Pediatric Hodgkin Lymphoma (PHL21)
Version 1.1

Introduction

Outcome of children with Hodgkin Lymphoma (HL), improved with risk- and response adaptive therapy. Recent large collaborative group studies demonstrated that reduction in chemotherapy cycles, doses and radiation are feasible and resulted in excellent survival and minimized toxicity.

Classical Hodgkin Lymphoma (cHL)

Low Risk

GPOH-HD-2002, TG-1 who were treated with two cycles of OEPA who were in CR (residual tumor volume ≤95% and ≤2 mL of the initial volume), the overall event-free survival (EFS) was 92% ± 2.0%, with no significant impact of RT on EFS. Building on the GPOH-HD studies, an international intergroup study for CHL in children and adolescents (EuroNet-PHL C1), In a report from an interim analysis, in TG-1 the 4-year overall survival (OS) and EFS were 98% and 87.5% respectively. In TG-1, ESR >30 or bulky disease was associated with inferior EFS. This trial suggests that RT can be eliminated in patients who are PET-negative after chemotherapy.

COG with 3-cycles of AVPC in AHOD0431, the four-year EFS being 79.9%, but the four-year overall survival (OS) was excellent at 99.6%. The study was temporarily closed on December 4, 2008, due to the high relapse risk among CR patients who had a positive result on PET after one cycle of chemotherapy (PET1), based on COG consensus AVPC alone has not been adopted as the overall standard of care for low-risk HL.

Low-risk patients, TG1 patient with stage IA and IIA and NO risk factors (ESR > 30; bulk volume > 200 mL; > 3 sites of disease) will be treated as per EuroNet-PHL C1 with two cycles of OEPA

Intermediate Risk

The phase III COG AHOD0031 study evaluated the role of early chemotherapy response in tailoring subsequent therapy in pediatric intermediate-risk HL Patients with newly diagnosed intermediate-risk HL received 2 cycles of ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, cyclophosphamide, and prednisone) followed by early response assessment with PET/CT. The overall 4-year EFS was 85% (86.9% for RERs and 77.4% for SERs; P < .001), and the 4-year OS was 97.8% (98.5% for RERs and 95.3% for SERs; P < .001).42 In RER patients who experienced CR at the end of chemotherapy, there was no significant difference in the 4-year EFS rate between patients who received IFRT versus those who did not receive IFRT (87.9% vs. 84.3%, respectively). For SER patients who received either DECA or no DECA, the 4-year EFS was 79.3% versus 75.2%, respectively (P = .11). PET response imaging was not required but was obtained for most patients as part of clinical care. Analysis of these data demonstrated that SER patients with PET-positive lesions after two cycles had a marginal improvement in EFS on the DECA arm (70.7% vs. 54.6%, P = .05). Overall, this study showed that RT can be omitted in RERs with CR at the end of chemotherapy, and that augmenting chemotherapy in SERs with PET-positive disease may be beneficial, RT was avoided in 30%-40% of intermediate-risk patients using the AHOD0031 regimen. Furthermore, based on this trial, stage IIB with bulk and IVA patients were moved to the high-risk category for subsequent trials.

Intermediate-risk will be treated with risk-response adapted chemotherapy using the backbone of AHOD0031

High risk

COG study, AHOD0831, the investigators aimed to limit alkylator exposure and decrease radiation volumes in pediatric patients with high-risk HL, defined as stage IIIB and IVB. All patients received 2 cycles of ABVE-PC; if they experienced CR (RER), they received an additional 2 cycles of ABVE-PC and ISRT (21 Gy) only to sites of initial bulk. Patients with SER received 2 cycles of ifosfamide and vinorelbine followed by 2 more cycles of ABVE-PC and RT to sites of initial bulk disease and slow-responding sites. According to intent-to-treat analysis, the 4-year second EFS (ie, freedom from second relapse or malignancy) was 91.9% (95% CI, 86.1%–95.3%).45 The 5-year first EFS and OS rates were 79.1% (95% CI, 71.5%–84.8%) and 95% (95% CI, 88.8%–97.8%),

AHOD0831 COG study showed significant reduction in radiation volume and alkylator resulted in similar outcome to successor COG study P9425, this regimen and treatment plan was taken forwarded as standard arm in AHOD1313, the study evaluated the use of Anti-CD30 antibody brentuximab vedotin (Bv) in combination with chemotherapy (Bv-AVE-PC) data in abstract was presented in ASCO 2022, showed high event-free survival in Brentuximab arm 3-year EFS 92.1% compared to the standard ABVE-PC 3-year EFS 82.5%.

High-risk will be treated with risk-response adapted chemotherapy using the Bv-AVE-PC arm of AHOD1331

Nodular Lymphocyte Predominant Hodgkin lymphoma (NLPHL)

The use of combination chemotherapy and/or radiation therapy can achieve excellent long-term progression-free survival and OS in patients with nodular lymphocyte-predominant Hodgkin lymphoma.

Low risk patients (stage I and II) will be treated as per AHOD03P1 protocol, advanced stage will be treated as per the corresponding stage of classical HL

Risk Stratification

	IA	IB	IIA	IIB	IIIA	IIIB	IVA	IVB
Low Risk								
Intermediate Risk	RF or X		RF or X					
High Risk				Bulky				

X Bulky disease or extranodal involvement

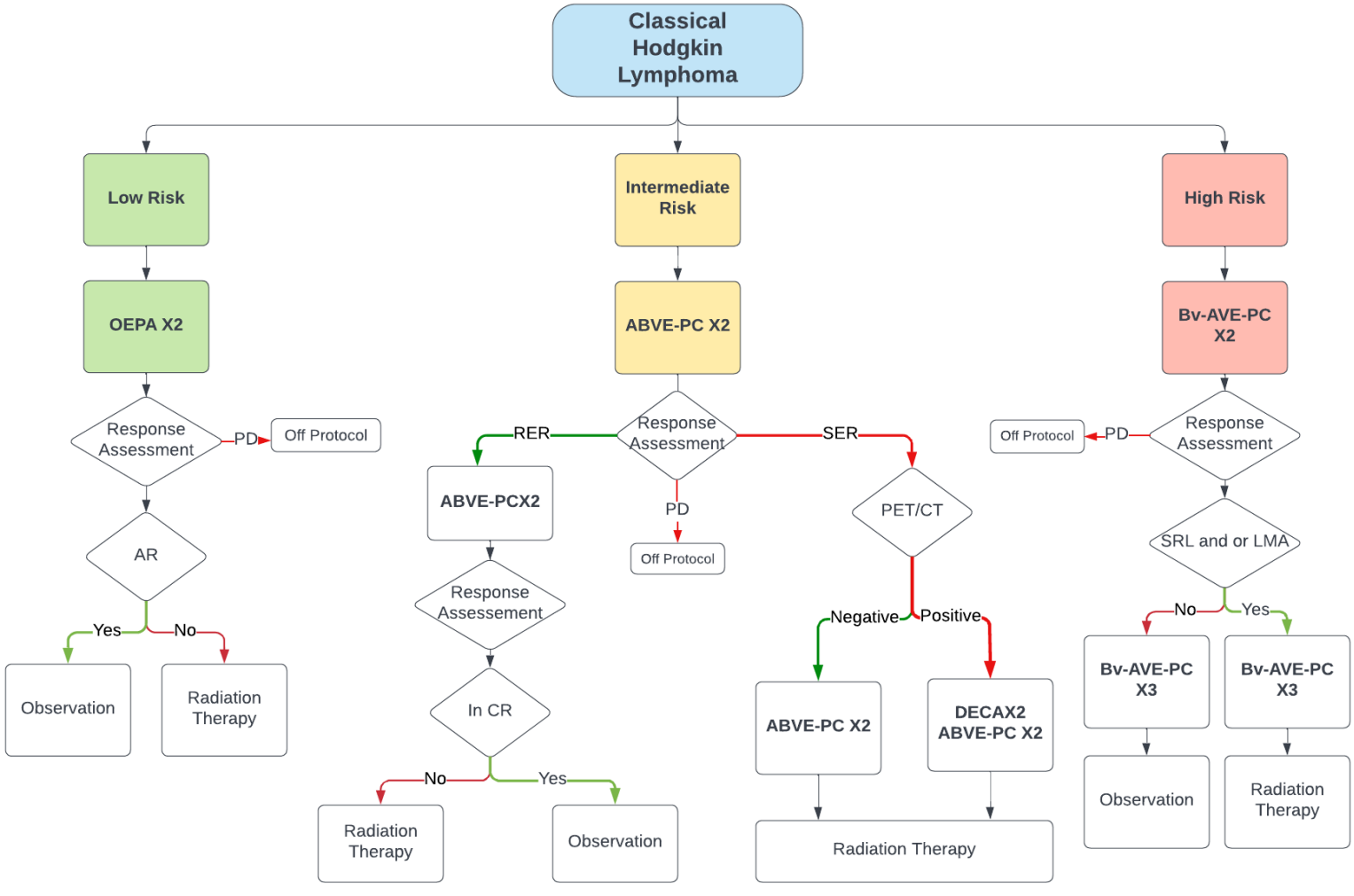
RF; Risk factors (ESR > 30 **or** bulk volume > 200 mL **or** > 3 sites of disease)

Low Risk.

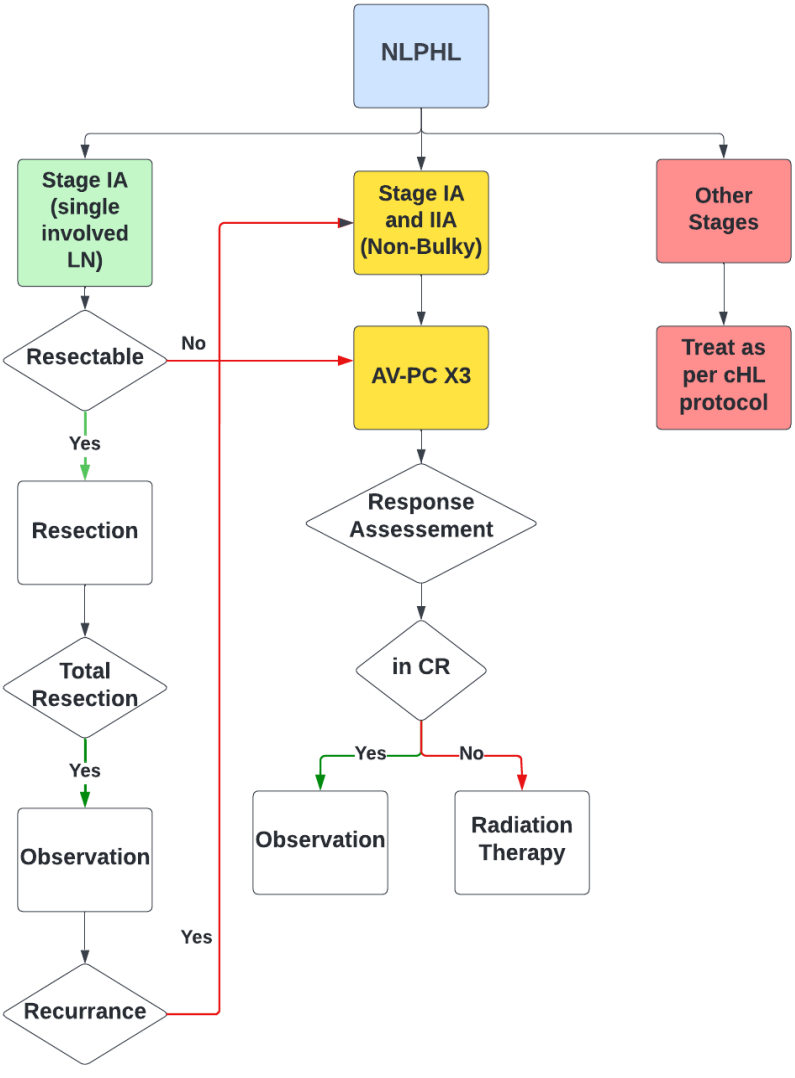
Intermediate Risk

High Risk

Treatment Schema



See Protocol for definition: AR; Adequate response **RER;** Rapid Early Response **SER;** Slow Early Response **SRL**; Slow Responding Lesion **LMA**; Large Mediastinal Adenopathy



See Protocol for definition: CR; Complete Response

Reference

[1] Keller FG, Castellino SM, Chen L, et al. Results of the AHOD0431 trial of response adapted therapy and a salvage strategy for limited stage, classical Hodgkin lymphoma: A report from the Children's Oncology Group. Cancer 2018;124:3210-3219.

[2] Mauz-Körholz C, Hasenclever D, Dörffel W, et al. Procarbazine-free OEPA-COPDAC chemotherapy in boys and standard OPPA-COPP in girls have comparable effectiveness in pediatric Hodgkin's lymphoma: the GPOH-HD-2002 study. J Clin Oncol 2010;28:3680-3686.

[3] Landman-Parker J, Wallace H, Hasenclever D, et al. First International Inter-Group Study for Classical Hodgkin Lymphoma in Children and Adolescents: EuroNet- PHL-C1 European protocol Euronet PHL-C1; Report of the latest interim Analysis [Abstract# P064]. Haematologica; 10th International Symposium on Hodgkin Lymphoma Symposium (ISHL10) 2016;101:35.

[4] Friedman DL, Chen L, Wolden S, et al. Dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate-risk hodgkin lymphoma: a report from the Children's Oncology Group Study AHOD0031. J Clin Oncol 2014;32: 3651-3658.

[5] Kelly KM, Cole PD, Pei Q, et al. Response-adapted therapy for the treatment of children with newly diagnosed high risk. Hodgkin lymphoma (AHOD0831): a report from the Children's Oncology Group. Br J Haematol 2019;187:39-48.

[6] Flerlage J, Kelly K, Beishuizen A, et al. Staging Evaluation and Response Criteria Harmonization (SEARCH) for Childhood, Adolescent and Young Adult Hodgkin

[7] Lymphoma (CAYAHL): Methodology statement. Pediatr Blood Cancer 2017;64(7):e26421.

[8] Appel BE, Chen L, Buxton AB, et al.: Minimal Treatment of Low-Risk, Pediatric Lymphocyte-Predominant Hodgkin Lymphoma: A Report From the Children's Oncology Group. J Clin Oncol 34 (20): 2372-9, 2016.

[9] Pediatric Hodgkin Lymphoma. NCCN Guidelines Version 3.2021

[10] Sharon M, et al Journal of Clinical Oncology 2022 40:16_suppl, 7504-7504

Diagnosis: Excisional or incisional biopsy for Immunohistochemistry evaluation.

Immunohistochemical Considerations and Ancillary Testing

- Consider clinical differential diagnoses (eg, T lymphoblastic lymphoma) and pathologic differential diagnoses: HL vs. non-Hodgkin lymphoma (NHL), CHL vs. NLPHL, HL vs. infection (cytomegalovirus [CMV], Epstein-Barr virus [EBV]), and HL vs. reactive proliferations.

- **Diagnosis is based on MORHHOLOGIC AND IMMUNOHISTOCHEMICAL findings.**
- Typical immunophenotype of HL:

CHL:
Neoplastic cells are PAX5+ (weak), **CD30+**, **CD15+**, CD3-, or CD20- (majority). This serves as an essential panel of markers for immunohistochemical evaluation of CHL. Evaluation of an expanded panel of markers (ie, CD45-, CD79a-, ALK-, MUM1+, OCT2-/weak, BOB1-/weak) should be considered in cases with equivocal or imperfect morphologic or immunophenotypic features or to exclude entities in the differential diagnosis.

NLPHL:
Neoplastic cells are **PAX5+, CD20+,** OCT2+ (strong), **CD30-, CD15-,** or CD3-. They are also CD45+, CD79a+, BCL6+, EMA+, or MUM1-/ weak.

- EBV+ CHL cases (EBV often assessed by EBER ISH) may benefit from additional studies, such as EBV serology and evaluation for underlying immunodeficiency.
- Flow cytometry is not helpful in diagnosing HL. However, it may be helpful in the evaluation of other entities in the clinical or pathologic differential diagnosis.
- There are six immunoarchitectural patterns of NLPHL and a mixture of patterns is commonly seen histologically b,2:

1. B-cell-rich nodular (pattern A)
2. Serpiginous/interconnected nodular (pattern B)
3. Nodular with prominent extranodular LP cells (pattern C)
4. T-cell-rich nodular (pattern D)
5. T-cell-rich diffuse or T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL)-like (pattern E)
6. Diffuse B-cell-rich (pattern F)

- Variant histologic patterns in NLPHL should be documented in the pathology report, where possible, as patterns C–F may be associated with higher risk of disease progression and relapse and shorter time to relapse.

Pathology Considerations in the Relapse/Refractory Disease Setting

- Pathologic confirmation is necessary to confirm relapse, particularly if >12 months after original diagnosis, given the high false-positive rate of PET-CT. Re-biopsy is also recommended for residual PET-avid disease at the end of therapy.
- If original diagnosis slides are available, limited immunohistochemical evaluation may be performed on the relapse/refractory specimen.
- For CHL cases, consider the possibility of misdiagnosis at original presentation, to consider mediastinal gray zone lymphoma and other lymphoma subtypes. For NLPHL cases, consider the possibility of diffuse large B-cell lymphoma transformation from NLPHL or reactive lymph node with progressive transformation of germinal centers.
- Prior monoclonal antibody therapy targeting CD30 (for CHL) or CD20 (for NLPHL) may result in weak or negative staining for these antigens by immunohistochemistry .
- There is insufficient data to recommend PDL1 testing by immunohistochemistry as a pre-requisite for checkpoint inhibitor therapy. Robust cut-offs for optimally predicting response to checkpoint inhibitor therapy have not been established

Workup

Essential:

- H&P including B symptoms (unexplained recurrent fever >38°C within last month; drenching night sweats; or weight loss >10% of body weight within 6 months of diagnosis) Examination of lymphoid regions, spleen
- CBC with differential
- Erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP)
- Comprehensive metabolic panel
- Echocardiogram (especially if anthracycline-based chemotherapy is indicated)
- Chest x-ray posteroanterior (PA) and lateral views (if cross-sectional imaging not available or necessitated to determine bulk of disease for a clinical trial)
- CT neck/chest/abdomen/pelvis with contrast or CT chest and MRI neck/abdomen/ pelvis
- PET/CT scan or PET/MRI
- PFTs (including diffusing capacity [DLCO] if bleomycin indicated)
- ECG
- HIV, hepatitis B/C testing (encouraged) and QuantiFERON-TB
- **Only consider bilateral bone marrow biopsy if there are cytopenias and negative PET**

Staging
Ann Arbor Staging Classification for Hodgkin Lymphoma

Stage	Description
I	Involvement of a single lymphatic site (i.e., nodal region, Waldeyer's ring, thymus, or spleen) (I); or localized involvement of a single extralymphatic organ or site in the absence of any lymph node involvement (IE).
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II); or localized involvement of a single extralymphatic organ or site in association with regional lymph node involvement with or without involvement of other lymph node regions on the same side of the diaphragm (IIE).
III	Involvement of lymph node regions on both sides of the diaphragm (III), which also may be accompanied by extralymphatic extension in association with adjacent lymph node involvement (IIIE) or by involvement of the spleen (IIIS) or both (IIIE,S).
IV	Diffuse or disseminated (multifocal) involvement of one or more extralymphatic organs or tissues, with or without associated lymph node involvement; or isolated extralymphatic organ involvement in the absence of adjacent regional lymph node involvement, but in conjunction with disease in distant site(s). Stage IV includes any involvement of the liver or bone marrow, lungs (other than by direct extension from another site), or cerebrospinal fluid.
Designations applicable to any stage	
A	No symptoms.
B	Fever (temperature >38.0ºC), drenching night sweats, unexplained loss of >10% of body weight within the preceding 6 months.
E	Involvement of a single extranodal site that is contiguous or proximal to the known nodal site.
S	Splenic involvement.

From AJCC: Hodgkin and non-Hodgkin lymphomas. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 607-11.

Bulky Disease

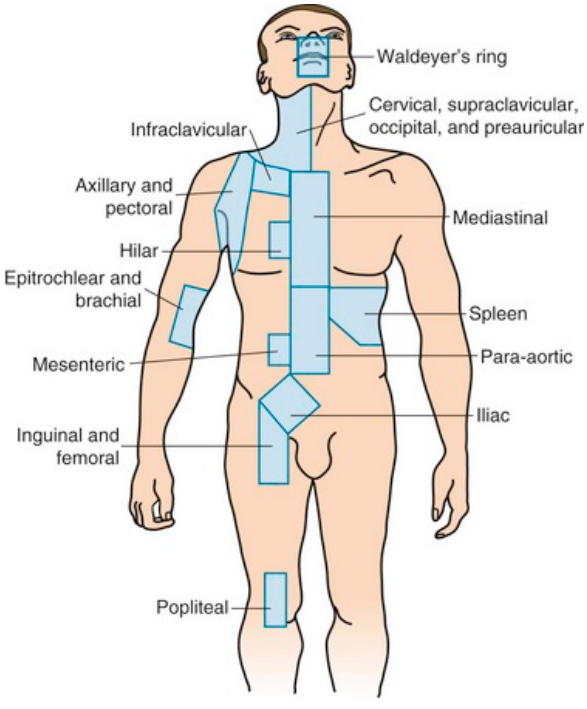
Site involvement	Definition
Peripheral nodes	• Contiguous extra-mediastinal nodal aggregate >6 cm in the longest transverse diameter (trans-axial measurement) or craniocaudal dimension (measured on reformatted CT)
Mediastinal mass	• Tumor diameter >1/3 of the maximal thoracic diameter of an upright PA chest radiograph (***portable exam is not acceptable)***

Extra nodal involvement (E)

Extra-lymphatic structures contiguous with sites of lymph node involvement are considered E-lesions (particularly lung). Exception: liver and/or bone marrow involvement is considered Stage 4.

- Pleural and pericardial effusions alone are not considered E-lesions.
- Pleural, pericardial, or chest wall infiltration by an adjacent nodal lesion that is PET positive is considered an E-lesion.

Lymph Node Anatomical Group (Lymph Node Site)



Rosenberg, S.A. (1966) Report of the committee on the staging of Hodgkin's disease. Cancer Research, 26, 1310

Regions of Nodal Involvement

Peripheral Upper Regions (indicate laterality: right or left)

- Neck: cervical (upper, lower/supraclavicular), occipital, and pre-auricular
- Infraclavicular
- Axilla
- Pectoral
- Epitrochlear
- Brachial

Central Regions

- Waldeyer's ring (including base of tongue)
- Mediastinum (anterior; hilar; cardiophrenic; subcarinal)
- Hilar
- Mesenteric
- Paraaortic (including retrocrural, portal and celiac)
- Splenic/splenic hilar

Peripheral Lower Regions (indicate laterality: right or left)

- Iliac
- Inguinal
- Femoral
- Popliteal

Other Non-Nodal Sites

- Lung (right, left, or bilateral)
- Bone
- Bone marrow

PRINCIPLES OF IMAGING

Staging or Initial Workup (should be performed within 2–4 weeks prior to initiation of therapy)

- CT neck/chest/abdomen/pelvis with contrast or CT chest and MRI neck/abdomen/pelvis
- Chest x-ray posteroanterior (PA) and lateral views (if cross-sectional imaging not available or necessitated to determine bulk of disease for a clinical trial)
- PET/CT[a,b] or PET/MRI[c] Whole-body is recommended
- Diagnostic-quality CT or MRI is still needed for initial staging

Interim and End-of-Therapy

- PET/CT[a,b] or PET/MRI[c]
- Schedule patient for appropriate evaluation timing (see protocol for details)
- Wait at least 8–12 weeks after end of RT to perform PET to minimize false-positive results.
- Diagnostic-quality CT with contrast or MRI only for original sites of disease.

Follow-up/Surveillance

- Imaging should only be obtained if significant clinical concern for relapse.
  Example: Follow-up imaging may include diagnostic-quality CT or MRI at 3- to 6-month intervals for up to 2 years.
- PET/CT[a,b] or PET/MRI is not advised due to risk of false positives.
  May consider repeat PET with persistent positive disease or equivocal finding on post-therapy PET.[a,b]

Relapsed or Refractory (confirmed or highly suspected)

- CT neck/chest/abdomen/pelvis with contrast or CT chest and MR neck/abdomen/pelvis
- PET/CT[a,b] or PET/MRI[c]

PET should be read by an experienced nuclear diagnostic radiologist experienced in reading Deauville scores for PET-adapted therapy. PET/CT should be obtained in accordance with American College of Radiology (ACR) practice guidelines.[b] In cases of PET positivity where sites of disease are inconsistent with usual presentation of Hodgkin lymphoma or if there is an unusual disease presentation (ie, HIV), additional clinical evaluation may be required to stage the patient. **See definition of involvement**. If PET negative at anatomic lesion of concern, biopsy should be considered. In most instances, if the PET/CT displays a homogeneous pattern of marrow uptake (thought to be secondary to cytokine release) bone marrow involvement is not assumed. If there are multifocal (>2–3) skeletal PET lesions without cortical destruction on CT, marrow involvement may be assumed. [c] If PET/MRI obtained, diagnostic CT of chest is needed.

Staging Considerations

- Measurable disease indicates the presence of at least one measurable lesion. Superficial lesions (e.g., palpable lymphadenopathy) measurable only by clinical exam or ultrasound are operator dependent and are not admissible as target lesions. A measurable lesion by CT is a lesion that can be accurately measured in 2 orthogonal dimensions. For extranodal sites, this typically involves lesions of at least 1 cm diameter. Lymph nodes are considered abnormal if the long axis is > 2.0 cm, regardless of the short axis. Lymph nodes with a long axis measuring between 1.0-2.0 cm are only considered abnormal if they are part of a conglomerate of nodes and are FDG-PET positive.

- Non-measurable evaluable lesions include permeative bone lesions, malignant ascites, malignant pleural/pericardial effusions, pulmonary or cutaneous lymphangitic spread, and lesions too small to accurately measure in 2 dimensions by CT. All non-target and non-measurable assessable lesions will be recorded at baseline and noted on follow-up.

Definition of disease involvement
(Based on AHOD1331 and AHOD0031)

Site involvement	Imaging modality[b, c,d]	
Peripheral nodes	PET/CT or PET/MRI	lymph node is considered involved if and only if it is FDG-PET positive. • For moderately sized (≥ 2 cm in greatest transverse diameter by CT) regardless of their location, mild and diffusely increased FDG uptake with intensity higher than that of mediastinal blood pool structures should be considered positive • For smaller masses or normal sized lymph nodes (< 2 cm in greatest transverse diameter by CT), any FDG uptake more than that of surrounding background activity should be considered positive. • ≥2 cm is considered involved on CT scan (if PET/CT is not available)
Spleen and liver or kidney	Ultrasound	• Any lesion large enough to characterize unless imaging characteristics indicate an alternative etiology
	PET/CT or PET/MRI	FDG-PET positive is defined as: a. For hepatic or splenic lesions ≥ 1.5 cm on CT, FDG uptake greater than or equal to that of normal liver or spleen parenchyma, respectively, should be considered positive. b. For hepatic or splenic lesions < 1.5 cm on CT, FDG uptake greater than that of normal liver or spleen parenchyma, respectively, should be considered positive. c. In the absence of focal splenic involvement at diagnosis, diffusely increased splenic FDG uptake greater than normal liver parenchymal FDG uptake but in the absence of lesions seen on CT will not be considered evidence of involvement. • Splenomegaly without focal lesions does not indicate splenic involvement with disease.
Lung	PET/CT	• Lung involvement is assumed if there is at least one intrapulmonary focus that is >1 cm and is PET positive or 3 or more lesions between 0.5 and 1 cm regardless of FDG-PET activity. Solitary lung nodules that are < 1 cm in transverse diameter, but are FDG avid, are also considered disease. E-lesions: Extra-lymphatic structures (lung lesions) contiguous with nodal masses are considered **E-lesions**
Bone marrow	Bilateral biopsy	• Positive by histopathology on previous high-risk trials; current trial recommendations are based on FDG-PET alone
	PET/CT or PET/MRI	• ≥3 FDG-PET–positive lesions in bone marrow without cortical bone destruction
Bone	PET/CT or PET/MRI	• Focal bone lesions that are permeative, sclerotic, or both and are PET positive are considered involved

Clinical interpretation of staging at diagnosis should not be based on reports alone. Treating clinician notes should summarize interpretation of sites of involvement prior to initiation of treatment.

[b] PET should be read by an experienced nuclear diagnostic radiologist experienced in reading Deauville scores for PET-adapted therapy.

[c] There may be PET-avid lesions that need clinical correlation to determine if it is related to lymphoma.

[f] Lewis J et al. Pediatr Blood Cancer 2020;67(4):e28142.

PET 5-POINT SCALE (DEAUVILLE CRITERIA)

Deauville 5-point scale from 1 to 5 as follows:

1) No uptake.
2) Uptake ≤ mediastinal blood pool.
3) Uptake > mediastinal blood pool and ≤ normal liver.
4) Moderately increased uptake > normal liver.
5) Markedly increased uptake > normal liver.

CLINICAL STAGING OF CLASSIC HODGKIN LYMPHOMA

Risk stratification is evolving. This table represents clinical trials with published data.

Clinical Stage	Bulk	RF	E-lesions	Treatment Group
IA IIA	No	No	No	Low risk (per EuroNet-PHL-C1)
	Yes	Yes	Yes	Intermediate risk (per AHOD0031)
IB	Yes	N/A	Yes	Intermediate risk AHOD0031
	Any	N/A	No	Intermediate risk AHOD0031
	Any	N/A	Any	Intermediate risk (per AHOD0031)
IIB	No	N/A	No	Intermediate risk per AHOD0031)
	No	N/A	Yes	Intermediate risk (per AHOD0031)
	Yes	N/A	Any	High risk (per AHOD1331)
	Yes	N/A	Yes	High risk (per AHOD1331)
IIIA	Any	N/A	No	Intermediate risk (per AHOD0031
	Any	N/A	Yes	Intermediate risk (per AHOD0031)
IIIB, IV	Any	N/A	Any	High risk (AHOD1331)

RF; Risk factors (ESR > 30 **or** bulk volume > 200 mL **or** > 3 sites of disease

Treatment for Classical HL

Organ Function Requirements

Adequate renal function defined as:

- Creatinine clearance or radioisotope GFR 70ml/min/1.73 m2 **or** A serum creatinine based on age/gender
- A serum creatinine based on age/gender as follows:

Age	**Maximum Serum Creatinine (mg/dL)**	
	Male	**Female**
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

Adequate liver function defined as:

- Total bilirubin ≤ 1.5 x normal, and
- AST or ALT < 2.5 x normal.

Adequate cardiac function defined as:

- Shortening fraction of 27% by echocardiogram
- No pathologic prolongation of QTc interval on 12-lead ECG

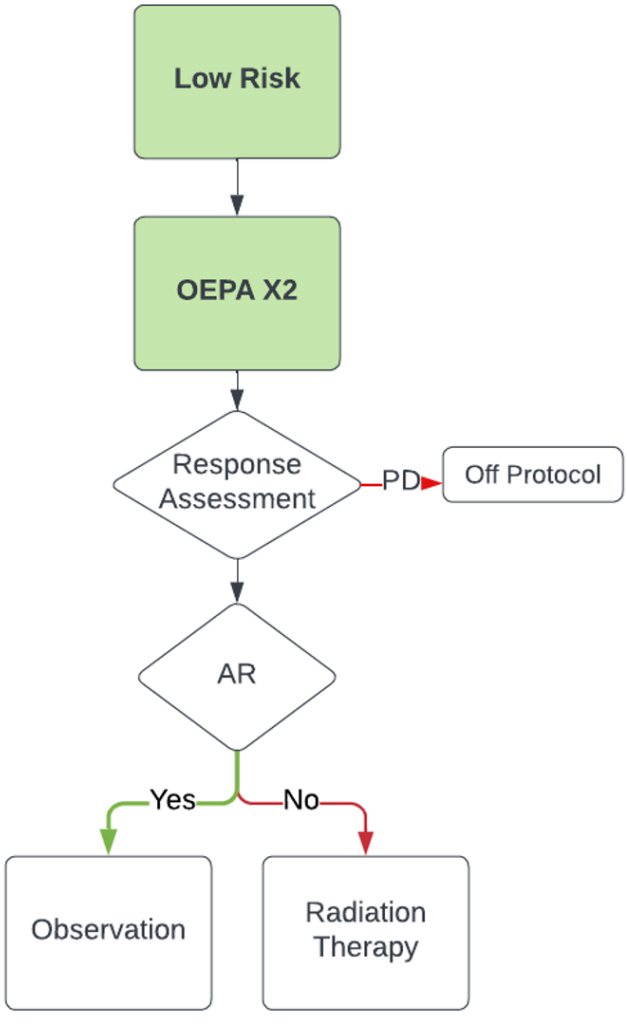
Adequate pulmonary function defined as:

- FEV1/FVC > 60% by pulmonary function test, unless due to large mediastinal mass from HD.
- For children who cannot adequately perform PFTs, no evidence of dyspnea at rest, no exercise intolerance, and a pulse oximetry > 94%. PFTs should not be attempted for children under the age of 7 years.

Low Risk

Induction treatment:

Stage IA, IIA, No bulky disease or extra-lymphatic lesion and No Risk Factors (ESR < 30; bulk volume ≤ 200 mL; < 3 sites of disease)



See Protocol for definition: AR; Adequate response **PD;** Progressive Disease

OEPA for 2 cycles (all patients) (**repeated every 28 days**)

Drug	Dose	Day(s)
VinCRIStine	1.5 mg/m2 (max dose 2 mg) IV push	1, 8 and 15
Etoposide	125 mg/m2 IV over 2 hours	Daily 1- 5
PredniSONE	30 mg/m2/dose (BID, no max dose) po	1-15
DOXOrubicin	40 mg/m2 IV (CVL over 15 min; PIV push) Days	1 and 15

Response assessment for low risk (Performed 4 weeks after the start of last cycle**)**

Recent Euro-Net C2 supports the use of PET in response assessment. Both modalities will be considered in assigning response and planning about prescription of RT**.**

Response	Definition
Inadequate response (IR)	• PET at Deauville ≥ 4 • At least one nodal site with largest diameter of ≥ 2 cm and non-assessable PET-value due to brown fatty tissue.
Adequate response (AR)	No IR criterion fulfilled
Progression	At least one initially involved mass increases by more than 25% compared to the best previous response

PET Assessment

Baseline PET (PET0) response visual threshold utilizes mediastinal blood pool as the reference activity:

 FDG-PET positive is defined as visual score 3, 4, 5.

 FDG-PET negative is defined as visual score 1, 2.

End of chemotherapy PET response visual threshold utilizes mediastinal blood pool as the reference activity:

 FDG-PET positive is defined as visual score ≥ 4

Radiation Therapy Indication

- If patient has Adequate response (AR) no RT, if inadequate response (IR) than to receive ISRT **Doses of RT (refer to RT guideline)**

Radiation Therapy timing

- Treatment should begin latest by week 5 after the last dose of chemotherapy.

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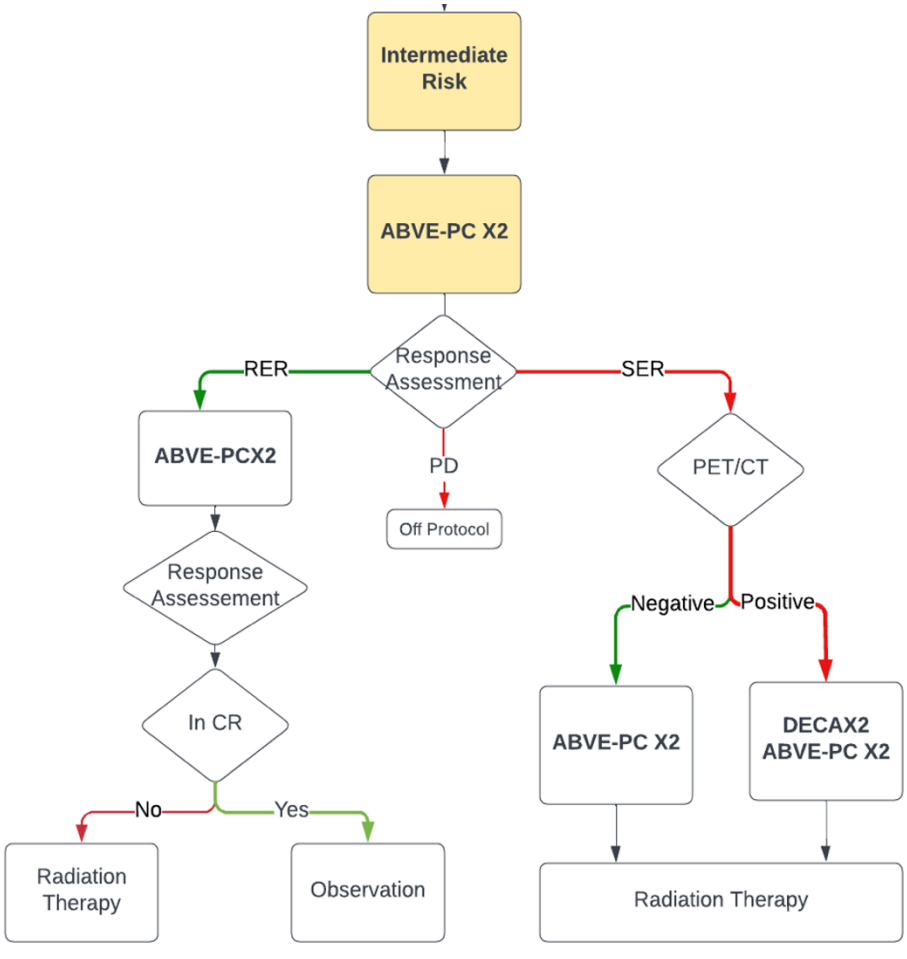
Intermediate Risk

Stage IA, IIA with Extra-lymphatic lesion or any of the risk factors (Bulky disease > 200 ml; ESR >30; or >3 sites of disease), IB and IIIA
Regimen repeated every 21 days



See Protocol for definition: RER; Rapid Early Response **SER;** Slow Early Response, **PD**; Progressive Disease

Intermediate Risk (AHOD-0031)

Drug	Dose	Day(s)
Doxorubicin	25 mg/m^2 IV	1 and 2
Bleomycin	5 U/m^2 IV Over 10 min 10 U/m^2	1 8
Vincristine	1.4 mg/m^2 IV (Max 2.8 mg)	1 and 8;
Etoposide	125 mg/m^2 IV Over 2 hour	1-3
Prednisone	40 mg/m^2 PO divided into two doses	1–7
Cyclophosphamide	800 mg/m^2 IV Over 1 hour	1

G-CSF 5 ug/kg Day +4, hold day 8 and resume day +9 till ANC > 1X10^9/L
Pegfilgrastim is permitted: Dose: 100 microgram/kg x 1 dose

Overview of Treatment Plan
All patient who meet the intermediate risk HL staging will initially receive **two cycles of 2 cycles of ABVE-PC**
To start each the ANC 0.75 $X10^9$/L (with patients off G-CSF for at least 2 days) and platelets are 75 $X10^9$/L
After Cycle 2 (approximately Days 18-22), FDG-PET will be done to determine response

Subsequent Treatment of Rapid Early Responders (RER) (See response criteria)

- At the conclusion of 2 cycles of ABVE-PC patients who have rapid early response to start two cycle ABVE-PC **(total of 4 cycles of ABVE-PC)**, those who have sustained a complete response (CR) end of therapy will not receive RT, and for those who are less than complete response (<CR) will receive RT

N.B: Exception – all patients with Large Mediastinal Adenopathy (LMA) will receive radiation therapy regardless of response.

Subsequent Treatment of Slow Early Responders (SER)

- At the conclusion of 2 cycles of ABVE-PC patients who have sustained a slow early response and negative PET/CT to start two cycle ABVE-PC followed by RT
- At the conclusion of 2 cycles of ABVE-PC patients who have sustained a slow early response and **POSITIV PET/CT** to start two cycles of DECA followed by two cycles of ABVE-PC Followed by RT

For Emergent Treatment Cycle 1 only: Patients who present with need for emergent treatment for respiratory distress or spinal cord compression may receive 4 days of Prednisone prior to completion of diagnostic work-up and before other chemotherapy agents are given. In these cases, a chest X-ray and a CT scan of the neck, chest, abdomen and pelvis must have been performed and if feasible, a biological specimen obtained for definitive diagnosis prior to the administration of Prednisone. The remainder of the diagnostic work-up should proceed as quickly as tolerated. If oral corticosteroids cannot be tolerated, methylprednisolone may be substituted at equipotent Prednisone doses. The cumulative dose of Prednisone administered for emergent respiratory distress or spinal cord compression should be considered part of the total 280 mg/m2 for this cycle. If methylprednisolone was used, the dose should be converted to prednisone-equivalent dose and this should be considered part of the total Prednisone dose noted above.

DECA for two cycles (for **SER and PET+ end of two cycles**)
Starts after 21 days from the previous cycles and if ANC 0.75 $X10^9$/L (with patients off G-CSF for at least 2 days) and platelets are 75 $X10^9$/L

Drug	Dose	Day(s)
Dexamethasone	10 mg/m2/dose IV (prior to etoposide/cytarabine)	1 and 2
Etoposide	100 mg/m2/dose IV over 2 hours	1 and 2
Cytarabine	3000 mg/m2 /dose IV over 3 hours Dexamethasone eye drops – 2 drops each eye q6h (until 24hr after completion of cytarabine)	1 and 2
Cisplatin	90 mg/m2/dose IV over 6 hours	1

(G-CSF) 5 mcg/kg/dose subcutaneous once daily (to start day 3 and continue until ANC > 1.5 x109 /L post nadir)
Pegfilgrastim is permitted: Dose: 100 microgram/kg x 1 dose

Response Assessment

Response assessment by CT

Will be based on the previously published experience with the COG HL protocols. Up to 6 target lesions will be identified at diagnosis based on size expressed as the product of the perpendicular diameters (on axial imaging).

RER is defined as CR or VGPR by CT criteria after 2 cycles of chemotherapy. In sum, these patients will have a decrease in the product of the perpendicular diameters of each of the target lesions by at least 60% **or** return to normal size with no nodal mass greater than 2cm (transverse diameter in axial plane) except for mediastinal disease where larger masses are acceptable if they have decreased by greater than 60%. There must be resolution of pathologic clinical exam findings, and resolution of liver and splenic lesions.

PET response assessment (**Performed around day 18-21 from start of cycle 2)**

PET results will be documented following 2 cycles of chemotherapy. If disease remains PET avid or PET equivocal, the PET scan should be repeated at the end of therapy to document status. See visual scoring criteria below. Residual areas of PET avidity should be considered for biopsy. Visual PET criteria are scored according to uptake involved by lymphoma from the Deauville 5-point scale from 1 to 5 as follows:

1) No uptake.
2) Uptake ≤ mediastinal blood pool.
3) Uptake > mediastinal blood pool and ≤ normal liver.
4) Moderately increased uptake > normal liver.
5) Markedly increased uptake > normal liver.

Baseline PET (PET0) response visual threshold utilizes mediastinal blood pool as the reference activity:

- PET positive is defined as visual score 3, 4, 5.
- PET negative is defined as visual score 1, 2.

Interim post Cycle 2 PET (PET2) response visual threshold uses normal liver as the reference activity (on approximately Day 18-21from start of cycle 2)

- FDG-PET positive is defined as visual score 4, 5.
- FDG-PET negative is defined as visual score 1, 2, 3.

End of chemotherapy PET response visual threshold utilizes mediastinal blood pool as the reference activity (on approximately Day 18-21from start of last cycle)

- FDG-PET positive is defined as visual score 3, 4, 5.

Splenic response

- In the instance where there is diffuse splenic uptake secondary to recent G-CSF administration the FDG-PET studies may not be of sufficient quality to adequately assess for response to therapy. In those circumstances CT criteria of macroscopic nodular should be used to assess for response to therapy. Decrease of all measurable splenic lesions by 50% in largest transverse diameter is considered a favorable response or < 1 cm is considered a favorable response. Alternative imaging with MRI or ultrasound may be used instead of or in addition to CT scan for assessment.

Response Assessment

Complete Response (CR) define as

- Resolution of pathologic palpable lymphadenopathy.
- At least 80% reduction in the PPD of each of the nodal masses including the mediastinum, or return to normal size with no residual nodal mass greater than 2.0 cm in maximal transverse diameter as measured in the axial plane on CT. Within the mediastinum, a > 2.0 cm residual nodal mass is permissible provided, the PPD has decreased by at least 80%.
- Individual nodes that were previously confluent must have regressed by more than 80% in their SPPD compared with the size of the original mass.
- Nodal masses that have not regressed at least 80% in their PPD or returned to normal size may reflect residual disease or fibrotic changes and biopsy should be considered.
- Any focal lesions of the liver or spleen or other organ considered due to lymphoma have resolved.
- No new lesion(s).
- Gallium or FDG negative.

Very Good Partial Response (VGPR)

- At least 60% reduction in the PPD of each of the areas of measurable disease, or return to normal nodal size, but not constituting a CR.
- Individual nodes that were previously confluent must have regressed by more than 60% in their SPPD compared to the size of the original mass.
- Small nodal masses that have not regressed by at least 60% in their PPD or returned to normal size may reflect lack of VGPR or fibrotic changes.
- No progression of nonmeasurable assessable disease sites.
- No new lesion(s).

Partial Response (PR)

- At least 50% reduction in the PPD of each of the areas of measurable disease, or return to
- normal nodal size, but not constituting a CR.
- Individual nodes that were previously confluent must have regressed by more than 50%
- in their SPPD compared to the size of the original mass.
- No progression of nonmeasurable assessable disease sites.
- No new lesion(s).

Stable Disease (SD)

- Less than a partial response but not progressive disease.

Progressive Disease (PD) (any of the following)

- At least 50% increase in the PPD of any of the involved nodes or nodal masses.
- At least 50% increase in the in the PPD of any of the focal organ lesions.
- New lesion(s).
- Progression of a nonmeasurable assessable disease site.

Treatment Failure

- Progressive disease anytime during therapy.
- Less than complete response with biopsy confirmed active disease at the end of therapy.
- Relapse that is biopsy confirmed anytime after the completion of therapy.

Rapid Early Responder (RER) define as

- Complete Response (CR) or very good partial response (VGPR) following 2 cycles of chemotherapy.

Slow Early Responder (SER) define as

- Less than very good partial response (<VGPR) following 2 cycles of chemotherapy.

Involved site radiation (ISRT) based on disease response:

All patients should be referred for a radiation oncology consult. Decisions regarding radiation will be based on initial stage and disease involvement and assessment of disease response.

Guidelines for radiation listed:

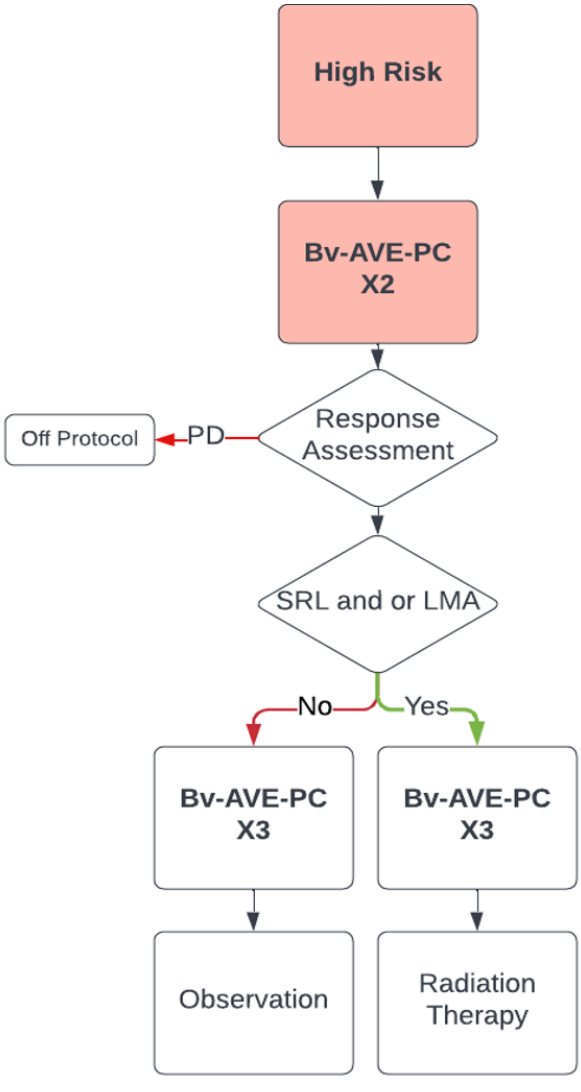
- **RER and PET negative post 2 cycles induction**: CR post 4 cycles – No Radiation
- Exception – all patients with Large Mediastinal Adenopathy (LMA) will receive radiation therapy regardless of response.
  RER and PET positive or equivocal post 2 cycles induction – will be considered for ISRT
- **SER** will receive ISRT upon completion of chemotherapy

Timing of Radiotherapy and Starting Criteria

- Treatment should begin **no later than 6 weeks** from the start of chemotherapy or when blood counts have recovered. Criteria include an ANC > 750/μL and platelets > 75,000/μL prior to treatment for each site

High Risk

Stage IIB with bulk, IIIB and IVA and IV



SRL; Slow Responding Lesion. **LMA;** Large mediastinal adenopathy (At diagnosis). **PD;** Progressive Disease

*Alternatively, in case of unavailability of Brentuximab, standard ABVE-PC could be used

High Risk (AHOD-1331)

Drug	Dose	Day (s)
Brentuximab vedotin	1.8 mg/kg/dose. (Maximum dose is 180 mg)	1 (prior to other chemotherapy)
Doxorubicin	25 mg/m^2 IV	1 and 2
Vincristine	1.4 mg/m^2 IV (Max 2.8 mg)	8
Etoposide	125 mg/m^2 IV Over 2 hour	1-3
Prednisone	20 mg/m^2 PO twice per day	1–7
Cyclophosphamide	600 mg/m^2 IV Over 1 hour	1 and 2

G-CSF 5 ug/kg Day +4, hold day 8 and resume day +9 till ANC > 1X10^9/

Pegfilgrastim is permitted: Dose: 100 microgram/kg x 1 dose

High Risk (AHOD-1331) (Alternatively, in case of unavailability of Brentuximab, standard ABVE-PC could be used)

- Regimen repeated every 21 days for 5 cycles

Drug	Dose	Day (s)
Doxorubicin	25 mg/m^2 IV	1 and 2
Bleomycin	5 U/m^2 IV Over 10 min 10 U/m^2	1 8
Vincristine	1.4 mg/m^2 IV (Max 2.8 mg)	1 and 8
Etoposide	125 mg/m^2 IV Over 2 hour	1-3
Prednisone	20 mg/m^2 PO twice per day	1–7
Cyclophosphamide	600 mg/m^2 IV Over 1 hour	1 and 2

G-CSF 5 ug/kg Day +4, hold day 8 and resume day +9 till ANC > 1X10^9/L
Pegfilgrastim is permitted: Dose: 100 microgram/kg x 1 dose

Overview of Treatment Plan

Therapy will consist of **five** cycles of ABVE-PC. Each cycle is 21 days. After Cycle 2 (approximately Days 18-22), FDG-PET will be done to determine response, patient with initial large mediastinal adenopathy and or Slowly Responding Lesion (SRL) based on interim PET after two cycles will receive RT end of therapy (see indication of RT)

For Emergent Treatment Cycle 1 only: Patients who present with need for emergent treatment for respiratory distress or spinal cord compression may receive 4 days of Prednisone prior to completion of diagnostic work-up and before other chemotherapy agents are given. In these cases, a chest X-ray and a CT scan of the neck, chest, abdomen and pelvis must have been performed and if feasible, a biological specimen obtained for definitive diagnosis prior to the administration of Prednisone. The remainder of the diagnostic work-up should proceed as quickly as tolerated. If oral corticosteroids cannot be tolerated, methylprednisolone may be substituted at equipotent Prednisone doses. The cumulative dose of Prednisone administered for emergent respiratory distress or spinal cord compression should be considered part of the total 280 mg/m2 for this cycle. If methylprednisolone was used, the dose should be converted to prednisone-equivalent dose and this should be considered part of the total Prednisone dose noted above.

Response Assessment

PET response assessment

PET results will be documented following 2 cycles of chemotherapy using the Deauville criteria (see below) Residual areas of PET avidity should be considered for biopsy.
Visual PET criteria are scored according to uptake involved by lymphoma from the Deauville 5-point scale from 1 to 5 as follows:

1) No uptake.
2) Uptake ≤ mediastinal blood pool.
3) Uptake > mediastinal blood pool and ≤ normal liver.
4) Moderately increased uptake > normal liver.
5) Markedly increased uptake > normal liver

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Baseline PET (PET0) response visual threshold utilizes mediastinal blood pool as the reference activity:

- FDG-PET positive is defined as visual score 3, 4, 5.
- FDG-PET negative is defined as visual score 1, 2.

Interim post Cycle 2 PET (PET2) response visual threshold uses normal liver as the reference activity (on approximately Day 18-21from start of cycle 2)

- FDG-PET positive is defined as visual score 4, 5.
- FDG-PET negative is defined as visual score 1, 2, 3.

End of chemotherapy PET (PET5) response visual threshold utilizes mediastinal blood pool as the reference activity *Only for those who are PET2 positive* (on approximately Day 18-21from start of cycle 5)

- FDG-PET positive is defined as visual score 3, 4, 5.

Splenic response

In the instance where there is diffuse splenic uptake secondary to recent G-CSF administration the FDG-PET studies may not be of sufficient quality to adequately assess for response to therapy. In those circumstances CT criteria of macroscopic nodular should be used to assess for response to therapy. Decrease of all measurable splenic lesions by 50% in largest transverse diameter is considered a favorable response or < 1 cm is considered a favorable response. Alternative imaging with MRI or ultrasound may be used instead of or in addition to CT scan for assessment.

Interim FDG-PET/CT After 2 cycle (PET2)

Deauville score of PET at Baseline	PET 2 result	CT with contrast result*	Interim Response Stratification
Any PET Positive Lesions**	Deauville 1, 2, 3	Mass of any size	Rapidly Responding Lesion (RRL)
Deauville 4, 5	Deauville 4, 5	< 50% increase in PPD (product of perpendicular diameter) of any of the nodal masses relative to baseline CT	Slowly Responding Lesion (SRL)
Deauville 4, 5	Deauville 4, 5	≥ 50% increase in PPD of any of the nodal masses relative to prior measurement OR appearance of new lesion(s) > 1.5 cm in any axis.	Progressive Disease (PD)
Deauville 1, 2, 3	Deauville 4, 5	Any	Progressive Disease (PD)
N/A	Deauville 3, 4, 5	**New Lesion(s)** > 1.5 cm in any axis not seen on baseline CT	Progressive Disease

** See Baseline Imaging Lesion Evaluation at Diagnosis criteria

End of Chemotherapy FDG-PET/CT (PET5) *

PET 2 result	PET 5 result	CT with contrast result	End of therapy Response
RRL and SRL	Deauville 1, 2	Mass of any size	Complete Metabolic Response (CMR)
Deauville 3	Deauville 3	< 50% increase in PPD of any of the nodal masses compared with baseline	Complete Metabolic Response (CMR)
SRL	Deauville 3, 4, 5	< 50% increase in PPD of any of the nodal	Incomplete Metabolic Response (IMR)^

		masses compared to CT 2	
RRL and SRL	Deauville 3, 4, 5	≥ 50% increase in PPD of any of the nodal masses compared to CT 2	Progressive Disease (PD)
RRL	Deauville 4, 5	Any	Progressive Disease (PD)@
N/A	Deauville 3, 4, 5	**New Lesion(s)** > 1.5 cm in any axis compared to any previous CT	Progressive Disease

* PET5 is limited to patients with Deauville ≥ 4 PET2 results. PET5 is required for any SRL (Deauville score 4, 5)

Radiation therapy

Indications for Radiotherapy for HR HL

- Initial large mediastinal adenopathy defined as Mediastinal Bulk (LMA) = transverse tumor diameter > 1/3 the thoracic diameter at the dome of the diaphragm. **All patients with LMA will receive** involved site RT (**ISRT) regardless of RRL status.**
- SRL as determined by FDG-PET scan residual avidity (Deauville score 4 or 5) after the first 2 cycles of chemotherapy (PET2) and after 5 cycles PET 5 is negative (Deauville score 1-2)
    - Radiotherapy will consist of 2100 cGy in 14 fractions of 150 cGy per day
- SRL as determined by FDG-PET scan residual avidity (Deauville score 4 or 5) after the first 2 cycles of chemotherapy (PET2) and after 5 cycles PET 5 is positive (Deauville score 3- 5)
    - For patients receiving RT (who have not been removed from study due to PD) who have PET score 3-5 at the end of chemotherapy, a boost of an additional 900 cGy in 6 fractions is to be prescribed to bring the total dose to 3000 cGy to PET avid sites.

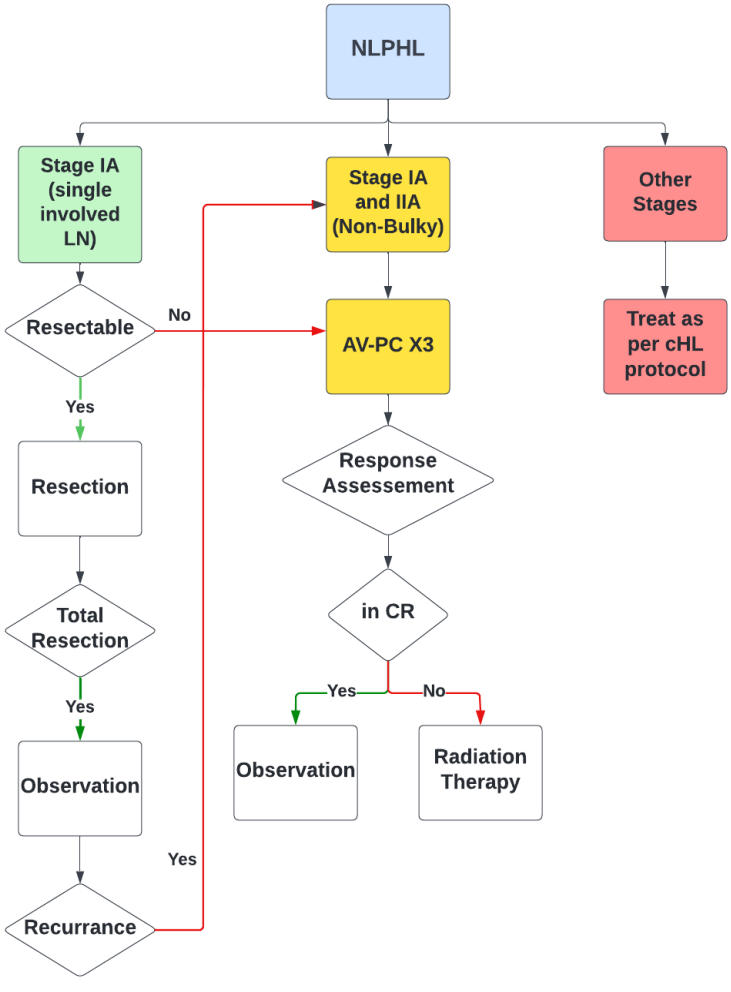
Note: Lesions which were Deauville 3 (and hence RRL by definition) at PET2 will be considered as such even if the lesions remain Deauville 3 on PET5; these lesions will **not** receive RT unless they demonstrate progression at PET5.

Timing of Radiotherapy and Starting Criteria

Treatment should begin no later than 6 weeks from the start of Cycle 5 of chemotherapy or when blood counts have recovered. Criteria include an ANC > 750/μL and platelets > 75,000/μL prior to treatment for each site.

Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL)

For stage IA and IIA (other stages will follow appropriate cHL risk stratifications)
Regimen repeated every 21 days for 3 cycles



See Protocol for definition: CR; Complete Response

Overview of Treatment Plan

Patients with stage I disease and total resection (TR) of a single involved lymph node (confirmed by CT and PET scans) proceeded to observation. If postoperative imaging was not definitive (i.e., findings consistent with either residual lymphoma or postoperative change), CT and PET scans repeated 6-7 weeks postoperatively were used to evaluate TR. Patients with TR after reimaging proceeded to observation.

Patients with stage I LPHL and more than one lymph node or stage II LPHL were treated with three cycles of AV-PC chemotherapy, given every 21 days.

Patients with a CR to chemotherapy did not receive RT. Patients with less than CR received 21-Gy involved-field/site radiation therapy; biopsy of residual adenopathy was not required.

AVPC (AHOD03P1)

Drug	Dose	Day
Doxorubicin	50 mg/m^2 IV	1
Vincristine	1.4 mg/m^2 IV (Max 2.8 mg)	1 and 8
Prednisone	20 mg/m^2 PO twice daily	1-7
Cyclophosphamide	800 mg/m^2 IV	1

Response Assessment

Complete Response (CR) define as

- Resolution of pathologic palpable lymphadenopathy.
- At least 80% reduction in the PPD of each of the nodal masses including the mediastinum, or return to normal size with no residual nodal mass greater than 2.0 cm in maximal transverse diameter as measured in the axial plane on CT. Within the mediastinum, a > 2.0 cm residual nodal mass is permissible provided, the PPD has decreased by at least 80%.
- Individual nodes that were previously confluent must have regressed by more than 80% in their SPPD compared with the size of the original mass.
- Nodal masses that have not regressed at least 80% in their PPD or returned to normal size may reflect residual disease or fibrotic changes and biopsy should be considered.
- Any focal lesions of the liver or spleen or other organ considered due to lymphoma have resolved.
- No new lesion(s).
- Gallium or FDG negative.

Very Good Partial Response (VGPR)

- At least 60% reduction in the PPD of each of the areas of measurable disease, or return to normal nodal size, but not constituting a CR.
- Individual nodes that were previously confluent must have regressed by more than 60% in their SPPD compared to the size of the original mass.
- Small nodal masses that have not regressed by at least 60% in their PPD or returned to normal size may reflect lack of VGPR or fibrotic changes.
- No progression of non-measurable assessable disease sites.
- No new lesion(s).

Partial Response (PR)

- At least 50% reduction in the PPD of each of the areas of measurable disease, or return to
- normal nodal size, but not constituting a CR.
- Individual nodes that were previously confluent must have regressed by more than 50%
- in their SPPD compared to the size of the original mass.
- No progression of non-measurable assessable disease sites.
- No new lesion(s).

Stable Disease (SD)

- Less than a partial response but not progressive disease.

Progressive Disease (PD) (any of the following)

- At least 50% increase in the PPD of any of the involved nodes or nodal masses.

- At least 50% increase in the in the PPD of any of the focal organ lesions.
- New lesion(s).
- Progression of a non-measurable assessable disease site.

Treatment Failure

- Progressive disease anytime during therapy.
- Less than complete response with biopsy confirmed active disease at the end of therapy.
- Relapse that is biopsy confirmed any time after the completion of therapy.

Involved field/ site radiation based on disease response:

All patients should be referred for a radiation oncology consult. Decisions regarding radiation will be based on initial stage and disease involvement and assessment of disease response.

Guidelines for radiation listed:

- **CR negative post 3 cycles induction**:– No Radiation
- **Less than CR-** RT

Timing of Radiotherapy and Starting Criteria

Treatment should begin no later than 6 weeks from the start of Cycle 3 of chemotherapy or when blood counts have recovered. Criteria include an ANC > 750/μL and platelets > 75,000/μL prior to treatment for each site

DOSAGE MODIFICATIONS:

Hematologic Toxicity:
Full dose chemotherapy should begin on day 21 if the ANC > 0.75 x109 /L (with patient off G-CSF for at least 2 days before a cycle of chemotherapy) and platelets are >75 x109 /L. If a patient has not recovered by day 21, check CBC at least twice weekly and begin chemotherapy as soon as hematological recovery is documented.
Patients who experience delayed neutrophil recovery and did not receive filgrastim as primary prophylaxis should be considered for secondary prophylaxis of neutropenia for subsequent cycles.

Hepatic Toxicity:
If patients has bilirubin > 1.5 x upper limit of normal (ULN) when chemotherapy is due to be given, hold chemotherapy and check bilirubin twice weekly until it is < 1.5 x ULN.

Hematuria:
Microscopic hematuria:
For transient microscopic hematuria (more than 2 abnormal urinalyses on 2 separate days during a cycle of therapy), do not modify the cyclophosphamide dose. Administer with increased hydration (3500 – 4000 mL/m2/day) using a total daily Mesna dose equal to 60 % of the daily cyclophosphamide dose.
For persistent microscopic hematuria (more than 2 abnormal urinalyses during a cycle of therapy), do not modify the cyclophosphamide dose. Administer with increased hydration (3500 – 4000 mL/m2/day) using a total daily Mesna dose equal to 100 % of the daily cyclophosphamide dose.
Gross hematuria:
For all episodes of gross hematuria, require further evaluation in consultation with urology.
For gross hematuria during or following a cycle of therapy, hold cyclophosphamide until hematuria clears. When hematuria clears, restart at 50% of the previous cyclophosphamide dose. Use hydration of 3500 – 4000 mL/m2 /day and Mesna at 100% the cyclophosphamide dose as a continuous infusion over 24 hrs. The cyclophosphamide dose may be escalated back to 100%, if tolerated, and Mesna given at 100 % as continuous infusion.
For persistent or recurrent gross hematuria on the Mesna continuous infusion regimen, discontinue cyclophosphamide.

Pulmonary:
If DLCO in any diffusion capacity test is < 50% of the initial value or predicted value or if both DLCO and FEV/FEV1 show rapid parallel decrease, obtain blood gases, discontinue further bleomycin.

Cardiac:
Patients will get an echocardiogram following 2 cycles of ABVE-PC. If the fractional shortening is < 28%, or the lower limit of institutional normal on 2 successive echocardiograms at least a week apart, the doxorubicin in the 4th cycle of therapy should be held. If at any time the patient develops signs and symptoms of congestive heart failure (i.e. pulmonary or peripheral edema,

dyspnea on exertion, poor feeding, increased liver size, deterioration in exercise tolerance or grade IV cardiac toxicity) or prolongation of QTc, which are not attributable to other causes such as sepsis or renal failure, hold doxorubicin and perform repeat ECG and echocardiogram.

Peripheral Neurotoxicity:
Toxicity grading of neurotoxicity is to be based on the modified Balis scale of peripheral neuropathy.
Vincristine should be held or reduced only for incapacitating neurotoxicity (e.g., ≥ Grade 3 by Balis Scale). Vincristine can be resumed when the symptoms have improved to Grade 1 toxicity or completely resolved. If held, the subsequent dose will be given at a 25% dose reduction (maximum dose 2.1 mg).

Constipation
Constipation or ileus (≥ Grade 3) or typhlitis: Hold vincristine dose(s); institute aggressive regimen to treat constipation if present. When symptoms improve to Grade 1 toxicity or less resume vincristine at 25% dose reduction (maximum dose 2.1 mg); escalate to full dose with subsequent courses as tolerated.

Ototoxicity:
For Grade II ototoxicity, reduce cisplatin to 45 mg/m2. For Grade III or IV ototoxicity discontinue cisplatin.

Renal toxicity:
If the calculated creatinine clearance using the Schwartz formula is < 70 mL/min/1.73 m2 hold cisplatin for 1 week. If renal function does not improve, omit cisplatin. If the calculated creatinine clearance using the Schwartz formula is greater ≥ 70 mL/min/1.73 m2 prior to the next course, cisplatin can be resumed at a 25% dose reduction If it remains < 70 mL/min/1.73 m2, omit cisplatin.

Hypersensitivity Reaction to Etoposide:
If with any dose, patient exhibits signs/symptoms of hypersensitivity reaction (HSR) in relation to administration of etoposide the infusion should be discontinued and appropriate treatment per institutional guidelines initiated. If additional doses of etoposide are scheduled for the patient to complete therapy, Etoposide phosphate (Etopophos) should be substituted at equivalent doses. Pretreatment will consist of patient's first morning scheduled treatment steroid dose (prednisone or dexamethasone according to applicable cycle for patient) and diphenhydramine 1 mg/kg IV or PO. Appropriate monitoring for HSR signs/symptoms should be instituted during the Etoposide phosphate infusion with emergency anaphylactic treatment available. Drug administration should be discontinued and appropriate treatment instituted should a reaction also occur with this product. No further doses of Etoposide or Etoposide phosphate should be attempted.

Hypersensitivity Reaction to Bleomycin:
If with any dose, patient exhibits signs/symptoms of HSR in relation to administration of bleomycin the infusion should be discontinued and appropriate treatment and supportive care given. If additional doses of bleomycin are scheduled for the patient to complete therapy, pretreatment will consist of patients' first morning scheduled treatment prednisone dose and

diphenhydramine 1mg/kg IV or PO. Appropriate monitoring for HSR signs/symptoms should be instituted during the bleomycin infusion with emergency anaphylactic treatment available. Drug administration should be discontinued and appropriate treatment instituted should a reaction also occur with this product. No further doses of bleomycin should be attempted.

Brentuximab Vedotin

Treatment Modification Guidelines for brentuximab vedotin-related Adverse Events are outlined in the tables below.

Dose Level Dose

Starting Dose	1.8mg/kg (max dose 180 mg)
Dose Reduction for Toxicity #1	1.2mg/kg (max dose 120 mg)
Dose Reduction for Toxicity #2	0.8mg/kg (max dose 80mg)

Event	CTCAE.v4.0 Grade	Action to be Taken
Allergic reactions, or Acute infusion reactions/ cytokine release syndrome	Grade 1-2	**For first reaction:** • Hold the infusion and wait 30 to 60 minutes (depending upon the reaction severity). • Treat reactions with diphenhydramine 1 mg/kg (max50 mg) or follow local institution guidelines. Depending on the reaction severity, dexamethasone 0.2 mg/kg (max10 mg) or equivalent corticosteroid IV should be used. • Upon resolution of the symptoms, at the physician's discretion, it may be possible to resume treatment by administering an H2 blocker such as ranitidine or famotidine approximately 30 minutes before restarting the infusion. Acetaminophen can also be considered. Resume brentuximab vedotin infusion at half the previouslyadministered rate until completion **For subsequent doses:** • Utilize diphenhydramine with or without acetaminophenas pre-treatment for all subsequent infusions. • Dosing should be administered over the shortest period that was well tolerated. **If Grade 1-2 infusion reactions recur despite the above measures, either during re-challenge or subsequent treatments:** • Take the measures outlined above. • With subsequent dosing, add dexamethasone 0.2 mg/kg (max 10 mg) IV or equivalent to medications above priorto infusion.

	Grade 3	• Stop infusion immediately. • Administer diphenhydramine 1 mg/kg IV (max 50 mg), dexamethasone 0.2 mg/kg (max 10 mg) IV (or equivalent), bronchodilators for bronchospasms, and other medicationsas medically indicated. • Once symptoms recover, brentuximab vedotin should not be resumed for that cycle. • Subsequent cycles of brentuximab vedotin may be considered at physicians' discretion, after a discussion and • approval by CTEP • All subsequent infusions should use the following pre-medications prior to infusion, acetaminophen, diphenhydramine 1 mg/kg IV (max 50 mg), dexamethasone 0.2 mg/kg (max 10 mg) IV (or equivalent). In addition, the infusion should be administered at 50% of the previous infusion rate.
	Grade 4	• Stop infusion immediately. • Administer diphenhydramine 1 mg/kg (max 50 mg) IV, dexamethasone 0.2 mg/kg (max 10 mg) IV (or equivalent), and other anaphylaxis medications as indicated. • Epinephrine or bronchodilators should be administered as indicated. • Hospital admission for observation may be indicated. • Permanently discontinue brentuximab vedotin.

Anaphylaxis	Any Grade	• If anaphylaxis occurs, immediately and permanently discontinue administration of brentuximab vedotin and administer appropriate medical therapy.
Pancreatitis	Grade 2	• Withhold dose until toxicity has returned to baseline, then continue protocol therapy but should resume at one dose reduction. • If Grade 2 pancreatitis recurs after one dose reduction, the patient must be removed from protocol therapy.
	Grade 3-4	• Permanently discontinue brentuximab vedotin.

Peripheral Neuropathy
Use The modified Bails scale of to grade peripheral neuropathy and to use dose level adjustment based on toxicity grade

Dose Level	Dose
Starting Dose	1.8 mg/kg (max dose 180 mg)
Dose Reduction for Toxicity #1	1.2 mg/kg (max dose 120 mg)
Dose Reduction for Toxicity #2	0.8 mg/kg (max dose 80 mg)

Peripheral Neuropathy	Grade 1*		• Continue at same dose level.
	Grade 2*	Day 1	• Continue Brentuximab vedotin at same dose level. Day 8 vincristine of this cycle should be dose reduced to 1 mg/m^2 (max 2 mg) or held if already dose reduced on a prior cycle. Increase vincristine to full dose with next cycle if neuropathy improves to ≤ Grade 1.
		Day 8	• Decrease vincristine to 1 mg/m^2 (max 2 mg). If neuropathy has improved to ≤ Grade 1 by Day 8 of the next cycle, then resume vincristine at full dose.
	Grade 3*	Day 1	• Treatment should be delayed up to 1 week after all other parameters to proceed are met to see if neuropathy improves to ≤ Grade 2. If neuropathy returns to ≤ Grade 2 then proceed with next cycle and reduce brentuximab vedotin by one dose level (see above). If neuropathy remains Grade 3, then brentuximab vedotin should be held for this cycle and then reduced by one dose level for subsequent treatments assuming neuropathy has returned to ≤ Grade 2. • Day 8 vincristine should be held for this and all subsequent cycles. • Patients who develop Grade 3 neuropathy after 2 dose reductions of brentuximab vedotin, will have brentuximab vedotin discontinued. If treatment must be delayed for peripheral neuropathy more than once, then brentuximab vedotin should be held for the remainder of treatment.
		Day 8	• Hold vincristine for this and all subsequent cycles.
	Grade 4*		• Discontinue brentuximab vedotin and vincristine.
Pneumonitis	Grade 1		• Continue at same dose level.

	Grade 2	• If suspected, strongly consider administration of oral or intravenous corticosteroid in single daily or two divided doses. The suggested dose for patients who develop pulmonary toxicity is methylprednisolone 1 mg/kg IV every 12 hours for a minimum of seven days.
	Grade 3-4	• If suspected, strongly consider administration of oral or intravenous corticosteroid in single daily or two divided doses. The suggested dose for patients who develop pulmonary toxicity is methylprednisolone 1 mg/kg IV every 12 hours for a minimum of seven days. • Discontinue brentuximab vedotin.
Progressive Multifocal Leukoencephalopathy (PML)	Any Grade	If PML is suspected, a diagnostic work-up should be performed. The work-up may include, but not limited to, the following: • Neurologic examinations and neurology consultation, as warranted. • Brain MRI. Features suggestive of PML include presence of unifocal or multifocal lesions, mainly of the white matter, that are typically non-enhancing and do not have mass effect. • PCR analysis. JCV DNA, detectable in CSF or in a brain biopsy, is suggestive of PML. Brentuximab vedotin dosing should be held if any grade of PML is suspected. If PML is confirmed, brentuximab vedotin should be permanently discontinued
Lymphopenia	Grade 1-4	• Continue at same dose level.
Neutropenia	Grade 1-2	• Continue at same dose level.
	Grade 3-4	• Patients who are unable to start a cycle > 35 days after the start of the previous cycle (> 14 day delay) with myeloid growth factor support due to neutropenia with no other dose-limiting toxicity should have brentuximab vedotin reduced by 1 dose level.
Thrombocytopenia	Grade 1-2	• Continue at same dose level.
	Grade 3-4	• Thrombocytopenia is expected on this protocol. Continue at current dose level.
Non-hematologic events (not including electrolyte abnormalities)	Grade 1-2	• Continue at same dose level.
	Grade 3-4	• Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline, then continue on protocol therapy but should resume at one dose reduction. • If same non-hematological Grade 3-4 toxicity recurs after one dose reduction, brentuximab vedotin should be omitted.

Electrolyte Abnormalities	Grade 1-4	• Continue at same dose level, provided electrolyte toxicity is not medically consequential and has been readily corrected. • If electrolyte abnormality is medically consequential, refer to guidelines above for non-hematologic events.

MODIFIED ("BALIS") PEDIATRIC SCALE OF PERIPHERALNEUROPATHIES

Peripheral Motor Neuropathy:

Grade 1: Subjective weakness, but no deficits detected on neurological exam, other than abnormal deeptendon reflexes.
Grade 2: Weakness that alters fine motor skills (buttoning shirt, coloring, writing or drawing, using eatingutensils) or gait without abrogating ability to perform these tasks.
Grade 3: Unable to perform fine motor tasks (buttoning shirt, coloring, writing or drawing, using eatingutensils) or unable to ambulate without assistance.
Grade 4: Paralysis.

Peripheral Sensory Neuropathy:

Grade 1: Paresthesias, pain, or numbness that do not require treatment or interfere with extremity function.
Grade 2: Paresthesias, pain, or numbness that are controlled by non-narcotic medications (without causingloss of function), or alteration of fine motor skills (buttoning shirt, writing or drawing, using eating utensils) or gait, without abrogating ability to perform these tasks.
Grade 3: Paresthesias or pain that are controlled by narcotics, or interfere with extremity function (gait, fine motor skills as outlined above), or quality of life (loss of sleep, ability to perform normal activities severely impaired).
Grade 4: Complete loss of sensation, or pain that is not controlled by narcotics

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End of therapy evaluation and Surveillance

H&P:
▪ Every 3–4 months for 1–2 years,
▪ then every 6–12 months until year 3,
▪ then annually until 5 years
Laboratory studies:
▪ CBC with differential, ESR or CRP, chemistry profile as clinically indicated.
▪ Thyroid-stimulating hormone (TSH) at least annually if RT to neck.
▪ Consider PFTs (if bleomycin, pulmonary RT, significant pulmonary involvement, or other clinical concerns)
Imaging
▪ Consider end of therapy ECHO.
▪ Imaging studies are only recommended when relapse is suspected, because most patients will clinically declare themselves and there is no survival advantage in pre-emptive imaging.
▪ If clinical concern, CT with contrast or MRI of original sites of disease may be performed and followed at 3- to 6-mo intervals up to 2 y following completion of therapy. MRI is acceptable in place of CT scan for neck/abdomen/pelvis, but not for chest; diagnostic CT of chest is needed.
▪ PET/CT or PET/MRI if previous PET was positive (Deauville 3–5), to confirm complete response (CR) at end of all prescribed therapy including RT. Once negative, repeat PET should not be done unless evaluating suspicious findings on H&P or CT or MRI.
▪ Wait at least 8–12 weeks after end of RT to perform PET to minimize false-positive results.
▪ Surveillance PET is not recommended due to risk for false positives.
Monitoring for Late Effects (≥2 years after completion of systemic therapy) **Children's Oncology Group Survivorship Guidelines)**

Principle of radiation

All cases of Hodgkin lymphoma should be referred early on to radiation therapy, appropriate discussion should be done to review response, radiation field and dose

General Principles

- Treatment with photons, electrons, or protons may all be appropriate, depending on clinical circumstances.
- In specific instances, advanced RT technologies may be used to spare important organs at risk (OARs) and decrease the risk for late normal tissue damage while still achieving the primary goal of local tumor control.
- OARs: heart (including coronary arteries, valves, and left ventricle), lungs, kidneys, spinal cord, esophagus, carotid arteries, bone marrow, breasts, stomach, muscle/soft tissue, and salivary glands.
- Advanced technologies include intensity-modulated RT (IMRT)/volumetric modulated arc therapy (VMAT), breath hold or respiratory gating and/or image-guided RT (IGRT), or proton therapy may offer significant and clinically relevant advantages.
- Dose-sparing for OARs reflects best clinical practice, as it reduces the risk of late complications from normal tissue damage. Achieving highly conformal dose distributions is especially important for patients who are being treated with curative intent or who have long life expectancies following therapy.

PRINCIPLES OF RADIATION THERAPY

In general, RT fields and doses should be delivered per protocol guidelines used for systemic therapy. As Involved-site RT (ISRT) showed to be effective in reduction of radiation field without compromising response, it should be considered in all risk-response therapy for children with HL. All risk group will follow AHOD1331 radiation dose and field. For low and Intermediate risk ISRT delivered to involved sites, while for high risk (due to large involvement sites) response-adaptive ISRT will be used. Patient with Large Mediastinal Adenopathy will receive radiation regardless response.

Risk Stratification	RT Indication	RT dose		RT field
Low-Risk	Patient not in CR post two cycles	21 Gy in 14 fractions of 1.5 Gy per day to all sites *	Treatment should begin latest by week 5 after the last dose of chemotherapy.	ISRT
Intermediate-Risk	**RER** not in CR after 4 cycles ALL patients with Large Mediastinal Adenopathy (LMA) will receive radiation therapy regardless of response.	21 Gy in 14 fractions of 1.5 Gy per day to all sites.	Treatment should begin later than 6 weeks from the start of last chemotherapy or when blood counts have	ISRT

	SER will receive ISRT upon completion of chemotherapy		recovered. Criteria include an ANC > 750/µL and platelets > 75,000/µL prior to treatment for each site	
High-Risk	Initial large mediastinal adenopathy defined as Mediastinal Bulk (LMA) = transverse tumor diameter > 1/3 the thoracic diameter at the dome of the diaphragm. **All patients with LMA will receive** involved site RT **(ISRT) regardless of RRL status.** SRL as determined by FDG-PET scan residual avidity (Deauville score 4 or 5) after the first 2 cycles of chemotherapy (PET2) and after 5 cycles PET 5 is negative (Deauville score 1-2) **Note:** Lesions which were Deauville 3 (and hence RRL by definition) at PET2 will be considered as such even if the lesions remain Deauville 3 on PET5; these lesions will **not** receive RT unless they demonstrate progression at PET5.	Radiotherapy will consist of 21 Gy in 14 fractions of 1.5 Gy per day. For SRL as determined by FDG-PET scan residual avidity (Deauville score 4 or 5) after the first 2 cycles of chemotherapy (PET2) and if after 5 cycles **PET 5 is positive (Deauville score 3- 5)** a boost of an additional 9 Gy in 6 fractions is to be prescribed to bring the total dose to 30 Gy to PET avid sites.	Treatment should begin no later than 6 weeks from the start of Cycle 5 of chemotherapy or when blood counts have recovered. Criteria include an ANC > 750/µL and platelets > 75,000/µL prior to treatment for each site	ISRT
NLPHL	< CR after cycle 3	21 Gy in 14 fractions of 1.5 Gy per day to all sites.	No later than 6 weeks from the start of Cycle an ANC > 750/µL and platelets > 75,000/µL prior to treatment	ISRT

*Due to major differences in RT dose and field in Euro-Net compared to COG protocols, we will follow COG radiation guidelines for all risk groups.