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# ADCETRIS® (BRENTUXIMAB VEDOTIN) SUBSTITUTING VINCRISTINE IN THE OEPA/COPDAC REGIMEN [TREATMENT GROUP 3 (TG3) OF EURO-NET C1] WITH INVOLVED NODE RADIATION THERAPY FOR HIGH RISK PEDIATRIC HODGKIN LYMPHOMA (HL)
## IND# 118603

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**Protocol summary**

| **HLHR13, ADCETRIS® (BRENTUXIMAB VEDOTIN) SUBSTITUTING VINCRISTINE IN THE OEPA/COPDAC REGIMEN [TREATMENT GROUP 3 (TG3) OF EURO-NET C1] WITH INVOLVED NODE RADIATION THERAPY FOR HIGH RISK PEDIATRIC HODGKIN LYMPHOMA (HL)** |
|---|
| **Principal investigator:** Matt Ehrhardt, MD |
| **IND holder:** St. Jude Children's Research Hospital, #118603 |
| **Brief overview:** Targeted therapy in the OEPA/COPDac regimen for high risk patients with Hodgkin lymphoma will lead to an increased number of patients with HL to achieve CR at the end of 2 cycles and therefore reduce the number of patients requiring RT for cure. |
| **Intervention:** Substitution of vincristine with Adcetris® in each cycle of OEPA/COPDac (see GPOH-HD therapy as published in Mauz-Koerholz et al. JCO 2010) for patients with high risk Hodgkin lymphoma. |
| **Brief outline of treatment plan:** Adcetris® will substitute every vincristine in the OEPA/COPDac regimen according to the GPOH-HD2002 treatment group 3 (TG3) regimen. Involved node radiotherapy (25.5 Gy) will be given at the end of all chemotherapy to involved nodes that are not in CR after 8 weeks of therapy. Radiotherapy will be administered after completion of all chemotherapy following recovery of counts. |
| **Objectives:**<br><br>Primary objectives<br><br>• To evaluate the safety of AEPA/CAPDAC, as well as the efficacy (early complete response) after 2 cycles of AEPA chemotherapy in high risk patients with Hodgkin lymphoma (HL).<br>• To compare the event-free survival in high risk HL patients treated with AEPA/CAPDac to the historical control HOD99 unfavorable risk 2 arm (UR2).<br><br>Secondary objectives<br><br>• To estimate the number of patients with adequate response according to the definitions in the Euro-Net C1 after 2 cycles of AEPA.<br>• To evaluate the safety of Adcetris® in the AEPA/CAPDac regimen in children with high risk HL.<br>  o To describe acute hematologic, neuropathic, and infectious toxicities as they relate to transfusion requirements, growth factor support, episodes of febrile neutropenia and hospitalizations, according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.<br>  o To study the association between local failure and original lymph node region and volume of radiation (patterns of treatment failure).<br>• To assess patient-reported symptoms and health-related quality of life in children with high risk HL compared to those treated on the unfavorable HOD99 treatment arm.<br><br>Exploratory objectives<br><br>• To compare the ratings of neuropathic toxicity according to the NCI Common Terminology Criteria for Adverse Events, version 4.0 to the Pain Quality Assessment Scale (PQAS©).<br>• To describe the pharmacokinetics of Adcetris® when used as part of AEPA/CAPDac for |

| HLHR13, ADCETRIS® (BRENTUXIMAB VEDOTIN) SUBSTITUTING VINCRISTINE IN THE OEPA/COPDAC REGIMEN [TREATMENT GROUP 3 (TG3) OF EURO-NET C1] WITH INVOLVED NODE RADIATION THERAPY FOR HIGH RISK PEDIATRIC HODGKIN LYMPHOMA (HL) |
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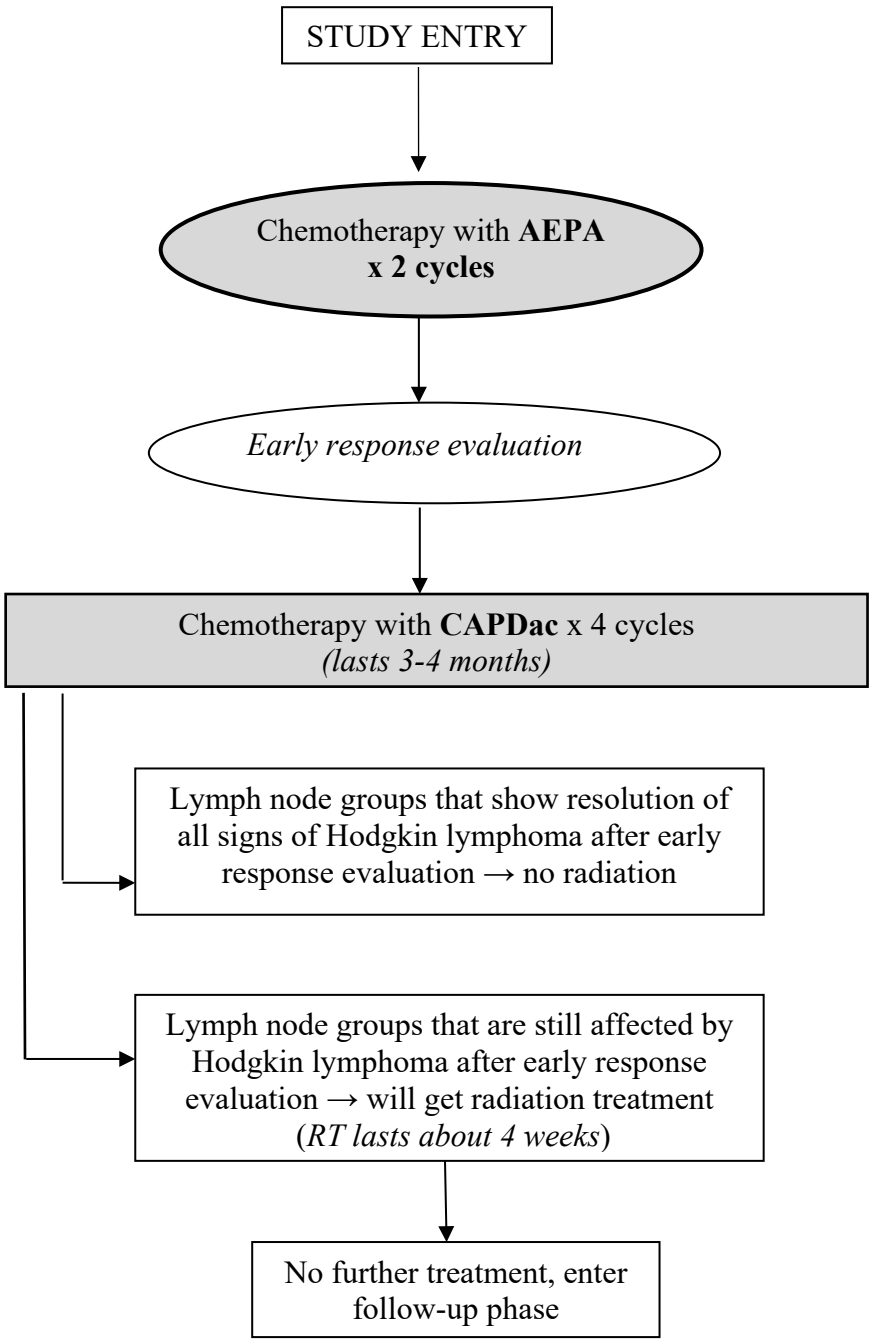
| pediatric HL patients.<br>• To describe the immunogenicity of Adcetris® and the relationship between early response and presence of anti-chimeric anti-body.<br>• To explore the association between CD30 density in Reed Sternberg cells in paraffin embedded tumor tissue and early response and event-free survival.<br>• To explore the association between soluble CD30 (in serum/plasma) and early response, event-free survival.<br>• To identify pharmacogenetic predictors for treatment-related outcomes in the context of AEPA/CAPDac. |
| **Study design:** This is a single-arm phase II study. The endpoint of primary objective 1.1.1 is complete response (CR) rate after OEPA. The sample size is calculated based on a binomial distribution to test the hypothesis: H0: p=17% versus Ha: p>17%, where p is the true CR rate of patients after 2-cycles of AEPA. A total of 32 patients are needed to detect a 20% increase in CR rate (to 37% or higher) with 80% power and 5% type I error. If this primary objective is successful, we will proceed to evaluate primary objective 1.1.2 which is event-free survival. A historical control phase II design was utilized to compare the EFS of patients treated with AEPA/CAPDac to that of unfavorable arm of HOD99. A sample size of 77 patients is sufficient to detect a 12% increase of 3-year EFS (from 79% to 91%) with 80% power and 10% type I error. |
| **Sample size:** A total of 32 are needed for the primary objective 1.1.1. A total of 77 (including 32 patients for the primary objective 1.1.1) patients are needed for primary objective 1.1.2. Thus, a total of 77 patients are needed for the study. |
| **Data management:** Provided by St. Jude Children's Research Hospital, Comprehensive Cancer Center research personnel, Leukemia/Lymphoma Division. |
| **Human subjects:** The risks to participants will be related to the toxicity of multi-modality chemotherapy and radiation. There is also the risk that reducing the number of patients who receive radiation therapy will increase the risk of relapse. Participants will be informed of this and other potential side effects during informed consent. Adverse events will be monitored and reported and treated appropriately. |

**General overview of treatment**



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**APPENDICES**

# 1.0 OBJECTIVES

## 1.1 Primary Objectives

1.1.1 To evaluate the safety of AEPA/CAPDAC, as well as the efficacy (early complete response) after 2 cycles of AEPA chemotherapy in high risk patients with Hodgkin lymphoma (HL).

1.1.2 To compare the event-free survival in high risk HL patients treated with AEPA/CAPDac to the historical control HOD99 unfavorable risk 2 arm (UR2).

## 1.2 Secondary Objectives

1.2.1 To estimate the number of patients with adequate response according to the definitions in the Euro-Net C1 after 2 cycles of AEPA.

1.2.2 To evaluate the safety of Adcetris® in the AEPA/CAPDac regimen in children with high risk HL.

1.2.2.1 To describe acute hematologic, neuropathic, and infectious toxicities as they relate to transfusion requirements, growth factor support, episodes of febrile neutropenia and hospitalizations, according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

1.2.2.2 To study the association between local failure and original lymph node region and volume of radiation (patterns of treatment failure).

1.2.3 To assess patient-reported symptoms and health-related quality of life in children with high risk HL compared to those treated on the unfavorable HOD99 treatment arm.

## 1.3 Exploratory Objectives

1.3.1 To compare the ratings of neuropathic toxicity according to the NCI Common Terminology Criteria for Adverse Events, version 4.0 to the Pain Quality Assessment Scale (PQAS©).

1.3.2 To describe the pharmacokinetics of Adcetris® when used as part of AEPA/CAPDac for pediatric HL patients.

1.3.3 To describe the immunogenicity of Adcetris® and the relationship between early response and presence of anti-chimeric anti-body.

1.3.4 To explore the association between CD30 density in Reed Sternberg cells in paraffin embedded tumor tissue and early response and event-free survival.

1.3.5 To explore the association between soluble CD30 (in serum/plasma) and early response, event-free survival.

1.3.6 To identify pharmacogenetic predictors for treatment-related outcomes in the context of AEPA/CAPDac.

1.3.7 Compare dosimetrically, the ability of PBRT to spare adjacent normal tissues compared to photon-based radiation therapy.

# 2.0 BACKGROUND AND RATIONALE

## 2.1 Combined Modality Therapy

Historically children and adults with Hodgkin lymphoma (HL) were treated with the same chemotherapy regimens, radiation therapy (RT) fields, and doses. However, irradiation techniques suitable for adults produced significant morbidities in children such as impaired musculoskeletal development, an increased risk for subsequent benign and malignant neoplasms, and cardiopulmonary toxicities. A desire to reduce these morbidities motivated the development of risk-adapted combined modality treatment strategies for pediatric HL.[17;38]

Chemotherapy with mechlorethamine, Oncovin (vincristine), procarbazine, and prednisolone (MOPP) was abandoned as frontline therapy due to its associated leukemogenesis and gonadal toxicity (azoospermia in more than 90% of males treated at any age; and age-related risk of ovarian failure in females).[27] Subsequently, Adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine (ABVD), which was not associated with secondary leukemia and sterility in adults, became the preferred chemotherapy regimen.[37] The predominant adverse effects of ABVD are pulmonary toxicity related to bleomycin and cardiovascular toxicity secondary to Adriamycin. These side effects may be exacerbated by the addition of mediastinal or mantle irradiation.[26] Overtime, contemporary pediatric regimens have evolved to further limit exposure to agents in the MOPP and ABVD regimens in an effort to reduce the risk of sterility, leukemia and cardiopulmonary toxicity.

Because of differences in the age-related developmental status of children, and the gender-related sensitivity to gonadal chemotherapy toxicity, no single treatment is ideal for all children. The use of RT and chemotherapy can broaden the spectrum of potential toxicities but reduce the severity of individual toxicities. Most current approaches entail chemotherapy in conjunction with reduced RT doses. The volume of RT and the intensity and duration of chemotherapy are risk- and response-adapted and determined by prognostic factors at presentation.

## 2.2 Risk Adapted Therapy - Intermediate and Unfavorable Risk

In risk-adapted treatment regimens, patients with localized disease presenting with unfavorable features are often grouped into an intermediate risk category and includes those with localized (stage IA, IIA) disease with unfavorable features and those with stage IIIA disease. The criteria for unfavorable clinical presentations vary per

investigation, but typically include the presence of "B" symptoms, bulky lymphadenopathy, hilar lymphadenopathy, involvement of 3 or more nodal regions, extranodal extension to contiguous structures, or advanced stage (IIIB and IV). In our studies, the unfavorable or high risk group (both terms used interchangeable) comprises all patients with stage IIB, IIIB and any IV. The COG has been using an approach of dose density to support early-response adapted therapy. A dose dense regimen of doxorubicin, bleomycin, vincristine, etoposide, prednisone and cyclophosphamide (ABVE-PC) chemotherapy was used for both intermediate and high risk patients in the POG9425 study which provided encouraging clinical outcomes using response based therapy (Table 1).[39] In the recently completed COG AHOD 0031 study, intermediate risk patients received 2 cycles of ABVE-PC followed by response assessment. Patients with RER received 2 additional cycles of ABVE-PC followed by a second response assessment; those with a CR were randomized to 21 Gy involved field RT (IFRT) or no further therapy. Patients with a RER who did not have a CR were all assigned to receive IFRT. SER patients were all randomized to either 2 additional cycles of ABVE-PC or dexamethasone, etoposide, cisplatin, and cytarabine (DECA) followed by an additional 2 cycles of ABVE-PC. All SER patients received 21 Gy IFRT after chemotherapy. 3-year EFS was 87.1% for RER patients versus 77.8% for SER patients (P=0.0001). OS for RER patients was 98.7% versus 96.9% for SER patients (P=0.02). 3-year EFS was 87.9% for RER/CR patients randomized to receive IFRT versus 85.4% for those randomized to no IFRT (P=0.07). These results suggest that early response to chemotherapy defined by early reduction (60%) in tumor size by CT after 2 cycles can be a powerful predictor of outcome and inform optimization of subsequent treatment. A secondary analysis of PET response after 2 cycles of ABVE-PC demonstrated that PET may further inform treatment. Analyses of the AHOD0031 cohort are still ongoing, including an "as treated" analysis; we await further information on the influence of disease characteristics, such as bulk, and treatment-related factors on clinical outcome.[13]

Patients with unfavorable and advanced disease presentations either receive a twice-monthly chemotherapy schedule for 6–8 months or a weekly chemotherapy regimen condensed to enhance dose intensity and reduce the risk of developing resistant disease. COG investigators recently assessed results of a dose-intense, response-based regimen employing BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) in children with high-risk disease.[23] Females with a rapid response, received 4 cycles of COPP/ABV following BEACOPP without IFRT and males received 2 cycles of ABVD and IFRT. All patients with a slow response received 4 additional cycles of BEACOPP and IFRT. A high 5-year EFS of 94% was achieved and OS was 97%.[23] A summary of treatment results of published trials is provided in Table 1, which demonstrates EFS rates ranging from 70%-90%.

The GPOH, building up on their original experience with the OPPA/COPP regimen, showed that 6 cycles OEPA/COPDAC together with 20-30 Gy IFRT also produced excellent results, with 5-year EFS of approximately 87%.[28]

Risk adapted treatment regimens as described above have allowed patients with localized disease receive less intensive therapy compared to patients with advanced disease without compromising outcome. Furthermore, response adapted therapy has been incorporated to allow tailoring of radiotherapy in patients that achieve a complete response after a couple of

cycles or are considered rapid early responders according to predefined criteria. These strategies aim at balancing cure and acute and late effects of therapy.

**Table 1: Treatment Results for Intermediate and High Risk Pediatric Hodgkin Lymphoma**

| Group or Institution | Patients (n) | Stage | Chemotherapy | Radiation (Gy), Field | Survival (%) | | F-up (year) |
|---|---|---|---|---|---|---|---|
| | | | | | OS | DFS, EFS or RFS | |
| GPOH-HD 2002[28] | 239 | $IIB_E$, $IIIA_E$, IIIB, IV | 2 OEPA/OPPA + 4 COPP/COPADC | 20-35 IF | 97 | 87 | 5 |
| POG 8725[43] | 80 | IIB, $IIIA_2$, IIIB, IV | 4 MOPP/4 ABVD | 21 EF | 87 | 80 | 5 |
| | 81 | $IIB/IIIA_2$, IIIB, IV | 4 MOPP/4 ABVD | None | 96 | 79 | 5 |
| POG 9425[39] | 216 | IB, $IIA/IIIA_1$ with bulky mediastinum or $IIIA_2$, IIB/IIIB/IVB | 3 ABVE-PC for RER<br>5 ABVE-PC for SER | 21 IF<br>21 IF | 95<br>95 | 86<br>83 | 5 |
| CCG 521[20] | 54<br>57 | III/IV | 6 ABVD<br>12 MOPP/ABVD | 21 EF<br>None | 90<br>84 | 87<br>77 | 4 |
| CCG 5942[32] | 109 | IIB, III | 6 COPP/ABV | 21 IF | 95 | 87 | 3 |
| | 33 | IV | COPP/ABV + CHOP + Ara-C/VP-16 | 21 IF | 100 | 90 | 3 |
| | 110 | IIB, III | 6 COPP/ABV | None | 100 | 83 | 3 |
| | 34 | IV | COPP/ABV + CHOP + Ara-C/VP-16 | None | 94 | 81 | 3 |
| CCG 59704[23] | 99 | IIB or IIIB with bulky disease or IV | All: 4 BEACOPP then<br>(1) RER: Female: 4 COPP/ABV<br>(2) RER: Male: 2 ABVD<br>(3) SER: 4 BEACOPP | (1) None<br>(2) 21 IF<br>(3) 21 IF<br>(<CR: boost 14 Gy) | 97 | 94 | 5 |
| AHOD0031 | 1712 | IA/IIA with bulk disease, $IA_E/IIA_E$, IB/IIB, IIIA/IVA | All: 2 ABVE-PC then<br>1. RER: 2 ABVE-PC<br>2. SER:<br>(2a) 2 DECA + 2 ABVE-PC<br>(2b) 2 ABVE-PC | If CR: (1a) None (1b) 21 IF<br>(2) 21 IF | RER: 99<br>SER: 97 | RER: 87<br>SER: 78 | 3 |
| HOD99 | 141 | IIB, IIIB, IV | Stanford V | If CR: 15 IF<br>< CR: 25 IF | 97 | 79 | 3 |

*GPOH-HD, German Pediatric Oncology-Hematology Hodgkin Lymphoma Study Group; POG, Pediatric Oncology Group; CCG, Children's Cancer Group; COG, Children's Oncology Group; HOD, Studies by the Pediatric Hodgkin Consortium;*
*OEPA, Oncovin, etoposide, prednisone, Adriamycin; OPA, Oncovin, prednisone, Adriamycin; OPPA, Oncovin, procarbazine, prednisolone and Adriamycin; COPDac, cyclophosphamide, Oncovin, prednisone and dacarbazine; COPP, cyclophosphamide, Oncovin, prednisone and procarbazine; MOPP, nitrogen mustard, Oncovin, procarbazine and prednisone; ABVD, Adriamycin, bleomycin, vinblastine and dacarbazine; ABVE-PC, Adriamycin, bleomycin, vincristine, etoposide, prednisone and cyclophosphamide; C/VP-16, cyclophosphamide and etoposide; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; CHOP, cyclophosphamide, doxorubicin, Oncovin, prednisone; DECA, dexamethasone, etoposide, cyclophosphamide, Adriamycin;*
*RER, rapid early response; SER, slow early response; IF, involved field; EF, extended field; CR, complete response; OS, overall survival; DFS, disease-free survival; EFS, event-free survival; RFS, relapse-free survival; F-up, follow up*

## 2.3 Results of Pediatric Hodgkin Group Collaborative Trials

In 1990, investigators from Stanford, Dana Farber, and St. Jude initiated studies with objectives of reducing cardiopulmonary, gonadal, and neoplastic treatment sequelae with the use of combination chemotherapy regimens that eliminated or reduced exposure to alkylating agents, anthracyclines and bleomycin. Patients with favorable (peripheral nodal disease < 6 cm or mediastinal mass to thoracic cavity ratio < 33% by chest radiograph) localized disease received 4 cycles of vinblastine, Adriamycin, methotrexate, and prednisone (VAMP) chemotherapy.[10] At a median follow-up of 9.6 years, 5- and 10-year EFS were 92.7% and 89.4%, respectively.[10] Patients with localized, unfavorable bulky presentations and advanced disease received 6 cycles of vinblastine, etoposide, prednisone, and Adriamycin (VEPA) chemotherapy.[14] All patients received involved-field radiation with the prescribed dose based on disease response after 2 cycles of chemotherapy. Patients with a complete response received 15 Gy; those with a partial response or bulky disease at presentation received 25.5 Gy. Accrual to the VEPA plus radiotherapy regimen was closed in 1993 because of the inferior event-free survival experienced by advanced and unfavorable patients.[14] Mature results of this trial suggest that disease control in patients with advanced stage HL is compromised when patients are treated with regimens that do not contain alkylating agent chemotherapy. The 5-year EFS for this cohort was 67.8%$\pm$6.3% and overall survival was 81.3%$\pm$5.2%, survival rates below the range typically observed for pediatric patients with advanced stage disease treated with combined modality therapy. The subsequent study for unfavorable and advanced disease prescribed alternating cycles of VAMP and COP chemotherapy with low-dose involved-field radiation therapy and started in 1993.[19] The dose of radiation was the same as that given on the earlier study: 15 Gy for patients achieving a complete response after the first 2 cycles, and 25.5 Gy for patients with a partial response and to all sites of bulky lymphadenopathy. The 5-year EFS for the entire VAMP/COP + RT cohort (n=159) was 75.6% ± 4.1% and 5-year overall survival was 92.7%$\pm$2.5%. Event-free survival was somewhat higher for the 77 patients with localized unfavorable stage I/II disease than that of the 88 patients with advanced stage III/IV disease though the difference was not statistically significant (5-year estimates: 82.5% ± 5.0% versus 68.4% ± 6.5%, p=0.093).[19] Overall, treatment outcomes following the VAMP/COP + RT regimen were inferior to other reports for unfavorable and advanced stage pediatric HL. Surviving patients are continuing with follow-up to determine if regimen-related long-term toxicity will be significantly less than that observed after combined modality treatment protocols including higher doses of alkylating agents and radiation doses and volumes. Accrual to this study has been closed. Subsequent studies utilized more dose-intensive therapy that may improve long-term outcomes (since 2002 for unfavorable patients and in 2004 for intermediate-risk patients).

The favorable risk arm of HOD99 closed in February 2009. In this arm favorable risk patients were treated with four cycles of VAMP. Patients who had a complete response after the first two cycles did not receive RT, whereas patients with a partial early response received low-dose (25.5 Gy) involved-field radiotherapy. Five-year OS and EFS for the whole cohort are 100% and 88% (SE=4.2%), respectively; the EFS for patients who achieved early CR and did not receive IFRT is 89% (SE=5.7%), compared with 87% (SE=6.4%) for those who did not achieve CR. All 5 relapsed non-irradiated patients were

retrieved with multi-agent chemotherapy and IFRT without an autologous stem cell transplant.[30]

In our closed intermediate risk study patients with stage IB, IIIA, plus IA/IIA patients with bulky mediastinal adenopathy, "E" lesions, or 3 or more nodal sites were treated with 12 weeks of Stanford V chemotherapy plus low-dose, involved node radiation therapy, with the radiotherapy dose based on response after 8 weeks (15 Gy if CR, 25.5 Gy if PR) of chemotherapy. The unfavorable risk arm of HOD99 reached accrual in May of 2011. The 3–year EFS of HOD99 unfavorable risk patients is 79.4% (SE +/- 4%) with a total of 27 events among 142 patients (results unpublished).

## 2.4 Proposed Study and Definition of Prognostic Groups

The aim of this high risk (previously called unfavorable risk) study is to: 1) estimate the number of patients (stages IIB, IIIB or IV) who achieve complete response to 8 weeks of chemotherapy with AEPA/CAPDac thereby reducing the number of patients requiring radiation therapy as well as the volume to the patients receiving radiation by inducing higher rates of early complete response and tailoring the volume of treatment only to sites that achieve less then CR after 2 cycles of AEPA (early response).

### 2.4.1 Adcetris® for the Treatment of Hodgkin Lymphoma

Adcetris® (generic name is Brentuximab vedotin, also previously known as SGN35) is an antibody-drug conjugate containing an anti-CD30 murine/human chimeric monoclonal antibody (cAC10; brentuximab) linked to monomethylauristatin E (MMAE; vedotin). CD30 is a transmembrane receptor highly expressed in both HL and anaplastic large cell lymphoma (ALCL). After binding CD30, brentuximab is internalized and is transported to lysosomes, where the peptide linker is selectively cleaved, releasing MMAE into the cytoplasm. Like vinorelbine, MMAE exerts its antineoplastic effect through inhibition of tubulin polymerization, leading to M-phase arrest and apoptosis.

The safety and efficacy of Adcetris® has been evaluated in adults with HL or ALCL, using the MTD of 1.8 mg/kg every three weeks. Among 102 patients with HL, the observed ORR was 76% (95% CI 65-83%), with a CR rate of 34% (95% CI 25-45%).[6] The ORR among patients with ALCL was 88% (95% CI: 75-94%), with a CR rate of 53% (95% CI: 40-67%).[40] Treatment related toxicity in these older heavily pretreated patients included peripheral sensory neuropathies (44%), fatigue (42%), nausea (41%), diarrhea (34%), pyrexia (31%), neutropenia (21%) and vomiting (20%). Based partly on these results, the FDA has approved Adcetris® for the treatment of patients with refractory HL or ALCL.

An adult phase I dose escalation study looking for the maximum tolerated dose (MTD) on a weekly schedule in 43 patients (38 HL and 5 ALCL) found it to be 1.2 mg/kg. The most common observed adverse events were peripheral sensory neuropathy, fatigue, nausea, diarrhea, arthralgia, and pyrexia; and the majority of events were mild to moderate in severity. Tumor regression occurred in 85% of patients and the overall objective response rate was 59% (n = 24), with 34% (n = 14) complete responses. The median duration of response was not reached at a median follow-up of 45 weeks on study.[12]

The pediatric experience to date is based on nine pediatric patients included in the Phase I or II trials of brentuximab vedotin (5 HL, 4 ALCL). Six were treated with 1.8 mg/kg every 3 weeks, for a median of 15 cycles.[11] The most frequent treatment-related adverse events were fatigue, nausea, and peripheral neuropathy. Three of 9 patients experienced ≥ Grade 3 toxicity (hyperesthesia, leukopenia, and neutropenia). Six of 9 pediatric patients obtained a CR (2/5 HL patients and 4/4 ALCL patients). In this pediatric cohort, pharmacokinetic parameters for the antibody-drug conjugate, including volume of distribution and clearance, were within approximately 20% of the values measured among adults (Personal communication, Seattle Genetics, September, 2011). The Children's Oncology Group has recently opened AHOD1221, a phase I/II trial for pediatric patients with relapsed Hodgkin lymphoma in which Adcetris® is given in combination with gemcitabine.

Combination trials with Adcetris® for adults with newly diagnosed advanced stage HL are ongoing.[47] The objectives of these studies are to assess the safety profile of the combination of Adcetris® with ABVD or AVD as well as to determine the MTD and the antitumor activity of the combination. Forty-four patients were enrolled on one study and received biweekly 1.2 mg/kg brentuximab vedotin concurrent with the chemotherapy. The most common grade 3/4 adverse events were neutropenia and anemia with no report of grade 3 neuropathy. In the ABVD cohort 40% developed significant pulmonary toxicity, and none in the AVD cohort, this prompted the company to warn about the combination with bleomycin (black box warning). The results on 37 of the evaluable patients is 97% of the patients were PET negative after 2 cycles of therapy.[47]

### 2.4.2 Rationale for Testing a Modified OEPA/COPDac and Involved Node Radiation Therapy Incorporating Adcetris® Instead of Vincristine in High-Risk Pediatric HL

The OEPA/COPDac regimen is a well-established pediatric HL treatment regimen widely used in Europe, Latin America and at St Jude. The combination of vincristine, etoposide, prednisone and doxorubicin (OEPA) followed by cyclophosphamide, vincristine, prednisone and dacarbazine (COPDac) was first successfully implemented in the GPOH-HD-2002 study for boys with omission of radiotherapy only in patients with favorable risk (stage IA, IB , and IIA without extranodal extension) features that achieved a complete response to chemotherapy.[28] This regimen was further refined in the ongoing Euro-Net C1 study open in numerous European countries in which radiotherapy decision is based on early response assessment – after 2 cycles of OEPA (now given to all patients). For consolidation COPDac is given to all boys while girls are randomized between COPDac and COPP (procarbazine instead of dacarbazine). Preliminary results suggest excellent outcomes with this strategy with and without radiotherapy in patients achieving an early complete response; however only 33% of high risk patients (TG3) could be spared radiotherapy (personal communication Mauz-Körholz) altogether. Since the closure of our last high risk study (HOD99) and the unavailability of mechlorethamine that prompted us to substitute cyclophosphamide leading to inferior outcomes,[29] we have been using the GPOH-HD 2002 approach in our intermediate and high risk patients successfully.

While we would have liked to continue building on our Stanford V backbone experience, addition of Adcetris® to this combination would not have been safe and feasible due to the interaction with bleomycin leading to unacceptable pulmonary toxicity and the risk of unacceptable neuropathic toxicity with the alternating weekly vincristine and vinblastine. Of all the agents included in the Stanford V regimen, bleomycin has the lowest single agent activity (approximately 40% response rate against HL as a single agent).[45] While bleomycin-induced pulmonary toxicity is not very common in patients treated with Stanford V, it is significant in the ABVD regimen. In our previous HOD99 study with Stanford V we had no grade 3 pulmonary toxicity reported. In a recent study of Adcetris® along with ABVD, approximately 40% of patients experienced pulmonary toxicity, compared to a 10-25% historical incidence for patients receiving ABVD alone. As a result of the finding, the study protocol was amended to remove bleomycin. According to data presented at the American Society for Hematology (ASH) conference, patients treated with Adcetris® plus AVD has not been associated with pulmonary toxicity.[2] The package insert has therefore been revised to indicate that Adcetris® shall not be combined with bleomycin. The other toxicity of concern is neuropathy. To date Adcetris® has not been combined with vincristine. In combination with AVD, which includes vinblastine, it appears to be tolerable; however, there is no combination data for vincristine and Adcetris®. In our previous Stanford V experience the incidence of grade 3 neuropathy (constipation, motor or sensory neuropathy, and pain) was reported in 9% of patients. According to the investigator brochure the neuropathy associated with single-agent Adcetris® is primarily sensory and in phase I clinical trials reaches 54% (any grade) which is mostly cumulative and observed after 10 weeks of therapy (for grade 2) and 36 weeks of therapy (for grade 3). Most patients experiencing complete resolution after discontinuation of the drug. Therefore, in this protocol we have replaced the vincristine in the OEPA/COPDac regimen with Adcetris® leading to the new combination AEPA/CAPDac. The cumulative doses of anthracyclines are not significantly higher than in the Stanford V combination while below other American cooperative group regimens, so that no significant cardiotoxicity is expected. Furthermore, the use of dacarbazine instead of a classical alkylator promises to be less gonadotoxic then procarbazine, though no definitive data are of yet available to prove this. To date there is no report of secondary leukemias in patients treated with OEPA. (Please see Tables 2 and 3 for comparative drug intensities and cumulative doses of pediatric standard regimens).

**Table 2: Dose Intensities of Pediatric HL Regimens (mg/m²/week)**

| | Stanford V | OEPA (GPOH HD-2002) | **AEPA** | COPDac (GPOH HD-2002) | **CAPDac** | COPP/ ABV (CCG5942) | DBVE+PC (POG9425) | BEACOPP (CCG 59704) |
|---|---|---|---|---|---|---|---|---|
| Doxorubicin | 12.5 | 20 | **20** | | | 8.75 | 20 | 11.7 |
| Bleomycin | 2.5 | | | | | 2.5 | 5 | 3.3 |
| Vincristine | 0.7 | 1.125 | **---** | 0.75 | **---** | 0.35 | 0.93 | 0.67 |
| Vinblastine | 3 | | | | | 1.5 | | |
| Etoposide | 30 | 156 | **156** | | | | 125 | 200 |
| Cyclophosphamide | | | | 250 | **250** | 150 | 267 | 400 |
| Procarbazine | | | | | | 175 | | 233 |
| Dacarbazine | | | | 187.5 | **187.5** | | | |
| Mustargen | 1.5 | | | | | | | |
| Adcetris® (mg/kg) | | 0.6 | **0.6** | | **0.6** | | | |

**Table 3: Cumulative Doses Associated with Long-Term Sequelae in Pediatric HL Regimens (mg/m²)**

| | Stanford V | DBVE-PC (POG 9425) | DBVE-PC (POG 9425) | COPP/ABV (CCG5942) | GPOH-HD 2002 | HLHR13 | CCG 59704 | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | RER | | SER |
| | +RT | RER +RT | SER +RT | Inter-mediate risk ± RT | OEPA/ COPDac ±RT | **AEPA/ CAPDac** | *BOYS* BEACOPP+ ABVD + RT | *GIRLS* BEACOPP+ COPP/ABV | *ALL* BEACOPP +RT |
| Doxorubicin | 150 | 180 | 300 | 210 | 160 | **160** | 340 | 280 | 280 |
| Bleomycin | 30 | 45 | 75 | 60 | | | 120 | 80 | 80 |
| Etoposide | 360 | 1125 | 1875 | | 1250 | **1250** | 2400 | 2400 | 4800 |
| Cyclophosphamide | | 2400 | 4000 | 3600 | 2000 | **4000** | 4800 | 7600 | 9600 |
| Procarbazine | | | | 4200 | | | 2800 | 4480 | 5600 |
| Dacarbazine | | | | | 3000 | **3000** | 1500 | | |
| Mustargen | 18 | | | | | | | | |
| Adcetris® (mg/kg) | | | | | | **16.8** | | | |

### 2.4.3 Response Adapted Involved Node Radiation

Traditional radiation therapy fields were delivered on the Hodgkin Collaborators' trial up through HOD99. This involved treatment with anterior and posterior oriented radiation beams designed based on simulation radiographs or digitally reconstructed simulation radiographs. This approach contributed to the high disease control rates and low infield failure rates (10.9%) seen in our reported combined modality clinical trials.[24] Despite the excellent results with radiation therapy, long-term toxicities are anticipated with a wide field anterior / posterior treatment approach.[24] Starting with the HOD05 trial for intermediate risk patients we began to further tailor our radiation therapy volumes to individual lymph nodes with a safety margin. This included moving away from the concept of contiguous irradiation

of nodal regions. This approach was further refined in the on-going HOD08 trial with smaller safety margins. Though data is not yet released for these trials, no apparent efficacy concerns have been identified with this more limited volume approach. In this trial we build on this approach incorporating PET response, CT residual disease and conformal radiation treatment.

## 2.5 Patient Reported Outcomes and Health Related-Quality of Life

The standard reporting for adverse symptoms during a treatment trial has been through clinical reporting using terms from the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). However, the CTCAE reporting does not describe symptoms from the perspective of the patient, with suggestions that the patient's perspective is most relevant in informing clinicians of anticipated effects.[3;4;15] This has led to the establishment of Federal Drug Administration (FDA) guidelines on the incorporation of patient reported outcomes (PROs) into clinical trials and for labeling purposes (US Dept. of Health).[1] Furthermore, the National Cancer Institute has begun development of a patient-reported version of the Common Terminology Criteria for Adverse Events.[9;41]

Patient reported outcomes (PROs) are defined as self-report of disease and/or treatment effects during clinical research.[8] Ultimately, the effect of treatment upon an individual is best described through self-report. The measurement of PROs is especially important when evaluating the efficacy and toxicity of newly prescribed therapy. Patient reported-outcomes may also include Health-related quality of life (HR-QoL), defined as a multi-domain concept that represents the patient's perception and the impact of a given illness and treatment on their life.[35]

Cancer therapy causes medical as well as psychosocial complications that may result in adverse effects on a patient's perception of health and quality of life. Roper et al (2009) identified 35 studies describing the health-related quality of life (HR-QoL) among survivors of HL.[36] The review found adult HL survivors to have decreased HR-QoL, most specifically within the domain of physical function. Fatigue was the most common complaint within the physical HR-QoL domain. Among childhood cancer survivors, disrupted sleep and fatigue have been found to be common complaints. Mulrooney et al, using the Childhood Cancer Survivor Study cohort, reported the prevalence of cancer related fatigue and sleep disturbance among adult childhood cancer survivors to a sibling comparison group.[31]

The study found that 19% of the survivors were in the most fatigued range, with female gender, congestive heart failure, pulmonary fibrosis, depression and being unmarried significantly predicting fatigue. Disrupted sleep was reported by 17% of the survivors and 14% reported increased daytime sleepiness. Compared to other diagnostic groups, survivors of HL were found to score lower on the Functional Assessment of Chronic Illness Therapy-Fatigue FACIT-Fatigue and higher on the Pittsburg Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (EES) suggesting increased fatigue, sleep disruption, and daytime sleepiness. Clanton et al further described the impact of fatigue and sleep on neurocognitive function among childhood cancer survivors. In the recent HOD99 protocol, we explored PROs and HR-QoL among patients treated with risk-

adapted therapy for HL.[7] Over the trajectory of treatment, patients treated on the favorable and intermediate arm had higher physical function than those treated on the unfavorable arm. Females reported an overall lower QoL when compared to males and also reported poorer emotional, physical and psychosocial functioning. Females also reported pain and nausea more often than males. The most common symptom reported on the symptom distress scale was feeling tired and trouble sleeping. Overall, QoL improved across treatment time points and PROs of symptoms improved. (Mandrell, unpublished)

Identifying patient reported outcomes of symptoms and QoL is of importance when introducing a new therapeutic drug in the treatment of HL. In the regimen of the current protocol, peripheral neuropathy is a dose limiting toxicity associated with brentuximab. Chemotherapy induced peripheral neuropathy is commonly evaluated using the National Cancer Institute's Common Toxicity Criteria ™, version 4.0 (NCI-CTC). The NCI-CTC quantifies neuropathy signs and symptoms according to a 0-5 score. According to the NCI-CTC neuropathy is graded according to cranial nerve function, as well as sensory and motor function. Neuropathic pain is graded as pain. The 0-5 scales is as follows: 0= no signs or symptoms, 1= neuropathy that does not interfere with activities of daily living; 2 = neuropathy that interferes with instrumental activities of daily living; 3= neuropathy that interferes with self-care, 4= disabling neuropathy, and 5= death. While the NCI-CTC toxicity criteria are widely used, published evidence of validity is limited.[5]

Descriptive study of PROs and HR-QoL is important during the introduction of new therapeutic agents. Therefore, patient reported symptoms and quality of life will be evaluated during the trajectory of therapy and compared to those treated on the HOD 99 unfavorable arm. In addition we will compare the ratings of the CTC toxicity criteria with the Pain Quality Assessment Scale. This scale measures pain quality and perceived depth of neuropathic pain. The use of this scale may be found to be more useful in detecting neuropathic pain and pain management assessment.[22]

## 2.6 Toxicity and Tumor Specific, Pharmacological and Pharmacogenetic Predictors of Outcome

Intra-patient variability in clinical response has been observed in previous trials of Adcetris®,[12;46] although the underlying causes for such variations are largely unknown. More recently, central nervous system and pulmonary toxicities have been reported in a small fraction of patients receiving Adcetris®, prompting the FDA to add a boxed warning to the Adcetris® drug label. Again, the source of inter-patient variability in toxicities is unclear. In this trial pulmonary toxicity is unlikely, as there is no combination with other known pulmonary toxic therapies like bleomycin or gemcitabine, but neurotoxicity may occur.

### 2.6.1 Progressive Multifocal Leukoencephalopathy (PML)

In January 2012, the US Food and Drug Administration (FDA) issued a warning to health care professionals noting that three cases of PML have been described among patients treated with Adcetris®, including two diagnosed with PML after the FDA approval of Adcetris® for patients with relapsed/refractory lymphoma. A mechanism by which Adcetris® causes PML is not known. Due to the serious nature of PML, a new Boxed Warning highlighting this risk has been added to the drug label. The FDA recommends

that healthcare professionals suspend Adcetris® dosing if PML is suspected, and discontinue the drug therapy if a diagnosis of PML is confirmed.

### 2.6.2 Predictors of Adcetris® Response and Toxicities

We propose to evaluate the following pharmacological and genetic variables as potential predictors of Adcetris® clinical response/toxicities:

*Adcetris® plasma clearance:* To characterize pharmacokinetics of Adcetris® in pediatric patients, we will determine serum concentration of Adcetris® at baseline, and at predetermined time points of the first cycle, using ELISA assay by an independent vendor.

*Immunogenicity of Adcetris®:* In a recent Phase I study of Adcetris® in CD30 positive hematologic malignancies, anti-therapeutic antibodies were observed during treatment in 5% of patients. However, it was unclear whether immunogenicity adversely affected tumor response due to the small sample size.[12] To address this question, we propose to prospectively examine serum concentration/titer of anti – Adcetris® antibody at predetermined time points. This assay is ELISA-based and will be performed by an independent vendor.

*Soluble CD30:* Soluble CD30 is known to be expressed in patients with Hodgkin lymphoma and represent a poor prognostic factor. Evaluation of this marker at diagnosis and prior to therapy, after 2 cycles of AEPA, and at the end of therapy in the context of targeted therapy may show an association with response and outcome. This assay will be performed at St Jude Molecular Clinical Trial Core.

*Tumor cell CD30:* Because CD30-mediated endocytosis is required for Adcetris® activation[33] it is speculated that tumor CD30 density might be related to efficacy, although this has not been definitively observed in clinical studies. We plan to perform a semi-quantitative immunohistochemical scoring (scale 1 – 5) of the CD30 density of individual Hodgkin Reed-Sternberg cells as well as the microenvironment. This assay will be performed at St. Jude Molecular Clinical Trial Core.

*Germline genetic polymorphisms:* Pharmacogenetic variants have long been recognized as important predictors for drug response in various hematologic malignancies.[34] For example, tumor response to gentuzumab ozogamicin, another antibody-targeted cytotoxic agent, has been linked to germline genetic variation in CD33 in children with AML, plausibly via regulating CD33 internalization.[25] As an explorative aim, we plan to interrogate a small panel of inherited genetic variations (coding variants in the *CD30* gene) for possible associations with Adcetris® response and toxicities (e.g. peripheral neuropathy).

# 3.0 ELIGIBILITY CRITERIA AND STUDY ENROLLMENT

According to institutional and NIH policy, the study will accession research participants regardless of gender and ethnic background. Institutional experience confirms broad representation in this regard.

## 3.1 Inclusion Criteria

3.1.1 Histologically confirmed, previously untreated CD30+ classical HL.

(*Participants receiving limited emergent RT or steroid therapy - maximum of 7 days - because of cardiopulmonary decompensation or spinal cord compression will be eligible for protocol enrollment*).

3.1.2 Age ≤ 18 years at the time of diagnosis (i.e., participants are eligible until their 19th birthday).

3.1.3 Ann Arbor stage IIB, IIIB, IVA, or IVB.

3.1.4 Adequate renal function based on GFR ≥ 70 ml/min/1.73m$^2$ or serum creatinine adjusted for age and gender as follows:

| Age | Maximum Serum Creatinine (mg/dL) | |
|---|---|---|
| | Male | Female |
| 1 to < 2 years | 0.6 | 0.6 |
| 2 to < 6 years | 0.8 | 0.8 |
| 6 to < 10 years | 1 | 1 |
| 10 to < 13 years | 1.2 | 1.2 |
| 13 to < 16 years | 1.5 | 1.4 |
| ≥ 16 years | 1.7 | 1.4 |

3.1.5 Adequate hepatic function (total bilirubin < 1.5 x ULN for age, and SGOT/SGPT < 2.5 x ULN for age).

3.1.6 Female participant who is post-menarchal must have a negative urine or serum pregnancy test.

3.1.7 Female or male participant of reproductive potential must agree to use an effective contraceptive method throughout duration of study treatment.

## 3.2 Exclusion Criteria

3.2.1 CD30 negative HL.

3.2.2 Has received prior therapy for Hodgkin lymphoma, except as noted above.

3.2.3 Inadequate organ function as described above in 3.1.4 and 3.1.5.

3.2.4 Inability or unwillingness of research participant or legal guardian / representative to give written informed consent.

### 3.3 Recruitment and Screening

Six institutions will participate in the protocol: St. Jude Children's Research Hospital (coordinating center and sponsor) and collaborating sites Dana-Farber Cancer Institute, Maine Children's Cancer Program, Massachusetts General Hospital, Stanford University Medical Center, and Children's Hospital of Illinois in Peoria.

### 3.4 Enrollment at St. Jude

A member of the study team will confirm potential participant eligibility as defined in Section 3.1-3.2, complete and sign the 'Participant Eligibility Checklist'. The study team will enter the eligibility checklist information into the St. Jude Clinical Trials Management System (CTMS). Eligibility will be reviewed, and a research participant-specific consent form and assent document (where applicable) will be generated. The complete signed consent / assent form(s) must be faxed or emailed to the CPDMO at 595-6265 to complete the enrollment process.

The CPDMO is staffed 7:30 am-5:00 pm CST, Monday through Friday. A staff member from the St. Jude Cerner Millennium (MILLI) helpline is on call Saturday, Sunday, and holidays from 8:00 am to 6:00 pm. If you have a prospective research enrollment and need assistance releasing your consent, please call the MILLI helpline [redacted] on call number.

### 3.5 Enrollment Instructions for Collaborating Sites

Collaborating Site research participants should be registered at St. Jude within 24 hours of enrollment at the site. The completed Eligibility Checklist and entire signed Informed Consent should be faxed to [redacted]. Please call [redacted] if confirmation of the enrollment information is needed. The Protocol Eligibility Coordinator will then register the research participant in the St. Jude CTMS.

## 4.0 TREATMENT PLAN

### 4.1 General Overview

One dose of Adcetris® will replace each vincristine in the OEPA/COPDac regimen (2 cycles of AEPA and 4 cycles of CAPDac) according to GPOH-HD2002 treatment group 3 (TG3). Involved node radiotherapy (25.5 Gy) will be given at the end of all chemotherapy to involved nodes that are not in CR after 8 weeks of therapy. Radiotherapy will be administered after completion of all chemotherapy following recovery of counts.

### 4.2 Chemotherapy Administration

| Table 4: Chemotherapy Administration | | | | |
|---|---|---|---|---|
| Agent* | Dosage and route | Route | Schedule (days) | Max. Dose |
| **AEPA x 2** (cycle length 28 days) | | | | |
| **(A)dcetris®** | **1.2 mg/kg** | **IV** over 30 min | **1, 8, and 15** | **120 mg** |
| (E)toposide | 125 mg/m$^2$ | IV over 1 to 2 hrs. | 1 to 5 | |
| (P)rednisone | 60 mg/m$^2$/day | PO | 1 to 15 (divided TID) | **30 mg TID** |
| (D)oxorubicin (Adriamycin) | 40 mg/m$^2$ | IV over 1 to 6 hrs. | 1 and 15 | |
| | | | | |
| **CAPDac x 4** (cycle length 21 days) | | | | |
| (C)yclophosphamide | 500 mg/m$^2$ | IV over 60 min** | 1 and 8 | |
| **(A)dcetris®** | **1.2 mg/kg** | **IV** over 30 min | **1 and 8** | **120 mg** |
| (P)rednisone | 40 mg/m$^2$/day | PO | 1 to 15 (divided TID) | **20 mg TID** |
| (Dac)arbazine | 250 mg/m$^2$ | IV over 15 to 30 min | 1 to 3 | |
| Filgrastim | 5 mcg/kg | SC | as clinically indicated | |

**All agents should be given according to institutional guidelines or as recommended herein*
***Post hydration with intravenous glucose or saline solution according to institutional guidelines*

#### 4.2.1 Adcetris® Administration Guidelines:

Adcetris® will be administered on days 1, 8 and 15 during the first 2 cycles (AEPA) and days 1 and 8 of the following 4 cycles (CAPDac). The dose of Adcetris® is 1.2 mg/kg (120 mg max.) and should be rounded to the nearest whole number of milligrams. It is administered by outpatient IV infusion given over approximately 30 minutes. In the absence of infusion toxicities, the infusion rate for all patients must be calculated in order to achieve a 30-minute infusion period. Adcetris® must not be administered as an IV push or bolus.

**Adcetris® cannot be mixed with other medications.**

##### 4.2.1.1 Required Pre-medication and Post-medication

Routine premedication should not be administered prior to the first dose of Adcetris®. However, participants who experience a Grade 1 or Grade 2 infusion-related reaction may receive subsequent Adcetris® infusions with premedication as described below. Patients who experience a Grade 3 or Grade 4 infusion-related reaction may potentially receive additional treatment with Adcetris® at the discretion of the treating investigator, after discussion with the principal investigator.

4.2.1.2 Management of Adcetris® Infusion Reactions

Infusion-related reactions may occur during the infusion of Adcetris®. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. The patient should be observed for 60 minutes following the first infusion of Adcetris®.

During this observation period, the IV line should remain open for at least 1 hour to allow administration of IV drugs if necessary. All supportive measures consistent with optimal patient care will be given throughout the study according to institutional standards. Medications for infusion-related reactions, such as epinephrine, antihistamines, and corticosteroids, should be available for immediate use. Patients who experience a Grade 1 or Grade 2 infusion-related reaction may receive subsequent Adcetris® infusions with premedication consisting of acetaminophen (15 mg/kg orally; max. 650 mg) and diphenhydramine (1-2 mg/kg orally max. 50 mg; or max. 25 mg IV) or according to institutional standards, administered 30–60 minutes prior to each 30-minute Adcetris® infusion.

The routine use of steroids as premedication is discouraged.

4.2.2 Management of Etoposide Infusion Reactions

Cardiovascular effects

Transient hypotension has occurred in about 1 to 2 % of patients following rapid IV administration of etoposide during clinical trials. However, hypotension has not been associated with cardiac toxicity or electrocardiogram changes. Blood pressure usually normalizes within a few hours after discontinuation of the infusion. To avoid this complication, etoposide should be infused over 60 – 120 minutes. If hypotension should occur, stop the infusion, and if necessary, give 10 mL/kg NS bolus over 15 minutes. Repeat as necessary. Once symptoms resolve, resume infusion at ½ previous infusion rate until full dose administered. If hypotension recurs, stop infusion and administer 10 mL/kg NS bolus as indicated. Once hypotension resolves, resume infusion at ½ previous infusion rate until complete. Consider infusing NS at 1 – 1.5 x maintenance during remainder of infusion. For all subsequent doses, infuse over 2 hours.

Sensitivity reactions

Anaphylactoid reactions consisting principally of chills, rigors, diaphoresis, pruritis, loss of consciousness, nausea, vomiting, fever, bronchospasm, dyspnea, tachycardia, hypertension, and/or hypotension have occurred in 0.7 – 3% of patients receiving etoposide. Other manifestations include flushing, rash, substernal chest pain, lacrimations, sneezing, coryza, throat pain, back pain, abdominal cramps, and auditory impairment. Facial/lingual swelling, coughing, diaphoresis, cyanosis, tightness in the throat, and laryngospasm have also occurred.

If an anaphylactoid reaction should occur:

- Stop the infusion immediately and notify prescriber
- Administer the following as indicated:
  - diphenhydramine 1mg/kg IV (max dose 50 mg)
  - hydrocortisone 50 – 100 mg/m$^2$ IV
  - epinephrine 0.01 mg/kg of a 1:1000 concentration for SQ administration
  - fluid bolus 10 mL/kg NS infused over 15 minutes
- Once symptoms have resolved, resume infusion at ½ previous rate until infusion complete. Consider infusing NS at 1 – 1.5 x maintenance during remainder of infusion.
- If anaphylaxis recurs, stop the infusion and re-treat as above. Do not administer remainder of dose. Consider substituting etoposide with etoposide phosphate (Etopophos®) for all subsequent doses.
- If anaphylaxis does not recur, pre-medicate all subsequent doses with diphenhydramine 1mg/kg (max 50 mg) and hydrocortisone 50 – 100 mg/m$^2$. Consider slowing the loading dose to be administered over 2 hours.
- Have at bedside all of the following for all subsequent infusions:
  - Diphenhydramine 1mg/kg IV (max 50 mg)
  - Hydrocortisone 50 – 100 mg/m$^2$ IV
  - Epinephrine 0.01 mg/kg of a 1:1000 concentration for SQ administration

Note: anaphylactoid reactions are still possible with etoposide phosphate. If the patient cannot tolerate the substitution, drug is contraindicated and must be discontinued.

4.2.3 Dose Rounding

Dose rounding for chemotherapeutic agents will be allowed according to each institution's policy (For St. Jude see Policy # 20.109, Institutional Policy and Procedure Manual). Dose rounding for standard of care medications may follow each institution's written policy.

4.2.4 Chemotherapy Administration Guidelines and Supportive Medical Care:

- The first cycle of AEPA starts immediately after completion of staging.
- Start subsequent cycles when ANC $\geq$ 500/mm$^3$, and platelets $\geq$ 80,000/mm$^3$. (28 days between AEPA and 21 days between CAPDac)
- Chemotherapy should only be interrupted in case of severe inter-current infections or other severe complications.
- Treatment is not interrupted for cytopenias during each cycle.
- Delay cycle if necessary, to give full dose of standard chemotherapy. For dose modifications on Adcetris® see 4.3.
- Filgrastim (5 mcg/kg) should be used if needed to shorten treatment delays due to myelosuppression (likely no need to give longer than 2-3 days). It should be discontinued if the ANC is $\geq$ 2,000/mm$^3$ on any one measurement or $\geq$ 1000/mm$^3$ two days in a row. Filgrastim should not be given within 24 hours of chemotherapy administration.
- Drugs with a maximum dose are: Adcetris® at 120 mg.

- Administer *Pneumocystis juroveci* prophylaxis as follows or as recommended by institutional guidelines: Trimethoprim-sulfamethoxazole 150 mg TMP/$m^2$: 750 mg SMX/$m^2$ for 3 consecutive days per week at the onset of therapy and continue for 6 weeks after chemotherapy or radiotherapy is completed.
- If the treating physician feels that trimethoprim-sulfamethoxazole is contributing to significant neutropenia, an alternative prophylaxis, such as atovaquone or pentamidine (IV or inhaled) may be substituted.

4.2.5 Guidance During Times of Drug Shortages and Unavailability

Treating investigators are urged to consult with the PI and use their best clinical judgment in optimizing therapeutic intent and ensuring patient safety in managing the protocol-specified therapy. Although these decisions may constitute "protocol violations," they are unavoidable and made in consideration of the best interest of an individual patient. These will not be considered monitoring/audit findings if appropriately documented. All protocol deviations must be documented in the clinic note and noted in the research database so that the alterations in therapy due to the agent shortage can be captured. This should be accomplished by entering "dose modified" and details noted in the comments field. These deviations will also be noted in the Deviation Log with the notation "Drug substitution/reduction due to unavoidable drug shortage/ unavailability".

## 4.3 Adcetris® Dose Modifications

4.3.1 Non-Hematologic Toxicities (except neuropathy)

| Toxicity | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Non-hematologic (except neuropathy) | Continue at same dose level | Continue at same dose level | Withhold dose until toxicity is Grade $\leq$ 2 or has returned to baseline, then resume treatment at the same dose level | Withhold until toxicity if Grade $\leq$ 2, then reduce dose to 1.2 mg/kg and resume treatment, or discontinue at the discretion of the treating investigator |

4.3.2 Sensory and Motor Peripheral Neuropathy

According to the NCI CTCAE 4.0 grading criteria, neuropathy characterized by loss of deep tendon reflexes or paresthesias (for sensory) or weakness on exam or testing (for motor) that does not interfere with activities of daily living is assigned Grade 1; neuropathy that interferes with instrumental activities of daily living, is assigned Grade 2; neuropathy that interferes with self-care is assigned Grade 3, and neuropathy that is disabling is assigned Grade 4.

Grade 1 toxicities will be managed clinically as indicated with pain control. For new or worsening Grade 2 neuropathy reduce the dose to 0.9 mg/kg. For new or worsening Grade 3 neuropathy dosing should be held until neuropathy improves to Grade 1 or baseline and then restarted at the 0.9 mg/kg dose level. For Grade 4 peripheral neuropathy, Adcetris® should be discontinued.

#### 4.3.3 Pulmonary Toxicity

The incidence of Adcetris®-related pulmonary toxicity will be monitored in all patients treated with at least one dose of Adcetris®. Unacceptable pulmonary toxicity will be defined according to the NCI CTCAE 4.0 grading criteria: Grade 3 dyspnea (shortness of breath limiting self-care), pneumonitis (severe respiratory symptoms requiring oxygen and limiting self-care), and/or hypoxia (oxygen saturation <88% on pulse oximetry) that persist for at least three days; any Grade 4 toxicity characterized by life threatening airway compromise requiring urgent intervention. There must be no evidence of other etiologies, including left atrial hypertension, congestive heart failure, infection, metabolic abnormalities, or cancer related causes (e.g., malignant pericarditis).

#### 4.3.4 Hematologic Toxicity

At first occurrence of severe neutropenia (ANC < 500/mm$^3$) consider starting filgrastim 24 hours after chemotherapy administration for 2-3 consecutive days or until count recovery and repeat after each subsequent week of chemotherapy in order to avoid administration delays and dose modifications.

#### 4.3.5 Progressive Multifocal Leukoencephalopathy

The incidence of Adcetris® related progressive multifocal leukencephalopathy will be monitored in all patients treated with at least one dose of Adcetris®. The FDA recommends that healthcare professionals suspend Adcetris® dosing if PML is suspected, and discontinue the drug therapy if a diagnosis of PML is confirmed. The clinical manifestation is of an encephalopathy that limits instrumental activities of daily living and is characterized on MRI by focal T2/FLAIR hyperintensities, involving periventricular white matter extending into centrum semiovale or involving 1/3 to 2/3 of susceptible areas of cerebrum +/- moderate increase in SAS and/or moderate ventriculomegaly

### 4.4 Radiation Therapy

Involved node radiation therapy is delivered on this trial. Doses and volumes of treatment are based on the response obtained after 2 cycles of AEPA (early response evaluation) measured by PET scan and diagnostic CT. Radiation doses will be selected for each individual lymph node, though this will be limited at times due to nodal conglomerates and shifting of nodal masses that have responded. ICRU style target volumes are required on this study. The intent of this radiotherapy approach is to reduce both the radiation dose and volume, treating residual lymph node disease that responded slowly or incompletely at 8 weeks of therapy.

4.4.1 Timing of Initiation of Involved Node Radiation Therapy:

Radiation therapy will be initiated approximately 2-3 weeks after completion of the last chemotherapy week or as soon as counts have recovered to ANC $\geq$ 1000/mm$^3$, and platelets $\geq$ 100,000/mm$^3$ and radiation treatment planning is complete.

4.4.2 Application of Response for Radiation Volume and Dose Selection

Response criteria are applied to each individual node as opposed to nodal regions based on the clinical and imaging response at early response evaluation. A lymph node is classified in CR if it meets BOTH the PET and CT criteria for complete response (both PET – CR and CT – CR).

PET criteria: PET - CR – no evidence of residual disease in the lymph node, spleen (either focally or diffusely), extra-nodal site or metastatic site at early response evaluation. PET activity consistent with brown fat, normal background activity or a non-cancer related finding will still be considered a "PET CR" as long as disease PET activity is not present.

PET - PR – Residual PET activity, above background, in an initially involved site of disease, felt to be consistent with HL.

PET - PD - New activity or an enlarging area of activity consistent with HL.

CT criteria: CT - CR – > 75% reduction (as measured by the product of 2 perpendicular diameters of lesions by CT or MR imaging) in the original lymph node, spleen, extra nodal site or metastatic site at the early response evaluation will be considered a complete response. Response to bony metastatic lesions will not be based on CT criteria but by PET alone. Any residual lymph node that measures <4 cm$^2$ (e.g. < 2 cm x 2 cm) as measured by the product of 2 perpendicular diameters will also be considered in CT - CR, regardless of the percent reduction from baseline. Any metastatic lesion (e.g. lung, liver) that is <1 cm in maximal dimension at the 8 week response time point will be considered to be in CT-CR.

CT - PR – Reduction of > 50% (but $\leq$ 75%) in the original tumor product of 2 perpendicular diameters by CT (or MRI) scan.

CT - PD - An increase in the product of 2 perpendicular diameters of any measured lesion by >25% over the size present at entry on study or the appearance of new areas of disease consistent with HL.

4.4.3 Volume Definition

The selection of the lymphatics requiring radiation occurs at the early response time point, yet the planning and delivery of radiation therapy occurs ~ 2 weeks after completion of all chemotherapy. This may result in continued shifting of nodal volumes and further shrinkage of individual lymph nodes or lymph node conglomerates. It may

be helpful to co-register (image fusion) the early response diagnostic CT, early response PET-CT or obtain the early response imaging in the radiation treatment position. The objective in this trial is reduction of the volume of radiation treatment only to those lymph nodes with a less than complete response. Even with these aids in planning it is anticipated that the radiation oncologist will have to use some judgment in defining the location of the residual lymph nodes assigned a mixed or inadequate response.

Lymphatics – involved nodal irradiation

CR (both a PET – CR and CT – CR) – these sites will not receive radiation therapy and will not be contoured.

PR (a PR in any lymph node by EITHER PET or CT criteria):

- GTV - Individual lymph nodes that are classified as PR will be contoured as the GTV based on their residual shape after completion of all chemotherapy (at the time of simulation). This may include one node in a larger group of nodes or may include the entire nodal conglomerate if it had residual PET avidity at early response evaluation point or continues to meet the CT criteria for PR (CT – PR). If there is significant uncertainty about delineation of the PET residual, the entire lymph node mass may be contoured. These volumes do not need to be contiguous.
- CTV - The GTV will be surrounded by a 1 cm CTV that is anatomically constrained to lymphatic regions of tissue at risk for invasion by HL.
- The CTV will be surrounded by an institution specific margin accounting for positional uncertainty and target motion (an ITV may be contoured)

Spleen

CR (both a PET – CR and CT – CR) – If the spleen has no residual focal activity and any lesion meets CT – CR response criteria, the spleen will not be contoured or irradiated.

PR (a PR in the spleen by EITHER PET or CT criteria):

- GTV - Regardless of whether the spleen was focally or diffusely involved, the entire spleen will be contoured as a GTV.
- CTV - For the spleen the CTV = GTV and no margin is added. If there are splenic hilar lymph nodes that required radiation, these will be targeted as noted above in the guidelines for lymphatics.
- PTV - The CTV will be surrounded by an institution specific margin accounting for positional uncertainty and target motion (an ITV may be contoured).

"E" lesions and metastatic sites

CR (both a PET – CR and CT – CR) – these sites will not receive radiation therapy and will not be contoured.

PR (a PR in any metastatic site or "E" lesion by EITHER PET or CT criteria with the exception of bone which will be assessed only by PET) – Metastatic sites or "E" lesions

with either residual PET activity or dimension that do not meet CT – CR criteria will be radiated.

- GTV - Individual metastatic sites and "E" lesions that are classified as PR at early response evaluation will be contoured as the GTV based on its residual shape after completion of all chemotherapy (at the time of simulation). This may include bone (not bone marrow involvement), lung (individual lesions, not the entire lung), or liver lesions (not the entire liver) as examples.
- CTV - For metastatic and "E" lesions the CTV = GTV and no margin is added.
- PTV - The CTV will be surrounded by an institution specific margin accounting for positional uncertainty and target motion (an ITV may be contoured).

Whole lung radiation therapy is not used in this trial. If individual lung nodules felt to be residual Hodgkin's lymphoma remain and meet size criteria, they will be treated according to the guidelines above. If the metastatic sites are too numerous to target safely, or if at the end of chemotherapy the metastatic sites have resolved and cannot be targeted (previously present at the 8 week response time point), no radiation may be given to those sites.

Normal tissue volumes

The following normal tissues should be delineated based on the location of the lymphatics requiring radiation. Delineation of other normal tissues is at the discretion of the radiation oncologist:

| | | | |
|---|---|---|---|
| Neck | Thyroid | Abdomen | Liver<br>Kidneys |
| Chest | Heart<br>Lungs | Pelvis | Bladder<br>Ovaries<br>Testes |

4.4.4 Dose: PTV - 25.5 Gy at 1.5 Gy per in 17 fractions

4.4.5 Treatment technique*:* All forms of conformal radiation therapy are allowed on this trial including proton beam radiation, intensity modulated radiation (IMRT), and conformal photon radiation, including tomotherapy and arc therapy.

Prescription point – The prescription point is to a point within the PTV with the goal of coverage of 95% PTV with the 95% isodose volume. This allows for the anticipated under-dosing of the PTV at superficial nodal sites, not a risk for invasion by HL.
Proton beam radiation is prescribed using Cobalt-Gray-Equivalents (CGE). Planning will additionally incorporate a distal target margin for each beam in place of the PTV to determine the distal range of each beam (described below).

Proton distal target margin - This is the distal edge of the CTV + Range Uncertainty + Internal Margin + Set-up Margin

- Range uncertainty = 1.5% of the water-equivalent range of the CTV at max depth (> 1mm)
- Set-up margin = set-up, mechanical, dosimetric and registration uncertainties (> 1mm)
- Internal margin = compensates for all variations in site, size and shape of the tissues contained in or adjacent to the CTV (> 1mm)

Tissue heterogeneity - Dose corrections are required for tissue heterogeneity.

Dose heterogeneity - Treatment plans must have no more than 10% of the combined GTV, CTV and PTV volume exceed 110% of the prescribed dose.

4.4.6 Dose Limitations and Treatment Interruptions.

Normal tissues should be maximally shielded as allowed by the target volume. Portions of the target volume may be partially shielded if necessitated by normal tissue tolerance. The following are recommended guidelines for normal tissue tolerances but individual patient and tumor circumstances may require deviation from these normal tissue limits.

- *Heart*: The whole heart may not receive more than 20 Gy and 50% of the heart may not receive more than 25 Gy.
- *Lung*: The volume of the total lung receiving more than 24 Gy should be limited to less than 30% (V24Gy<30%)[18]
- *Liver*: The entire liver should not receive more than 15 Gy.
- *Kidney*: Maximum of 15 Gy to the entire kidney volume bilaterally.
- Oophoropexy should be offered prior to pelvic radiotherapy in all females who require pelvic radiotherapy. A testicular shield should be used for male patients requiring radiation therapy to the pelvic region during that course of therapy when feasible.

Treatment interruptions – Treatment interruptions should be kept to a minimum, but may be necessary for significant events such as infection, neutropenia or thrombocytopenia.

4.4.7 Position Verification

Some method of patient localization should be used at a minimum of weekly, but is allowed more frequently based on institutional standard. This may include (but is not limited to) implanted fiducials, cone beam CT, in-room CT, EPIDs, or port films.

4.4.8 Urgent Radiotherapy

Urgent radiotherapy at the time of presentation and prior to chemotherapy will be given for those presenting with life threatening conditions such as airway compromise, spinal cord compression, or disease interfering with optimal and timely work-up of the patient.

4.4.9 Collection of Volumetric Radiation Therapy Data

The composite volumetric radiation therapy treatment plan will be submitted in a DICOM format to the Radiation Oncology PI (Matthew Krasin) in a manner determined appropriate for each participating institution. This information will include:

- DICOM RT dataset (structures, targets, dose, CT simulation study)
- Copy of the total dose record (treatment chart)
- The 8 week PET-CT in DICOM format

This information should be submitted within 6 weeks of completion of radiation therapy.

### 4.5 Participation of St. Jude Affiliates in the Treatment Plan

St Jude participants may receive standard chemotherapy, as well as laboratory/tests to monitor for toxicity at St. Jude affiliates and local physicians' offices, as recommended by treating investigator. Adcetris® must be administered at St. Jude unless special permission is granted to the affiliate site.

Radiotherapy for St. Jude patients and all protocol required response assessments will be done at St. Jude or a site approved by the PI.

## 5.0 DRUG/DEVICE/BIOLOGIC AGENT INFORMATION

### 5.1 Brentuximab vedotin (SGN-35, ADCETRIS®)

Description: Brentuximab is a sterile, preservative-free, white to off-white lyophilized cake for reconstitution for IV administration. Brentuximab is supplied by Seattle Genetics in single-use, Type 1 borosilicate glass vials with FluroTec®-coated butyl rubber stoppers and aluminum seals. Each vial of the product contains brentuximab, trehalose, sodium citrate, and polysorbate 80. See the Pharmacy Manual and Investigator's brochures for further information.

Storage and handling: Vials containing brentuximab must be refrigerated at 2–8oC in an appropriate locked room accessible only to the pharmacist, the investigator, or a duly designated person. Reconstituted brentuximab should not be stored at room temperature. The effect of light on brentuximab has not been assessed; therefore, it is recommended that brentuximab vials and solutions be stored in the dark until the time of use. Reconstituted vials must not be shaken. Drug accountability instructions are provided in the Pharmacy Manual.

Packaging and labeling: Refer to the Pharmacy Manual for information regarding packaging and labeling.

Preparation: Please refer to the Pharmacy Manual, Sections 3.5 – 3.8.

Toxicity: The most commonly reported side effects are tiredness, fever, diarrhea, nausea, abnormal nerve function in arms or legs, low white blood cells, muscle pain, vomiting,

back pain, rash, constipation, cough, shortness of breath, chills, upper respiratory tract infection, dizziness, joint pain, itching, low platelets, alopecia, high blood sugar, low red blood cells, stomach pain, and weight loss.

**See investigator's brochure for complete safety information**.

Dosage and route of administration: See section 4.2.

### 5.2 Etoposide (VP-16) (Vepesid®)

Source and pharmacology: Etoposide is an epipodophyllotoxin derived from *Podophyllum pelatatum*. It is thought to act mainly by inhibiting topoisomerase II, causing double and single strand DNA breaks. Etoposide is cell cycle, phase-specific, with activity in the G2 and S phases. Absorption of etoposide is approximately 30-40% and is highly variable and somewhat dose-dependent. It is extensively bound to serum proteins and is metabolized in the liver, including cytochrome P450 3A metabolism to several moieties that include a reactive oxidized species. Etoposide and its metabolites are excreted mainly in the urine with a smaller amount excreted in the feces. Dosage adjustments should be considered in patients with liver dysfunction, kidney dysfunction or hypoalbuminemia.

Formulation and stability: Etoposide is available in multi-dose vials containing 100mg, 150mg, 500mg and 1000mg of etoposide as a 20mg/ml solution and 30% alcohol. Etoposide is also available as a 50 mg capsule. The intact vials of etoposide solution should be stored at room temperature. The capsules should be stored under refrigeration. Etoposide solution should be diluted in D5W or 0.9% NaCl prior to administration. Solutions with a final concentration of 0.2 and 0.4 mg/ml are stable at room temperature for 96 hours and 24 hours respectively.

Supplier: Commercially available.

Toxicity: Dose limiting toxicity is myelosuppression. Nausea and vomiting (usually of low to moderate severity), diarrhea, mucositis (particularly with high doses), alopecia and anorexia are fairly common. Hypotension can occur with rapid infusions. Other side effects reported less commonly include hepatitis, fever and chills, anaphylaxis and peripheral neuropathy. Secondary leukemia has been reported.

Dosage and route of administration: See section 4.2.

### 5.3 Prednisone, Prednisolone

Source and pharmacology: Prednisone is a synthetic congener of hydrocortisone, the natural adrenal hormone. Prednisone is a white or yellowish crystalline powder. It binds with steroid receptors on nuclear membranes, impairs cellular mitosis and inhibits protein synthesis. Prednisone also has potent anti-inflammatory effects and suppresses the immune system. Prednisone is well absorbed orally. It is converted to prednisolone, the pharmacologically active metabolite, in the liver. Prednisolone is further metabolized to inactive compounds in the liver. The metabolites are excreted mainly in the urine.

Formulation and stability: Prednisone is available as various strength tablets and oral solution from multiple manufacturers. All dosage forms can be stored at room temperature. Prednisolone oral solution may be substituted for prednisone liquid at equal doses due to its superior palatability.

Supplier: commercially available

Toxicity: Side effects of prednisone vary depending on the duration of its use. Side effects that can occur with short term use include sodium and water retention with associated hypertension, peptic ulcer with possible perforation and hemorrhage, increased susceptibility to infections, emotional instability, insomnia, increased appetite, weight gain, acne and hyperglycemia. Side effects more commonly associated with prolonged use include cataracts, increased intraocular pressure and associated glaucoma, development of a "cushingoid" state, compression fractures, menstrual irregularities, suppression of growth in children, secondary adrenocortical and pituitary unresponsiveness particularly in times of stress as in trauma, surgery or illness, osteoporosis and muscle wasting.

Dosage and route of administration: See section 4.2

### 5.4 Doxorubicin (Adriamycin®)

Source and pharmacology: Doxorubicin is an anthracycline antibiotic produced by *Streptomyces peucetius*. Doxorubicin exerts its anti-tumor effects in several different ways. Doxorubicin intercalates between base pairs of DNA causing steric obstruction, disruption of DNA function and inhibition of RNA synthesis. In addition, doxorubicin inhibits topoisomerase II, an enzyme responsible for allowing strands of DNA to pass through one another as they unwind. Lastly, doxorubicin undergoes enzymatic electron reduction to generate highly reactive species, including the hydroxyl free radical, which is thought to be responsible for the drug's cardiac toxicity, but may play a role in its anti-tumor activity as well. Doxorubicin is cell-cycle, phase non-specific. Doxorubicin is widely distributed in the tissues and plasma, but does not cross the blood brain barrier to an appreciable extent. It is metabolized to doxorubicinol, which is thought to be the major active metabolite, and aglycones. Doxorubicin and its metabolites are excreted mainly in the bile and feces (≈80%). The remainder is excreted in the urine. Dosage should be reduced in patients with liver dysfunction (bilirubin > 1.2 mg/dl) or renal dysfunction (creatinine > 3 mg/dl).

Formulation and stability: Doxorubicin is available in vials containing 10 mg, 20 mg, 50 mg and 200 mg as a 2mg/ml red-orange solution. It is also available in vials containing 10 mg, 20 mg, 50 mg, 100 mg and 150 mg of doxorubicin as a red-orange lyophilized powder. Intact vials of doxorubicin solution should be stored under refrigeration while the lyophilized product should be stored at room temperature. Both products should be protected from light. Lyophilized doxorubicin can be reconstituted by adding 5, 10, 25, 50 or 75 ml of 0.9% NaCl respectively to the 10, 20, 50, 100 and 150 mg vials to produce a final concentration of 2 mg/ml. Bacteriostatic diluents are not recommended. After reconstitution, the resultant solution should be protected from light and is stable for 7 days at room temperature and 15 days if refrigerated.

Supplier: Commercially available.

Toxicity: Dose-limiting toxicities include myelosuppression and cardiotoxicity. Two forms of cardiac toxicity can occur. Acute toxicity may take the form of arrhythmias, heart block or pericarditis and may be fatal. The chronic form of cardiotoxicity is related to total cumulative dose and is characterized by heart failure. Mediastinal radiotherapy and/or other cardiotoxic drugs may increase the risk of cardiotoxicity. In general, total lifetime dosages of 450-550 mg/m$^2$ should not be exceeded. Other toxicities include nausea and vomiting, mucositis, alopecia, diarrhea and red discoloration of the urine and other body fluids. Severe tissue damage and necrosis can occur upon extravasation. Radiation recall reactions can occur and can be severe. Rarely, allergic reactions have occurred. Typhilitis can occur when combined with cytarabine.

Dosage and route of administration: See section 4.2

### 5.5 Cyclophosphamide (Cytoxan®)

Source and pharmacology: Cyclophosphamide is a nitrogen mustard derivative. It acts as an alkylating agent that causes cross-linking of DNA strands by binding with nucleic acids and other intracellular structures, thus interfering with the normal function of DNA. Cyclophosphamide is cell-cycle, phase non-specific. Cyclophosphamide is well absorbed from the GI tract with a bioavailability of > 75%. Cyclophosphamide is a prodrug that requires activation. It is metabolized by mixed-function oxidases in the liver to 4-hydroxycyclophosphamide, which is in equilibrium with aldofosfamide. Aldofosfamide spontaneously splits into cyclophosphamide mustard, which is considered to be the major active metabolite, and acrolein. In addition, 4-hydroxycyclophosphamide may be enzymatically metabolized to 4-ketocyclophosphamide and aldofosfamide may be enzymatically metabolized to carboxyphosphamide which are generally considered to be inactive. Cyclophosphamide and its metabolites are excreted mainly in the urine. Dosage adjustments should be made in patients with a creatinine clearance of < 50 mL/min/1.73m$^2$.

Formulation and stability: Cyclophosphamide is available in 25 and 50 mg tablets. Cyclophosphamide is also available in vials containing 100, 200, 500, 1000 and 2000 mg of lyophilized drug and 75 mg mannitol per 100 mg of cyclophosphamide. Both forms of the drug can be stored at room temperature. The vials are reconstituted with 5, 10, 25, 50 or 100 ml of sterile water for injection respectively to yield a final concentration of 20 mg/ml. Reconstituted solutions may be further diluted in either 5% dextrose or 0.9% NaCl containing solutions. Diluted solutions are physically stable for 24 hours at room temperature and 6 days if refrigerated, but contain no preservative, so it is recommended that they be used within 24 hours of preparation.

Supplier: Commercially available.

Toxicity: Dose-limiting toxicities of cyclophosphamide are bone marrow suppression and cardiac toxicity. Cardiac toxicity is typically manifested as congestive heart failure, cardiac necrosis or hemorrhagic myocarditis and can be fatal. Hemorrhagic cystitis may occur and necessitates withholding therapy. The incidence of hemorrhagic cystitis is

related to cyclophosphamide dose and duration of therapy. Forced fluid intake and/or the administration of MESNA decrease the incidence and severity of hemorrhagic cystitis. Other toxicities reported commonly include nausea and vomiting (may be mild to severe depending on dosage), diarrhea, anorexia, alopecia, immunosuppression and sterility. Pulmonary fibrosis, SIADH, anaphylaxis and secondary neoplasms have been reported rarely.

Dosage and route of administration: See section 4.2.

### 5.6 Dimethyl Triazeno Imidazole Carboximide (DTIC) (DACARBAZINE®)

Description: The chemical structure of DTIC is 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide. Three hypotheses have been offered as the mechanism(s) ofaction of DTIC: inhibition of DNA synthesis by acting as a purine analog, action as an alkylating agent, and/or interaction with SH groups.

Source and pharmacology: Kinetics: After IV administration, plasma disappearance is biphasic with the initial half-life of 19 minutes and terminal half-life of 5 hours. In patients with renal and hepatic dysfunction half-life is lengthened to 55 minutes and 7.2 hours. 40% of unchanged DTIC is excreted in the urine in 6 hours. The drug is not apparently bound to plasma proteins. Formulation: 100 and 200 mg ampules containing a white powder.

Formulation and stability: Dacarbazine 100 mg/vial and 200 mg/vial are reconstituted with 9.9 ml and 19.7 ml, respectively, of Sterile Water for Injection, USP. The resulting solution contains 10 mg/ml of dacarbazine. The reconstituted drug may be given as a rapid intravenous injection (although this may be quite painful) or more preferable as an infusion in 150-200 cc of diluent over a 15 - 30 minute period. This latter form of administration is rarely associated with any pain along the infusion site. The drug must be stored in a refrigerator 2° to 8°C (36° - 46°F) at a temperature of 4°C or less and protected from the light while stored. Once reconstitution occurs, the drug should be utilized within an 8-hour period.

Supplier: DTIC is commercially available.

Toxicity: Myelosuppression is the dose-limiting toxicity. The predominant side effect observed in humans has been anorexia, nausea and vomiting. This occurs with maximal intensity on the first day of a five-day course, and in many patients, it is less with each subsequent day. Myelosuppression consisting of thrombocytopenia and leukopenia occurs in approximately one quarter of patients after a five-day course of 250 mg/m$^2$. The time course for this myelosuppression is generally maximal approximately three weeks after administration with the period of recovery variable. Other side effects reported included infrequent flu-like syndrome associated with fever and myalgia, phlebitis, tissue necrosis, hepatic toxicity, anaphylaxis, photosensitivity, alopecia, and facial flushing. Rarely, DTIC has caused diarrhea.

Dosage and route of administration: See section 4.2.

## 5.7 Filgrastim (Neupogen®)

Source and pharmacology: Filgrastim (granulocytic colony stimulating factor) is a biosynthetic hematopoietic agent that is made using recombinant DNA technology in cultures of *Escherichia coli.* Filgrastim stimulates production, maturation and activation of neutrophils. In addition, endogenous filgrastim enhances certain functions of mature neutrophils, including phagocytosis, chemotaxis and antibody--dependent cellular cytotoxicity.

Formulation and stability: Filgrastim is supplied in vials containing 300 mcg and 480 mcg of filgrastim at a concentration of 300 mcg/ml. The intact vials should be stored under refrigeration. The vials can be left out of refrigeration for 24 hours, but should be discarded if left at room temperature for longer periods of time. Filgrastim can be drawn up into tuberculin syringes for administration and stored under refrigeration for up to 7 days prior to usage. Filgrastim can be further diluted for IV infusion in 5% dextrose. Do not dilute in saline---precipitate may form. If the final concentration of this product is < 15 mcg/ml, it is recommended that albumin be added to a final concentration of 2mg/ml (0.2%) to minimize adsorption of the drug to infusion containers and equipment.

Supplier: Commercially available.

Toxicity: Filgrastim causes marked leukocytosis. Adverse reactions reported commonly include bone pain, thrombocytopenia, diarrhea, nausea, rash, alopecia, fever, anorexia and pain or bruising at the injection site. Allergic reactions, MI, atrial fibrillation, and splenomegaly have been reported rarely. Filgrastim is contraindicated in participants with allergy to E. coli derived products.

Dosage and route of administration: See section 4.2

# 6.0 REQUIRED EVALUATIONS, TESTS, AND OBSERVATIONS

## 6.1 Pre-treatment Evaluations

See Table 5 below. All entry/eligibility studies should be performed within 4 weeks prior to entry onto the trial.

6.1.1 Required Clinical Staging Evaluations:

- History and physical exam
- Complete blood count with differential
- Complete metabolic profile (including electrolytes, BUN, creatinine, bilirubin, SGOT and SGPT)
- C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)
- LDH, alkaline phosphatase and albumin
- Chest x-ray* (mediastinal adenopathy must be expressed as equal to, greater than or less than 33% of the maximum intra-thoracic diameter or no mediastinal involvement)
- CT scan or MRI of the neck and chest with contrast
- CT scan or MRI of the abdomen and pelvis with contrast
- PET scan
- Blood or urine pregnancy test for female patients more than 10 years old or post-pubertal, regardless of age.
- Echocardiogram and EKG

Surgical staging: Staging laparotomy with splenectomy is not recommended; however, untreated patients who have been surgically staged are eligible.

Initial staging: Initial staging will be based on the primary physician's interpretation of physical examination, laboratory and diagnostic imaging evaluations.

6.1.2 Other pre-therapy evaluations recommended but not required for good clinical care or as clinically indicated may include the following:

- Urinalysis
- Pulmonary function studies
- Referral for sperm cryopreservation for male patients when appropriate
- Introductory visit with radiation oncology
- Bone marrow biopsies

## 6.2 Evaluations during therapy

See Table 5 below. History and physical examinations as well as CBCs are recommended for good patient care or as clinically indicated prior to chemotherapy administration as deemed necessary by the treating physicians.

**Table 5: Evaluations before, during, and at the end of therapy**

| | Pre-treatment | Before each chemotherapy/ Adcetris® | Early response Evaluation (after 2 AEPA) | Off therapy evaluation* |
|---|---|---|---|---|
| History & physical | X | X | X | X |
| CBC with diff | X | X | O | X |
| ESR or CRP | X | | O | X |
| Bone marrow biopsy | O | | | |
| Chest X-ray | X | | O | O |
| Pregnancy test | X | X** | | |
| LDH, alkaline phosphatase, albumin | X | | O | O |
| Urinalysis | O | | O | O |
| Complete metabolic profile (including renal and liver function) | X | O | O | O |
| Pulmonary function tests | O | | | O |
| ECHO/EKG | X | | X | O |
| CT or MRI neck/chest | X | | Areas positive at diagnosis | Areas positive at diagnosis |
| CT or MRI abdomen/pelvis | X | | Areas positive at diagnosis | Areas positive at diagnosis |
| PET scan | X | | If positive at diagnosis | If positive at early response evaluation and no subsequent negative scan |
| Radiation oncology consultation | O | | X | O |

** For patients with complete response at all sites after 2 AEPA, end of therapy evaluation will be performed 4-6 weeks after 4th cycle of CAPDac*

** For patients not with complete response at all sites after 2 AEPA end of therapy evaluation will be performed 4-6 weeks after finishing all prescribed radiotherapy*

***Pregnancy testing required at a minimum of every 4 weeks in females of childbearing potential during chemotherapy*

*X = Required study evaluations  O = Evaluations recommended for good patient care or as clinically indicated.*

### 6.3 Early Response and Off-Therapy Evaluations

All participants will be evaluated for chemotherapy response after 2 cycles of AEPA to determine fields and volumes of radiotherapy. It is required to perform history and physical exam at the time, laboratory tests are recommended for good clinical practice. PET scan is required for everybody, as is CT or MRI of sites involved at diagnosis. For patients with complete response at all sites that will not require radiotherapy, off therapy evaluation is performed 4-6 weeks after the end of the 4th cycle of CAPDac, while patients requiring radiotherapy will have their off therapy evaluation performed 4 to 6 weeks after the end of all prescribed radiotherapy. Required evaluations at this point will comprise history and physical exam, CBC with differential, and ESR or CRP. CT or MRI of areas positive at diagnosis need to be repeated, PET scans will only be repeated if previous scan positive.

### 6.4 Suggested Long-Term Follow-Up Evaluations

See Table 6 below. After confirmation of disease status at the first off therapy evaluation, participants should have regular follow-up with a recommended schedule of every 3 months for 1 year, every 4 months for the next 2 years, every 6 months for the 4th year, and annually thereafter. Follow-up studies are recommended as clinically indicated for patients with abnormal values at baseline and to monitor for organ dysfunction related to the toxic effects of chemotherapy and include a physical examination, CBC with differential and ESR/CRP. Chest radiograph is recommended for good patient care and *as clinically indicated* during follow-up for patients with mediastinal disease.

CT or MRI of initially involved sites of disease is required at 1 year off therapy evaluation. Follow-up PET is only recommended if CT or MRI shows suspicious lesions requiring further characterization.

**Table 6: Recommended schedules for off-therapy evaluation for disease status**

| Time since end of therapy | H&P | CBC | ESR/CRP | CXR | CT or MRI neck/chest | CT or MRI abd/pelvis | PET scan |
|---|---|---|---|---|---|---|---|
| 3 months | X | O | O | | | | |
| 6 months | X | O | O | O | | | |
| 9 months | X | O | O | | | | |
| 1 year | X | X | X | O | X[1] | X[1] | X[2] |
| 16 months | X | O | O | | | | |
| 20 months | X | O | O | | | | |
| 2 years | X | X | X | O | X[1] | X[1] | X[2] |
| 28 months | X | O | O | | | | |
| 32 months | X | O | O | | | | |
| 3 years | X | X | X | O | | | |
| 3 ½ years | X | O | O | | | | |
| 4 years | X | X | X | O | | | |
| 4 ½ years | X | O | O | | | | |
| 5 years and yearly thereafter | X | X | X | O | | | |

*[1] 1 year off therapy CT or MRI, only re-image sites that were positive at diagnosis.*
*[2] PET scan only necessary if CT or MRI shows suspicious lesions requiring further characterization.*

*X = Required study evaluations  O = Evaluations recommended for good patient care or as clinically indicated.*

## 6.5 Recommended Late Effects Evaluations

See Table 7 below. Participants will be followed for at least 10 years after completion of therapy and follow up captured at least yearly. Specific late effects' testing should follow the Children's Oncology Group Long-Term Follow-up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers http://www.survivorshipguidelines.org or institutional guidelines.

**Table 7: Recommended Late Effects Evaluations**

| Off therapy follow-up for late organ toxicity | Physical exam (includes growth and fertility information) | ECHO/ EKG | $T_4$/TSH | PFT |
|---|---|---|---|---|
| Annually | O | | O | |
| 1-year evaluation | | O | | O |
| 2-year evaluation | | O | | O |
| 5-year evaluation | | O | | O |
| 10 -year evaluation | | O | | O |

O = Evaluations recommended for good patient care or as clinically indicated

- Heart: echocardiogram, electrocardiogram at 1, 2, 5 and 10 years.
- Lung: pulmonary function studies at 1, 2, 5 and 10 years for patients with respiratory symptoms or that have received significant pulmonary radiation
- Growth: physical examination with attention to growth abnormalities of soft tissues and bones with every physical exam.
- Thyroid: Free $T_4$ and TSH yearly if patient received radiation possibly encompassing the thyroid, but should be captured only at 1, 2, 5, and 10 years when available.
- Document initiation date for thyroid hormone replacement therapy, if applicable.
- Fertility: Record menstrual cycle and pregnancy information. Referral of men for semen analysis or measurement of testosterone levels is optional and should be performed when appropriate.
- Obtain pathology of second tumors for histological review.

Late effects follow-up evaluations for patients in first remission should be captured at years 1, 2, 5 and 10.

Evaluations at 1, 2, 5, and 10 years should be performed within 6 months of the Off-Therapy anniversary date. We recognize, however, that patients may be monitored more frequently and that off therapy evaluations and diagnosis of treatment-related toxicity may not adhere exactly to 1, 2, 5, or 10 years after completion of therapy. For patients in first remission, whose off therapy evaluations are performed beyond the 6 month anniversary date, a HLHR13 Late Organ Function Screening Form for Patients in First Remission and a HLHR13 Late Effects Follow-Up Form can be submitted as part of good

clinical practice. Follow-up after relapse or progressive disease should be captured on an annual basis for as long as the study is open for follow-up.

## 6.6 Patient-Reported Symptoms and Health-Related Quality of Life

The described instruments will be administered in conjunction with the scheduled clinic visit (± 7 days) (Table 8), then at 4-6 weeks after the completion of chemotherapy for those that had CR after 8 weeks of therapy and 4-6 weeks after completion of radiation for those that did not have a CR after 8 weeks of chemotherapy, 1 year, 2 years and 5 years scheduled off therapy visit (Table 9). It should take no more than 15-20 minutes to complete all instruments. Participation in the Quality of Life part of the trial is voluntary for participating institutions and voluntary by patient.

### 6.6.1 The Symptom Distress Scale (SDS)

The SDS is a 10-item, self-report, Likert type scale developed to measure the patient's degree of discomfort from specific treatment-related symptoms i.e., nausea, sleep disturbances, appetite, etc. In our previous work using the SDS with adolescents receiving treatment for cancer, the scale achieved coefficient alphas of 0.81 to 0.82. The SDS also was noted to have construct validity, as hypotheses predicting negative relationships with measures of hopefulness, self-esteem, and self-efficacy were all supported. The SDS may be completed in 3 to 5 minutes.[16]

### 6.6.2 The Peds QL Multidimensional Fatigue Scale (MFS)

The Peds QL MFS is an 18-item Likert type scale with three subscales which include general fatigue, sleep/rest fatigue and cognitive fatigue. The patient and parent proxy forms are for three different age groups (5- to 7-year-olds, 8- to 12-year-olds, and 13- to 21- year- olds). There is a parent form only for age group 2-4 year olds. Internal consistency and reliability have been reported ($\alpha = 0.89$ child, $\alpha = 0.92$ parent) and validity demonstrated using the known groups method.[42]

### 6.6.3 Peds QL V4.0 Module

The Peds QL v4.0 Module is a 23-item Likert scale with four subscales measuring physical, emotional, social and school function. . The patient and parent proxy forms are for three different age groups (5- to 7-year-olds, 8- to 12-year-olds, and 13- to 21- year-olds). There is a parent form only for age group 2-4 year olds. Both patient and parent forms have been found to be internally consistent with $\alpha = 0.91$ to 0.92, respectively.[42]

### 6.6.4 Peds QL Cancer Module

The Peds QL Cancer Module is a 27-item Likert scale with eight subscales which include pain and hurt, nausea, procedural anxiety treatment anxiety, worry, cognitive problems, physical appearance, and communication. The patient forms are for three different age groups (5- to 7-year-olds, 8- to 12-year-olds, and 13- to 21- year- olds). There is a parent form only for age group 2-4 year olds.[42]

6.6.5 The Short-Form 36 (SF-36)

The Short Form 36 health survey questionnaire (SF-36) is a generic measurement of QOL and is a 36-item Likert-type scale measuring physical functioning, role physical function, bodily pain, general health perception, mental health, role emotional function, energy, and social functioning. The SF-36 will be administered to adolescents ages 13-21 and is reported to have high validity and internal consistency.[21]

6.6.6 Pain Quality Assessment Scale (PQAS©)

The PQAS© is a 20-item scale for assessment of neuropathic pain with additional pain assessment qualities associated with non-neuropathic pain. This scale was developed from modification of the Neuropathy Pain Scale, with additional pain descriptors to ascertain non-neuropathic pain. This assessment scale will help in better describing the pain that patients at risk for neuropathy might experience.[22]

**Table 8: Schedule for Symptom and Quality of Life Measurements during Therapy**

| Symptom/QoL | Entry | Course 1 Day 8 | Course 1 Day 15 | Course 2 Day 1 | Course 2 Day 15 | Course 3 Day 1 | Course 3 Day 8 | Course 6 Day 1 | Course 6 Day 8 |
|---|---|---|---|---|---|---|---|---|---|
| **PedsQL 4.0 Generic** Patient (5-21) Parent (2-21) | X | | | X | | X | | X | |
| **Cancer QL Generic** Patient (5-21) Parent (2-21) | X | | | X | | X | | X | |
| **Multidimensional Fatigue Acute** Patient (5-21) Parent (2-21) | X | X | X | X | X | X | X | X | X |
| **Pain Quality Assessment** Scale ≥ 8 years | X | X | X | X | X | X | X | X | X |
| **Symptom Distress Scale** Patient only ≥ 8 years | X | X | X | X | X | X | X | X | X |
| **SF-36** ≥ 13 years | X | | | X | | X | | X | |

**Table 9: Schedule for Symptom and Quality of Life measurements off Therapy**

| Symptom/QoL | Evaluation 4-6 weeks after chemotherapy (*participants who do not receive radiation*) | Evaluation 4-6 weeks after radiation | 1 year | 2 year | 5 year |
|---|---|---|---|---|---|
| **PedsQL 4.0**<br>Generic Patient (5-21)<br>Parent (2-21) | X | X | X | X | X |
| **Cancer QL Generic**<br>Patient (5-21)<br>Parent (2-21) | X | X | | | |
| **Multidimensional Fatigue Generic**<br>Patient (5-21)<br>Parent (2-21) | X | X | X | X | X |
| **Pain Quality Assessment**<br>Scale ≥ 8 years | X | X | X | X | X |
| **Symptom Distress Scale**<br>Patient only ≥ 8 years | X | X | X | X | X |
| **SF-36**<br>≥ 13 years | X | X | X | X | X |

## 6.7 Expression of CD30 in Tumor Tissue (CD30 density)

Archival formalin-fixed, paraffin embedded tumor sections will be assessed by immunohistochemistry for CD30 expression in Reed Sternberg cells. Immunohistochemistry will be performed on formalin-fixed, paraffin embedded tissue specimens using commercially available antibodies to CD30, evaluated and graded semi-quantitatively for the percentage of RS cells stained and the intensity (0, +, ++, +++) of staining. The density of CD30 expression in RS cells and potential correlation with PR or CR will be explored via descriptive methods. See Appendix III for details on collection, processing and shipment of samples.

## 6.8 Soluble CD30 Assessments

**Table 10: Soluble CD30 (all sites) Sampling Time points**

| Cycle | Day | Time | Relative Time | sCD30 |
|---|---|---|---|---|
| C1 | 1 | Pre-dose | Prior to Adcetris | **X** |
| C3 | 1 | Pre-dose | Prior to Adcetris | **X** |
| EOT[b] | | | | **X** |

[b]*EOT, End of Therapy – at off therapy evaluation*

### 6.9 Pharmacogenetics

All research participants at St. Jude Children's Research Hospital will be asked to enroll on the institutional protocol PGEN5, while patients from external sites will be consented for pharmacogenetics research as part of this therapeutic protocol. Participation on this part of the protocol is voluntary.

## 7.0 EVALUATION CRITERIA

### 7.1 Early Response Criteria

Early response at the end of 2 cycles of AEPA will be determined for each individual nodal group. The response evaluation will be based on the multidisciplinary (oncologist, radiotherapist, and radiologist) interpretation of physical examination, laboratory and diagnostic imaging as described below (see Appendix II for response evaluation for the secondary objective 1.2.1).

7.1.1 Complete Response (CR):

Disappearance of all measurable or evaluable disease, signs, symptoms and biochemical changes related to the tumor. Biopsy confirmation is not mandatory. Residual PET-negative CT scan abnormalities representing ≥ 75% reduction (as measured by the product of 2 perpendicular diameters of lesions by CT or MR imaging) in the original tumor volume will be considered scar tissue without active tumor.

7.1.2 Complete Response Unconfirmed (CRu):

Persistent radiographic abnormalities (PET negative) at a site of previous disease not thought to represent active disease as long as residual abnormalities are stable or improved when compared to previous evaluations. Biopsy is not required to confirm a complete remission status.

7.1.3 Partial Response (PR):

Reduction of 50% to 75% in the original tumor volume of any measurable lesion by CT scan regardless of PET avidity. Persistence of PET avidity in residual nodal masses that shrunk ≥ 75% (as measured by the product of 2 perpendicular diameters of lesions by CT or MR imaging) from original tumor volume.

7.1.4 Stable Disease (SD):

Neither sufficient shrinkage (<50%) to qualify for partial response, nor sufficient increase (<25%) or appearance of new lesions to qualify for progressive disease.

7.1.5 Progressive Disease (PD):

An increase in the product of two perpendicular diameters of any measured lesion by >25% over the size present at entry on study or the appearance of new areas of biopsy

proven disease. Recurrence within 3 months from the end of therapy is also considered progressive disease.

## 7.2 Remission Evaluation after Completion of Therapy

All patients will undergo a complete disease evaluation 4 to 6 weeks after completing all prescribed therapy. For patients that achieved a complete response after 2 cycles of AEPA and will not undergo radiotherapy, this will be performed 4 to 6 weeks after finishing the 4$^{th}$ cycle of CAPDac, while for patients that did not achieve a complete response after 2 cycles of AEPA and went on to receive radiotherapy, this will be done 4 to 6 weeks after completing all prescribed radiotherapy.

### 7.2.1 Complete Remission:

Patients will be designated to be in complete remission after the completion of all of the protocol-prescribed chemotherapy and radiotherapy as long as off therapy evaluations do not reveal new abnormalities suggestive of disease progression. This definition allows for persistent radiographic abnormalities (PET negative) at a site of previous disease not thought to represent active disease as long as residual abnormalities are stable or improved when compared to previous evaluations. Biopsy is not required to confirm a complete remission status.

## 7.3 Evaluation of Progressive Disease or Relapse

Biopsy is required for confirmation of progression during planned therapy, or for relapse following completion of therapy.

Participants with progressive disease on therapy will be taken off treatment, but will remain on study and followed for survival. Participants who relapse off therapy will continue on study and followed for survival. Participants will receive salvage therapy according to investigator preference. When progression or relapse occurs, a protocol outcomes event form and off-treatment date will be entered into CRIS.

## 7.4 Response Criteria for Secondary Objective

See Appendix II for detailed response definition according to Euro-Net C1. This objective will not be evaluated in real time, but will be centrally reviewed retrospectively.

## 7.5 Toxicity Evaluation Criteria

Common Terminology Criteria for Adverse Events v4.0 (CTCAE): This study will utilize the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the current version of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page (http://ctep.info.nih.gov). Additionally, toxicities are to be reported on the appropriate data collection screens.

### 7.6 Acceptable Percentage of Missed Doses for Study Drugs

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB. However, it is expected that participants will occasionally miss some doses or receive the wrong dose of oral chemotherapy. Compliance with oral medication will be captured in the CRIS database and appropriately documented in the participants' medical records. Appropriately documented doses of missed or wrong doses of chemotherapy will not constitute a deviation unless the amount in question is over 10% of the expected total dose due in the respective protocol cycles (these are specified in the CRIS HLHR13 database). Missed doses do not include doses held or reduced for medical reasons (toxicity, illness) and will not be considered protocol deviations or violations.

## 8.0 OFF THERAPY AND OFF-STUDY CRITERIA

### 8.1 Off-Study Criteria

- Death
- Withdrawal of consent
- Found to be ineligible (e.g., incorrect diagnosis)
- Completion of protocol-required interventions and follow-up period (10 years)
- Lost to follow-up

### 8.2 Off-Therapy Criteria

- Progressive disease or relapse
- Second malignancy
- Completion of all protocol prescribed treatment
- Development of unacceptable toxicity during treatment (with concurrence of the PI)
- Participant/family decision to withdraw from protocol treatment at any time for any reason
- Discretion of the study PI or co-PI, such as the following:
    - The researcher decides that continuing in the study would be harmful
    - A treatment is needed that is not allowed on this study
    - The participant misses so many appointments that the data cannot be used in the study – Lost to follow up
    - The participant's condition gets worse
    - New information is learned that a better treatment is available, or that the study is not in the participant's best interest

# 9.0 SAFETY AND ADVERSE EVENT REPORTING REQUIREMENTS

## 9.1 Reporting Adverse Experiences (AEs) and Deaths to St. Jude IRB

Only "unanticipated problems involving risks to participants or others" referred to hereafter as "unanticipated problems" are required to be reported to the St. Jude IRB promptly, but in no event later than 10 working days after the investigator first learns of the unanticipated problem. Regardless of whether the event is internal or external (for example, an IND safety report by the sponsor pursuant to 21 CFR 312.32), only adverse events that constitute unanticipated problems are reportable to the St. Jude IRB. As further described in the definition of unanticipated problem, this includes any event that in the PI's opinion was:

- Unexpected (in terms of nature, severity, or frequency) given (1) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, as well as other relevant information available about the research; (2) the observed rate of occurrence (compared to a credible baseline for comparison); and (3) the characteristics of the subject population being studied; and
- Related or possibly related to participation in the research; and
- Serious; or if not serious suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unrelated, expected deaths do not require reporting to the IRB. Though death is "serious", the event must meet the other two requirements of "related or possibly related" and "unexpected/unanticipated" to be considered reportable.

Deaths meeting reporting requirements are to be reported immediately to the St. Jude IRB, but in no event later than 48 hours after the investigator first learns of the death.

The following definitions apply with respect to reporting adverse experiences:

**Serious Adverse Event:** Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical

intervention to prevent one of the other outcomes listed in this definition (examples of such events include: any substantial disruption of the ability to conduct normal life functions, allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse), a congenital anomaly/birth defect, secondary or concurrent cancer, medication overdose, or is any medical event which requires treatment to prevent any of the medical outcomes previously listed.

**Unexpected Adverse Event**:

- Any adverse event for which the specificity or severity is not consistent with the protocol-related documents, including the applicable investigator brochure, IRB approved consent form, Investigational New Drug (IND) or Investigational Device Exemption (IDE) application, or other relevant sources of information, such as product labeling and package inserts; or if it does appear in such documents, an event in which the specificity, severity or duration is not consistent with the risk information included therein; or
- The observed rate of occurrence is a clinically significant increase in the expected rate (based on a credible baseline rate for comparison); or
- The occurrence is not consistent with the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

**Internal Events**: Events experienced by a research participant enrolled at a site under the jurisdiction of St. Jude IRB for either multicenter or single-center research projects.

**External Events:** Events experienced by participants enrolled at a site external to the jurisdiction of the St. Jude Institutional Review Board (IRB) or in a study for which St. Jude is not the coordinating center or the IRB of record.

**Unanticipated Problem Involving Risks to Subjects or Others:** An unanticipated problem involving risks to subjects or others is an event which was not expected to occur and which increases the degree of risk posed to research participants. Such events, in general, meet all of the following criteria:

- unexpected;
- related or possibly related to participation in the research; and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. An unanticipated problem involving risk to subjects or others may exist even when actual harm does not occur to any participant.

Consistent with FDA and OHRP guidance on reporting unanticipated problems and adverse events to IRBs, the St. Jude IRB does not require the submission of

external events, for example IND safety reports, nor is a summary of such events/reports required; however, if an event giving rise to an IND safety or other external event report constitutes an "unanticipated problem involving risks to subjects or others" it must be reported in accordance with this policy. In general, to be reportable external events need to have implications for the conduct of the study (for example, requiring a significant and usually safety-related change in the protocol and/or informed consent form).

Although some adverse events will qualify as unanticipated problems involving risks to subjects or others, some will not; and there may be other unanticipated problems that go beyond the definitions of serious and/or unexpected adverse events. Examples of unanticipated problems involving risks to subjects or others include:

- Improperly staging a participant's tumor resulting in the participant being assigned to an incorrect arm of the research study;
- The theft of a research computer containing confidential subject information (breach of confidentiality); and
- The contamination of a study drug. Unanticipated problems generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.

## 9.2 Reporting Requirements to the FDA

Any unexpected fatal or unexpected life-threatening event (e.g. progressive multifocal leukoencephalopathy or pulmonary toxicity as described on page 47) judged by the PI to possibly be due to the investigational agent, will be reported to the FDA by telephone or fax as soon as possible but no later than seven calendar days after notification of the event and followed by a written safety report as complete as possible within eight additional calendar days (i.e. full report 15 calendar days total after notification of event).

Unexpected, non-fatal and non-life-threatening SAEs, which occur in on-study participants during the time periods specified in Section 9.1 that are considered due to or possibly due to the investigational agent, will be reported to the FDA by written safety report as soon as possible but no later than 15 calendar days of the notification of the occurrence of the event. Expected SAEs, even unexpected fatal SAEs, considered by the PI to be not related to the study, will be reported to the FDA in the Annual Review Report along with non-serious AEs. All FDA correspondence and reporting will be conducted through the St. Jude Office of Regulatory Affairs.

## 9.3 Reporting to St. Jude Regulatory Affairs Office (RAO)

Copies of all correspondence to the St. Jude IRB, including SAE reports, are provided to the St. Jude Regulatory Affairs office by the St. Jude study team. FDA-related correspondence and reporting will be conducted through the Regulatory Affairs office.

## 9.4 Reporting to Seattle Genetics by St. Jude

Safety Reporting Requirements:

**Reporting Timeframe:** The Principal Investigator will report all Serious Adverse Event (SAE)s that occur in a study subject within the following timeframe:

| | |
|---|---|
| Individual expedited SAE reports required by competent health authority (i.e. FDA, Health Canada) | At time of submission to competent authority:<br><br>Seattle Genetics Drug Safety by:<br>Facsimile [redacted]<br>[redacted] (USA only toll free)<br>Email: [redacted] |
| Aggregate listing of all SAEs | Monthly:<br><br>[redacted] or portal |

**Reporting Forms for individual expedited submissions:** The Principal Investigator will report such SAEs on the approved local regulatory form (i.e. FDA MedWatch form or CIOMS) *to include an assessment of causality to the Product*.

**Reporting format for monthly SAEs:** St. Jude will provide a study-specific cumulative SAE line listing of all SAEs including an *assessment of causality* to the Product.

**Reporting Period:** The reportable events that are subject to this provision are those that occur from the start of administration of the first dose of the Product through thirty (30) days after discontinuation of the Product. SAEs occurring more than thirty (30) days after discontinuation of the Product that are assessed by the Investigator as related to the Product should also be reported.

**Follow-up Information:** The IST Sponsor-Investigator will assist Seattle Genetics in investigating any SAE and will provide any follow-up information reasonably requested by Seattle Genetics.

**Regulatory Reporting:** Reporting an SAE to Seattle Genetics does not relieve the IST Sponsor-Investigator conducting the study of the responsibility for reporting it to the FDA, local regulatory authority, or IRB/IEC as required.

<u>St. Jude Investigator Responsibilities</u>

The Sponsor-Investigator of the study, and/or Institution must ensure that the study is conducted in accordance with the provisions of the ICH GCP Guidelines and all applicable local and regulatory requirements. The Sponsor-Investigator must assume all regulatory responsibilities including, but not limited to, IRB/IEC approvals, regulatory approvals, monitoring responsibilities and any and all reporting obligations to local Regulatory Authorities.

Seattle Genetics Requirements for IST Collaboration

*Study initiation*

The Sponsor-Investigator and/or Institution must provide the following to Seattle Genetics prior to initiation of Seattle Genetics support (provision of Product and/or funding):

- Final study protocolFully executed IST Agreement
- Regulatory Response Documentation (IND or CTA documentation if applicable)
- IRB/IEC approval

*Study maintenance*

Throughout the study, Seattle Genetics requires the following:

- For studies administering study drug: At least one safety study status update per year, to include information on enrollment and study completion dates.
- Notification of any amendment to the original protocol after the research has begun; and *immediate* notification of any amendments made due to safety reasons.

*Study closure*

Any Sponsor-Investigator and/or Institution conducting an IST is contractually required to provide Seattle Genetics a copy of the IND Annual Report (or equivalent in rest of world regions). Upon study closure, the Sponsor-Investigator and/or Institution will be required to certify that all safety reporting obligations were met.

## 9.5 Reporting AEs to and from Collaborating Sites to St. Jude

Adverse events from collaborating sites will also be reviewed by the PI and discussed in study team meetings as described above. SAE report from collaborating sites for AEs that are serious, unexpected, and at least possibly related to protocol treatment or interventions will be reported to site IRB and the St. Jude IRB within the reporting requirements described above. The PI will determine if this is an event that will need to be reported expeditiously to all participating sites, considering the following criteria:

- Is the AE serious, unexpected, and related or possibly related to participation in the research?
- Is the AE expected, but occurring at a significantly higher frequency or severity than expected?
- Is this an AE that is unexpected (regardless of severity that may alter the IRB's analysis of the risk versus potential benefit of the research *and*, as a result, warrant consideration of substantive changes in the research protocol or informed consent process/document?

With the submission of the "Reportable Event" in St. Jude TRACKS application, the PI will indicate if all sites should be notified to report to their IRBs, and if the protocol and/or consent should be amended (consent will be amended if event is information that should be communicated to currently enrolled subjects). Generally, only events that warrant an amendment to the protocol and/or consent will be reported expeditiously to all sites. However, any event may be reported expeditiously to all sites at the discretion of the PI.

A cumulative summary of Grade 1-5 AEs and expected/unrelated deaths that occur more than 30 days off last protocol treatment will be reported to all sites with study progress report at the time of continuing review.

Contact information for SAEs meeting reporting requirements:

Collaborating sites should send SAE reports to St. Jude IRB promptly, **but in no event later than 10 working days** after the investigator first learns of the unanticipated problem.

**Deaths meeting reporting requirements are to be reported immediately to the St. Jude IRB, but in no event later than 48 hours after the investigator first learns of the death.**

E-mail reports to the HLHR13 study team:

[redacted]

### 9.6 Recording AEs and SAEs

Adverse events (AEs) will be evaluated and documented by the clinical staff and investigators throughout inpatient hospitalizations and each outpatient visit. CRAs are responsible for reviewing documentation related to AEs and entering directly into CRIS protocol-specific database. The data to be recorded are:

- The event description
- The NCI CTCAE v4.0 code and grade
- The onset date, 4) the resolution date (or ongoing)
- Action taken for event
- Participant outcome
- Relationship of AE to protocol treatment/interventions
- If AE was expected or unexpected (see investigator's brochure, package inserts, informed consent document)
- Comments, if applicable.

AEs that are classified as **serious, unexpected, and at least possibly related** will be notated as such in the database as "SAEs". These events will be reported expeditiously to the St. Jude IRB within the timeframes as described above.

Cumulative summary of all adverse events (Grades 1-5) during treatment and for 30 days after the last therapeutic intervention will be recorded and reported as part of the progress reports to IRB at the time of continuing review. Specific data entry instructions for AEs and other protocol-related data will be documented in protocol-specific data entry guidelines, which will be developed and maintained by study team and clinical research informatics.

The study team will meet regularly to discuss AEs (and other study progress as required by institutional DSMP). The PI will review Adverse Event reports generated from the research database, and corrections will be made if applicable. Once the information is final the PI will sign and date reports, to acknowledge his/her review and approval of the AE as entered in the research database.

Any unexpected fatal or unexpected life-threatening event judged by the PI to possibly be due to the investigational agent, will be reported to the FDA by telephone or fax as soon as possible but no later than seven calendar days after notification of the event and followed by a written safety report as complete as possible within eight additional calendar days (i.e. full report 15 calendar days total after notification of event).

Unexpected, non-fatal and non-life-threatening SAEs, which occur in on-study participants during the time periods specified in Section 9.1 that are considered due to or possibly due to the investigational agent, will be reported to the FDA by written safety report as soon as possible but no later than 15 calendar days of the notification of the occurrence of the event. Expected SAEs, even unexpected fatal SAEs, considered by the PI to be not related to the study, will be reported to the FDA in the Annual Review Report along with non-serious AEs. All FDA correspondence and reporting will be conducted through the St. Jude Office of Regulatory Affairs.

## 10.0 DATA COLLECTION, STUDY MONITORING & CONFIDENTIALITY

### 10.1 Data Collection

Electronic case report forms (e-CRFs) will be completed by the SJCRH Leukemia/Lymphoma CRAs. Data will be entered from record directly into a secure CRIS database, developed and maintained by St. Jude Clinical Research Informatics.

Data management will be supervised by the Director of Clinical Trials Management, and Manager of Clinical Research Operations for the Leukemia/ Lymphoma Division, working with Dr. Ehrhardt or his designee. All protocol-specific data and all grade 1-5 adverse events will be recorded by the clinical research associates into the CRIS database, ideally within 2-4 weeks of completion of study phase. All questions will be directed to the attending physician and/or PI and reviewed at regularly-scheduled working meetings. The attending physicians (or their designees) are responsible for keeping up-to-date roadmaps in the patient's primary SJCRH medical chart.

Regular (at least monthly) summaries of toxicity and protocol events will be generated for the PI and the department of Biostatistics to review.

## 10.2 Data Collection Instructions for Collaborating Sites

Collaborating sites will collect data by using e-CRFs via remote electronic data entry. All protocol-specific data and all grade 1-5 adverse events during treatment and for 30 days post last dose of protocol therapy will be recorded by the clinical research associates into the CRIS database, ideally within 2-4 weeks of completion of study phase.

## 10.3 Study Monitoring

This study is considered high risk (HR-3) for monitoring purposes. Protocol and regulatory compliance, including essential regulatory documentation, will be assessed as well as the accuracy and completeness of all data points relating to the primary and secondary objectives semi-annually. If the study design has strata, accrual will be tracked continuously. The first two enrollees will be monitored and 15 % of the study enrollees thereafter, semi-annually.

The PI and study team are responsible for protocol and regulatory compliance, and for data accuracy and completeness. The study team will meet at appropriate intervals to review case histories or quality summaries on participants and retain copies of the minutes which are signed by the PI.

The Eligibility Coordinators in the Central Protocol and Data Monitoring Office (CPDMO) will verify informed consent documentation and eligibility status on 100% of St. Jude participants within 5 working days of enrollment completion.

The Clinical Research Monitor (CRM) will verify informed consent documentation and eligibility status of all non-St. Jude participants and perform a quality verification of select St. Jude participants during routine monitoring intervals (every 6 months). Overall study conduct, compliance with primary and secondary objectives, age of majority consenting, safety assessments and reporting, and the timeliness and accuracy of database entries are monitored routinely.

Study documents routinely monitored on selected participants include medical records, database entries, study worksheets, and case report forms. Study documents are monitored for participant status, demographics, staging, subgroup assignment, treatments, investigational drug accountability, evaluations, responses, participant protocol status, off-study and off-therapy criteria, and for all other specifics as detailed in a separate study-specific monitoring plan. The study-specific monitoring plan may be revised over time, to adapt monitoring frequency and/ or intensity to a changing environment when appropriate (for example: new safety signals; positive history of compliance; all participants are in long term follow-up; or the enrollment period has ended).

The recording and reporting of Adverse Events, Serious Adverse Events (SAEs), and Unanticipated Problems (UPs) to include type, grade, attribution, duration, timeliness and appropriateness will be reviewed by the Monitor/ CRM. The CRM will generate a formal report which is shared with the Principal Investigator (PI), study team and the Internal Monitoring Committee (IMC).

Continuing reviews by the Internal Review Board (IRB) and Clinical Trials- Scientific Review Committee (CT-SRC) will occur at least annually. In addition, unanticipated problems are reviewed in a timely manner by the IRB.

St. Jude affiliates and domestic collaborating study sites will be monitored on-site by a representative of St. Jude as needed. International collaborators will be monitored by a Contract Research Organization (CRO), or other mechanism according to the study specific monitoring plan.

### 10.4 Confidentiality

Study numbers will be used in place of an identifier such as a medical record number. No research participant names will be recorded on the data collection forms. The list containing the study number and the medical record number will be maintained in a locked file and will be destroyed after all data have been analyzed.

The medical records of study participants may be reviewed by the St. Jude IRB, FDA, and St. Jude clinical research monitors.

## 11.0 STATISTICAL CONSIDERATIONS

The objective of this pilot phase II study is to study the safety and efficacy of the incorporation of Adcetris® into frontline therapy as AEPA/CAPDac in pediatric patients with high risk HL. The first 32 patients will be used to answer the first primary objective as described below; the total of 77 patients will contribute to answer the second primary objective relating to EFS. The trial is written to allow publication of the first primary objective as soon as the results are available.

It is foreseeable to have a successful primary objective of increasing the proportion of patients that achieve a complete response to 8 weeks of chemotherapy that will not translate into increased EFS if omission of radiotherapy proves to be unsafe in this patient population under these given circumstances.

On the other hand if the first primary objective is not successful, then the second primary objective no longer is of interest, as the paradigm in pediatric HL, to improve survival without radiation therapy, could not be achieved.

### 11.1 Safety Monitoring

The thresholds for safety monitoring were chosen after careful consideration of the potential risk/benefit ratio for the trial. All eligible patients who receive any AEPA/CAPDAC therapy will be included in safety monitoring described below from the initiation to the end of all chemotherapy.

Critical for the timely safety monitoring described in this section is up-to-date and accurate data for analysis. Each of the monitoring analyses will be conducted as follows:

- The triggering event will be confirmed by the attending physician and the protocol PI. Upon confirmation, all associated information for the event (dates, grade, etc.) will be locked (frozen) in the HLHR13 database.

    - If the safety stopping threshold is not reached, the trial continues unabated and this will conclude the analysis for this event.
    - If the safety stopping threshold is exceeded, the analysis is repeated by assuming that patients who do not have data in the HLHR13 database current to the date of the triggering event are "safe" on that date.

        - If the analysis of these data still exceeds the stopping threshold, then the appropriate action described below is executed.
        - If the analysis of these data does not result in the stopping threshold being exceeded, then the relevant data in the HLHR13 database is immediately (within several days) updated and the analysis repeated. This will constitute the final analysis triggered by the event and appropriate action will be taken pending on whether the stopping threshold is or is not exceeded.

    - Safety monitoring rules provide a statistical framework in which to consider whether observed toxicities are excessive. Upon completion of an interim analysis, the findings will be reported to the St. Jude DSMB that will make recommendations to the protocol PI and advise the St. Jude leadership on continuing, stopping or amending the trial.

- For monitoring purposes we will count the first episode of a monitored toxicity should the same toxicity occur multiple times on a single patient. The monitored toxicities will be pulmonary toxicity (see Section 4.3.2) and progressive multifocal leukoencephalopathy (see Section 4.3.4) as these are the only life threatening toxicities or toxicities possibly associated with long term morbidity. Both toxicities will be monitored independently.

    - Given the drug combinations, no pulmonary toxicity is expected; however in the rare event of having any grade ≥3 pulmonary toxicity, the trial shall be closed if this happens in 2 out of the first 32 patients, or is greater than 5% in subsequent cohort with additional 10 more cumulative patients than the previous cohort if the trial is extended to a cohort of 77 patients for the event-free survival evaluation.
    - Progressive multifocal leukoencephalopathy is a rare but serious adverse event. A single event could be tolerated and considered to have happened by chance alone; however, in the event of a second patient presenting with this toxicity, the stopping criteria will be reached.

## 11.2 Primary Objectives

*11.2.1 To evaluate the safety of AEPA/CAPDac, as well as the efficacy (early complete response) after 2 cycles of AEPA chemotherapy in high-risk patients with HL.*

*Responsible investigator: Matt Ehrhardt, M.D.*
*Responsible statistician: Hui Zhang, Ph.D.*

*Study design:* The proportion of historical control of HOD99 unfavorable risk patients had CR at week 8 of 17% (24/141). The sample size for this primary objective is calculated based on a binomial distribution to test following hypothesis: H0: p=17% vs. Ha: p>17%, where p is the true CR rate of high risk patients treated on this protocol after 2 cycles of AEPA chemotherapy. A total of 32 patients are needed to detect 20% increase CR rate with 80% power and 5% type I error. After 32 evaluable patients had CR assessment, the CR rate will be estimated and exact 90% and 95% confidence intervals of the CR rate will be provided. After the first 32 patients had response assessment, an analysis will be conducted to determine the efficacy of 2 cycles of AEPA chemotherapy. If it shows efficacy, the response results will be reported in a national/international meeting and the study will continue to enroll for a total of 77 patients (see primary objective 11.2.2) to assess response and event-free survival. If it shows futility, the study accrual will be closed and the study will be amended or closed.

*11.2.2 To compare the event-free survival in high-risk HL patients treated with AEPA/CAPDac to the historical control HOD99 unfavorable risk 2 arm (UR2).*

*Responsible investigator: Matt Ehrhardt, M.D.*
*Responsible statistician: Hui Zhang, Ph.D.*

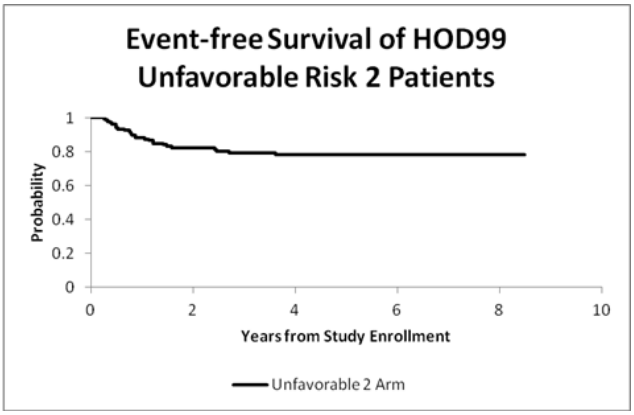
*Study design:* In this protocol, an event is defined as a relapse, disease progression, second malignance (except basal cell carcinoma) or death. The EFS is defined as the time interval from on study to the first event or last follow-up if a patient without an event. Based on the current HOD99 follow-up data (cut-off date is 9/19/2011, data are frozen for future interim analysis and final analysis. The follow-up of the historical data will also be updated for the final analysis.), the 3–year EFS of historical control HOD99 unfavorable risk 2 arm (UR2) patients is 79.4% (se=4%) with a total of 27 events among 142 patients (see Table 11 and Figure 1). Sample size for this objective is then determined to detect 12% increase of 3-year EFS (from 79% to 91% of 3-year EFS or equivalently to detect a hazard ratio 0.4). Under the proportional hazard model assumption, using a two-sample log-rank test comparing with historical control of HOD99 unfavorable risk 2 arm (UR2) patients, a total of 77 patients (or 7 events, relapse/progression or death) are needed to detect a 11% increasing 3-year EFS with study power of 80% and 10% type I error, assumed a 2-year follow-up period for current study[45].

*Table 11: Event-free Survival of HOD99 UR2 Patients*

| *Unfavorable risk 2 Arm* | | | | | |
|---|---|---|---|---|---|
| Years from Study Enrollment | Risk | Fail | Cens | Prob | SE |
| 0 | 142 | 0 | 0 | 1.000 | 0.000 |
| 1 | 142 | 16 | 13 | 0.881 | 0.028 |
| 2 | 113 | 7 | 15 | 0.823 | 0.036 |
| 3 | 91 | 3 | 13 | 0.794 | 0.041 |
| 4 | 75 | 1 | 9 | 0.782 | 0.045 |
| 5 | 65 | 0 | 14 | 0.782 | 0.051 |
| 6 | 51 | 0 | 19 | 0.782 | 0.064 |

| *Unfavorable risk 2 Arm* | | | | | |
|---|---|---|---|---|---|
| Years from Study Enrollment | Risk | Fail | Cens | Prob | SE |
| 7 | 32 | 0 | 13 | 0.782 | 0.082 |
| 8 | 19 | 0 | 11 | 0.782 | 0.122 |
| 9 | 8 | 0 | 8 | 0.782 | 0.365 |

*Figure 1: EFS of HOD99 UR2 patients*




### *11.2.4 Accrual and study duration*

Table 12 shows the observed annual accrual rate for unfavorable risk patients treated on HOD99 protocol. An average of 15-16 patients were enrolled annually, therefore the study will need approximate 2 years to accrual 32 patients for primary objective 1 and approximate 5-6 years to accrual 77 patients for primary objective 2. For the primary objective 2, the final analysis of EFS will be conducted after last evaluable patient enrolled on the study and followed 2 years.

***Table 12: Yearly Accrual for HOD99 Unfavorable Risk 2 Arm***

| **Year** | **# of Eligible Patients Enrolled** |
|---|---|
| **Year 1**: 6/11/2002 – 6/10/2003 | 13 |
| **Year 2**: 6/11/2003 – 6/10/2004 | 15 |
| **Year 3**: 6/11/2004 – 6/10/2005 | 19 |
| **Year 4**: 6/11/2005 – 6/10/2006 | 17 |
| **Year 5**: 6/11/2006 – 6/10/2007 | 20 |
| **Year 6**: 6/11/2007 – 6/10/2008 | 9 |
| **Year 7**: 6/11/2008 – 6/10/2009 | 16 |
| **Year 8**: 6/11/2009 – 6/10/2010 | 16 |
| **Year 9**: 6/11/2010 – 6/10/2011 | 17 |
| **Total** | **142** |
| ***Average yearly accrual: 15.78*** | |

## 11.3 Secondary Objectives

*11.3.1 To estimate the number of patients with adequate response according to the definitions in the Euro-Net C1.*

*Responsible investigator: Matt Ehrhardt, M.D.*
*Responsible statistician: Hui Zhang, Ph.D.*

The proportions of patients with adequate response according to the definitions in the Euro-Net C1 will be estimated together with a 95% confidence interval.

*11.3.2 To evaluate the safety of Adcetris® in the AEPA/CAPDac regimen in children with unfavorable risk HL.*

*Responsible investigator: Matt Ehrhardt, MD*
*Responsible statistician: Hui Zhang, Ph.D.*

To describe acute hematologic, neuropathic, and infectious toxicities as they relate to transfusion requirements, growth factor support, episodes of febrile neutropenia and hospitalizations, according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Summary statistics will be provided for hematologic, neuropathic and infectious toxicities as they relate to transfusion requirements, growth factor support, episodes of febrile neutropenia and hospitalizations, according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

*11.3.3 To study the association between the incidence and patterns of local failure and original lymph node region and volume of radiation.*

*Responsible investigator: Matt Ehrhardt, MD and Matthew Krasin, M.D.*
*Responsible statistician: Hui Zhang, Ph.D.*

Cumulative incidence model will be used to study the association between local failure and original lymph node region and volume of radiation. Person Chi-square test will be used to study the association between patterns of local failure and original lymph node region and volume of radiation.

*11.3.4 To assess the patient reported symptoms and health-related quality of life in children with high risk HL compared to those treated on the unfavorable HOD99 treatment arm.*

*Responsible investigator: Belinda Mandrell, PhD*
*Responsible statistician: Hui Zhang, Ph.D.*

The patient reported symptoms distress scale (SDS) and responses to the items of the PedsQL physical functioning subscale will be summarized by descriptive statistics. Spearman correlation coefficients will be used to assess the correlation of the physical functioning subscale between time points. The mixed effects linear model for repeated measures will also be used to assess the change in QoL and symptom distress over time and to investigate the association between symptom distress and QoL. The results will be compared to that of those treated on the unfavorable arm 2 of HOD99.

### 11.4 Exploratory Objectives

*11.4.1 To compare the ratings of neuropathic toxicity according to the NCI Common Terminology Criteria for Adverse Events, version 4.0 to the Pain Quality Assessment Scale (PQAS©).*
*Responsible investigator: Belinda Mandrell, PhD*
*Responsible statistician: Hui Zhang, Ph.D.*

Summary statistics will be provided to compare the ratings of neuropathic toxicity according to the NCI CTC v4.0 to the PQAS©.

*11.4.2 To describe the pharmacokinetics of Adcetris® when used as part of AEPA/CAPDac for a pediatric HL population*
*Responsible investigator: Matt Ehrhardt,MD*
*Responsible statistician: Hui Zhang, Ph.D.*

Summary statistics will be provided for PK data of Adcetris®. This will be done according to previous protocols involving Adcetris®.

*11.4.3 To describe the immunogenicity of Adcetris® and the relationship between early response and presence of anti-chimeric anti-body.*
*Responsible investigator: Matt Ehrhardt, MD*
*Responsible statistician: Hui Zhang, Ph.D.*

Summary statistics will be provided for this objective.

*11.4.4 To explore the association between CD30 density in Reed Sternberg cells in paraffin embedded tumor tissue and early response and event-free survival.*
*Responsible investigator: Matt Ehrhardt, MD*
*Responsible statistician: Hui Zhang, Ph.D.*

The association between CD30 density in Reed Sternberg cells within paraffin-embedded tumor tissue and early response/EFS will be explored by regression analysis. We will request 10 unstained slides of 5-7 microns thick tissue sections for immunohistochemical analysis of CD30 expression. These studies will be completed by the Molecular Clinical Trials Core at St. Jude Children's Research Hospital under the direction of

*11.4.5 To explore the association between soluble CD30 and early response, event-free survival and symptom/quality of life.*
*Responsible investigator: Matt Ehrhardt, MD*
*Responsible statistician: Hui Zhang, Ph.D.*

The association between soluble CD30 and early response, EFS and symptom/quality of life will be explored by regression analysis.

*11.4.6 To identify pharmacogenetic predictors for treatment-related outcomes in the context of AEPA/CAPDac.*
*Responsible investigator: Matt Ehrhardt, MD*
*Responsible statistician: Hui Zhang, Ph.D.*

Regression model will be used to study the pharmacogenetic predictors for treatment-related outcomes in the context of AEPA/CAPDac.

Estimated completion of accrual date is May 2020 (7 years). Estimated study completion date is May 2030.

*11.4.7 Objective: Compare dosimetrically, the ability of PBRT to spare adjacent normal tissues compared to photon based radiation therapy*
*Responsible investigator: Matthew Krasin, M.D., Chia-ho Hua, Ph.D., and Jonathan Farr, Ph.D.*
*Responsible statistician: Hui Zhang, Ph.D.*

The dosage derived to spare adjacent normal tissues using PBRT based radiation therapy will be compared to photon therapy. Summary statistics of dosage will be given and non-parametric test will be to test the difference.

# 12.0 OBTAINING INFORMED CONSENT

## 12.1 Consent/Assent at Enrollment

The process of informed consent for HLHR13 will follow institutional policy. The informed consent process is an ongoing one that begins at the time of diagnosis and ends after the completion of therapy. Informed consent should be obtained by the attending physician or his/her designee, in the presence of at least one non-physician witness. Initially, informed consent will be sought for the institutional banking protocol (research study), blood transfusion and other procedures as necessary. After the diagnosis of high risk HL is established, we will invite the patient to participate in the HLHR13 protocol. Throughout the entire treatment period, participants and their parents receive constant education from health professionals at SJCRH and collaborating sites, and are encouraged to ask questions regarding alternatives and therapy. All families have ready access to chaplains, psychologists, social workers, and the St. Jude ombudsperson for support, in addition to that provided by the primary physician and other clinicians involved in their care.

We will also obtain verbal assent from children 7 to 14 years old and written assent for all participants ≥14 years of age. Participants who reach the age of majority while on study will be re-consented for continued participation on HLHR13, according to Cancer Center and institutional policy.

## 12.2 Consent at Age of Majority

The age of majority in the state of Tennessee is 18 years old. Research participants must be consented at the next clinic visit after their 18th birthday. If an affiliate or collaborating site is located in a country or state where a different age of majority applies, that location must consent the participants according to their local laws.

## 12.3 Consent When English is Not the Primary Language

When English is not the patient, parent, or legally authorized representative's primary language, the Social Work department will determine the need for an interpreter. This information documented in the participant's medical record. Either a certified interpreter or the telephone interpreter's service will be used to translate the consent information. The process for obtaining an interpreter and for the appropriate use of an interpreter is outlined on the Interpreter Services, OHSP, and CPDMO websites.

Collaborating sites will follow institutional policy for consenting non-English speaking participants (and will provide institutional policy to St. Jude).

## 12.4 Collection of Collaborating Institutions' Consent Forms

Signed collaborating institution's consent forms will be faxed to the CPDMO Eligibility Office at [redacted].

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## APPENDIX I: Ann Arbor Staging Classification of Hodgkin Lymphoma

### A. Stage Grouping

(See the diagram below for definitions of regions.)

Stage I: Involvement of single lymph node region (I) or localized involvement of a single extra-lymphatic organ or site (IE).

Stage II: Involvement of 2 or more lymph node regions on the same side of the diaphragm (II) or localized contiguous involvement of a single extra-lymphatic organ or site and its regional lymph node(s) with involvement of 1 or more lymph node regions on the same side of the diaphragm (IIE).

Stage III: Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized contiguous involvement of an extra-lymphatic organ or site (IIIE), by involvement of the spleen (IIIS), or both (IIIE+S).

Stage IV: Disseminated (multifocal) involvement of 1 or more extra-lymphatic organs or tissues, with or without associated lymph node involvement, or isolated extra-lymphatic organ involvement with distant (non-regional) nodal involvement.

### B. Symptoms and Presentations

"A" Symptoms: Lack of "B" symptoms.

"B" Symptoms: At least one of the following:

- Unexplained weight loss > 10% in the preceding 6 months;
- Unexplained recurrent fever > 38°C in the preceding month; or
- Recurrent drenching night sweats in the preceding month.

### C. Bulk disease

Each of the following presentations is considered "bulk" disease:

- **Large mediastinal mass:** tumor diameter > 1/3 the thoracic diameter (measured transversely at the level of the dome of the diaphragm on a 6 foot upright PA CXR). In the presence of hilar nodal disease the maximal mediastinal tumor measurement may be taken at the level of the hilus. This should be measured as the maximum mediastinal width (at a level containing tumor and any normal mediastinal structures at the level) over the maximum thoracic ratio.
- **Large extra-mediastinal nodal aggregate:** A continuous aggregate of nodal tissue that measures > 6 cm in the longest transverse diameter in the axial plane in any nodal area.
- **Macroscopic splenic nodules:** focal defects in the spleen seen on CT, PET or MRI imaging studies consistent with Hodgkin lymphoma will be deemed to be the functional equivalent of “bulk” disease in this study.

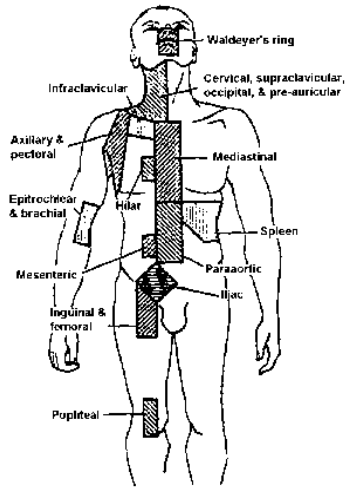
**D. Enumeration of Number of Regions of Nodal Involvement**

*Each of these 20 regions is counted separately for purposes of determining clinical group.*

Peripheral regions
- Right neck; cervical, supraclavicular, occipital, and pre-auricular
- Left neck; cervical, supraclavicular, occipital, and pre-auricular
- Right infraclavicular
- Left infraclavicular
- Right axilla and pectoral
- Left axilla and pectoral
- Right epitrochlear and brachial
- Left epitrochlear and brachial

Central regions
- Waldeyer's ring (including base of tongue)
- Mediastinum (including paratracheal)
- Right hilar
- Left hilar
- Mesenteric
- Paraaortic (including retrocrural, portal and celiac)
- Splenic/splenic hilar

Lower regions
- Right iliac
- Left iliac
- Right inguinal and femoral
- Left inguinal and femoral
- Right popliteal
- Left popliteal




**Anatomical Regions for the Staging of Hodgkin's Disease**

Clinical criteria for nodal involvement – upper torso

The following will be considered Hodgkin lymphoma positive nodes, provided they are not obviously infected.

- Any cervical or axillary node > 1.5 cm in longest transverse diameter on physical examination, ultrasound, CT or MRI scan
- Any cluster of matted or adherent nodes
- Any enlarged supraclavicular nodes
- Any mediastinal adenopathy
- Any FDG-positive nodes

Clinical criteria for nodal involvement – lower torso

Below the diaphragm the following areas of involvement will be considered positive for Hodgkin lymphoma unless they are pathologically proven to be negative. With the exception of the mesenteric region, nodes > 1.0 cm in the longest transverse diameter should be considered as lymphomatous in the absence of a compelling alternative explanation.

- Any FDG-positive nodes, liver or spleen
- A spleen or liver that has focal defects on CT or ultrasound or MRI. A maximum of 3 target lesions per organ should be measured and will be utilized for response

# APPENDIX II: Response Criteria According to Euro-NET C1

Response assessment for secondary objective 1.2.1 will be done blinded and retrospectively by central review. Images will be collected and assessed according to the definitions outlined below.

## A. DEFINITION OF TREATMENT RESPONSE

### A.1. Local response definitions for nodal involvement with measurable tumor volume

At staging all measurable nodal sites (i.e. all nodal except for the spleen and Waldeyer's ring) are grouped in **separately measurable reference volumes**. Reference volumes can include multiple sites if these are contiguous. The composition of these reference volumes is defined and documented. Initial volumes of reference volumes are measured. Volumes are approximated as ellipsoids. If a, b, c denote the principal axes of the ellipsoid the volume is calculated as V= (a x b x c)/2. In this protocol overall response to treatment is determined according to a systematic assessment of tumor response in all involved sites. In those sites where the tumor is measurable from CT/MRI scanning the change in tumor volume is compared the original pre-treatment reference volume and then assigned a treatment response for that local site.

#### *A.1.1. Local Complete remission (local CR)*

A reference volume is in "local complete remission"(in short: local CR) if:

- the residual tumor volume is less or equal 5% of the reference volume (CT/MRI) and
- the residual tumor volume is less or equal 2 ml

#### *A.1.2. Local complete remission unconfirmed (local CRu)*

A reference volume is in "local complete remission unconfirmed "(in short: local CRu) if:

- No local CR **and**
- the residual tumor volume is less or equal 25% of the reference volume (CT/MRI) **or** the residual tumor volume is less or equal to 2 ml

#### *A.1.3. Local partial remission (local PR)*

A reference volume is in "local partial remission"(in short: local PR) if:

- No local CR or local CRu **and**
- the residual tumor volume is less or equal 50% of the reference volume (CT/MRI) **or** the residual tumor volume is less or equal 5 ml (to safeguard against artifacts due to measurement errors).

#### *A.1.4. Local no change (local NC)*

A reference volume is in "local no change" (in short: local NC) if

- no local CR or local CRu or local PR **and**
- no local Progression

#### *A.1.5. Local Progression (local PRO)*

A reference volume is in "local progression" (in short: local PRO) if

- The residual tumor volume is larger than 125% of the reference volume or significantly increases compared to the best previous response – be aware of possible measurement error in small tumor volume.

### A.2. Local response definitions for extra-nodal involvement or for nodal involvement with non-measurable tumor volume

For all extra-nodal sites or for nodal involvement with non-measurable tumor volume three response categories are distinguished by radiological or clinical criteria:

- **Locally undetectable**
- **Locally detectable**
- **Locally progressive**

Only "Locally undetectable" is consistent with overall CR.

**Note: In case of multi-focal bone or bone marrow involvement multiple sites are assessed separately.** Initial bone or bone marrow involvement is only assessed be FDG-PET assuming it is still detectable by conventional imaging.

### A.3. Overall (patient level) response definitions

Overall (patient level) response categories are obtained from the worst local response in reference volumes and the worst local response in non-measurable nodal or extra-nodal disease as illustrated in the following figure:

**Fig. 1. Definition of overall response**

| | | worst local response in nodal reference volumes | | | | | |
|---|---|---|---|---|---|---|---|
| | | no involvement | local CR | local CRu | local PR | local NC | local PRO |
| worst local response in extranodal or non-measurable nodal regions | no involvement | | overall CR | overall CRu | overall PR | overall NC | overall PRO |
| | undetectable | overall CR | overall CR | overall CRu | overall PR | overall NC | overall PRO |
| | still detectable | overall CRu | overall CRu | overall CRu | overall PR | overall NC | overall PRO |
| | local PRO | overall PRO | overall PRO | overall PRO | overall PRO | overall PRO | overall PRO |

**legend:** overall CR, overall CRu, overall PR, overall NC, overall PRO

### *A.3.1. Complete remission (CR)*

"Complete remission"(in short: CR) is achieved if in restaging

- all disease symptoms have disappeared **and**
- no new lymphatic or extra-lymphatic lesions have occurred **and**
- ***all*** initially involved extra-nodal sites or involved regions with non-measurable tumor volume are locally undetectable **and**
- ***all*** reference volumes are in local CR

### *A.3.2. Complete remission unconfirmed (CRu)*

"CR unconfirmed"(in short: CRu) is achieved if in restaging

- no CR **and**
- all disease symptoms have disappeared **and**
- no new lymphatic or extra-lymphatic lesions have occurred **and**
- ***all*** initially involved extra-nodal sites or involved regions with non-measurable tumor volume are not locally progressive **and**
- ***all*** reference volumes are at least in local CRu

### *A.3.3. Partial remission (PR)*

"Partial remission" (in short: PR) is achieved if in restaging

- no CR or CRu **and**
- all disease symptoms have disappeared **and**
- no new lymphatic or extra-lymphatic lesions have occurred **and**
- ***all*** initially involved extra-nodal sites or involved regions with non-measurable tumor volume are not locally progressive **and**
- ***all*** reference volumes are at least in local PR

### *A.3.4. No change (NC)*

"No change" (in short: NC) is achieved if in restaging

- no CR or CRu or PR **and**
- no PRO

### *A.3.5. Progression (PRO) / Relapse (R)*

Progression / Relapse of the disease occurs if

- recurrence or occurrence of new disease symptoms which cannot be explained otherwise **or**
- occurrence of new lymphatic or extra-lymphatic lesions **or**
- ***at least one*** initially involved extra-nodal site or involved region with non-measurable tumor volume is locally progressive **or** at least one reference volume is in local PRO

**A progression / relapse of the disease is called**

- **progression** if it occurs until three months after the end of therapy (last day of chemotherapy application (including Prednisone/prednisolone) or last day of radiotherapy respectively).
- **early relapse** if it occurs between three and twelve months after the end of therapy.
- **late relapse** if it occurs later than twelve months after the end of therapy.

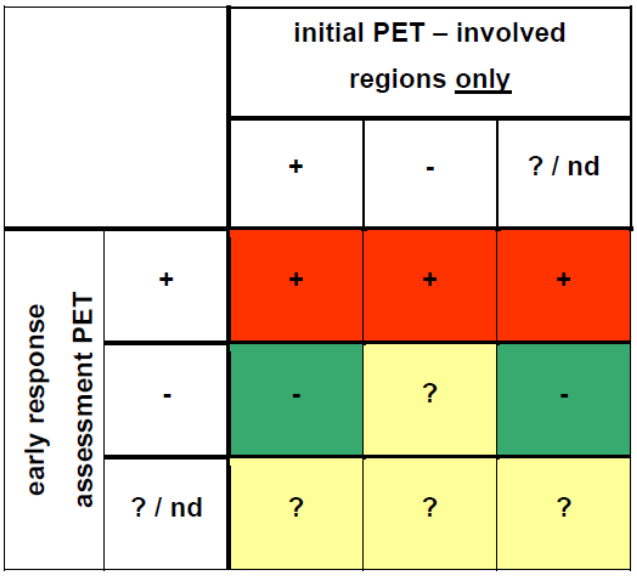
## B. EARLY FDG-PET RESPONSE ASSESSMENT

After two cycles of chemotherapy early response reassessment including FDG-PET is performed. **FDG-PET examinations are assessed only for initially involved regions** (except in case of suspected progression).

### B.1. Definition local FDG-PET response

For each initially involved reference volume or non-measurable nodal or extra-nodal site a local PET response is defined based on the initial PET and the response assessment PET results as illustrated in:

**Fig. 2: Definition local FDG-PET response**




+ = positive FDG-PET

- = negative FDG-PET

? / nd = questionable FDG-PET or FDG-PET not done

**Definition local FDG-PET response**

- **Local PET response positive** if the response assessment PET is positive anywhere in the reference volume or involvement site.
- **Local PET response unclear,** if the response assessment PET is unclear **or** the response assessment PET is negative, but the initial PET was discordantly negative.
- **Local PET response negative** if the response assessment PET is negative **and** the initial PET was positive or unclear (i.e. not discordantly negative).

NOTE: A PET examination is locally **unclear** if:

- Not done
- Not evaluable due to technical problems in rare cases of questionable PET results.

### B.2. Definition worst local FDG-PET response

In case of **Local PET response unclear** a further distinction is made by local CT/MRI response**:**

- **Locally PET unclear, but local CR or locally undetectable (by CT/MRI)**
- **Locally PET unclear, but not local CR or locally detectable (by CT/MRI)**

The **worst local PET response** is defined based on the following order relation:
"Local PET response positive" worse than
"Locally PET unclear, but not local CR or locally detectable" worse than
"Locally PET unclear, but local CR or locally undetectable" worse than
"Local PET response negative"

## C. RESPONSE GROUP DEFINITION

If **no tumor progression** is found, response groups are obtained from the overall response and the worst local PET response in reference volumes and in non-measurable nodal or extranodal disease as illustrated in Fig. 5 and Table 14:

**Figure 3: Response group definition**

| | | worst local PET response | | | |
|---|---|---|---|---|---|
| | | PET negative | PET unclear, but local CR / undetectable | PET unclear, detectable and not local CR | PET positive |
| overall response | CR | ☐ AR1 | ☐ AR1 | | ☐ AR1 |
| | CRu | ☐ AR2 | ☐ AR2 | ☐ IRu | ☐ IR |
| | PR | ☐ AR2 | ☐ AR2 | ☐ IRu | ☐ IR |
| | NC | ☐ IRu | ☐ IRu | ☐ IRu | ☐ IR |

AR1 = adequate response group 1 ⇨ no radiotherapy
AR2 = adequate response group 2 ⇨ no radiotherapy
IRu = inadequate response qroup unconfirmed ⇨ radiotherapy
IR = inadequate response group ⇨ radiotherapy

**Table Response groups in non-progressing patients**

| | |
|---|---|
| **Adequate response 1 (AR1)** | Patients in overall complete remission irrespective of PET results. |
| **Adequate response 2 (AR2)** | Patients in overall CRu or overall PR for whom **all** initially involved regions are<br>▪ **PET-negative** or<br>▪ **PET-unclear** and<br>o in local CR or<br>o undetectable |
| **Inadequate response (IR)** | Patients<br>▪ not in overall complete remission **and**<br>▪ at least one initially involved region is **PET-positive**. |
| **Inadequate response unconfirmed (IRu)** | ▪ Patients in overall CRu or overall PR **and**<br>▪ **no** initially involved region is **PET-positive and**<br>▪ at least one initially involved region is **PET-unclear and**<br>o not in local CR or<br>o still detectable<br>**or**<br>▪ Patients in overall No Change **and**<br>▪ **no** initially involved region is **PET-positive**. |

The distinction between AR1 and AR2 is made because in TG-1 AR1 the GPOH 95 study has already shown that omitting radiotherapy is safe, while in TG-1 AR2 this is an open study question.

## APPENDIX III: Collection, Processing, Storage and Shipment of Biologic Samples

### A. Expression of CD30 in tumor tissue (CD30 density)

Tumor tissue

Archival formalin-fixed, paraffin embedded tumor sections will be assessed by immunohistochemistry for CD30 expression in Reed Sternberg cells. Immunohistochemistry will be performed on formalin-fixed, paraffin embedded tissue specimens using commercially available antibodies to CD30, evaluated and graded semi-quantitatively for the percentage of RS cells stained and the intensity (0, +, ++, +++) of staining. The incidence of CD30 expression in RS cells and potential correlation with PR or CR will be explored via descriptive methods.

Shipment of samples

Please send 8-10 unstained slides of 5 micron thickness from FFPE tissue to the following address:

Tissue Resources Core Facility (TCRF)
St. Jude Children's Research Hospital
MS315, Room D1053
262 Danny Thomas Boulevard
Memphis, TN 38105
Phone: [redacted]
E-mail: [redacted]

### B. Soluble CD30 (all sites) Assessments

| Cycle | Day | Time | Relative Time | sCD30[a] |
|---|---|---|---|---|
| C1 | 1 | Pre-dose | Prior to Adcetris | **X** |
| C3 | 1 | Pre-dose | Prior to Adcetris | **X** |
| EOT[b] | | | | **X** |

*[a]soluble CD30- samples – collected at all participating sites*
*[b]EOT, End of Therapy – at off therapy evaluation*

Blood for sCD30 (all sites)

Blood will be drawn pre cycle one, pre cycle 3 and end of therapy for evaluation of sCD30.

Draw one 2.5 ml gold top serum separation tube, invert the tube five times and allow blood to clot for 30 minutes at room temperature. Within 1 hour of collection, centrifuge SST a minimum of 1500 x g for 15 minutes until clot and serum are well separated.

Following centrifugation for sCD30 obtain at least 0.5 ml. Freeze the samples immediately at -70°C (samples can be batched and sent at the end of the study period for all patients together).

***Each site will store the samples at their institution and send batch to Covance at the end of the study:***

Katherine T. Landschulz, PhD
Principal Scientist and Manager
Biomarker Center of Excellence
Covance Laboratories, Inc
671 S. Meridian Road
Greenfield, IN 46140

Tel: [redacted]

**C. Pharmacogenetics**

All research participants at St. Jude Children's Research Hospital will be asked to enroll on the institutional protocol PGEN5, while patients from external sites will be consented for banking of specimens for research as a part of the therapeutic protocol. Participation on this part of the protocol is voluntary. A blood sample will be collected *at any time point* in all consenting research participants. A total of 10 ml whole blood will be obtained in EDTA (purple top) vacutainer. Blood samples from external sites will be shipped overnight to St. Jude on coldpack. DNA extraction from mononuclear cells will be performed according to standard techniques. Genotyping for pharmacogenetic polymorphisms will be performed using standard molecular techniques in the Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital. Samples from collaborating sites should be shipped to:

Jun J. Yang Ph.D.
Assistant Member
Dept. of Pharm. Sci., Room I5506
St. Jude Children's Research Hospital
262 Danny Thomas Pl., MS313
Memphis, TN 38105
Tel: [redacted], Fax: [redacted]

St. Jude Children's Research Hospital
Department of Pathology, Tissue Resources Core Facility
262 Danny Thomas Place
Memphis, TN 38105 Tel: 901-595-4827 Fax: 901-595-2432

# HLHR13 Specimen Data and Shipping Form
# CD30 Density (Tumor Tissue)

Patient demographics

Referring Institution's Patient ID#: _____

Patient Name: _____ Sex: M F

Date of birth: _____

Hospital/clinic: _____

Patient physician: _____ Phone : _____

Fax: _____

……

*Specimen demographics*

Date specimen obtained: _____ Date specimen shipped: _____

Anatomic Site of Tumor: _____

Diagnosis: _____

| Collection Time point | Specimen Type |
|---|---|
| Initial diagnostic specimen | No. of FFPE slides: |

***Shipping Address:***

Tissue Resources Core Facility (TRCF)
St. Jude Children's Research Hospital
MS 315, Room D1053
262 Danny Thomas Place
Memphis, TN 38105
[redacted]

***Shipping Instructions:***

Ship specimens Monday through Thursday via FedEx priority overnight, at ambient temperature.
Inform the TRCF of shipment and FedEx tracking number at email address above.