 40).

A phase 3, randomized, placebo-controlled study evaluating efficacy and safety of brentuximab vedotin in the treatment of patients with HL who are at risk of disease progression following autologous stem cell transplant (ASCT) has been completed (Ref. 39). A total of 329 patients were randomized (164 patients to brentuximab vedotin and 165 to placebo) and 327 patients received study treatment (167 patients received at least 1 dose of brentuximab vedotin and 160 patients received placebo). The median progression-free survival (PFS) per independent review facility (IRF) for patients randomized to the brentuximab vedotin arm was 42.9 months (95% CI, 30.4, 42.9) (range, 0.03+ to 42.94) compared with 24.1 months (95% CI, 11.5, -) (range, 0.03+ to 42.35+) for patients randomized to the placebo arm. The difference between the 2 arms was statistically significant by stratified log-rank test (P=0.001). As assessed by Cox regression analysis, the stratified HR was 0.57 (95% CI, 0.40, 0.81). AEs that had a higher relative risk of occurring in patients in the brentuximab vedotin arm of Study SGN35-005 compared with patients in the placebo arm (as indicated by a relative risk >1 and confidence intervals that do not include 1) were peripheral motor neuropathy, paresthesia, abdominal pain, constipation, peripheral sensory neuropathy, weight decreased, neutropenia, nausea, myalgia, vomiting, diarrhea, and arthralgia.

A phase 1, open-label, dose-escalation study evaluated the safety and dose of brentuximab vedotin in combination with standard ABVD (ABVD-A) or a modified-standard treatment where bleomycin was omitted (AVD-A = BrAVD) in patients with newly diagnosed stage III/IV and II with risk factors HL (Ref. 40). Patients were enrolled into the cohorts sequentially. In the first cohort (ABVD-A) an unacceptable number of patients experienced pulmonary toxic effects (11 out of 25 patients = 44%) and this clearly exceeded the historical incidence of pulmonary toxicity for ABVD alone. In the following cohort (26 patients) no patients experienced pulmonary toxic effects when treated with brentuximab vedotin plus AVD. The most common grade 3 or worse events in the latter cohort were neutropenia (77%), anemia (12%), febrile neutropenia (8%), syncope (8%), fatigue (4%), and leukopenia (4%). Serious events occurred in seven (27%) patients in the brentuximab vedotin and AVD group, with no single serious event occurring in 10% of patients or more. Assessment of efficacy was not the aim of the study, but interestingly the end-of-treatment response rate in the AVD-A (BrAVD) cohort was 96%. Based on these data, Seattle Genetics and Millennium Pharmaceuticals (now Takeda) launched a phase III trial (Echelon-1), comparing the experimental regimen BrAVD, where bleomycin is replaced by BV, with standard ABVD

in advanced HL, aiming to show a PFS benefit (primary endpoint is modified PFS, including start of second line treatment in patients not in CR after completing front line therapy), with OS and safety as secondary endpoints. The final analysis of the Echelon-1 study was published in December 2017 (Ref. 57). At a median follow-up of 24.9 months the 2-year modified progression-free survival rates (the primary endpoint of the study) in the A+AVD and ABVD groups were 82.1% (95% confidence interval [CI], 78.7 to 85.0) and 77.2% (95% CI, 73.7 to 80.4), respectively, a difference of 4.9 percentage points (hazard ratio for an event of progression, death, or modified progression, 0.77; 95% CI, 0.60 to 0.98; P=0.03). There were 28 deaths with A+AVD and 39 with ABVD (hazard ratio for interim overall survival, 0.72 [95% CI, 0.44 to 1.17]; P=0.19). All secondary efficacy end points trended in favor of A+AVD. In the Echelon1 trial, the combination of Br+AVD shows a safety profile in consistence with that of each drug individually with respect to the nature of treatment emergent adverse events and serious adverse events (SAEs) observed. Neutropenia and associated complications, including febrile neutropenia and infections, and peripheral neuropathy (PN) were considered the most clinically important adverse events for the Br+AVD treatment arm. Neutropenia occurred in 58% of the patients receiving A+AVD and in 45% of those receiving ABVD; in the A+AVD group, the rate of febrile neutropenia was lower among the 83 patients who received primary prophylaxis with granulocyte colony-stimulating factor than among those who did not (11% vs. 21%). Peripheral neuropathy occurred in 67% of patients in the A+AVD group and in 43% of patients in the ABVD group; 67% of patients in the A+AVD group who had peripheral neuropathy had resolution or improvement at the last follow-up visit. Pulmonary toxicity of grade 3 or higher was reported in less than 1% of patients receiving A+AVD and in 3% of those receiving ABVD. Among the deaths that occurred during treatment, 7 of 9 in the A+AVD group were associated with neutropenia and 11 of 13 in the ABVD group were associated with pulmonary-related toxicity.

The German Hodgkin Study Group (GHSG) developed two modified BEACOPP regimens: In a more conservative variant (BrECAPP: BV, etoposide, cyclophosphamide, adriamycin, procarbazine, prednisone), vincristine was replaced by BV and bleomycin omitted. A more experimental variant (BrECADD: BV, etoposide, cyclophosphamide, adriamycin, dacarbazine, dexamethasone) was designed to reduce procarbazine induced gonadal toxicity. In a randomized phase II study, both regimens were administered every three weeks for 6 cycles, with the primary objective to assess the PET-based complete response rate (CRR) after chemotherapy and the complete remission rate (CR/CRu rate) at final restaging including early follow-up for each of the regimens. Safety and feasibility were secondary trial objectives (Ref. 42). In the most recently presented analysis, 104 patients had been enrolled and were evaluable (52 patients in each treatment arm). Median age was 29 years (range 18-60 years), 61% were male, and 83% had Ann-Arbor stage III or IV disease. 102 patients qualified for the safety analysis (BrECADD n=52, BrECAPP n=50). All 52 patients with BrECADD received the planned number of cycles, 2/50 terminated BrECAPP after 2 and 3 cycles due to toxicity and revision of initial staging by expert panel, respectively. 70% and 60% with complete cycles of BrECADD and BrECAPP received the last treatment cycle at full dose level. The majority of patients did not have treatment delays.

101 patients qualified for the efficacy analysis (BrECADD n=52, BrECAPP n=49). CRR was 88% (95%-CI: 77% - 96%) for the BrECADD regimen and 86% (95%-CI: 73% - 94%) for BrECAPP. Regarding the co-primary endpoint CR/CRu, the corresponding rates were 88% for BrECADD (95%-CI: 77% - 96%), and 94% (95%-CI: 83% to 99%) for BrECAPP. Survival analyses for the BrECADD regimen revealed a PFS of 94% (95%-CI: 87% - 100%) at 12 months, and 89% (95%-CI: 77% - 100%) at 18 months. Corresponding numbers for BrECAPP were 98% (95%-CI: 94% - 100%), and 93% (95%-CI: 83% - 100%). OS after a median follow-up time of 18 months for BrECADD was 100%. In the BrECAPP group the median follow-up was 16 months and one patient died. This patient had never received the study treatment. However, this event led to a 1-year OS of 98% (95%-CI: 94% - 100%) in the BrECAPP group.

Hematological toxicity grade 3 or 4 occurred in 42/52 (88%) of BrECADD treated patients, and in 47/50 (96%) with BrECAPP. Main hematotoxicity was leukopenia resulting in 15% (BrECADD) and 8% (BrECAPP) grade 3 or 4 infections. Organ toxicity grade 3 or 4 occurred in 4% of BrECADD treated patients (all events grade 3), and in 17% in the BrECAPP group (5% grade 4). Severe neurotoxicity (i.e., grade 3 or 4) was not observed in the BrECADD group and in one patient (2%) in the BrECAPP group (grade 3 sensory neuropathy). Grade 1 or 2 sensory neuropathy occurred in 35% and 30%, respectively.

While BrECAPP and BrECADD demonstrated similar efficacy profiles, BrECADD was preferred over BrECAPP because of its superior organ toxicity profile. On this basis, the GHSG has launched a large phase III trial (HD21) in advanced HL, challenging the standard BEACOPPesc regimen with BrECADD in patients with advanced HL.

There is little doubt that BV will find its place in first-line treatment of advanced HL and that multi-agent chemotherapy will remain the principle of first-line treatment of advanced HL in the foreseeable future. However, it is also more than likely that after the introduction of BV into first-line therapy there will still be a conflict between the more aggressive and more toxic approach on one side, and the less toxic and possibly less effective approach on the other side. In this era it is difficult to imagine a randomized trial comparing BrAVD with BrECADD, and such a trial would not be very desirable anyway, since - also in the upcoming era a first-line BV based - advanced HL treatment - should be patient-tailored, risk-tailored, and response-adapted.

1.3.3.1 Use of growth factors with BrAVD

Based on the experience from the Echelon-1 study, primary G-CSF prophylaxis should be used to prevent neutropenia, per institutional guidelines.

1.3.3.2 Radiotherapy after BrAVD regimen

A study of involved-site radiotherapy to 30Gy given after BrAVD to patients with stage I-IIA Hodgkin lymphoma was published by Kumar et al. and showed no signs of aggravated radiation-induced toxicity when historically compared to standard radiotherapy given after standard ABVD. Importantly, no patients experienced clinically significant pulmonary toxicity (Ref. 41, Ref. 57).

1.4 Benefit – Risk Assessment

As detailed above, brentuximab vedotin monotherapy has demonstrated therapeutic activity in Hodgkin lymphoma. The final analysis of the Echelon-1 study showed a statistically significant improvement in the efficacy of the BrAVD arm compared with the standard ABVD arm, with acceptable toxicity as detailed above. The German "Targeted BEACOPP" phase II study demonstrated that the activity of BrECADD is as high as BEACOPPesc, with less toxicity (Ref. 42). The BrECADD regimen is currently being investigated in a large, international randomized phase III trial from the German Hodgkin Study Group (HD21), with upfront randomization between BrECADD and BEACOPPesc for patients with advanced HL. With BrAVD and BrECADD being presumably the most active regimens to treat advanced HL, the main benefit of the present study lies in the combination of those two regimens in a patient- and response-adapted approach. Both BrAVD and BrECADD omit bleomycin, a drug which has hitherto been part of all accepted first-line regimens for treatment of HL. This is another important added benefit, since bleomycin-induced lung toxicity is a major cause of treatment-related morbidity and mortality.

Brentuximab vedotin treatment causes a peripheral neuropathy that is predominantly sensory. Cases of peripheral motor neuropathy have also been reported. Brentuximab vedotin-induced peripheral neuropathy is typically cumulative and generally reversible. Infusion-related reactions, including anaphylaxis, have occurred with brentuximab vedotin. Monitoring of patients during infusion is required. If anaphylaxis occurs, the administration of brentuximab vedotin should be immediately and permanently

discontinued and appropriate medical therapy administered. If an infusion-related reaction occurs, the infusion should be interrupted and appropriate medical management instituted. Patients who have experienced a prior infusion-related reaction should be premedicated according to institutional guidelines for subsequent infusions. Premedication may include paracetamol, an antihistamine and a corticosteroid. Clinically significant laboratory analyses have been observed under treatment with BV, as detailed in section 1.3.3. These should be monitored as detailed in chapter 6. Progressive multifocal leukoencephalopathy (PML) has been reported with brentuximab vedotin use. PML is a rare demyelinating disease of the brain that is caused by the John Cunningham virus (JCV). It typically occurs in immunocompromised individuals and can be fatal. Presenting features may include altered mental status, motor deficits such as hemiparesis or ataxia, visual disturbances, or higher cortical dysfunction such as dysphasia or agnosia. Seizures have also been reported in patients with PML. If PML is suspected, expert neurologist diagnostic work-up should be performed. Acute pancreatitis has been reported in patients treated with brentuximab vedotin and has contributed to fatal outcomes in some cases. Onset typically occurred after 1 to 2 doses of brentuximab vedotin. Early symptoms included severe abdominal pain, nausea, and vomiting. The majority of pancreatitis cases were complicated by other possible contributory factors, including cholelithiasis and alternate etiologies (e.g., pancreatic lymphoma progression, displacement of bile duct stent, etc.). Monomethyl auristatin E (MMAE) is primarily metabolized by CYP3A. Coadministration of brentuximab vedotin with ketoconazole, a potent CYP3A4 inhibitor, increased exposure to MMAE by approximately 34%. Patients who are receiving strong CYP3A4 inhibitors concomitantly with brentuximab vedotin should be closely monitored for adverse reactions. Coadministration of brentuximab vedotin with rifampin, a potent CYP3A4 inducer, reduced exposure to MMAE by approximately 46%. The effects of brentuximab vedotin on embryogenesis, reproduction, and spermatogenesis in humans are unknown. In addition, no mature data about the effects of brentuximab vedotin in pregnant women are available (Ref. 32, Ref. 36, Ref. 37, Ref. 38).

Brentuximab vedotin has demonstrated acceptable safety profile when administered in combination with conventional multiagent chemotherapy to patients with Hodgkin lymphoma (Ref. 40, Ref. 42).

Based on previously published studies, early PET-response adapted treatment of advanced HL is already accepted in routine clinical practice. Based on the preliminary safety and efficacy data on BrAVD and BrECADD, the shift from the standard regimens to PET-response adapted treatment with the novel, targeted regimens is a logical evolution and the benefit/risk profile for participating patients is considered favorable.

1.5 Rationale

This single-arm phase II study investigates the value of early FDG-PET-response adapted BV-based therapy for advanced HL. All patients will receive one cycle of BrAVD followed by an FDG-PET/CT. Patients with a negative early FDG-PET(Deauville score 1-3) will continue with five more BrAVD cycles (total six cycles) while patients with a positive FDG-PET should shift to six cycles of BrECADD.

The hypothesis is that the efficacy will be comparable to the efficacy of BEACOPPesc and BrECADD, while using the intensive chemotherapy regimen only for those patients who do not achieve a negative FDG-PET after one cycle (estimated 25% of patients).

The choice to assess the treatment sensitivity by PET after a single cycle of BrAVD is based on results from a recent international multicenter study comparing FDG-PET/CT after one and two cycles of ABVD chemotherapy in HL (Ref. 40). There is no reason to suspect that FDG-PET1 should be less prognostic after BrAVD than after ABVD.

With this trial, we believe we can add important information about the optimal treatment of BV-containing first-line treatment for advanced HL, and thus answer important therapeutic questions that

are likely to otherwise remain unanswered even after the Echelon-1 and HD21 trials reach mature results. This relatively large single-arm phase II trial of 150 patients will allow a meaningful comparison with the BrAVD and BrECADD regimens based on modified progression-free survival (primary endpoint) and progression-free survival (secondary endpoint) respectively.

2 Objectives of the trial

2.1 General objectives

2.1.1 Primary objective

The main objective of this trial is to assess whether treatment adaptation based on a very early FDG-PET/CT results in improved efficacy while minimizing treatment toxicity in advanced stage HL patients treated with BV-containing regimens, BrAVD and BrECADD.

This will be primarily assessed by modified progression-free survival.

2.1.2 Secondary objectives

The secondary objectives are:

- To assess the rate of FDG-PET negativity (Deauville score 1-3) after 1 cycle of BrAVD
- To assess response according to Lugano Criteria at end of protocol treatment i.e., after chemotherapy and after radiotherapy (if administered), as defined by FDG-PET/CT
- To assess the safety and tolerability of the different BV containing regimens
- To assess the safety and tolerability of radiotherapy in the context of BrAVD and BrECADD
- To assess efficacy in terms of PFS and OS

2.1.3 Exploratory objectives

- To assess response according to RECIL 2017
- to assess the degree of association between serum TARC level and FDG-PET result both after one cycle of BrAVD among patients with pre-treatment TARC elevation (see translational research in chapter 10)
- to identify markers that are potentially predictive for response or toxicity or markers that can be used for treatment response monitoring (see translational research chapter 10)

2.2 Endpoints

2.2.1 Primary endpoint

Modified progression-free survival rate at 2 years after start of treatment (2yr-mPFS for each patient).

The following are considered events for the primary endpoint: progression/relapse; start of new treatment for cHL when not in CR after completing protocol treatment; death from any cause.

2.2.2 Secondary endpoints

The secondary endpoints are:

- FDG-PET result (positive/negative) after 1 cycle of BrAVD (central assessment).
- Response according to Lugano Criteria at end of protocol treatment i.e., after chemotherapy and after radiotherapy (if administered), as defined by FDG-PET/CT
- Progression-free survival (where progression, relapse and death from any cause are considered events).

- Overall survival.
- Safety and tolerability
- Response according to RECIL 2017

3 Patient selection criteria

3.1.1 Inclusion criteria

- Previously untreated, histologically proven classical Hodgkin lymphoma;
- Staged by PET with diagnostic-quality CT

Note: in case of iodine allergy please refer to section 6.1.1

- Clinical stages according to Lugano 2014 and based on FDG/PET CT:
  - Stage IIB with large mediastinal mass > 1/3 max transverse diameter thorax and/or extranodal lesion(s) (GHSG, Refer to Appendix G)
  - Stage III – IV
- Participation in translational research is mandatory and therefore patient must consent to additional blood samples at multiple time points in the study. In addition, sufficient tissue must be available (15 blank formalin fixed paraffin embedded tissue samples mounted on APES slides or a tissue block).
- Age ≥18 and ≤60
- WHO performance status 0-2 (Appendix C)
- Patient demonstrates adequate organ function:

hemoglobin	≥ 8 g/dl (transfusions allowed) unless there is known HL marrow involvement
leukocyte concentration	≥ 3.0 x 10^9/L unless there is known HL marrow involvement
absolute neutrophil count	≥ 1.5 x 10^9/L unless caused by known HL marrow involvement
platelets	≥ 75 x 10^9 /L unless caused by known HL marrow involvement
Exception to above requirements: reduced values related to HL (e.g., BM infiltration, splenomegaly)	
total Bilirubin	< 1.5 x ULN unless the elevation is known to be due to HL liver involvement or Gilbert Syndrome
alanine aminotransferase (ALT, SGPT)	< 3 x ULN unless the elevation is known to be due to HL liver involvement or Gilbert Syndrome
aspartate aminotransferase (AST, SGOT)	< 3 x ULN unless the elevation is known to be due to HL liver involvement or Gilbert Syndrome
Exception to above requirements: elevated values up to 5 times the ULN due to HL liver involvement or Gilbert Syndrome	
serum creatinine	< 2mg/dL
creatinine clearance	> 40ml/min measured or calculated according to the method of Cockcroft-Gault Formula
calcium	< Upper Limit of Normal

- Women of childbearing potential (WOCBP) must have a negative serum pregnancy test within 72 hours prior to the first dose of study treatment.

Note: women of childbearing potential are defined as premenopausal females capable of becoming pregnant (i.e., females who have had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy). However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, antiestrogens, low body weight, ovarian suppression or other reasons.

- Patients of childbearing / reproductive potential should use two birth control methods, as defined by the investigator, from the time of signing the informed consent form, and throughout the entire study and for 6 months after the last dose of treatment. Two (2) of the following barrier methods in combination are allowed during the study. It is strongly recommended that at least one of these two methods be highly effective. A highly effective contraceptive method is one that has a failure rate of less than 1% and does not interfere with the proposed investigations.

Highly effective methods	**Other effective methods (barrier methods)**
Intra-uterine devices (IUD)	Latex condom
Hormonal (birth control pills/oral contraceptives, injectable contraceptives, contraceptive patches, or contraceptive implants)	Diaphragm with spermicide; Cervical cap; Sponge
If one of the highly effective methods cannot be used, using two other effective methods at the same time is required.	

Birth control methods as directed above must be used unless patient completely avoid having heterosexual intercourse.

Note: for sexual abstinence: occasional abstinence, the rhythm method and the withdrawal method are not acceptable methods of contraception.

- Female subjects who are breast feeding should discontinue nursing prior to the first dose of study treatment and until 6 months after the last study treatment.
- Absence of any medical, 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 registration in the trial
- Before patient registration, written informed consent must be given according to ICH/GCP, and national/local regulations.

3.1.2 Exclusion criteria

- Known cerebral or meningeal disease (HL or any other etiology), including signs or symptoms of Progressive Multifocal Leukoencenphalopathy
- Symptomatic neurologic disease compromising normal activities of daily living or requiring medications
- Sensory or motor peripheral neuropathy greater than or equal to grade 2 according to CTCAE version 5.0

Any of the following cardiovascular conditions or values:

within 6 months before registration:

- A left-ventricular ejection fraction <50%
- New York Heart Association (NYHA) Class III or IV heart failure (see Appendix D).
- Evidence of current uncontrolled cardiovascular conditions, including cardiac arrhythmias, congestive heart failure (CHF), angina, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities
- symptomatic coronary heart disease (stable angina pectoris is allowed)
- severe uncontrolled hypertension defined as blood pressure (BP) >150/100 mmHg despite optimal antihypertensive treatment

within 2 years before registration

- Myocardial infarction

- Patients with poorly controlled diabetes mellitus (HbA1c > 7.5 % or a fasting blood sugar > 200 mg/dL).
- Any active systemic viral, bacterial, or fungal infection requiring systemic antibiotics within 2 weeks prior to registration.
- Known HIV infection, chronic active hepatitis C, HBV positivity (HBsAg + patients; HBsAg -/HBcAb+/HBV DNA+ patients).
  Note: HBsAg-/HBV DNA – patients are eligible; patients who are seropositive due to vaccination are eligible
- Concomitant or previous malignancies within the past 5 years with the exception of adequately treated carcinoma in situ of the cervix, nonmelanoma skin cancer.
- Previous treatment with anti CD30 antibodies
- Known hypersensitivity to any excipient contained in Brentuximab Vedotin formulation and other study drugs. Refer to Summary Product Characteristics for list of excipients.
- Concurrent anti-cancer treatment or use of any investigational agent(s)

Important note: All eligibility criteria must be adhered to, in case of deviation discussion with Headquarters and study coordinator is mandatory.

4 Trial Design

4.1 Design

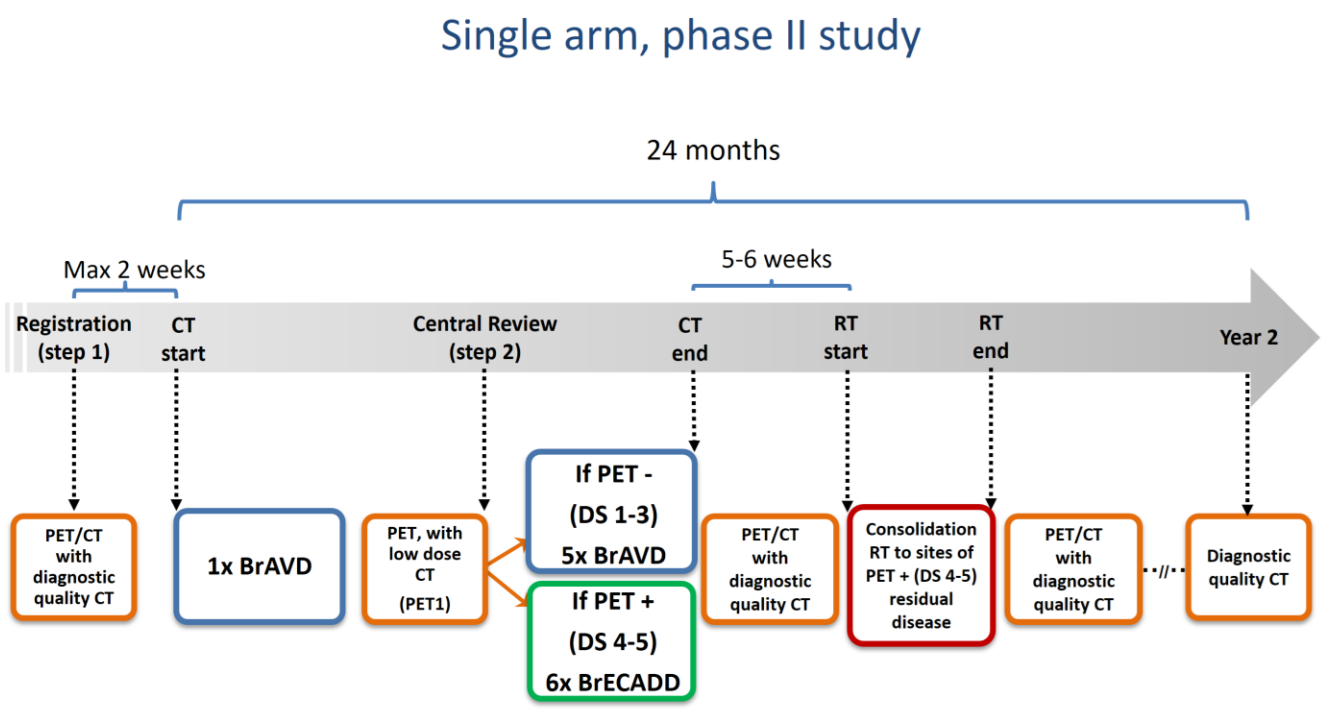
This is an international, open label, multi-center, single-arm phase II trial. Patients fulfilling the entry criteria, will be centrally registered at EORTC after written informed consent (IC) has been obtained.

All patients will receive 1 cycle of BrAVD followed by an FDG-PET with low-dose CT scan (PET1). Further treatment will be based on the centrally revised PET1 results scored according to the Deauville 5-point score (DS) as follows:

1. If PET1-negative (Deauville score: 1-3): patients will receive an additional 5 cycles of BrAVD

2. If PET1-positive (Deauville score: 4-5): patients will switch treatment and receive 6 cycles of BrECADD

Radiotherapy will be applied only to patients with residual PET positivity (Deauville score 4 or 5) at the end of chemotherapy. Only sites of residual PET positive disease will be irradiated.



4.2 Trial periods

4.2.1 Recruitment

The targeted 150 patients are expected to be accrued in 2.5 years: when all sites are open for recruitment, It is anticipated that 75 patients per year can be accrued; but during the first year accrual will stepwise increase according to site activation (half accrual rate during the first year).

4.2.2 Treatment period

1. for FDG-PET1 negative patients: approx. 24 wks of systemic therapy (6 x 4 weeks)

2. for FDG-PET1-positive patients: approx. 22 wks of systemic therapy (total: 1 x 4 + 6 x 3 weeks)

For patients receiving consolidation radiotherapy treatment duration will be approximately 8-10 weeks longer.

4.2.3 Follow-up

Patients are followed annually until 5 years.

4.3 End of study

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

- All patients have completed their end of study visit. If a participant discontinues the follow-up for one of the following reasons: withdrawal of consent, loss to follow-up, or death, the end of study participation is defined as the time point when one of these events occurred.
- The trial is mature for all analyses defined in the protocol and the database has been cleaned and frozen for these analyses.

4.4 Study suspension or study termination

EORTC reserves the right to terminate this study prematurely or discontinue parts of this study at any time for ethical/safety or unexpected operational/logistical reasons.

Any premature discontinuation will be appropriately documented according to local requirements (e.g., IRB/EC, regulatory authorities, etc.).

All the investigators will be immediately informed of the suspension or termination of the study using expedited means (e.g., e-mail, investigator letters, Ethics Committee information).

The patients should be contacted by the investigators to be informed of the suspension or the termination of the study and to inform them of the actions that need to be taken.

4.5 First act of recruitment

The start of the study is the first act of recruitment. This is the date of the first site authorized in the study.

5 Therapeutic regimens and concomitant therapy, expected toxicity, dose modifications

5.1 Drug authorization

Drug name	IMP or AMP	Authorization status	Used in accordance with Marketing Authorization (MA
Brentuximab vedotin	IMP	Authorized	Yes
Adriamycin	IMP	Authorized	Yes
Vinblastine	IMP	Authorized	Yes
Dacarbazine	IMP	Authorized	Yes
Cyclophosphamide	IMP	Authorized	Yes
Etoposide or etoposide phosphate	IMP	Authorized	Yes
Dexamethasone	IMP	Authorized	Yes
G-CSF	AMP	Authorized	Yes
pegylated G-CSF	AMP	Authorized	Yes

For each of the above-listed drug, complete information regarding indication, population, posology, treatment duration, contra-indications, warnings and precautions, contraceptive measures and administration method is reported below.

5.2 Drug information

5.2.1 Brentuximab vedotin

5.2.1.1 General information

Brentuximab vedotin (BV) is the International Nonproprietary Name (INN) assigned to SGN-35 and it is marketed as ADCETRIS®. Brentuximab vedotin is an antibody-drug conjugate (ADC) composed of a CD30-targeted chimeric monoclonal antibody (cAC10) covalently linked, via an enzyme-cleavable linker, to the

microtubule disrupting agent MMAE. It has been approved for the treatment of Hodgkin lymphoma and systemic anaplastic large cell lymphoma.

Brentuximab vedotin is administered as an IV infusion over a period of 30 minutes.

Therapeutic indications

BV is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):

1. following autologous stem cell transplant (ASCT) or

2. following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.

3. BV is indicated for the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT.

4. BV is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).

5. BV is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy.

For more information please refer to the investigator's brochure.

5.2.1.2 Drug supply

Brentuximab vedotin will be supplied by the sponsor to clinical sites, using a designated distribution center, as long as patients are on protocol treatment. Guidelines for drug supply will be provided in a separate document.

5.2.1.3 Packaging, dispensing and storage

Brentuximab vedotin is a sterile, preservative-free, white to off-white lyophilized cake for reconstitution for IV administration. Brentuximab vedotin for injection is supplied as single-use, borosilicate glass vials with FluroTec®-coated butyl rubber stoppers and aluminum seals. Each vial of the product contains brentuximab vedotin, trehalose, sodium citrate, and polysorbate 80. Brentuximab vedotin will be labeled as IMP according to the current regulatory requirements.

Vials containing brentuximab vedotin must be stored under refrigeration at 2-8°C. Chemical and physical stability of the reconstituted brentuximab vedotin drug product has been demonstrated for 24 hours at 2-8°C. However, brentuximab vedotin does not contain preservatives; therefore, from a microbiological standpoint, opened and reconstituted vials should be used immediately. If not used immediately, the in-use storage should not be longer than 24 hours under refrigeration at 2‑8°C. It is recommended that brentuximab vedotin vials and solutions be protected from direct sunlight until the time of use.

Each vial contains 50 mg of brentuximab vedotin. After reconstitution each vial contains 5 mg/ml of BV.

For further instructions regarding drug inventory, handling, storage, accountability and disposal, please refer to the IMP management guidelines (provided as a separate document) for brentuximab vedotin.

5.2.2 Chemotherapy drugs and dexamethasone

Adriamycin, vinblastine, dacarbazine, etoposide, cyclophosphamide will be administered as per standard practice.

Dexamethasone also as per standard practice.

5.2.2.1 Drug supply

Chemotherapies will not be supplied. Drugs composing the BrAVD or BrECADD regimen are approved standard medications and are available at the hospital pharmacy.

5.2.3 Drug reconciliation procedures

Accountability of the investigational study drugs is under the responsibility of the investigator and can be delegated to an appropriately qualified person.

Study drug accountability should be maintained by each site. Accountability records should include receipt date, batch numbers, expiry dates, patient SeqID, use by subject, dispensing dates, quantities (lowest unit) and stock balance.

In addition to internal accountability documentation on site, EORTC study-specific accountability and drug destruction forms will be supplied for this purpose, if site-specific forms are deemed not sufficiently detailed or do not provide enough information, according to EORTC Quality Assurance criteria.

The drug accountability and destruction forms will be verified during monitoring visits.

At the end of study, when all patients have stopped protocol treatment, complete drug reconciliation per batch should be available at the site for verification by EORTC in order to allow drug destruction or return procedure.

Both the unused and expired study medication must be destroyed, upon authorization of the sponsor (EORTC), according to local regulations and procedures, and a copy of the destruction form must be returned to the EORTC Headquarters.

The medication provided for this trial is to be used only as indicated in this protocol and only for the patients entered in this study.

5.3 Dose and schedule of BrAVD

The treatment must start no more than 2 weeks after registration.

All enrolled patients will first received one cycle BrAVD, then followed by FDG-PET/CT. Depending on the centrally reviewed result of the FDG-PET/CT:

- If FDG-PET1-negative (Deauville score 1-3): + 5 cycles of BrAVD
- If FDG-PET1-positive (Deauville score 4-5): + 6 cycles of BrECADD.

5.3.1 BrAVD regimen

One cycle of treatment is defined as 4 weeks and BrAVD will be administered intravenously on Days 1 and 15 of each cycle.

BrAVD (Q4 wks): Dose and schedule		
	Day 1	**Day 15**
Adriamycin 25 mg/m² IV in 50 ml NaCL 0.9% over 15 min	X	X
Vinblastine 6 mg/m² in 50 ml NaCl 0.9% over 15 min	X	X
Dacarbazine 375 mg/m² in 500 ml NaCl 0.9% over 60 min	X	X

BrAVD (Q4 wks): Dose and schedule		
	Day 1	**Day 15**
Brentuximab vedotin 1.2 mg/kg* (max 120 mg) IV in 100 ml NaCl 0.9% over 30 min starting 60 min after the completion of AVD therapy	X	X

* See section 5.3.1.1.2

5.3.1.1 Drug administration

No routine pre- or post-medications are required for BrAVD therapy.

Anti-emetics will be given as per institutional guidelines.

5.3.1.1.1 AVD

AVD will be administered first and as per institutional guidelines for ABVD.

AVD will be administered intravenously on Days 1 and 15 of each 28-day cycle. Patients may receive up to 6 cycles of therapy.

5.3.1.1.2 Brentuximab vedotin

Brentuximab vedotin is to be administered after AVD.

Brentuximab vedotin will be administered by IV at the dose of 1.2 mg/kg over approximately 30 minutes on days 1 and 15 of each 28-day cycle; the infusion is to start approximately 1 hour after the conclusion of the dacarbazine administration. In the absence of infusion toxicities, the infusion rate for all patients must be calculated in order to achieve a 30-minute (approximate) brentuximab vedotin infusion period.

Brentuximab vedotin must not be administered as an IV push or bolus. It must be administered through a dedicated IV line and cannot be mixed with other medications.

The dose of brentuximab vedotin in BrAVD is 1.2 mg/kg. Dosing is based on patients' weight according to the institutional standard; however, doses will be adjusted for patients who experience a ≥ 10% change in weight from baseline. Actual weight will be used except for patients weighing greater than 100 kg; dose will be calculated based on 100 kg for these individuals. The dose will be rounded to the nearest whole number of milligrams.

Patients who experience infusion-related reaction may potentially receive additional treatment with Brentuximab vedotin at the discretion of the investigator.

5.3.2 BrECADD regimen

One cycle of treatment is defined as 3 weeks and BrECADD will be administered intravenously on Days 1, 2, 3, 4 and 5 of each cycle.

BrECADD (Q3 weeks): Dose and Schedule					
	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**
Brentuximab vedotin 1.8 mg/kg (max 180 mg) IV over 30 min	X				

BrECADD (Q3 weeks): Dose and Schedule					
	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**
Cyclophosphamide 1250 mg/m² (max 2625 mg) IV in 100 ml NaCL 0.9% over 30 min		X			
Adriamycin 40 mg/m² (max 84 mg) IV in 50-100 ml NaCL 0.9% over 15 min		X			
Etoposide or etoposide phosphate* 150 mg/m² (max 315 mg) IV in 750 ml NaCL 0.9% over 60 min		X	X	X	
Dacarbazine 250 mg/m² (max 525 mg) IV in 500 ml NaCL 0.9% over 60 min			X	X	
Dexamethasone 40 mg PO		X	X	X	X
*Etoposide phosphate/etoposide conversion: 113 mg etoposide phosphate is equivalent to 100 mg etoposide					

5.3.2.1 Drug administration

Uromitexan (Mesna) prophylaxis with Cyclophosphamide for BrECADD therapy.

Mesna (urometixan) tablet or injection as per standard practice. In conjunction with cyclophosphamide treatment. The patient should ingest 2.5 liters of fluid on the day of administration.

Anti-emetics will be given as per institutional guidelines.

Antibiotic prophyllaxis with BrECADD is obligatory:

- Pneumocystis Jiroveci prophyllaxis: Sufamethazole/trimethoprim per institutional guidelines
- Gram-negative prophyllaxis: Fluoroquinolone: e.g., ciprofloxacin 500 mg 1-2 t.i.d. p.o. (per institutional guidelines)

5.3.2.1.1 ECADD

Administration as per standard practice.

The maximum upper limit for the calculation of chemotherapy is fixed at a body surface of 2.1 m², even if the calculated body surface exceeds this.

5.3.2.2 Brentuximab vedotin

Brentuximab vedotin will be administered by i.v. at the dose of 1.8 mg/kg over approximately 30 minutes on day 1 of each cycle. In the absence of infusion toxicities, the infusion rate for all patients must be calculated in order to achieve a 30-minute (approximate) brentuximab vedotin infusion period.

Brentuximab vedotin must not be administered as an i.v. push or bolus. It must be administered through a dedicated i.v. line and cannot be mixed with other medications. Steroids might have influence on the expression status of the target antigen CD30. Corticosteroid prephase must be stopped at least two days before Brentuximab vedotin administration.

The dose of brentuximab vedotin in BrECADD is 1.8 mg/kg. Dosing is based on patients' weight according to the institutional standard; however, doses will be adjusted for patients who experience a ≥10% change in weight from baseline. Actual weight will be used except for patients weighing greater than 100 kg; dose will be calculated based on 100 kg for these individuals. The dose will be rounded to the nearest whole number of milligrams.

Patients who experience infusion-related reaction may potentially receive additional treatment with Brentuximab vedotin at the discretion of the investigator.

5.3.3 Administration of growth factors

5.3.3.1 Administration of G-CSF

The administration of a G-CSF product is obligatory with both BrECADD and BrAVD, primary prophylaxis with G-CSF starting with the first dose for prevention of neutropenia. As an alternative to daily G-CSF, the pegylated form can be used.

The recommended dose is 150 µg/m² in subcutaneous from day 5 and day 19 for BrAVD, and from day 5 for BrECADD (timing of G-CSF according to experience with the individual patient):

- Four to five days for BrAVD
- Seven days for BrECADD

The administration of G-CSF is to be discontinued when the leukocyte count, after reaching the nadir, is over 1000/mm³ on 3 successive days. Chemotherapy is continued no earlier than 48 hours after G-CSF was discontinued.

5.3.3.2 Administration of pegylated G-CSF

As an alternative to daily G-CSF, pegylated G-CSF can be used. It is administered at a dose of 6mg s.c. on day 5 and day 19 for BrAVD, and on day 5 for BrECADD.

5.3.4 Dose and schedule modifications

5.3.4.1 Definition of febrile neutropenia

If febrile neutropenia (FN) occurs in a patient, this is to be documented e-CRF in connection with the respective chemotherapy cycle. Febrile neutropenia is defined as:

- Granulocytopenia ≤ 0.5 10^9 /L
- Leukocytopenia ≤ 1.0 10^9 /L

and

- at least one time fever ≥ 38.0°C

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

5.3.4.2 Retreatment criteria

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

- Leukocytes ≥ 2.5 10^9 / L

or

- Neutrophilic granulocytes (see section 5.3.4.3.16)

- Platelets ≥ 80 10^9 / L (unless thrombocytopenia is due to HL bone marrow involvement)

5.3.4.3 Brentuximab vendotin

5.3.4.3.1 Serious and Opportunistic Infections

Serious infections such as pneumonia, staphylococcal bacteremia, sepsis/septic shock (including fatal outcomes) and herpes zoster, cytomegalovirus (CMV) (reactivation) and opportunistic infections such as Pneumocystis jiroveci pneumonia and oral candidiasis have been reported in patients treated with brentuximab vedotin. Patients should be carefully monitored during treatment for the emergence of possible serious and opportunistic infections.

5.3.4.3.2 Infusion-related reactions

Immediate and delayed infusion-related reactions (IRR), as well as anaphylactic reactions, have been reported.

Patients should be carefully monitored during and after infusion. If an anaphylactic reaction occurs, administration of brentuximab vedotin should be immediately and permanently discontinued and appropriate medical therapy should be administered.

If an IRR occurs, the infusion should be interrupted and appropriate medical management instituted. The infusion may be restarted at a slower rate after symptom resolution. Patients who have experienced a prior IRR should be premedicated for subsequent infusions. Premedication may include paracetamol, an antihistamine and a corticosteroid.

IRRs are more frequent and more severe in patients with antibodies to brentuximab vedotin.

5.3.4.3.3 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) has been reported with brentuximab vedotin. Patients with rapidly proliferating tumor and high tumor burden are at risk of tumor lysis syndrome. These patients should be monitored closely and managed according to best medical practice. Management of TLS may include aggressive hydration, monitoring of renal function, correction of electrolyte abnormalities, anti-hyperuricaemic therapy, and supportive care.

5.3.4.3.4 Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

SJS and TEN have both been reported in patients treated with brentuximab vedotin. Fatal outcomes have been reported. If either occurs, **discontinue brentuximab vedotin and administer appropriate medical therapy.**

5.3.4.3.5 Progressive Multifocal Leukoencephalopathy

John Cunningham virus (JCV) reactivation resulting in progressive multifocal leukoencephalopathy (PML) and death can occur in brentuximab vedotin-treated patients. PML has been reported in patients who received this treatment after receiving multiple prior chemotherapy regimens. PML is a rare demyelinating disease of the central nervous system that results from reactivation of latent JCV and is often fatal (Ref. 44).

Patients should be closely monitored for new or worsening neurological, cognitive, or behavioral signs or symptoms, which may be suggestive of PML. **Brentuximab vedotin dosing should be held for any suspected case of PML**. Suggested evaluation of PML includes neurology consultation, gadolinium-enhanced magnetic resonance imaging of the brain and cerebrospinal fluid analysis for JCV DNA by polymerase chain reaction or a brain biopsy with evidence of JCV. A negative JCV PCR does not exclude PML. Additional follow up and evaluation may be warranted if no alternative diagnosis can be

established. Brentuximab vedotin dosing should be permanently discontinued if a diagnosis of PML is confirmed.

5.3.4.3.6 Peripheral neuropathy

Brentuximab vedotin treatment may cause peripheral neuropathy, both sensory and motor. Brentuximab vedotin-induced peripheral neuropathy is typically an effect of cumulative exposure to this medicinal product and is reversible in most cases. In clinical trials, the majority of patients had improvement or resolution of their symptoms. Patients should be monitored for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness. Patients experiencing new or worsening peripheral neuropathy may require a delay and a dose reduction of brentuximab vedotin or discontinuation of treatment.

5.3.4.3.7 Pulmonary Toxicity

Cases of pulmonary toxicity, including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome (ARDS), some with fatal outcomes, have been reported in patients receiving brentuximab vedotin. Although a causal association with brentuximab vedotin has not been established, the risk of pulmonary toxicity cannot be ruled out. In the event of new or worsening pulmonary symptoms (e.g., cough, dyspnea), a prompt diagnostic evaluation should be performed and patients should be treated appropriately.

Consider holding brentuximab vedotin dosing during evaluation and until symptomatic improvement.

5.3.4.3.8 Acute Pancreatitis

Acute pancreatitis has been observed in patients treated with brentuximab vedotin. Fatal outcomes have been reported.

Patients should be closely monitored for new or worsening abdominal pain, which may be suggestive of acute pancreatitis. Patient evaluation may include physical examination, laboratory evaluation for serum amylase and serum lipase, and abdominal imaging, such as ultrasound and other appropriate diagnostic measures. **Brentuximab vedotin should be held for any suspected case of acute pancreatitis**. **Brentuximab vedotin should be discontinued if a diagnosis of acute pancreatitis is confirmed.**

5.3.4.3.9 Hematological toxicities

Grade 3 or Grade 4 anemia, thrombocytopenia, and prolonged (≥1 week) Grade 3 or Grade 4 neutropenia can occur with brentuximab vedotin. Complete blood counts should be monitored prior to administration of each dose. If Grade 3 or Grade 4 neutropenia develops.

5.3.4.3.10 Febrile neutropenia

Febrile neutropenia defined as fever of unknown origin without clinically or microbiologically documented infection with an absolute neutrophil count <1.0 x 10^9/L, fever ≥38.5° C; has been reported with treatment with brentuximab vedotin. Complete blood counts should be monitored prior to administration of each dose of this treatment. Patients should be monitored closely for fever and managed according to best medical practice if febrile neutropenia develops.

5.3.4.3.11 Hepatotoxicity

Hepatotoxicity in the form of elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) has been reported with brentuximab vedotin. Serious cases of hepatotoxicity, including fatal outcomes, have also occurred. Pre-existing liver disease, comorbidities, and concomitant medications may also increase the risk. Liver function should be tested before initiating the treatment

and routinely monitored in patients receiving brentuximab vedotin. Patients experiencing hepatotoxicity may require a delay, change in dose or discontinuation of brentuximab vedotin.

5.3.4.3.12 Hyperglycemia

Hyperglycaemia has been reported during clinical trials in patients with an elevated Body Mass Index (BMI) with or without a history of diabetes mellitus. However, any patient who experiences an event of hyperglycaemia should have their serum glucose closely monitored. Anti-diabetic treatment should be administered as appropriate.

5.3.4.3.13 Gastrointestinal Complications

Gastrointestinal (GI) complications including intestinal obstruction, ileus, enterocolitis, neutropenic colitis, erosion, ulcer, perforation and hemorrhage, some with fatal outcomes, have been reported in patients treated with brentuximab vedotin. In the event of new or worsening GI symptoms, perform a prompt diagnostic evaluation and treat appropriately.

5.3.4.3.14 Hepatic Impairment

In patients with hepatic impairment, the recommended dose is 1.2 mg/kg. Patients with hepatic impairment should be closely monitored for adverse events.

Complete blood counts should be monitored prior to administration of each dose of this treatment

Patients should be monitored during and after infusion.

Treatment should be continued until disease progression or unacceptable toxicity

5.3.4.3.15 Renal Impairment

Patients with severe renal impairment (CrCl <30 mL/min) exhibited a trend toward moderate decreases in ADC exposure and increases in MMAE exposure. The recommended dose is 1.2 mg/kg administered .In patients experiencing decreased renal function during treatment, relevant dose reduction of brentuximab is recommended and patients should be closely monitored for AEs.

5.3.4.3.16 Dosing recommendation for neutropenia

Patients who develops Grade 3 or Grade 4 lymphopenia may continue treatment without interruption.

For thrombocytopenia, consider platelet transfusion and/or proceed according to institutional guidelines.

For anemia, manage as per institutional guidelines.

<table>
<tr><th>Severity grade of neutropenia</th><th>Modification dose and schedule</th></tr>
<tr><td>Grade 1 (<LLN-1.5 10^9/L)</td><td rowspan="2">Continue with same dose and schedule</td></tr>
<tr><td>Grade 2 (< 1.5-1.0 10^9/L)</td></tr>
<tr><td>Grade 3 (< 1.0-0.5 10^9/L)</td><td rowspan="2">Continue with same dose and schedule if responsive to G-CSF and in the absence of ongoing infection. If not withhold *dose until toxicity returns to ≤ Grade 2 or baseline then resume treatment at the same dose and schedule.</td></tr>
<tr><td>Grade 4 (<0.5 10^9/L)</td></tr>
<tr><td colspan="2">Patients who develop Grade 3 or Grade 4 lymphopenia may continue treatment without interruption.</td></tr>
</table>

LLN: Lower Limit of Normal

5.3.4.3.17 Dosing recommendation for non-hematologic events

Patients who develop clinically insignificant Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non hematologic (excluding neuropathy)	Continue at same dose level		Hold dosing until toxicity has resolved to ≤ Grade 2 or has returned to baseline.	

For Grade 3 or 4: it's recommended to also hold AVD and ECADD until toxicity has resolved to ≤ Grade 2 or has returned to baseline.

5.3.4.3.17.1 Peripheral neuropathy

In case the patients develop peripheral neuropathy (sensory or motor), the dose of Brentuximab vedotin should be modified as follows:

Severity of peripheral sensory or motor neuropathy	Modification of dose and schedule
Grade 1 (paraesthesia and/or loss of reflexes with no loss of function)	Continue with the same dose and schedule
Grade 2 (interfering with function but not with activities of daily living)	Withhold dose until toxicity returns to ≤ Grade 1 or baseline, then restart treatment at a reduced dose. In BrAVD, BV is to be given every 2 weeks and dose reduced to 0.9. In BrECADD, BV is to be given every 3 weeks and dose reduced to 1.2 mg
Grade 3 (interfering with activities of daily living)	Withhold dose until toxicity returns to ≤ Grade 2 or baseline, then restart treatment at a reduced dose. Resume at a dose of 0.9 mg In BrAVD and 1.2 mg in BrECADD. If BV is already given at reduced dose levels when a grade 3 PN event occurs, consult with medical monitor before restarting BV at a further reduced dose.
Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis)	Discontinue treatment

For Grade 3-4: it's left at the investigator discretion to hold individual components of AVD and ECADD.

5.3.4.4 AVD regimen

AVD treatment should be modified or discontinued per applicable label/Summary of Product Characteristics (SmPC) instructions/institutional or national guidelines.

5.3.4.5 ECADD regimen

Dose reduction for ECADD should follow 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 (leukocytes < 1,000/mm^3) for more than 4 days
- Thrombopenia (platelets < 25.000/mm^3) on one or more days
- Infection grade 4
- Other toxicity 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. No reduction is made for a treatment postponed up to 2 weeks.

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

Full dose (level 4):		
Cyclophosphamide	1250 mg/m^2 i.v.	Day 2
Adriamycin	40 mg/m^2 i.v.	Day 2
Etoposide	150 mg/m^2 i.v.	Day 2-4
Level 3		
Cyclophosphamide	1100 mg/m^2 i.v.	Day 2
Adriamycin	40 mg/m^2 i.v.	Day 2
Etoposide	125 mg/m^2 i.v.	Day 2-4
Level 2		
Cyclophosphamide	950 mg/m^2 i.v.	Day 2
Adriamycin	40 mg/m^2 i.v.	Day 2
Etoposide	100 mg/m^2 i.v.	Day 2-4
Level 1		
Cyclophosphamide	650 mg/m^2 i.v.	Day 2
Adriamycin	40 mg/m^2 i.v.	Day 2
Etoposide	100 mg/m^2 i.v.	Day 2-4
BrECADD (baseline)		
Cyclophosphamide	650 mg/m^2 i.v.	Day 2
Adriamycin	35 mg/m^2 i.v.	Day 2
Etoposide	100 mg/m^2 i.v.	Day 2-4

Examples of dose reductions for BrECADD:

Example 1:

Cycle	**1**	**2**	**3**	**4**	**5**	**6**
Dose level	4	4	4	**3**	3	3
Toxic event	No	No	**Yes**	No	No	No

Example 2:

Cycle	**1**	**2**	**3**	**4**	**5**	**6**
Dose level	4	4	4	**3**	3	**2**
Toxic event	No	No	**Yes**	No	**Yes**	No

Example 3:

Cycle	**1**	**2**	**3**	**4**	**5**	**6**
Dose level	4	4	4	**3**	**Baseline**	**Baseline**
Toxic event	No	No	**Yes**	**Yes**	No	No

5.4 Radiotherapy

Patients with residual lymphoma mass(es) showing metabolic activity of Deauville score 4 or 5 after completion of chemotherapy will be offered consolidation radiotherapy. The decision will be based on local assessment of the FDG-PET/CT scan. Radiotherapy to a dose of 36 Gy/18 fractions should be delivered only to residual lymphoma masses containing FDG-PET/CT-avid areas after the end of chemotherapy. FDG-PET/CT will be scored according to the Deauville 5-point scale (Ref. 54).

For this purpose, a score 4 and 5 will be considered FDG-PET/CT positive.

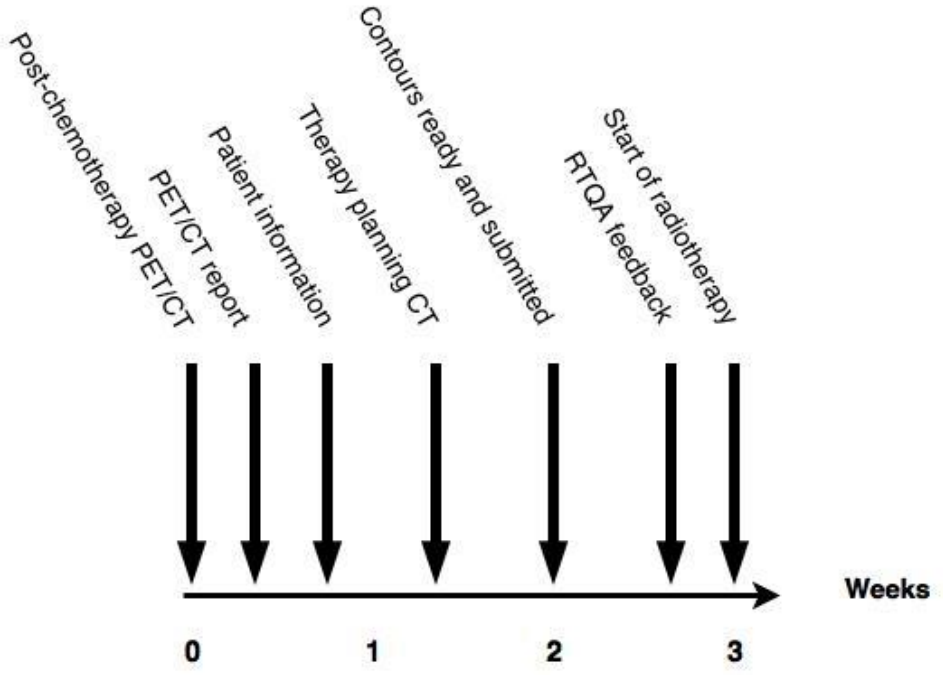
Bulky disease at presentation is not in itself an indication for radiotherapy. Irradiation of a residual mass without (a) FDG-PET/CT positive area(s) is not indicated.

The FDG-PET/CT scan after completing BV chemotherapy should be performed around day 21-28 of the last cycle.

Central and prospective individual case review (ICR) of radiotherapy plan will be performed for all patients that will be irradiated (see Section 15.4.1.1).

Radiotherapy should be started preferably 5-6 weeks 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.



5.4.1 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 is required. Proton therapy is allowed with appropriate calculation of radiobiological dose equivalence.

5.4.2 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 post-chemotherapy evaluation FDG-PET/CT and the treatment planning CT to allow for 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.
- Deep inspiration breath holding treatment should be considered for optimal OAR sparing depending on the circumstances.

5.4.3 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 IV 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 [ICRU 1993; ICRU 1999; ICRU 2010] (Ref. 43, Ref. 45, Ref. 46).

5.4.4.1 Target volume definitions and delineation guidelines

5.4.4.1.1 General provisions

GTV is considered to be equal to CTV.

Contouring should be done on a planning CT preferably 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 (applicable to standard radiotherapy) are described below. Local setup protocols should be taken into account when defining the PTV margins. Reduction of the PTV margins could be considered in case of 4-DCT, DIBH and extensive imaging procedures.

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

TARGET AREA	CTV	PTV
Nodal areas	residual lymphoma masses containing FDG-PET/CT-positive areas after completion of chemotherapy.	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 3-5 mm is sufficient provided an immobilization mask will be used. In the mediastinum a margin of 10-15 mm in lateral and antero posterior direction and 12-15 mm in cranio caudal direction should be used depending on the breathing movement.
Spleen	residual abnormality in the spleen as defined on FDG-PET/CT scan after completion of chemotherapy.	CTV + a margin of 12-20 mm, depending on the breathing movement
Lung	FDG-PET/CT-positive area in the lung after chemotherapy + surrounding residual abnormalities	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.

TARGET AREA	CTV	PTV
Liver	area of residual abnormality after chemotherapy containing FDG-PET/CT-positive areas	CTV + margin of 12-20 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	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.	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.

For proton therapy: PTV can be used for treatment plan generation, but robust optimization is preferred and recommended. In both cases robust evaluation is mandatory. For Single Field Optimized (SFO) and Multiple Field Optimized (MFO) IMPT, definition of beam-specific PTVs for planning could be useful.

5.4.4.1.2 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. The heart, lungs, breasts (in females <40 years old at treatment), kidneys, liver and other relevant organs at risk will be contoured only if they are situated within the region to be irradiated.

Lungs	Both the right and left lung should be contoured as one structure (2 structures are acceptable but should be added for DVH calculation). Contouring should be carried out using pulmonary window. All inflated lung should be contoured. In case of pulmonary involvement, GTV should be excluded from the OAR delineation. The use of automatic contouring software is allowed.
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. 47).
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.
Ovaries	The whole ovaries should be contoured.
Spinal cord	The spinal cord will be contoured at the level of the target volume.
Esophagus	The whole esophagus will be contoured.

5.4.5 Dosing

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).

5.4.5.1 Treatment planning

3D-CRT or IMRT should be applied, with Step-and-Shoot, Dynamic, 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 more advanced techniques, like inspiration breath hold technique, is allowed. Treatment will be planned using inhomogeneity corrections. Passive scattering, pencil beam scanning and IMPT are allowed for proton therapy.

5.4.5.2 Dose prescription to PTV

The prescription dose is to be specified and reported at the median dose of the PTV, as defined in ICRU Reports #50, #62 and in particular #83 (Ref. 43, Ref. 45, Ref. 46). Moreover the plan should meet the criteria that in the PTV D_max<107% of the prescribed dose and D_min>95% of the prescribed dose. The maximum dose could either be the D1% or D2% and the minimum dose D99% or D98%, according to institute standards. For proton therapy, the prescription and criteria reported above apply to the CTV.

5.4.5.3 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 as low as possible i.e., V5 < 55%, V20 < 30%, MLD < 13.5 Gy. (Ref. 59)
Heart	Mean heart dose should be kept as low as possible i.e., below 20 Gy and V30 ≤ 50%
Breasts	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%.
Ovaries	Dose should be kept as low as possible; in order to preserve fertility mean dose ≤ 2Gy and in order to preserve hormonal function mean dose ≤ 5 Gy
Spinal cord	Dose to this organ will be collected for the purpose of recording only since the normally used constraint of EQD2 Dmax ≤ 50 Gy will always be met.
Esophagus	Dose to this organ will be collected for the purpose of recording only.

5.4.5.4 Dose recording

Standard radiotherapy PTV / proton therapy CTV: The reported doses for the PTV/CTV shall include the prescription dose, the Dose near maximum ($D_{2\%}$) and the % target volume receiving <95% and >107%

For organs at risk, the hot spots outside the PTV/CTV 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
- Spinal cord: Dose near maximum (D2%)
- Esophagus: Dose near maximum (D2%)
- Ovaries: mean dose and dose near maximum dose (D2%)

5.4.6 Treatment verification and accuracy

Daily patient set-up shall be performed using laser alignment to reference marks on the skin/immobilization device. Patient positioning setup should be according to planning setup (see section 5.4.2).

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. 53).

5.4.7 Radiotherapy induced toxicity

Refer to section 7.2.3.

5.4.8 Dose and schedule modification

Lowering the daily dose per fraction is not allowed.

Radiotherapy treatment interruptions are expected to be necessary only very rarely. Treatment breaks should be kept as short as possible.

5.5 Withdrawal criteria

Patients may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice.

5.5.1 Treatment discontinuation

The primary reason for study treatment discontinuation should be documented in the patient’s medical notes and in the eCRFs. If the patient decides to prematurely discontinue study treatment, the investigator should ask her/him if he/she agrees to continue attending the study visits as per the schedule of assessments and/or to provide follow-up data (including: safety, disease assessments, subsequent anticancer therapies, and survival). The outcome of the discussion between the investigator and the patient should be documented in the patient’s medical notes and eCRF.

Patients who discontinue study treatment prematurely will not be replaced. Patients who discontinue study treatment but remain on the study will return to the site for an end of treatment visit and will enter the follow-up period.

Every effort should be made to obtain information on patients who discontinued the study treatment but do not withdraw from the study.

If a patient fails to attend scheduled visits, several attempts should be made by the investigator to contact the patient or a responsible relative or the patient’s physician to obtain follow-up information. Only after sufficient unsuccessful attempts have been made to contact the patient, can a patient be

declared “lost to follow-up” (at least 1 phone call and 2 certified letters). The attempts to contact the patient and collect data on their outcome should be documented in the patient’s medical notes. If the sponsor or investigator recommends treatment discontinuation, the patient should continue attending the study visits as per the schedule of assessments.

Patient must be discontinued from treatment (but may continue to be monitored in the trial) for any of the following reasons:

- Confirmed disease progression or relapse according to protocol section 7.1
- Excessive toxicity precluding further therapy, according to the investigator
- No FDG-PET scan performed after one cycle of BrAVD. This is considered as a major protocol deviation.
- Any medical conditions for which patient must permanently discontinue. Refer to section 5.2.
- Noncompliance of patient with study treatment or procedure requirements
- Patient's refusal
- Investigator's decision
- Sexually active patients who refuse to use medically accepted adequate birth control methods as described in the patient selection criteria during the course of the study
- Pregnancy or intent to become pregnant
- Initiation of any new anticancer therapy
- Occurrence of a new malignancy except in situ carcinoma
- Request by regulatory agencies for termination of treatment of an individual patient or all patients under the protocol

5.5.2 Study discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to:

- Patient withdrawal of consent to participate in the study
- Study termination or site closure
- Significant non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

The primary reason for withdrawal from the study should be documented in the eCRF.

If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced. When a patient withdraws from the study and also withdraws consent for disclosure of future information and/or use of collected biological material, no further evaluations should be performed, no additional data should be collected and collected samples should be returned/destroyed. The study staff may use a public information source to obtain information about survival status.

After study discontinuation, patient care will be left at the discretion of the treating physician.

5.5.3 Site closure

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to:

- Poor recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording

- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No further study activity (i.e., all patients have completed the study and all obligations have been fulfilled).

5.6 Concomitant treatments

5.6.1 Supportive care in case of toxicity

Supportive care is left to the physician's discretion.

An intensified antibiotic prophylaxis with a drug from the fluoroquinolone family according to the local standard is recommended during aplasia (day 7 to 13). If signs of fever occur, the patient should immediately go to see his treating physician. At the weekend or at night time, the patient should present himself at his local hospital.

The following accompanying medications are also recommended:

- Antiemesis with 5-HT3 receptor antagonists.
- The use of aprepitant (Emend) should be avoided. If it is being used, the dexamethasone dose should be reduced to 20 mg (due to drug interactions).
- Prophylaxis of hemorrhagic cystitis with uromitexanon day 2.
- Adequate hydration using fluids (i.v./oral) of at least 2.5 liters/day must be assured.
- Adequate nutritional support and timely referral to dietician is recommended.
- Treatment with allopurinol and H2-receptor blocker should be considered in individual cases.

Steroids should only be administered in addition to protocol medication in case of an emergency.

5.6.2 Other concomitant therapies

5.6.2.1 Permitted

- The use of topical, inhalational and ophthalmic steroids is permitted.
- Corticosteroids are permitted as part of a chemotherapy premedication regimen.
- Patients may receive concomitant hormonal therapy provided they have been on a stable dosage for at least 1 month prior to enrollment. No restrictions are placed upon the use of birth control.
- The use of platelet and/or red blood cell supportive growth factors or transfusions when applicable is allowed.
- The use of colony stimulating factors for the treatment of neutropenia per institutional practice is permitted during therapy.

5.6.2.2 Prohibited medications

- The concomitant use of brentuximab vedotin and bleomycin has resulted in increased pulmonary toxicity versus bleomycin alone. Coadministration of brentuximab vedotin and bleomycin is contraindicated.
- Anticancer treatment other than the study protocol treatment.
- Any investigational agent during the treatment.

5.6.2.3 Medications to use with caution

Interaction with medicinal products metabolized through CYP3A4 route (CYP3A4 inhibitors/inducers).

Co-administration of brentuximab vedotin with ketoconazole, a strong CYP3A4 and P-gp inhibitor, increased the exposure to the antimicrotubule agent MMAE by approximately 73%, and did not alter the

plasma exposure to brentuximab vedotin. Therefore, co-administration of brentuximab vedotin with strong CYP3A4 and P-gp inhibitors may increase the incidence of neutropenia.

Co-administration of brentuximab vedotin with rifampicin, a strong CYP3A4 inducer, did not alter the plasma exposure to brentuximab vedotin. Though PK data are limited, co administration of rifampicin appeared to reduce plasma concentrations of MMAE metabolites that could be assayed.

Co-administration of midazolam, a CYP3A4 substrate, with brentuximab vedotin did not alter the metabolism of midazolam; therefore brentuximab vedotin is not expected to alter the exposure to medicines that are metabolized by CYP3A4 enzymes.

6 Clinical evaluation, laboratory tests and follow-up

6.1 Within 4 weeks prior to registration

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

- Medical history: hypertension, diabetes mellitus, menstrual status, and smoking history
- Demographics (gender, age, year of birth)
- Physical examination: height, body weight, pulse rate, blood pressure
- WHO performance status
- Diagnosis of cHL confirmed by local hematopathologist
- Fertility tests (if patient agrees) and preservation: according to local practice
- Cardiac function: 12 lead ECG and LVEF (echo or MUGA scan)
- Pulmonary function tests (VC, FEV1, DLCO)
- Assessment of baseline symptoms according to the CTCAE v.5.0 including B-symptoms, cardiopulmonary complaints
- Concomitant medications

Translational research (Refer to chapter 10 & HBM Guidelines): collection of material is mandatory

- Serum sample storage
- Buffy coat storage
- Plasma for cfDNA analysis
- Tissue block or 15 blank FFPE slides

6.1.1 Within 2 weeks prior to registration

- Hematology test: ESR, hemoglobin, platelets, leukocyte count including neutrophils and lymphocytes
- Virology tests: HIV, Hepatitis B and C
- Serum chemistry: total bilirubin, creatinine, alkaline phosphatase, ALT, AST, LDH, serum albumin
- Hormonal tests: Thyroid function (T4 free, TSH)
- Imaging (see imaging guideline):
    - FDG-PET with diagnostic quality CT-scan less than 2 weeks before registration (neck, chest, abdomen and pelvis). Patient for whom the use of contrast (iv, oral) is not possible, images have to be uploaded on the EORTC imaging platform for assessment by the central review panel to confirm the study requirements are met.

6.1.2 Within 72 hours prior to treatment start

Pregnancy test: serum beta HCG in fertile female study participants.

It is recommended to repeat a urine pregnancy test on Day 1 of Cycle 1 prior to the first dose of brentuximab vedotin.

6.2 During treatment

The pregnancy test is to be repeated monthly during protocol treatment.

6.2.1 After Cycle 1 of BrAVD

At the end of the first cycle the following examination/tests will be performed:

- Physical examination (refer section 6.1 except height)
- WHO performance status
- Hematology (refer section 6.1.1)
- Serum chemistry (refer section 6.1.1)
- Assessment of adverse events (including B symptoms, cardiopulmonary complaints) according to CTCAE v 5.0
- Concomitant medications
- Imaging: FDG-PET with low-dose CT scan at day 22 to 23. For more information, please see the Imaging Guidelines for this trial.
- Uploading of FDG-PET/CT scans (baseline and PET1) for prospective central review

Translational research (Refer to chapter 10 & HBM Guidelines):

- Serum sample storage
- Plasma for cfDNA analysis

6.2.2 At the end of each subsequent cycle (BrAVD and BrECADD arms)

Following examination/tests will be performed:

- Physical examination (refer section 6.1 except height)
- WHO performance status
- Hematology (refer section 6.1.1)
- Serum chemistry (refer section 6.1.1)
- Assessment of adverse events (including B symptoms, cardiopulmonary complaints) according to CTCAE v 5.0
- Concomitant medications

Translational research (Refer to chapter 10 & HBM Guidelines):

Serum and plasma sample for cfDNA analysis will be collected at the following time-points:

- After 4th cycle i.e.:
  - BrAVD (3rd cycle after allocation to BrAVD arm)
  - BrECADD (3rd cycle after allocation to BrECADD arm)

6.3 End of treatment

There are two time-points for assessment of end of treatment:

1) at the end of systemic treatment, 21 days (BrECCAD arm) or 28 days (BrAVD arm) after the last dose of chemotherapy, tests and investigations will have to be performed as per Section 6.3.1.

2) in addition to above, for the patients that will receive consolidation radiotherapy, tests and investigations will have to be performed 8 weeks after last dose of radiotherapy as per Section 6.3.2.

6.3.1 End of systemic treatment

Evaluation should be performed 21-28 days (depending on the treatment arm) after start of last cycle.

- Physical examination (refer section 6.1 except height)
- WHO performance status
- Hematology (refer section 6.1.1)
- Serum chemistry (refer section 6.1.1)
- Pregnancy test
- Cardiac function: LVEF if clinically indicated
- Pulmonary function tests, if clinically indicated
- Assessment of adverse events (including B symptoms, cardiopulmonary complaints)
- Concomitant medications
- Imaging: FDG-PET/CT scan with diagnostic quality CT

Note: the FDG-PET/CT scan should be performed 21-28 days (depending on the treatment arm) after the start of the last chemotherapy 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.

Translational research (Refer to chapter 10 & HBM Guidelines):

- Serum sample storage
- Plasma for cfDNA analysis

6.3.2 End of radiotherapy (if radiotherapy is given)

Evaluation should be performed 8 weeks after completion of radiotherapy.

- Physical examination (refer section 6.1 except height)
- WHO performance status
- Hematology (refer section 6.1.1)
- Serum chemistry (refer section 6.1.1)
- Pregnancy test
- Cardiac function (LVEF) if clinically indicated
- Pulmonary function tests if clinically indicated
- Assessment of adverse events (including B symptoms, cardiopulmonary complaints)
- Concomitant medications

Imaging: FDG-PET/CT scan with diagnostic quality CT-scan

Translational research (Refer to chapter 10 & HBM Guidelines):

- Collection of serum sample and storage

6.4 Follow-up

In this section end of treatment time-point is defined as:

1) last dose of systemic treatment (BrAVD or BrECCAD) for the patients that will not receive consolidation radiotherapy

2) last dose of radiotherapy for the patients that will receive consolidation radiotherapy after the chemotherapy.

6.4.1 At progression/relapse

Progression must be documented by relevant imaging investigations.

Translational research (Refer to chapter 10 & HBM Guidelines):

- Serum sample storage
- Plasma for cfDNA analysis

6.4.2 3, 6, 9, 12 & 15 months after end of treatment

- Related adverse events (including incidences of cardiopulmonary disease, second malignancy, B-symptoms), physical examination and hematology test according to local practice
- WHO performance status
- Survival status
- New anti-tumor treatment and outcomes

Note: additional hormonal tests and toxicity studies are needed at 12 months after end of treatment (refer to section 6.4.5)

Translational research (Refer to chapter 10 & HBM Guidelines):

- Serum sample storage at 3, 6, 9, 12 and 15 months after end of treatment.
- Plasma for cfDNA analysis at 3, 6 and 12 months after end of treatment.

6.4.3 18 months after end of treatment (24 months after treatment start)

- Related adverse events (including incidences of cardiopulmonary disease, second malignancy, B-symptoms), physical examination and hematology test according to local practice
- WHO performance status
- Survival status
- New anti-tumor treatment and outcomes
- Diagnostic CT-scan (neck, chest, abdomen)

Translational research (Refer to chapter 10 & HBM Guidelines):

- Serum sample storage
- Plasma for cfDNA analysis

6.4.4 From 18 months to year 5th after end of treatment

From 18 months after end of treatment until 5 years after end of treatment follow-ups will be performed every 6 months.

- Related adverse events (including incidences of cardiopulmonary disease, second malignancy, B-symptoms), physical examination, and blood test according to local practice
- WHO performance status
- Survival status
- New anti-tumor treatment and outcomes

6.4.5 At 1, 3 and 5 years after end of treatment

- Hormonal tests: Thyroid function (T4free, TSH), fertility tests (FSH, LH, 17-beta-oestradiol, progesterone, testosterone)
- Toxicity studies: pulmonary function tests and LVEF
- Survival status
- New anti-tumor treatment and outcomes

6.4.6 End of study visit

When a subject completes the 5-year planned follow-up after end of treatment or is discontinued from the study, the last follow-up visit is considered as the end of study visit.

6.5 Summary table

6.5.1 Screening, during treatment and at the end of treatment

Required procedures	Prior registration			During treatment		End of treatment (EOT)		Upon progression/ relapse
	Within 4 wks	Within 2 wks	Within 72 hrs	End of cycle 1	End of each subsequent cycle	End of systemic treatment *21-28 days after start of last cycle (15)*	End of radiotherapy (if applicable) *8 weeks after end of RT*	
Medical history (1)	X							
Demographics	X							
Physical examination (2)	X			X	X	X	X	
WHO performance status	X			X	X	X	X	
Diagnosis of cHL confirmed by local hematopathologist	X							
Fertility tests and preservation (3)	X							
Virology tests (4)		X						
Cardiac function: 12 lead ECG and LVEF (5)	X					C (16)	C	
Pulmonary function tests (6)	X					C	C	
Adverse events according to CTCAE v5.0 (7)				X	X	X	X	
Concomitant medications	X			X	X	X	X	

Required procedures	Prior registration			During treatment		End of treatment (EOT)		Upon progression/ relapse
	Within 4 wks	Within 2 wks	Within 72 hrs	End of cycle 1	End of each subsequent cycle	End of systemic treatment	End of radiotherapy (if applicable)	
						21-28 days after start of last cycle (15)	*8 weeks after end of RT*	
Hematology (8)		X		X	X	X	X	
Serum chemistry (9)		X		X	X	X	X	
Thyroid function (10)		X						
Imaging (11)		X		X (13)		X (17)	X	X
Pregnancy test (12)			X			X	X	
Serum samples	X			X	X (14)	X	X	X
Buffy coat	X							
cfDNA samples	X			X	X (14)	X		X
Tissue block or 15 blank FFPE slides	X							

X All cases; **C** If clinically indicated

(1) Medical history: hypertension, diabetes mellitus, menstrual status, and smoking history

(2) Physical examination: height (only at baseline), body weight, pulse rate, blood pressure

(3) If patient agrees: fertility tests: FSH, LH, 17-beta-oestradiol, progesterone, testosterone and fertility preservation according to local practice

(4) Virology: HIV, Hepatitis B and C

(5): Cardiac function: 12 lead ECG and LVEF (echo or MUGA scan)

(6) Pulmonary function tests: VC, FEV1, DLCO

(7) Assessment of adverse events according to the CTCAE v.5.0 including B symptoms, cardiopulmonary complaints

(8) Hematology tests: ESR, hemoglobin, platelets, leukocyte count including neutrophils and lymphocytes

(9) Serum chemistry: total bilirubin, creatinine, alkaline phosphatase, ALAT, ASAT, LDH, serum albumin

(10) Thyroid function: T4 free, TSH

(11) Imaging (please see the Imaging Guidelines for this trial): FDG-PET with diagnostic quality CT-scan less than 2 weeks before registration (neck, chest, abdomen and pelvis)

(12) Pregnancy test within 72 hours prior to treatment start and be repeated monthly during protocol treatment. It is recommended to repeat a urine pregnancy test on Day 1 of Cycle 1 prior to the first dose of brentuximab vedotin.

(13) FDG-PET with low-dose CT scan at day 22 to 23/ Uploading of FDG-PET/CT scans (baseline and PET1) for central review

(14) Serum and cfDNA samples, should be performed at all required time points and at PD/relapse. After 4th cycle i.e.:

- BrAVD (3rd cycle after allocation to BrAVD arm), i.e., Cycle 5 day BraVD
- BrECADD (3rd cycle after allocation to BrECADD arm), i.e., Cycle 4 day 1 BrECADD

(15): 21 days (BrECCAD arm) or 28 days (BrAVD arm) after the start of last cycle

(16): only LVEF

(17): FDG-PET with diagnostic quality CT-scan performed 21 days (BrECADD arm) or 28 days (BrAVD arm) after the start of last cycle

6.5.2 Follow up period

	Follow up after end of treatment				
Required procedures	From 3 -18 months after EOT		From 18months - 5 years after EOT		
	3, 6, 9, 12, 15 months	18 months	Every 6 months	at 1,3 and 5 years	
Physical examination (1)	X	X	X		
WHO performance status	X	X	X		
Adverse events according to CTCAE v5.0 (2)	X	X	X		
Hematology tests as per local practice	X	X	X		
Survival status	X	X	X	X	
New anticancer treatment and outcomes	X	X	X	X	
Serum sample	X	X			
cfDNA sample	X(6)	X(6)			
Diagnostic CT-scan (neck, chest, abdomen)		X			
Cardiac function: LVEF				X	
Pulmonary function tests (3)				X	
Hormonal tests (4)				X	
Mammograms and MRI of breast (5)					

X All cases

(1): Physical examination: body weight, pulse rate, blood pressure

(2): Related adverse events (including incidences of cardiopulmonary disease, second malignancy, B-symptoms)

(3): Pulmonary function tests: VC, FEV1, DLCO

(4): Hormonal tests: Thyroid function (T4free, TSH), fertility tests (FSH, LH, 17-beta-oestradiol, progesterone, testosterone)

(5): According to local practice

(6) ctDNA samples only at 3,6,12 months after EOT (not at 9 and 15 months)

7 Criteria of evaluation

7.1 Evaluation of efficacy

Response assessment and time to progression will be measured according to Lugano classification (Ref. 5).

All patients included in the study must be assessed for response to treatment, even if there is a major protocol treatment deviation or if they are ineligible, or not followed/re-evaluated. Patients' response will be classified as "not evaluable" if insufficient data were collected to allow evaluation per these criteria.

Tumors will be re-evaluated with a FDG-PET/CT scan after 1 cycle of BrAVD, after completion of chemotherapy and after completion of radiotherapy (when applicable). After discontinuation of protocol treatment, patients who have not progressed will still be re-evaluated with a final diagnostic quality CT scan at month 24 after treatment start (approximately 18 months after end of treatment).

7.1.1 Chemotherapy sensitivity testing after 1 cycle of BrAVD

Evaluation of FDG-PET/low-dose CT after 1 cycle of BrAVD is performed according to the 5-point scale of the Deauville criteria (Ref. 54).

In this trial:

- a score of 1-3 is considered negative, qualifying for continuation of BrAVD
- a score of 4-5 is considered positive, qualifying for switching to BrECADD

According to these criteria, (18F)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 PET/CT interpretation (Ref. 24)	
Score	PET/CT scan result
1	No uptake above background
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

A prospective central review of FDG-PET scans (baseline and after 1 cycle of BrAVD) will be performed for all registered patients by a panel of 3 experts, using the 5-point Deauville Criteria.

Each scan will have to be uploaded to the EORTC imaging platform within 24 hours after acquisition (preferably the same day). This will allow for central review by our expert panel within 2 working days.

FDG-PET/CT scans will be centrally reviewed by an expert nuclear medicine core lab blinded to the local review results.

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.

7.1.2 Response assessment after chemotherapy, after radiotherapy, at the end of protocol treatment

After completion of chemotherapy and after completion of radiotherapy (when applicable), a local evaluation is performed with FDG-PET/diagnostic quality CT according to the Lugano classification (Ref. 5 - Table 3 PET-CT -Based response). Completion of chemotherapy refers to completion of planned chemotherapy with no more than 1 missed cycle (i.e., days 1 and 15 of a BrAVD cycle; days 1 to 5 of a BrECADD cycle).

Patients will be classified as: complete response (CR), partial response (PR), no response/stable disease (SD) or progressive disease (PD). Patients who discontinued treatment prematurely or not evaluable will be classified in a separate category.

Response at the end of protocol treatment is defined as:

- for patients with no radiotherapy: response after completion of chemotherapy
- for patients with radiotherapy: response after completion of radiotherapy

7.1.3 Response assessment at month 24 after treatment start

Patients who are not in PD at the end of protocol treatment will be evaluated locally with a diagnostic quality CT scan at month 24 after treatment start (approximately 18 months after end of treatment), according to the Lugano classification (Ref. 5 - Table 3 CT -Based response).

Patients will be classified as: complete response (CR), partial response (PR), no response/stable disease (SD) or progressive disease (PD), as follows:

- Patients in CR at the end of treatment will be considered in PD at month 24 only if CT-based response is PD; otherwise they remain in CR. PD detected on CT scan needs to be confirmed by biopsy or FDG-PET.
- Patients in less than CR (i.e., PR or SD) at the end of treatment will be classified using the CT-based response at month 24

Patients who are not evaluable will be classified in a separate category.

7.1.4 Date of progression/relapse

The date of progression/relapse will be the date of the first imaging study where PD was assessed, taking into account that PET positive after CT and before RT is not considered an event (not a PD). When PD is detected radiologically and later confirmed by biopsy or another imaging modality, the date of first imaging will be used.

7.1.5 Modified progression-free survival rate (mPFS)

The primary endpoint of the study is based on a modified version of progression-free survival, which includes "start of new treatment for cHL when not in CR after completing protocol treatment" as an event, consistently with the primary endpoint defined in the Echelon-1 trial conducted by Takeda (see section 1.3.3).

Modified PFS (mPFS) is defined as the time interval between the date of treatment start and the date of the first of:

- Progressive disease (PD)
- Start of new treatment for cHL when not in CR at the end of protocol treatment; in this case, the date of mPFS is the date of the FDG-PET/CT scan at the end of protocol treatment. Switching therapy prior to end of protocol treatment for reasons other than PD is not considered an event for mPFS. "End of protocol treatment" refers to completion of the planned protocol treatment with no more than 1 missed cycle, including radiotherapy on PET positive lesions if administered
- Death due to any cause

Patients without any of these events will be censored at the date of the last response assessment. Modified PFS (mPFS) at 2 years is the primary endpoint of the study and will be primarily estimated using the Kaplan Meier approach (see section 8.2 for more details).

7.1.6 Modified PFS (mPFS) at 2 years (defined as binary endpoint)

A binary version of the primary endpoint is defined where patients are classified as a failure or success depending whether they had an event for mPFS at 2 years or not. Two distinct definitions are considered:

1) Patients who drop-out early with no event are classified as failure

2) Patients who drop-out early with no event are classified as success

7.1.7 Progression-free survival (PFS)

PFS is defined as the time interval between the date of treatment start and the date of progression/relapse or death from any cause, whichever comes first. If neither event has been observed, then the patient is censored at the date of the last response assessment.

7.1.8 Overall survival (OS)

OS is defined as the time interval between the date of treatment start and the date of death for any cause. Patients still alive are censored at the date of last follow up.

7.1.9 Response according to RECIL 2017

Response after chemotherapy, after radiotherapy, at the end of protocol treatment and at month 24 after treatment start will also be assessed according to RECIL 2017 (Ref. 55).

7.2 Evaluation of safety

7.2.1 Adverse events

All adverse events will be recorded; the investigator will assess whether those events are drug related (reasonable possibility, no reasonable possibility) and this assessment will be recorded in the database for all adverse events.

The collection period will start from registration. All adverse events must be followed until resolution or stabilization.

7.2.2 General evaluation of adverse events

This study will use the International Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, for adverse event reporting. A copy of the CTCAE can be accessed from the EORTC home page https://www.eortc.be/services/doc/ctc/

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

7.2.2.1 Chemotherapy regimens

- Cardiac dysfunction
- Fertility
- Secondary malignancy

7.2.2.2 Expected side effects of radiotherapy

Any observations regarding radiation reactions will be recorded according to Criteria for Adverse Events version 5.0 (CTCAE) (see Appendix E).

7.2.2.2.1 Acute toxicity

Acute toxicity is defined as toxicity within 90 days after end of radiotherapy. 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
- Skin reaction

7.2.2.2.2 Late toxicity

Late toxicity is defined as toxicity after 90 days after end of radiotherapy. 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.

7.2.3 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 14, Reporting Serious Adverse Events)

7.2.4 Toxic deaths

Toxic death is defined as death due to toxicity (defined as adverse events that are not confirmed as unrelated). 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).

7.2.5 Evaluability for safety

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

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

8 Statistical considerations

8.1 Statistical design

8.1.1 Sample size

This is a single-arm multi-center phase II study.

The primary endpoint of the study is the modified progression-free survival rate at 2 years (2yr-mPFS). mPFS is defined in section 7.1.5.

The study is designed to reject an 80% or less 2yr-mPFS rate. This value is considered too poor for further development. The recent Echelon-1 trial conducted by Takeda showed mPFS rates at 2 years of 82.1% (95% CI:78.7-85.0) and 77.2% (95%CI:73.7-80.4) in the A+AVD (BrAVD) and ABVD arms respectively. Most recent clinical studies testing BEACOPPesc (EORTC 20012, GHSG HD15) have shown PFS rates in the range of 85%-90%; although not measured, outcome in terms of mPFS should be slightly poorer but still in the same range. A'Hern design was used with one-sided type I error of 10% and 82% power for the following null and alternative hypotheses:

- H0: 2 yr mPFS=80%
- H1: 2 yr mPFS=87%.

Using the exact binomial distribution, the study needs to enroll 143 evaluable patients (exact type I error=9.8%, exact power=83.5%). Assuming a 5% proportion of patients not evaluable (i.e., ineligible patients, patients who do not start the allocated treatment according to the result of the FDG-PET/CT after 1 cycle of BrAVD), a total of 150 patients will be registered in order to obtain the required 143 evaluable patients.

In order to avoid loss of statistical power for potential drop-outs during the 2 years of observation, the primary endpoint will be analyzed using time-to-event methods (see section 8.2.2.1 below). With this approach, the statistical power to reject H0 under H1 is still 81.6% when the rate of drop-out at 2 years is 5%, compared to the test based on the exact binomial distribution where the statistical power drops to 75.8% (based on 10000 simulations, assuming mPFS and drop-outs follow an exponential distribution).

The targeted 150 patients are expected to be accrued in 2.5 years: when all sites are open for recruitment, It is anticipated that 75 patients per year can be accrued; but during the first year accrual will stepwise increase according to site activation (half accrual rate during the first year).

8.1.2 Measures taken to minimize bias

Measures are put in place to ensure the minimization of bias in this single arm study:

- Prospective central assessment of the FDG-PET/CT scan after 1 cycle of BrAVD (section 15.5)
- Quality assurance in radiotherapy (section 15.4)
- Medical review of study data performed on a regular basis (section 9.2). This includes measures put in place to enhance protocol compliance and minimize the amount of missing data

8.2 Statistical analysis plan

Two statistical analyses will be conducted for this study:

- The main statistical analysis will be conducted when all registered patients have completed 2 years of follow-up. This analysis will include the analysis of: the primary endpoint (2yr-mPFS); response rate at the end of protocol treatment and at month 24 after treatment start. It will include an analysis of safety and disease/survival status using all available data up to the clinical data cut-off date, defined for this analysis as the date of treatment start of the last patient + 2 years.
- A second (long term) statistical analysis will be conducted when all registered patients have completed 5 years of follow-up post treatment start. This will be an updated analysis of safety and disease/ survival status endpoints, using all available data up to the clinical data cut-off date, defined for this analysis as the date of treatment start of the last patient + 5 years.

8.2.1 Analysis populations

- Intention-to-treat population: All registered patients.
- Evaluable population: All registered and eligible patients, who started the allocated treatment according to the result of the FDG-PET/CT after 1 cycle of BrAVD, as assessed by central review.
- Radiotherapy population: All registered and eligible patients who started radiotherapy.
- Safety population: All patients who have started BrAVD 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.

8.2.2 Statistical methods

Description of baseline characteristics will include (but not limited to) gender, age, histology, performance status, baseline adverse events and eligibility factors. Baseline characteristics will be summarized (either by incidence table, or by summary statistics, as applicable) in the intention-to-treat population, the evaluable population as well as the subset of patients excluded from the evaluable population.

Compliance to protocol treatment will be described separately for the first cycle of BrAVD; for the subsequent cycles of BrAVD (for patients with FDG-PET1-negative); for the subsequent cycles of BrECADD (for patients FDG-PET1-negative); for radiotherapy.

The study endpoints are listed in section 2.2 and defined in chapter 7. All summary tables and graphs will display all patients grouped together, irrespective of the result of the FDG-PET/CT scan after 1 cycle of BrAVD.

8.2.2.1 Analysis of the primary efficacy endpoint

The main analysis of the primary endpoint (2yr-mPFS) will be conducted on the evaluable population.

The Kaplan-Meier curve of mPFS will be plotted; the estimated mPFS rate at 2 years will be obtained based on the Kaplan Meier method and its two-sided 80% confidence interval (CI) will be calculated using the log-log transformation and the standard deviation of the Kaplan Meier estimate based on the Greenwood formula. The study will be considered successful if the lower bound of the 80% CI is greater than the reference value of the null hypothesis 80%. The two-sided 95% confidence interval will also be provided, as additional information.

Estimated mPFS rate at 5 years will also be provided with its 95% CI.

8.2.2.2 Analysis of secondary efficacy endpoints

FDG-PET/CT response after chemotherapy and at end of treatment (i.e., including radiotherapy, if administered) will be analyzed in the evaluable population. FDG-PET/CT response after radiotherapy will be analyzed in the radiotherapy population. The rate of patients with complete response will be reported together with its associated 95% confidence interval. The same method of analysis will be applied for the analysis of response according to Lugano criteria or to RECIL 2017.

Kaplan Meier curves of PFS and OS will be plotted in the evaluable population. Estimates of the survival rates at 2 and 5 years will be obtained using the Kaplan Meier technique and 95% CI will be calculated using the log-log transformation and the standard deviation of the Kaplan Meier estimate based on the Greenwood formula. If applicable, estimates of the median survival time will be obtained and presented with its 95% confidence interval (CI) calculated using the reflected CI method.

8.2.2.3 Analysis of safety

All tabulations of safety will be performed on the safety population. Adverse events and laboratory abnormalities will be tabulated using the worst CTCAE version 5.0 grade per patient.

The worst grade of adverse events and laboratory abnormalities will be tabulated overall and separately for:

- Adverse events with onset during the first 6 months after start of first cycle of BrAVD
- Adverse events with onset or increased grade more than 6 months after start of first cycle of BrAVD

A second tabulation of adverse events/ laboratory abnormalities related to treatment (excluding no reasonable possibility event, but including relationship not assessable) will be made.

A separate analysis of acute and late toxicity safety will be conducted in the Radiotherapy population (see section 5.4.7 for the definition of acute and late toxicity for patients receiving radiotherapy).

8.2.3 Pre-planned sensitivity or exploratory analyses

An analysis of the primary endpoint will also be conducted in the ITT population.

Analyses of the primary endpoint as a binary endpoint will be conducted to be consistent with the A'Hern design (see section 7.1.6). This binary endpoint will be presented as a percentage with its two-sided 80% exact confidence interval (based on exact binomial distribution). With 143 patients available for this analysis, at least 121 patients with no event are required to reject H0. Equivalently, H0 is rejected if the lower bound of the two-sided exact 80% confidence interval is greater than the reference value of the null hypothesis 80%. These analyses are considered as sensitivity analyses.

Additional analyses will be conducted with the purpose to examine the outcome of patients treated with 6 cycles of BrAVD and of patients treated with 1 cycle of BrAVD followed by 6 cycles of BrECADD:

- The efficacy and safety of treatment with 6 cycles of BrAVD will be evaluated by restricting the analysis of efficacy and safety endpoints to the subset of patients who continued on BrAVD after PET1.
- The efficacy and safety of treatment with 1 cycle of BrAVD followed by 6 cycles of BrECADD will be evaluated by restricting the analysis of efficacy and safety endpoints to the subset of patients who switched to BrECADD after PET1.

8.3 Data recording 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 registration – date of past event + 1) and presented using the median and range. For example, on the registration 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 registration – 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 (expressed in mg/m² /cycle) is the ratio of the total dose received to the total treatment duration, for example, for a dose in mg/m² and duration in number of cycles:

$$DI_{observed}\ (mg/m^2/cycle) = \frac{Total\ dose\ (mg/m^2)}{Actual\ total\ treatment\ duration\ (number\ of\ cycles)}$$

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., ≤ 80%, > 80-120%, > 120%).

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

9 Trial Governance and Data Monitoring

9.1 Study committees

9.1.1 Study Management Group (SMG)

The Study Management Group is set up for this study. It consists of the EORTC Headquarters team in charge of running the study (clinical research physician, statistician, clinical scientist, clinical operations manager and data managers) and the principal study coordinator.

The EORTC Headquarters team is responsible for the day -to-day conduct of the trial. The Study Coordinator will assist the team in case of problems with patient evaluation (eligibility, treatment compliance, safety).

The Study management Group also performs the medical review as indicated below.

9.1.2 Study Steering committee (SSC)

The Study Steering Committee for this study is composed of the study coordinator; experts from the areas of Hematology, Radiation Oncology, Pathology and Translational research; at least two representative of the EORTC Headquarters (Study Clinical Research Physician or Clinical Scientist, Statistician).

This committee provides the general oversight of the study and has the executive power. The SSC monitors study progress and conduct and advises on its scientific credibility. The SSC will consider and act, as appropriate, upon the recommendations of the independent data monitoring committee.

9.1.3 Independent data monitoring committee (IDMC)

According to EORTC policy “Policy on Independent Data Monitoring Committees”, this study will be submitted to the IDMC every year as part of the periodic review.

The independent data monitoring committee for EORTC studies (IDMC) is in charge of the independent oversight of this study, according to the EORTC Policy "Independent Data Monitoring Committees" and its functioning is ruled by the charter annexed to the Policy.

The study-specific experts on the IDMC performing this review will be selected for their relevant expertise with the disease and/or treatments assessed in the study.

The IDMC reports its recommendations in writing to the Study Management Group through the clinical operations manager to the Study Steering Committee and other relevant parties (supporting bodies, collaborative groups…).

9.2 Data Monitoring

9.2.1 Monitoring during medical review meetings

The medical review will be performed on a regular basis by the clinical research physician assisted as needed by the study management group. The study coordinator will, in particular, support the Study Clinical Research Physician during the medical review process and will assist the team in case of problems with patient evaluation (safety, eligibility, treatment compliance). The study coordinator is also responsible for the review and approval of the medical review plan and medical review reports.

If at any time during the course of the study, the medical review identifies safety signals or other elements that could affect the potential risks and benefits to the study participants. These will be reported to the Study Steering Committee and may trigger a review by the EORTC Independent Data Monitoring Committee (IDMC).

9.2.2 Monitoring by the IDMC

The study may be subject to periodic review for feasibility, data quality and evidence of treatment harm as per EORTC Policy "Independent Data Monitoring Committees". The IDMC will be asked to give advice on whether the accumulating data from the trial justifies continuing recruitment of further patients or further follow-up. These periodic reviews are to stop at primary study analysis but can be extended beyond that point in time by decision of the IDMC. The IDMC will review the trial whenever safety problems or other elements are identified during the medical review or by the SMG and/or SSC that could affect the potential risks and benefits for study participants. Such emergency IDMC review may be created upon request of the study team and upon decision of the IDMC chair.

While the trial is ongoing the accumulating data will generally remain confidential, unless the SSC and IDMC agree that the data should be made public.

10 Translational research

10.1 Background

There are several translational research projects embedded in the study including tissue, serum and DNA based biomarker studies. These projects aim to find markers that are predictive for response or toxicity or markers that can be used for treatment response monitoring.

First, the main objective of this translational research project is on serum Thymus and Activation-Regulated Chemokine (TARC). TARC is a serum biomarker which can be used to monitor treatment response. It is present in tissue in approximately 90-95% of classical Hodgkin's Lymphoma (HL) patients, but not in Nodular Lymphocyte Predominant Hodgkin's Lymphoma or most other B cell derived lymphomas (Ref. 48). 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 plasma or serum levels correlate well with tumor extensiveness (Ref. 49, Ref. 50, Ref. 51).

Recent data from a study performed in the University Medical Center Groningen (UMCG) show that final response to chemotherapy can already be observed by TARC response after one cycle of chemotherapy. A more recent study showed that TARC at mid-treatment showed a stronger positive predictive value for treatment failure and modified progression free survival than mid-treatment FDG-PET/CT imaging (Ref. 49). To further evaluate TARC as a treatment response biomarker there is a need to correlate TARC in current clinical trials with current standard of treatment response monitoring, i.e., FDG-PET imaging. Another small study indicated that TARC can be used during follow-up to detect early disease recurrence. More prospective studies are needed to validate these findings.

Secondly, we aim to identify the role of circulating tumor DNA (ctDNA) as a predictive biomarker for treatment response and as a biomarker for minimal residual disease. Prognosis of patients with Hodgkin lymphoma is highly dependent on initial treatment response (see study rationale) as detected with FDG-PET or TARC. However, advanced stage patients with a negative interim FDG-PET still have a 15-25% risk of (early) relapse. So there is still a need for specific and sensitive biomarkers to detect minimal residual disease (MRD). Genomic aberrations have the potential to serve as biomarkers for both predicting and monitoring response to treatment. Genomic aberrations in cell-free DNA (cfDNA) were initially detected in a pregnant individual, who was later diagnosed with early stage HL, indicating presence of ctDNA in the circulation. Subsequent testing on nine additional HL patients revealed presence of 2p and 9p gains, two commonly observed aberrations in tumor cells of HL, in cfDNA of seven and five of the nine HL patients, respectively. (Ref. 60). Two larger scale studies in recent years showed that mutations detected in cfDNA mirror the genetics of HL tumor cells by comparing the mutations in cfDNA to microdissected tissues enriched with tumor cells. (Ref. 61, Ref. 62). Together these studies show the feasibility of using cfDNA as a source of Hodgkin lymphoma tumor DNA.

A main advantage of cfDNA as compared to tissue biopsies is that it is easy to obtain and less invasive, allowing disease monitoring over time. Moreover, due to intra-tumor heterogeneity, a single biopsy might not be fully representative of all genomic aberrations in the total tumor mass. Considering that genomic aberrations can be readily detected in non-invasive liquid biopsies, this method may allow monitoring disease load and serve as a MRD marker. In DLBCL the cfDNA yield was significantly correlated with Ann Arbor stage of disease, as well as with serum lactate dehydrogenase (LDH), a commonly used non-specific biomarker for DLBCL. (Ref. 63). Moreover, persistent ctDNA levels were independently correlated with inferior progression-free survival in a multivariate analysis in DLBCL. Also in Hodgkin lymphoma, a decrease in ctDNA levels highly predicted for long lasting remission whereas persistent ctDNA levels correlated with relapsed disease despite FDG-PET negativity. (Ref. 64)

Third, other potential predictive or prognostic biomarkers will be analyzed on tissue, serum and blood samples in an explorative setting. These studies will include:

(1) exploration of predictive value of pre-treatment soluble CD30 (sCD30) levels for treatment response or toxicity. Pre-treatment sCD30 levels have been correlated with prognosis in previous studies. It is unknown whether sCD30 levels have predictive value for response with anti-CD30 targeted therapies such as Brentuximab vedotin. Next, toxicity or incidence of serious infusion reaction might be correlated with sCD30 levels.

(2) exploration of prognostic value of tissue RNA expression using Nanostring. A previous study has found prognostic value of a 22-gene set in ABVD treated advanced stage Hodgkin lymphoma (Ref. 56). The value of this gene set or total tissue RNA expression has not been validated in other studies or among patients treated with different treatment schedules. Analysis will include the then available gene set and will not necessarily be restricted to the 22-gene set predictor used by Scott et al. to identify possible new predictive gene sets.

(3) exploration of predictive value of several previously described immunohistochemistry 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 will be included for analysis in this study, i.e., CD68, HLA class II, cMET, IGF1-R, EBV-ISH, PD-1 and PDL-1.

(4) DNA analysis for HLA typing and a genome-wide association study (GWAS) approach. The latter may identify genetic determinants for treatment failure or other events. The DNA sample can also be used as a control to filter for personal variants in ctDNA analysis.

10.2 Objectives

10.2.1 Primary objective

The primary objective of this translational side-study is:

- to assess the degree of association between serum TARC level after one cycle of BrAVD and FDG-PET result after one cycle of BrAVD among patients with pre-treatment TARC elevation.

10.2.2 Secondary objectives

Secondary objectives of this translational side-study are of exploratory nature:

(1) to assess the ability of serial TARC levels during follow-up after completion of treatment to detect disease recurrence among patients that are positive for TARC by tissue immunohistochemistry

(2) to assess the correlation between TARC levels before, during and after completion of treatment with concurrent FDG-PET result (both Deauville score and quantified metabolic tumor parameters, i.e., SUVmax, metabolic volume and SUVmean) among patients with pre-treatment TARC elevation.

(3) to assess the correlation between TARC levels before, during and after completion of treatment and modified progression free survival for the BrAVD and BrECADD arm separately among patients with pre-treatment TARC elevation

(4) to correlate pre-treatment genomic aberrations in ctDNA with treatment response

(5) to correlate ctDNA levels with treatment response after one cycle of BrAVD and the end of chemotherapy

(6) to assess the ability of ctDNA to detect minimal residual disease after one cycle of BrAVD in patients who achieve a negative FDG-PET and experience relapse.

(7) to assess the ability of ctDNA to detect minimal residual disease after end of study treatment in patients who relapse

(8) to correlate cfDNA and ctDNA levels to TARC levels

(9) to explore predictive value of pre-treatment sCD30 to predict for FDG-PET response after one cycle of BrAVD in all patients

(10) to explore the correlation of pre-treatment TARC with clinical parameters including the international prognostic score, presence of B-symptoms, bulky disease and stage of disease in patients with pre-treatment TARC elevation

(11) to explore predictive value of sCD30 after one cycle of BrAVD for final treatment response and modified progression free survival in all patients in the BrAVD and BrECADD arm separately

(12) to explore the correlation of sCD30 levels with treatment toxicity and incidence of infusion reactions

(13) to explore predictive value of RNA expression using Nanostring to predict for FDG-PET result after one cycle of BrAVD in all patients

(14) to explore predictive value of several immunohistochemistry markers for FDG-PET result after one cycle of BrAVD in all patients

(15) to explore whether treatment failure is associated with genetic determinants in the host (HLA type and GWAS)

10.3 Participation in translational research

Participation in translational research is mandatory and part of the eligibility criteria.

10.4 Samples and time-points

	Tissue blocks/slides (biopsy)	**Buffy coat**	**Serum samples**	**Plasma**
Prior registration	x	x	x	x
During treatment				
After cycle 1 of BrAVD concomitant with FDG-PET/CT			x	x
After 4 cycles of BrAVD or 1 BrAVD cycle and 3 cycles of BRECADD			x	x
End of treatment				
After completion of chemotherapy concomitant with FDG-PET/CT			x	x
After completion of RT (if applicable) concomitant with FDG-PET/CT			x	

	Tissue blocks/slides (biopsy)	Buffy coat	Serum samples	Plasma
Follow up				
3 months after EOT			x	x
6 months after EOT			x	x
9 months after EOT			x	
12 months after EOT			x	x
15 months after EOT			x	
24 months after registration (app. 18 months after end of treatment) concomitant with CT			x	x
At progression/relapse (if applicable)			x	x

10.5 Sample processing, storage and shipment

10.5.1 Tissue sample

From the diagnostic biopsy material, formalin fixed paraffin embedded tissue samples mounted on tissue blocks are requested for central review and translational research purposes. Detailed information on shipment is defined in the HBM guidelines.

10.5.2 DNA sample

For every patient, 10 ml of blood will be collected in an EDTA-tube prior start of treatment. Buffy coat will be isolated by the local laboratory, split into 2 aliquots of 1.5 mL and stored at -80 °C. DNA will be isolated by the central lab. Detailed information on sample processing and shipment is defined in the HBM guidelines.

10.5.3 Serum samples

Serum will be collected at each time point as indicated in the sampling schedule. 8.5 ml of blood will be collected in a SST tube. After blood draw, samples have to be processed by the local laboratory in which serum will be isolated, split into 3 aliquots of 1.0 mL and stored at -80 °C until shipment according to the HBM guidelines.

10.5.4 cfDNA samples

Blood for cfDNA analysis will be collected at each time point as indicated in the sampling schedule. Samples have to be processed as per HBM guidelines.

10.5.5 Storage and shipment

Samples will be collected and, depending by the sample, processed according HBM guidelines. All samples will be stored locally and then shipped in batches by courier to the biobank of the University Medical Center Groningen upon EORTC greenlight (see HBM guidelines for central lab address, instructions and details).

Samples will be assayed at completion of the study.

10.6 Analyses of collected material

10.6.1 Serum biomarker levels

TARC and sCD30 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. Pre-treatment TARC levels will be considered elevated if level is above 1000 pg/ml (Ref. 56).

10.6.2 Immunohistochemistry studies

Immunohistochemistry analysis will be performed by the central lab. 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.

10.6.3 RNA studies

RNA will be isolated from tissue slides that are considered to contain enough amount of tumor cells. RNA expression studies using the then available gene sets will be performed according to Nanostring protocol and as previously described (Ref. 56).

10.6.4 ctDNA studies

DNA samples will be isolated from buffy coat samples by the central lab. DNA samples will be used for HLA typing, GWAS, controls for personal variants and/or correlative analysis of preceding regimens.

Cell-free DNA for ctDNA studies will be isolated from about 8ml of plasma with the QIAamp Circulating Nucleic Acid kit. This will be performed at the central lab. Samples will be subjected to quality control and used for library preparation using unique molecular indexes (UMIs) to allow selection of unique reads and sample specific indexes. After this first step, a size selection step will be done to enrich for the tumor DNA rich cfDNA fraction. An aliquote will be used for low-coverage WGA to detect copy number aberrations, and the remaining part will be used for target enrichment with a hybrid capture based next generation sequencing (NGS) platform. The targeted sequencing gene panel will include all coding exons and splice sites of genes recurrently mutated in HL. High-throughput sequencing will be performed with 100-bp paired-end runs. Copy number aberrations will be evaluated using low-pass whole genome sequencing using R package, CNAclinic. Somatic mutations will be identified at the central lab using pipelines established to analyze tumor NGS data (including multiple variant callers).

10.7 Statistical considerations

The primary objective of the TR is to assess the degree of association between serum TARC level (elevated versus low, as defined in section 10.6.1) and FDG-PET result (positive versus negative, as defined in section 7.1.1), both evaluated after one cycle of BrAVD, among patients with pre-treatment TARC elevation.

It is estimated that 85% of the patients will have pre-treatment TARC elevation in serum (Ref. 49, Ref. 50). TARC elevation after one cycle of chemotherapy is estimated to be about 75% of the FDG-PET positive patients and about 5% in the FDG-PET negative patients (unpublished observations). Finally, it is expected that 25% of the patients will be FDG-PET positive and 75% will be FDG-PET negative.

Based on these considerations, with 121 evaluable patients with pre-treatment serum TARC elevation, the chi-square test at 5% significance level two-sided has >99% power to detect an association between TARC and FDG-PET.

The statistical analysis will be restricted to the subset of evaluable patients with pre-treatment TARC elevation. The number of patients with pre-treatment serum TARC elevation or not and FDG-PET result positive or negative will be cross-tabulated. The estimated odds ratio with its 95% confidence interval will be presented together with the p-value resulting from the chi-square test.

The other objectives will be analyzed on an exploratory basis at 5% significance using bioinformatics and statistical methods described in the analysis plan (see section 10.8).

10.8 Data storage, transfer and development of technical appendices

The translational projects will be the result of the work of collaborating institutions and EORTC HQ. Project set-up, bio-informatics and statistical analysis plan will be jointly developed for each project. These documents will be reviewed and approved by EORTC trial statistician and bioinformatics expert before starting any analysis. They will specify analytical and methodological details. Clinical and patient-reported outcome data will be stored in the EORTC clinical database and genomic data will be stored at the European Genomic Archive (EGA). Transfer of data will be performed according to applicable policies (e.g., EORTC Policy L-01-POL-01) or according to jointly approved data transfer charters.

10.9 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/UMCG. 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 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 (GSSC) will be responsible for TR project review and prioritization, including the consideration of newly proposed TR projects not specified in the protocol. In the absence of a GSSC, responsibilities of the GSSC are transferred to the EORTC HQ as applicable.

Final decisions on the use of HBM will be determined by a majority vote of the GSSC. Additional expertise may be sought through advisory non-GSSC 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 appropriate GSSC.
- The GSSC will prioritize the TR projects. Access procedures defined by the GSSC 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 GSSC 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 Board will mediate any disagreements of opinion between TRAC, the EORTC HQ feasibility assessment, the GSSC and the TR project leader(s), as needed.

11 Investigator authorization procedure

Investigators will be authorized to register patients in this trial only once they have returned the following documents to the EORTC Headquarters:

- The updated signed and dated curriculum vitae of the Principal Investigator in English with a GCP training proof.
- The (updated) list of normal ranges for the investigator’s 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.
- The Confirmation of interest by Principal Investigator Form (CIF), 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 CIF.

- The Study Agreement between EORTC and investigator's institution.
- 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. In case patients receive treatment at a satellite institution, i.e., outside the authorized institution, details on the satellite institution, including the CV of the local investigator, normal lab ranges and the approval of an ethics committee will have to be transmitted to the EORTC Headquarters. Please keep in mind that all communication is done ONLY between the primary institution and the EORTC Headquarters.
- 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.

The center specific 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 patients in the trial as soon as

- All the above-mentioned documents are available at the EORTC Headquarters.
- All applicable national legal and regulatory requirements are fulfilled.

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

12 Patient registration procedure

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

Patients should be registered 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 registration/randomization program, the investigator needs a username and a password (which can be requested at http://orta.eortc.be/).

In case of problems investigators can phone the EORTC Headquarters from 9.00 am to 5.00 pm (Belgian local time) from Monday through Friday in order to register patients via the EORTC call center. Registration via the phone is not available on Belgian holidays. A list of these holidays is available on the EORTC web site (http://orta.eortc.be/) and it is updated annually.

Through Internet:	http://orta.eortc.be/
In case of problems by phone:	+32 2 774 16 00

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

STANDARD INFORMATION REQUESTED:

- institution number
- protocol number
- step number: 1
- name of the responsible investigator
- patient's code (*maximum 4 alphanumerics, a unique code to help identify the patient within your institution*)
- patient's birth date (*day/month/year*) or year of birth (as allowed per applicable legislation)

PROTOCOL SPECIFIC QUESTIONS:

- all eligibility criteria will be checked one by one
- actual values for the eligibility parameters will be requested when applicable
- date of written informed consent (*day/month/year*)
- date foreseen for protocol treatment start

Once eligibility has been verified, a **sequential patient identification number ("seqID")** will be allocated to the patient. This number 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.

13 Forms and procedures for collecting data

13.1 Case report forms and schedule for completion

Data will be reported on the forms specifically designed by the EORTC Headquarters for this study. Forms should be electronically sent to the EORTC Headquarters through the VISTA/RDC (Remote Data Capture) system, with the exception of the SAE form and the Pregnancy notification form which are paper CRFs.

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

A. Before the treatment starts:

- The patient must be registered 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 hour after the registration on http://rdc.eortc.be/ or on http://www.eortc.org in the section "Research Tools".

The paper CRF(s) 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 with the exception of the paper CRFs which need to be signed and dated individually by the responsible investigator or one of his/her authorized staff members.

13.2 Data flow

The forms must be completed electronically, with the exception SAE form and the Pregnancy notification form, 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 that 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. Corrections of obvious data errors will be done by the EORTC Data Manager, as outlined on the convention list, which

can be downloaded from the EORTC trial specific webpage: http://www.eortc.be/protoc/. Queries will be issued in order to resolve other 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.

13.3 HBM* sample registration and tracking

Once the patient is registered, this procedure might take up to one hour, the investigator or his/her authorized staff must log on "Samples" website at https://samples.eortc.be/ or by clicking on the link "Samples Website" at the bottom of the page http://rdc.eortc.be.

"Samples" is a web-based tracking tool designed to register, manage and track Human Biological Materials collected in the frame of EORTC clinical trials.

Details about access the "Samples" Website, register samples and tracking shipments are described on the guidelines of HBM* management.

(*) Human Biological Material

14 Reporting of Serious Adverse Events, Adverse Events of Clinical Interests and Pregnancy

ICH GCP and the EU Directive 2001/20/EC and the EU Regulation 536/201 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.

14.1 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.

ADR: An **Adverse Drug 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 was 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.

AECI: The following **Adverse Events of Clinical Interest** should be reported as a SAE **in an expedited way on a SAE form**:

The following adverse events are considered as Adverse events of clinical interest.

- Grade 3-4 peripheral neuropathy
- Progressive multifocal leukoencenphalopathy (PML)
- Grade 3-4 pulmonary AEs
- Grade 3-4 Cardiac AEs
- Secondary malignancies

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 timeframes specified by national legislations.

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

New 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.

14.2 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.
- Product complaints and medication errors in and of themselves are not AEs. If a product complaint or medication error results in an SAE, an SAE form should be completed.

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.

14.3 Severity assessment

The severity of all AEs (serious and non-serious) in this trial should be graded using CTCAE v5.0 https://www.eortc.be/services/doc/ctc/.

14.4 Causality assessment

The investigator is obligated to assess the relationship between protocol treatment and the occurrence of each SAE following the 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.

14.5 Expectedness assessment

The expectedness assessment is the responsibility of the sponsor of the study. The expectedness assessment will be performed against the following RSI (reference safety information):

- For Brentuximab vedotin: Summary of Product Characteristics (SmPC) section 4.8
- For Adriamycin: Summary of Product Characteristics (SmPC) section 4.8
- For Cyclophosphamide: Summary of Product Characteristics (SmPC) section 4.8.
- For Dacarbazine: Summary of Product Characteristics (SmPC) section 4.8.
- For Dexamethasone: Summary of Product Characteristics (SmPC) section 4.8.
- For Etoposide: Summary of Product Characteristics (SmPC) section 4.8.
- For Vinblastine: Summary of Product Characteristics (SmPC) section 4.8.
- For Radiotherapy: Safety information related to radiotherapy is compared to known complications of radiotherapy (depending or area irradiated). Anticipated adverse events related to radiotherapy are described in section 7.2.2.2)

14.6 Reporting procedure for investigators

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

Registration till 30 days after last protocol treatment administration:	All SAEs/AECIs
Any time after the 30 days period after the last protocol treatment administration (especially for BV):	Only SARs
From first dose administration until 3 years after last dose of IMP	All new primary malignancies

Any secondary malignancy should also be reported in expedited way on a SAE form with the appropriate seriousness criteria!

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

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

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

All 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.

All SAE forms must be sent to:

EORTC Pharmacovigilance Unit:

Fax No. +32 2 772 8027 or Email: Pharmacovigilance@eortc.org

To enable the Sponsor to comply with regulatory reporting requirements, all initial 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 SAE 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 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 principal investigator or any authorized staff member (i.e., on the signature list).

14.7 Reporting responsibilities for EORTC

As the Sponsor EORTC will be responsible for the reporting of SUSARs/unexpected SARs to the Competent Authorities, Ethics committees, EudraVigilance Clinical Trial Module (EVCTM), cooperating groups, and all participating investigators as applicable.

EORTC will also be responsible for the reporting of Annual Safety Report/Development Safety Update Report (ASR/DSUR) to the Competent Authorities, Ethics committees, CTIS portal and cooperating groups as applicable.

EORTC is not the marketing authorization holder for the Investigational Medicinal Product (IMP) and hence is a non-commercial sponsor. A single ASR/DSUR per trial will be prepared instead of per drug. The rationale is that the IMP is used amongst different EORTC trials which implies that there is no synchronous Development International Birth Date (DIBD) for the concerned IMP. As such EORTC has chosen to prepare for each EORTC trial a separate DSUR. This holds true for trials involving multiple drugs also.

The EORTC Pharmacovigilance will be compliant with the European Regulation 536/2014 and national legislation of the participating countries.

All forms must be signed by the principal investigator or any authorized staff member (i.e., staff on the signature list).

The EORTC Pharmacovigilance will forward all SAE reports to the appropriate persons within the EORTC Headquarters and to the pharmacovigilance contact at the Pharmaceutical Company.

- The EORTC Pharmacovigilance will report all SAEs in English (including pregnancies and suspected pregnancies) to Takeda Pharmaceuticals (or designee) regardless of expectedness or causality within 24 hours of the Sponsor's awareness of the event(s) from the first dose until 30 days after the last dose of BrAVD or BrECADD, as per any Agreements. Any SAE that occurs at any time during the study or after completion of brentuximab vedotin treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported to Takeda Pharmacovigilance (or designee) per any agreement. All new cases of primary malignancy must be reported to Takeda Pharmacovigilance (or designee) per any agreement.

The EORTC Pharmacovigilance will provide a six-monthly summary which will be added in the Newsletter and which will be accessible to all participating investigators.

The EORTC Pharmacovigilance Unit will take in charge the reporting of SUSARs/unexpected events to the Competent Authorities, Ethics committees, EudraVigilance Clinical Trial Module (EVCTM) and all participating investigators whenever applicable.

14.8 Adverse Events of Clinical Interest

The following adverse events of clinical interest should be reported on a SAE-form by following the procedure described in section 14.6:

- Grade 3-4 peripheral neuropathy
- Progressive multifocal leukoencenphalopathy (PML)
- Grade 3-4 pulmonary AEs
- Grade 3-4 Cardiac AEs
- Secondary malignancies

14.9 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 adverse outcome to the mother or the child should be reported. This also applies to pregnancies in female partners of a male patient participating in this trial.

- Any pregnancy in a female subject or in a female partner of a male subject diagnosed during the treatment period or until 6 months after last protocol 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/Email, to the Pharmacovigilance Unit on a Pregnancy Notification Form
- If an SAE occurs in conjunction with the pregnancy, please also complete an SAE form as explained in the SAE reporting chapter

14.10 Special situations requiring immediate reporting

List of special situations requiring reporting/immediate reporting e.g., they must be reported immediately or at latest within 24 hours from investigator being aware of the event:

- Abuse: is the persistent or sporadic, intentional excessive use of the study treatment which is accompanied by harmful physical or psychological effects.
- Misuse: the study treatment is intentionally and inappropriately used not in accordance with the authorized/approved product information.
- Use outside of what is foreseen in the protocol: this relates to situations where the study treatment is intentionally used for a medical purpose not in accordance with the protocol.
- Medication error: is any preventable incident that may cause or lead to inappropriate study treatment use or patient harm while the study treatment is in the control of the health care professionals or patients. Such incident may be due to health care professional practice, product labelling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use. As a general principle, unintentional misuse, unintentional off-label use, and unintentional overdose are medication errors. However, whether a scenario is an error or not may depend on the reason or cause.
- Product complaint: is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact Takeda Pharmacovigilance or designee (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Takeda Quality representative.

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

For Product Complaints or Medication Errors: E-mail: Cco.smbx.dk-ComplaintDK@takeda.com

Reporting procedure for investigator for above events: all these events must be reported in Vista Update as described in the CRF guidelines to the Sponsor regardless of whether or not an AE or SAE has occurred. If any of these events are associated with an SAE, an SAE report must be provided to the Sponsor within 24 hours of awareness.

15 Quality assurance

15.1 Control of data consistency

Data forms will be entered in the EORTC Headquarters database by using the VISTA/RDC (Remote Data Capture) 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.

15.2 On-site monitoring

The EORTC Headquarters or delegates will perform on-site monitoring visits according to the approved study-monitoring plan.

The first visit in a participating site will be performed within 3 to 6 months after the first patient's registration at this site. Frequency and number of subsequent visits will depend on site's accrual and quality observed during the first visit.

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

15.3 Audits

The EORTC is responsible for the performance of the EORTC investigators.

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 Compliance and Audits immediately (contact at: Complianceandaudits@eortc.org).

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

15.4 Other central review procedures

15.4.1 Quality assurance in radiotherapy (RTQA)

The RTQA procedures are summarized here and described in detail in the "RTQA Guidelines" document which will be supplied by EORTC prior to institution authorization. In case of questions or difficulties, please contact the trial RTQA team: rtqa1537@eortc.org.

The RTQA procedure consists of completing the following prior to institution authorization:

- Level I: Facility Questionnaire (FQ) and Beam Output Audit (BOA)

During the trial, the following RTQA patient-specific procedure must be performed:

- Level IV: Extensive prospective Individual Case Review (E-ICR)
- Level V: Complex Dosimetry Check through Virtual Phantom Procedure (VPP). This procedure, described in detail in the RTQA Guidelines, is in essence a phantom QC of a patient plan. For this specific study, due to the characteristics of the population and consequently the relatively small percentage of patients receiving radiotherapy, this procedure is going to be performed on the first patient to receive radiotherapy accrued by the institution.

Institutions failing to comply with the aforementioned procedures, including respect of timelines, delineation and dose limits, or failing to submit ALL data required for the VPP procedure before treatment start, can be excluded from accrual until resolution of all incompliances.

15.4.1.1 Prior to authorization

15.4.1.1.1 Facility questionnaire (FQ) and Beam Output (BOA)

All EORTC centers at authorization must have a valid EORTC FQ and a valid BOA performed by an external auditor. Both must be not older than 2 years. The questionnaire must be filled in electronically and submitted on line. Additional information can be found at the EORTC website under the Study Tools section.

To determine if a previously submitted FQ and or BOA is valid please contact rtqa1537@eortc.org and along with EORTC institution number.

15.4.1.2 Patient-specific RTQA program

All patient digital treatment data, FDG PET/CT fused with planning CT if in the same position, patient planning CT, complete with structures, dose and plan in DICOM format and completed Radiotherapy planning eCRF must be submitted prior to the start of RT treatment.

Should the review result in an “unacceptable protocol variation”, the institution 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” or "acceptable variation" review. The same rule will apply if case plans are not submitted within the requested timelines.

All details about the submission procedure, timelines and supplementary forms are described in the RTQA Guidelines.

15.5 Imaging Quality Assurance and Quality Control

15.5.1 Scan submission

The baseline PET/CT and the PET/CT after 1 cycle will be reviewed centrally and prospectively to determine with which treatment the patient will continue. These scans will have to be uploaded to the EORTC imaging platform within 24 hours after the acquisition of PET1 to make it possible for the central review to happen within 72 hours.

15.5.2 Imaging guidelines “read and understood” acknowledgment page signature

Every site participating in an EORTC study with imaging, must comply with the minimum requirements established as specified in the imaging guidelines. The 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 lead radiologist/nuclear medicine physician. This is mandatory from all institutions in this study before activation to participate in the trial.

15.5.3 Dummy run

Prior to enrolling patients to participate in this trial, centers are required to submit a test scan, called dummy run (DR) scan to be reviewed by the EORTC imaging officer, who will verify image quality, consistency of acquisition/reconstruction parameters and imaging guidelines compliance. Furthermore, the DR will act as a connectivity check. The DR scan will not be analyzed further. For more details on DR acquisition, reconstruction and submission please refer to the imaging guidelines.

15.5.4 Scan quality control

QC will be performed prospectively, on an on-going basis. As part of this study, the patients will have multiple visits. Only the baseline PET/CT and PET/CT after 1 cycle need to be uploaded to the EORTC imaging platform.

The EORTC Imaging Officer will be reviewing all centralized scans for all patients to check for artifacts and to ensure compliance with the imaging guidelines and study protocol.

Every subsequent scan on the same patient must be done with the same scanner across all visits. In case of scanner breakdown or change of scanners in the department, you need to notify the EORTC HQ.

15.5.5 Central review

The baseline scan and scan after 1 cycle will be centrally assessed within 72 hours after scan submission. The outcome of this assessment will determine the further treatment. A panel of 3 expert reviewers will be available to do the review in a timely manner. Step 2 will be completed by the experts.

16 Administrative responsibilities

16.1 The study coordinator

The Study Coordinator works closely with the study team to develop the outline and full protocol and discusses the contents of the reports with the study team. The Study coordinator is responsible for publishing the study results. He/she will assist the Clinical Research Physician for answering some clinical questions concerning eligibility, treatment, and contributes to the medical review of the patients.

Study coordinator:

[redacted]

Responsible Imaging physician:

[redacted]

16.2 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

16.3 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.org.

Lymphoma EORTC group

Chairman:

[redacted]

Secretary:

[redacted]

17 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.org

There is an education grant from Takeda pharmaceuticals

18 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.

19 Results dissemination policy

19.1 Study disclosure

19.1.1 Trial Registration

This trial will be registered in a public database (https://www.clinicaltrialsregister.eu). As the clinical trial (CT) regulation 536/2014 of the European Union (EU) becomes applicable, more information about this trial will be uploaded in this public database in compliance with European requirements on transparency. Information posted, among others, will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

In accordance with applicable EU regulations, a summary of the trial results, including intermediate analyses if available (i.e., not pertaining to confidential interim analyses reports), will be made publicly available within one year of the end of study declaration / intermediate data analysis data. EORTC as Sponsor of this trial will submit the summary of the results based on the relevant analysis report in compliance with the regulations.

19.1.2 Final Analysis Report

A Final Analysis Report that reports summary statistics of all the data collected for the study and presents an interpretation of the study results will be issued by the EORTC Headquarters. It will form the basis for the manuscript intended for publication. The Final Analysis Report or a summary thereof will be distributed to all participating groups, the supporting companies and ethics committees and the results will be posted in relevant public databases (as in section 19.1.119.1.1) as per contractual agreements / legal obligations

19.2 Publication policy

All publications must comply with the terms specified in the EORTC Policy J-03-POL-01 “Release of Results and Publication Policy” version 5.0 dated January 2022.

In accordance with the Policy J-03-POL-01, results of the present study will be made public once the study data are mature for the final analysis of the primary study endpoint (as described in the section “statistics” of the present protocol), irrespective of the findings (positive or negative). Deviations from the results disclosure rules specified in the Policy require authorization by the Independent Data Monitoring Committee (IDMC).

The primary trial publication will be written on the basis of the final analysis report and shall be published in a peer-reviewed scientific journal within 1 year of the date of the database lock.

Prior to submission, all publications (papers, abstracts, presentations…) will be submitted for review to the EORTC Headquarters statistician and clinical research physician, to all co-authors and to the designated representative of the pharmaceutical company supporting the study, if any as per contractual agreement. Approval of the manuscript by EORTC Headquarter representatives is required before submission of the manuscript reporting on an EORTC study for publication.

The authorship rules conform to the recommendations of the International Committee of Medical Journal Editors defining the roles of authors and contributors (http://icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html).

All other investigators and scientific contributors to the study who do not qualify for authorship will be acknowledged in the publication.

Sources of funding or support to the study will be disclosed and acknowledged in the publication.

The name “EORTC” and of any collaborative Group must be visible in the publication's header of all publications.

19.3 Data sharing

EORTC is committed to ensuring that the data generated from its studies be put to good use by the cancer research community and, whenever possible, are translated to deliver patient benefit.

It is therefore EORTC's policy to consider for sharing upon request from qualified scientific and medical researchers all data generated from its research whilst safeguarding intellectual property, the privacy of patients and confidentiality.

Considering that ongoing research contributing to the completion of datasets must not be compromised by premature or opportunistic sharing and analysis of data, the EORTC will not release the data of its study until the primary study results have been published; unless authorization for release has been granted according to the terms of EORTC Policy J-03-POL-01.

Requests for accessing the data of published trials should be filed through the data sharing tab on the EORTC website (www.eortc.org).

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Appendix B: Abbreviations

ABVD	Adriamicine, bleomycin, vinblastine, dacarbazine
ASCT	Autologous stem cell transplant
AVD	Adriamicine, vinblastine, dacarbazine
AE	Adverse event
AER	Absolute excess risk
ALCL	Anaplastic large cell lymphoma
AML	Acute myeloid leukemias
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
BEACOPP	Bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine
BrECADD	Brentuximab, etoposide, cyclophosphamide, adriamycin, dacarbazine, dexamethasone
BrECAPP	Brentuximab, etoposide, cyclophosphamide, adriamycin, procarbazine, prednisone
BV	Brentuximab vedotin
cfDNA	cell-free DNA
ctDNA	Circulating tumor DNA
CR	Complete remission
CRR	Complete response rate
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
DS	Deauville score
EBV	Epstein Barr virus
FDG	Fludeoxyglucose (^{18}F)
GI	Gastro-intestinal
G-CSF	Granulocyte-colony stimulating factor
GHSG	German Hodgkin study group
cHL	Classical Hodgkin Lymphoma
HRS	Hodgkin- or Reed-Sternberg cells
ICH GCP	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
IRR	Immediate and delayed infusion-related reactions

INRT	Involved node radiotherapy
IV	Intravenous
LLN	Lower limit of normal
LVEF	Left Ventricular Ejection Fraction
NHL	Non-Hodgkin lymphomas
MDS	Myelodysplastic syndrome
MMAE	Monomethyl auristatin E
MTD	Maximum tolerated dose
OS	Overall survival
PET CT	Positron emission tomography
PFS	Progression free survival
PML	Progressive Multifocal Leukoencephalopathy
RT	Radiotherapy
SMG	Study Management Group
SMR	Standardized mortality ratio
TARC	Thymus and Activation Regulated Chemokine
TNF-R	Tumor necrosis factor-receptor

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 5.0.

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

The EORTC Headquarters web site https://www.eortc.be/services/doc/ctc/ provides a link to the appropriate CTC web site. This link will be updated if the CTC address is changed.

Appendix F: Brentuximab vedotin - instructions for reconstitution

Each single use vial must be reconstituted with 10.5 ml of sterile water for injection to a final concentration of 5 mg/ml. Each vial contains a 10% overfill giving 55 mg of brentuximab vedotin per vial and a total reconstituted volume of 11 mL.

- Direct the stream toward the wall of the vial and not directly at the cake or powder.
- Gently swirl the vial to aid dissolution. DO NOT SHAKE OR VIGOROUSLY SWIRL.
- The reconstituted solution in the vial is a clear to slightly opalescent, colorless solution with a final pH of 6.6.
- The reconstituted solution should be inspected visually for any foreign particulate matter and/or discoloration. In the event of either being observed, discard the medicinal product.

Preparation of Infusion Solution

The appropriate amount of reconstituted brentuximab vedotin must be withdrawn from the vial(s) and added to an infusion bag containing sodium chloride 9 mg/ml (0.9%) solution for injection in order to achieve a final concentration of 0.4-1.2 mg/ml brentuximab vedotin. The recommended diluent volume is 150 ml. The already reconstituted brentuximab vedotin can also be diluted into 5% dextrose for injection or Lactated Ringer's for injection.

Gently invert the bag to mix the solution containing brentuximab vedotin. DO NOT SHAKE.

Any portion left in the vial, after withdrawal of the volume to be diluted, must be disposed of in accordance with local requirements.

Do not add other medicinal products to the prepared brentuximab vedotin infusion solution or intravenous infusion set. The infusion line should be flushed following administration with sodium chloride 9 mg/ml (0.9%) solution for injection, 5% dextrose for injection, or Lactated Ringer's for injection.

Following dilution, infuse the brentuximab vedotin solution immediately at the recommended infusion rate.

Total storage time under refrigeration 2◦C to 8◦C of the solution from reconstitution to infusion should not exceed 24 hours. Reconstituted brentuximab vedotin should not be stored at room temperature. Reconstituted vials must not be shaken.

Disposal

Adcetris is for single use only.

Any unused product or waste material should be disposed of in accordance with local requirements.

Appendix G: Extranodal disease (E-disease), bulk, large mediastinal mass

Definition: localized involvement of extralymphatic tissue (either by direct intrusion from a neighboring lymph node or with close anatomic connection). Also 2 or more E-lesions are compatible with stage II or III.

Bulky Disease (measured by CT)

Bulky disease is present if there is a:

- massive involvement of one lymph node with ≥ 5 cm greatest diameter, or
- conglomerate tumor ≥ 5 cm greatest diameter, or
- mediastinal tumor ≥ 5 cm diameter (hili and pericard not included in measurements).

Exact measurements for each bulky involvement are to be recorded on the ST form.

Large mediastinal mass

Definition: ≥ 1/3 of the greatest thorax cross-sectional diameter (measured on a sagittal chest X-ray image posterior-anterior in an upright position, not in CT). The maximum transverse diameter of the thorax is measured on a posterior-anterior image at the level of the diaphragm from the inside s of the ribs.

Mediastinal involvement

In the definition of irradiation regions, the upper mediastinum, above the tracheal bifurcation, is differentiated from the lower (infrabifurcal) mediastinum. If the mediastinum at the level of the tracheal bifurcation is involved, then the involvement is taken to involve the entire mediastinum.

Appendix H: Specific protocol instructions during the COVID-19 crisis

Note: all instructions listed in this Appendix will be solely applicable during the COVID-19 crisis.

Furthermore, please ensure that any protocol deviations resulting from COVID-19 are:

- **Adequately documented in the eCRF's, as well as in the patient's medical records or in a Note To File (NTF) to be stored in your Study binder (ISF).**
- **Always begin any deviation text with "COVID-19".**

1. Introduction

Current information suggests that cancer patients have a higher risk of infection and serious complications from infections including COVID-19, than other patients.

It is strongly recommended that investigators exercise medical/clinical judgement, and decisions regarding each patient should be individualized after considering the overall goals of treatment, the patient's current oncologic status and treatment tolerance as well as their general medical condition.

In addition, investigators should adhere to local and institutional guidelines for SARS-CoV-2 infection and suspected COVID-19 infection.

2. COVID-19 risk-benefit assessment

The study investigates a first-line treatment with curative intent for a curable disease. Protocol treatment with BrAVD or BrECADD does not lead to significantly more days in hospital or a higher level of risk than standard treatment with either ABVD or escBEACOPP. The omission of bleomycin in the study protocol is expected to put patients at lower risk for pulmonary complications compared to standard treatment.

Based on the above risk-benefit assessment, the following recommendations are proposed (see below):

The COBRA team strongly insist to follow the protocol as applicable and does not foresee any changes in the site handling of IMP, study patients treatment or changes to study visits.

On-site monitoring has been put on hold until further notice.

3. Proposed measures for patients already enrolled during the COVID-19 crisis

3.1 Recruitment of new patients

The EORTC confirms that this trial is open for recruitment.

The safety of the subject is of primary importance and the local investigator should weigh up the risks of involvement in the trial against anticipated benefit for the subject. The decision of enrolling a patient in the trial is left to participating investigator's judgment.

3.2 Strategy for patients already enrolled:

With respect to patient re-consent:

a. If additional consent is necessary for the implementation of new urgent changes in trial conduct (mainly expected for reasons related to COVID-19), alternative ways of obtaining such re-consents should be considered during the pandemic e.g., contacting the trial participants via phone or video-calls and obtaining oral consents supplemented with email confirmation. Any consent obtained this way should be documented and confirmed by way of normal consent procedures at the earliest opportunity when the trial participants will be back at the regular sites.

Please record in patients' medical records, major protocol deviations discussed with patients: Visits skipped, Images taken in other sites, IMP skipped/ provided to patient's home, patients' diaries completion. Please record in patients 'source documents all relevant information discussed with patients and the actions taken to conduct the trial during this period.

With respect to study imaging procedures:

It is preferred that the patient have imaging performed at the investigative site as directed in the protocol.

If imaging can NOT be performed at the investigative site as directed in the protocol, there are several possibilities, in order of preference:

- Have the imaging performed offsite/locally according to the protocol-specified timing. Guidance should be given by the site to the local imaging facility about conducting the scans according to all applicable requirements (modality etc… as per 1537-Cobra Imaging Guidelines).

  Important note: Due to the central review of the early PET-response, the upload of the scans (baseline and PET1) should occur within 24 hours. Please adhere to this as much as possible.

- Have the imaging performed at the site but delayed.

  Important note: For the PET1: if more than 23 days from the start of the first cycle of treatment due to travel restriction / safety of the participant, the site needs to report this in the comment fields of the applicable CRFs and in the Source Data.

- The scan can be done as late as possible before cycle 2, but as long as there is time to upload and review the scans. Therefore please contact EORTC as soon as possible so we can arrange the central review in due time.

- Have the imaging performed offsite but delayed.

  Important note: For the PET1: if more than 23 days from the start of the first cycle of treatment due to travel restriction / safety of the participant, the site needs to report this in the comment fields of the applicable CRFs and in the Source Data.

- The scan can be done as late as possible before cycle 2, but as long as there is time to upload and review the scans. Therefore please contact EORTC as soon as possible so we can arrange the central review in due time.

- Skip the imaging only if impossible to perform due to travel restriction / safety

Important note: For PET1 imaging, please note that in this case, patient must go off protocol treatment and an end of treatment form should be completed mentioning as reason for interruption 'COVID-19'.

! With regards to the PET 1 scan: If any changes are made (delay in performing the scan, delay in upload of the scan, … please contact imaging@eortc.org).

With respect to study treatments:

For IMP with parenteral administration (IV) it is recommended that upcoming scheduled administrations cannot be postponed for any other reason than mentioned in the study protocol. In case of any foreseen problems, please contact: medicalmonitor1537@eortc.org.

With respect to patient physical visits:

Whether a patient should postpone an assessment (e.g., due to unacceptable increased risk of infection) must be decided by the responsible physician in the best interest of the patient. Patient Physical Visits can be changed in phone visits where needed.

With respect to collection of biomaterial:

Participation in translational research is mandatory, if it is impossible to collect the sample(s) due to travel restriction / safety, the patient cannot be enrolled in the trial.

With respect to on-site monitoring visits

All on-site monitoring visits are currently suspended. CRAs will contact your staff to schedule the next monitoring visit, when the situation will evolve positively and in compliance with the Governments and sites recommendations. In the meantime, EORTC team will keep in touch with your staff to provide any support deemed necessary by the study team.

With respect to serious adverse event reporting:

Sites should follow the SAE reporting as described in the protocol e.g., the sites should continue to report SAEs immediately and no later than 24 hours from the time the investigator or site staff became aware of the event, as described in the protocol. There are no specific adaptations to the protocol defined SAE reporting procedure due to COVID-19.

Should sites have any SAE reporting related questions, please contact us at pharmacovigilance@eortc.org

Should there be a suspected or confirmed serious case of COVID-19 infection, report it as SAE:

Please remember to provide the mandatory SAE information as per protocol and as per the CRF completion guidelines.

Please indicate if the COVID-19 infection was confirmed by a test.

Please provide as much information as available.

With respect to RTQA:

Concerning the mandatory prospective central review of patients proceeding to have Radiotherapy, we acknowledge that timely submission of the RTdata data by investigators and review by our reviewers may not be feasible during this pandemic with reduced personnel. We ask that you continue to send the data for review as soon as possible and we will continue to send the cases to our reviewers asking also for their evaluation as soon as possible. Despite this, as a temporary measure, please do not hold up a patient's treatment waiting for review and proceed as planned. We will inform you when processes will be returned to timely prospective reviewing.

Appendix I: Regulatory and ethical considerations

1 Regulatory considerations

The study is submitted by the principal investigator or the national coordinator or the sponsor, in accordance with local regulations, for review and approval by an appropriate Independent Ethical Review Committee (IEC)/ Institutional Review Board (IRB) and a National Competent Authority if required by the national laws of the countries where the study is conducted. Other national approvals may also be required from the regulatory bodies within the member state.

The study cannot start at a participating site until written approval by the relevant Ethics Committee(s) has been obtained and the local regulatory requirements have been complied with.

The sponsor will provide a copy of the final protocol, protocol amendments, subject information sheets, consent forms, investigator brochure and all other applicable study documentation for locally required submissions.

The investigator and sponsor ensure that the study is conducted in full conformance with the principles of the Declaration of Helsinki, as revised from time to time (available on the World Medical Association web site (http://www.wma.net)) and with the laws and regulations of the country in which the research is conducted, whichever provides the greatest protection of the patient.

The sponsor and investigator ensure that the study is conducted in compliance with the protocol, the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP E6 (R2)), the EU Clinical Trial Directive (2001/20/EC) and/or the Regulation EU No 536/2014 when effective, and with the EU General Data Protection Regulation (GDPR) or other national laws and regulations as applicable.

2 Patient involvement in study design

EORTC encourages our patient partners to participate in the review of protocol synopsis and patient information sheet and informed consent.

To ensure the relevance and high quality of the research, protocol synopsis is reviewed by the EORTC Protocol Review Committee. It is composed of cancer specific experts, methodologists, and independent external patient experts whose contribution aims to add a unique patient's perspective to the study. Reviews of patient information sheet and informed consent are made by the EORTC Group of Patient Experts helping us to strike the balance between completeness of the information, document length and relevance of the research objectives for the patients.

Both groups are multinational, diverse, focus on different types of cancer and involve people with different personal experiences.

Furthermore, EORTC has an advisory patient panel whose main objective is to provide an independent voice of "lived experience" of cancer to EORTC and advise on different aspects of patient involvement, including the strategy. The patient panel is composed of independent patient advocates, former patients and caregivers of different age, gender and with different personal experiences of a range of cancers. Built in the spirit of co-creation, patient panel is supported in its work by one medical doctor and a HQ staff member.

3 Statement of compliance with EU General Data Protection Regulation (GDPR)

EORTC, in its role of Sponsor and Data Controller of the clinical study ensures that the processing activities on the personal data in scope of this study are compliant with, but not limited to, the requirements set by EU General Data Protection Regulation (GDPR EU 2016/679), its subsequent amendments and any additional national laws, recommendations and guidelines as applicable.

To comply with the applicable rules on the protection of personal data, specifically regarding the implementation of the organizational and technical arrangements aiming to avoid unauthorized access, disclosure, dissemination, alteration or loss of information and processed personal data, EORTC, in its role of Data Controller, declares that:

- It sufficiently involved and consulted the data protection officer with regards to all the aspects relevant to the compliance of data processing activities performed in the scope of study, it performed a data protection impact assessment and implemented the eventual mitigation actions prior start of the study.
- All clinical trial information is recorded, processed, handled, and stored by the sponsor or investigator, as applicable, in such a way that it can be accurately reported, interpreted and verified while the confidentiality of records and the personal data of the subjects remain protected in accordance with the applicable law on personal data protection.
- Ensured that appropriate technical and organizational measures are implemented to protect information and personal data processed against unauthorized or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss, in particular where the processing involves the transmission over a network, such as but not limited to:
    - restriction of physical access to the offices and information processing facilities to employees, personnel and visitors;
    - monitoring of the reception areas for offices and information processing facilities by a receptionist or security guard; controlling out of hours access;
    - provision of access cards and keys to data centers, server to authorized persons only; performing regular reviews of access rights;
    - allowing authorized access to personal data, as applicable and justified;
    - ensuring sustainable identification and authentication in virtual environment; centrally logging user access in virtual environment;
    - implementing the pseudonymisation and/or encryption of personal information, where applicable or required;
    - implementing network, application, database security by means of firewalls and antivirus/anti-malware;
    - ensuring detection of malware purposed for unauthorized deletion, blocking, copying of information, disabling security measures; and response to such attacks;
    - the ability to restore the availability and access to personal information in a timely manner in the event of a physical or technical incident;
    - logging of security events/incidents in information systems; implementing procedures that cover reporting, analysis, monitoring and resolution of security incidents;
    - ensuring that information systems, computers and software involved in the performance of the services provided in the Study are backed up;
    - a process for regularly testing, assessing and evaluating the effectiveness of technical and organizational measures for ensuring the security of the processing;
    - implementing procedures for reporting and handling personal data breaches;

  - implementing procedures and practices for secure destruction of paper documents containing personal data;
  - implementing business continuity procedures ensuring that Sponsor can continue to provide services through operational interruption; all locations, personnel and information systems that are used to perform services for the study will be covered.
- Ensured that staff involved in conducting the clinical study is suitably qualified by education, training and experience to perform their tasks, including but not limited to data protection and data privacy rules applicable to their tasks.

EORTC as Data Controller will ensure technical and organizational security measures described above are regularly reviewed and updated in accordance with evolving technology.

EORTC may apply additional statutory requirements, where applicable in the national laws, and implement necessary security measures.

Besides, EORTC as Data Controller in the study:

- ensures that data subject rights are informed about their rights and that the requests are addressed in a timely manner.
- processes personal data in a lawful, fair, and transparent manner;
- collects personal data only for purpose to conduct the study;
- ensures appropriate security of personal data and maintain its integrity and confidentiality; ensure that data collected and processed in scope of the study are accurate and up-to-date;
- ensures restricted access of its employees, processors, authorities, and subcontractors to personal data;
- maintain all records of processing activities necessary to demonstrate that personal data was only collected, processed and disclosed in compliance with the GDPR or other applicable data protection laws.

Before starting any new collaboration, EORTC performs processor and partner assessments, including the GDPR compliance assessment. Only qualified vendors will process data collected in scope of the study, as per contractual agreement between them and EORTC.

In the event of an actual or reasonably suspected personal data breach, breach of any data protection agreements in scope of the Study, or breach of applicable law, such as but not limited to GDPR, EORTC imposes to the processors and partners to:

- notify EORTC without undue delay (and in any event, within 24 business hours of Vendor/Supplier official confirmation of the actual or suspected personal data breach);
- at Vendors or Partners' sole cost and expense, undertake an appropriate investigation and all remediation efforts necessary to rectify and prevent a recurrence of the personal data breach or breach of applicable data protection laws;
- in the case of an actual or suspected personal data breach, as part of the remediation efforts, to collaborate with the Data Controller in the process of notification to all individuals whose personal information may have been affected, with content required under GDPR and satisfactory to the Data Controller.

For any questions regarding data protection in context of this study, please contact dpo@eortc.org.

4 Protection of patient's identity

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 and corresponding material and data associated with the patient. In order to avoid identification errors, the patient's code (maximum of 4 alphanumerics) and year of birth will also be reported on the case report forms.

EORTC monitors or delegates of EORTC have access to fully identifiable information only in the scope of the on-site monitoring visits, and only for the source data verification mandatory under the clinical trial framework, including the guidelines applying to the clinical research field, such as but not limited ICH-GCP obligations in scope of the study conduct. Staff involved in the performance of this task is sufficiently trained on personal data protection rules and is abided by additional stricter confidentiality clauses as compared with other staff members.

5 Informed consent form and procedure for obtaining patient's consent

5.1 Informed consent form

The Patient Information Sheet and Informed Consent Form (PISIC) describes the following items:

- the investigator and sponsor contact details
- the aims, description and course of the study (tests and procedures, treatment and mechanism of treatment allocation)
- the possible adverse events and potential hazards to which the patient will be exposed including risks related to a pregnancy
- benefits and interest in participating in the study
- costs related to study participation
- alternative treatment
- withdrawal from the study
- treatment after stopping or at the end of the study
- publication of study results
- translational research
- protection, privacy and confidentiality of any patient data
- insurance and liability
- notification of new information
- medical records possibly being reviewed for trial purposes by authorized individuals other than their treating physician

At time of site authorization, the sponsor will provide a copy of the approved version of the PISIC to be used. The investigators are not allowed to make any changes to the approved version of the PISIC unless these changes are non-substantial for the sponsor, such as but not limited to adding the hospital logo and completing contact person's details.

The PISIC to be provided to patients shall be revised whenever important new information becomes available that may be relevant to the patient's consent. Any substantial amendment to the PISIC shall receive the IRB/IEC's approval/favorable opinion in advance of use.

5.2 Recruitment and informed consent procedure

The provisions described below are subject to variations depending on the country and its national laws, but also on the hospitals where the patients will be recruited.

A description of this clinical study will be available on public registries (*section 19.1.1*). The sponsor, some participating sites and networks of investigators may also publish information about the trial on their own websites.

The informed consent process can only start once the study has been given a favorable opinion by the IRB/IEC's and has been approved by the National Competent Authorities as required by the national laws of the participating country(-ies). Also, the Investigator authorization procedure must have been completed by the Sponsor or its authorized representative(s) (Chapter 11).

Patients should be identified as potentially eligible by a healthcare professional who is responsible for the patient. This is to ensure that medical confidentiality is adhered to. Patients will be assessed for their potential eligibility by a healthcare professional that is authorized to recruit to the study.

Once a patient has been identified and assessed as potentially eligible for the study, the patient should be approached and informed about the study.

The person informing the subject on the study must be familiar with all aspects of the study as described in the latest IEC/IRB approved version of the protocol.

The investigator, or another member of the clinical team, should discuss the study with the patient and provide the patients with the opportunity to understand the objectives, risks and inconveniences of the study and the conditions under which it is to be conducted. The information should be provided to subjects in both oral and written forms. The language used to inform the subject, both oral and written, should be concise, should use layman's terms and should be understandable to the patient and an impartial witness/interpreter, when applicable. The person obtaining the informed consent must have the patient's medical notes and the current IEC/IRB approved versions of the PISIC available during the discussion. Other study documents may also be used during the interview (e.g., subject diaries, study schedule sheets).

All patients should receive the appropriate version of the written information and will be asked to read and review it.

Usually, if the patient is considering participating in a clinical study, he/she may take the PISIC home to discuss with family and friends.

All patients must have the cognitive ability to provide a legally effective informed consent for study participation. For patients not qualified to give or incapable of giving consent, written consent must be obtained from the patient's legal representative. The legal representative is an individual authorized under applicable law to consent to the patient's participation in the clinical study on behalf of the patient. This person should be designated by judicial decision or by a mandate (signed and dated by the two parties). By default, the national law may provide additional rules on the legal representatives. These rules must be followed, when applicable.

In the case where the patient (and the patient's legal representative as applicable) is unable to read, an impartial witness should be present during the entire informed consent discussion. An impartial witness is a person, who is independent of the study and cannot be unfairly influenced by people involved in the study, who attends the informed consent process if the patient cannot read the PISIC. After the patient (and/or legal representative, as applicable) has/have orally consented to participation in the study, the

witness's signature on the form will attest that the information in the consent form was accurately explained and understood.

Neither the investigator nor any member of the study team shall coerce or unduly influence a subject to participate or to continue to participate in a study. The investigator or designee must explain to the subject that the participation to the study is voluntary and that the subject is free to refuse to enter the study or to withdraw from it at any time, for any reason without any impact on the patient's subsequent care.

It is the responsibility of the investigator or a person designated by the investigator (if acceptable by national regulations) to obtain a signed, written informed consent from each potential subject prior to any study-related procedure being carried out. The informed consent is applicable throughout the subject's participation to the study. It is commonly accepted that subject should have a minimum of 24 hours between the date the PISIC is provided to the patient and the actual date when the patient (and/or the patient's legal representative as applicable) signs the PISIC. The date and time the study was discussed and the date the PISIC was given to the subject must be documented in the patient's medical records.

In addition, the person obtaining the patient's consent should inform relevant team members of the treatment decision for the patient.

The written PISIC must be dated and personally signed by the investigator or authorised sub-investigator and the patient giving consent (or patient legal representative or impartial witness).

An original copy of the signed PISIC will be retained in the Investigator's Study File (ISF) and must be made available for monitoring, audit or inspection. Another copy of the signed PISIC is given to the patient.

EORTC HQ does not collect any data about patients before the patient consented to participate to the study. To confirm patients' eligibility to the study, the investigator or a person designated by the investigator transmits their personal data to the EORTC HQ in a coded (pseudonymised) form.

In case of new information that might affect the patient's willingness to continue participating in the study or results in significant changes in the risk/benefit assessment, the PISIC will be reviewed and updated if necessary by the sponsor. All patients, including those already being treated, should be informed of the new information, given a copy of the revised PISIC or PISIC addendum (as applicable per national regulations), and give their consent to continue in the study.