COG-AHOD2131: A Randomized Phase 3 Interim Response Adapted Trial Comparing Standard Therapy with Immuno-oncology Therapy for Children and Adults with Newly Diagnosed Stage I and II Classic Hodgkin Lymphoma

FAST FACTS
Eligibility Reviewed and Verified By
_____ MD/DO/RN/LPN/CRA Date _____
_____ MD/DO/RN/LPN/CRA Date _____
Consent Version Dated_____

PATIENT ELIGIBILITY:
Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical research record which will serve as the source document for verification at the time of audit.

___1. Timing
Study enrollment must take place within five (5) calendar days of beginning protocol therapy. If enrollment takes place before starting therapy, the date protocol therapy is projected to start must be no later than **five (5)** calendar days after enrollment.

All laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.

___2. PRO/HRQoL Timing
Immediately upon study consent, age- and language-eligible participants should be asked to complete the Quality of Life Contact Information Form found in Appendix XII-A. The information collected in this form is required for administration of assessments by the PRO/HRQoL team via planned electronic data capture. We strongly encourage sites to scan and upload this form to Medidata Rave within 24 hours of enrollment to ensure timely completion of the baseline instruments.

Please note that the first PRO/HRQoL assessment (T0) must be completed prior to start of protocol therapy. See Section 14.1 for complete PRO/HRQoL eligibility, administration, and timing details.

___3. Callback for Treatment Assignment and Randomization
There will be a callback procedure performed during this study. The callback is performed after completion of the initial 2 cycles of ABVD and PET2 scan. The callback will:
1. Assign favorable risk, RER patients to Arm A or B
2. Assign favorable risk, SER patients to Arm C or D
3. Assign unfavorable risk, RER patients to Arm E or F
4. Assign unfavorable risk, SER patients to Arm G or H

___4. **Laboratory Studies**
The following laboratory studies must be repeated prior to the *start of protocol therapy* if >28 days have elapsed from their most recent prior assessment: CBC with differential, bilirubin, ALT (SGPT) and serum or plasma creatinine. Laboratory tests need not be repeated if therapy starts within twenty-eight (28) days of their most recent prior assessment.

If the result of a laboratory study that is repeated at any time *post-enrollment* and prior to the *start of protocol therapy* is outside the limits for eligibility, then the evaluation must be rechecked within 48 hours prior to initiating protocol therapy. The results of the recheck must be within the limits for eligibility to proceed. If the result of the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy.

___5. **Clinical Studies**
Clinical studies (eg, cardiac imaging, pulmonary function tests), if applicable, must be obtained within 42 days prior to *enrollment* and *start of protocol therapy* (repeat if necessary).

___6. **Disease/Staging Imaging**
Disease/staging imaging studies, if applicable, must be obtained within 42 days prior to *enrollment* and *start of protocol therapy* (repeat if necessary).

___7. Age
Patients must be 5 to 60 years of age at the time of enrollment.

___8. Diagnosis
- Patients with newly diagnosed untreated histologically confirmed classic Hodgkin lymphoma (cHL) (nodular sclerosis, mixed cellularity, lymphocyte-rich, or lymphocyte-depleted, or not otherwise specified (NOS)) with Stage I or II disease.
- Patients must have bidimensionally measurable disease (at least one lesion with longest diameter ≥ 1.5 cm).
- Patients must have a whole body or limited whole body PET scan performed within 42 days prior to enrollment. PET-CT is strongly preferred. PET-MRI allowed if intravenous contrast enhanced CT is also obtained.
- Pediatric patients (age 5-17 years) must have an upright PA CXR for assessment of bulky mediastinal disease. Adult patients must have either a CXR or CT chest.

___9. Performance Score
- Patients ≥ 18 years must have a performance status corresponding to Zubrod scores of 0, 1 or 2.
- Patients ≤ 17 years of age must have a Lansky performance score of ≥ 50.

See Appendix IV for details.

___10. Organ Function Requirements
Please note that eligibility criteria and the timing of documentation prior to enrollment differ by age.
- Adequate renal function defined as:
  - For pediatric patients (age 5-17 years):
    - 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

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR utilizing child length and stature data published by the CDC.
*Plasma creatinine is also acceptable.

OR - a 24 hour urine Creatinine clearance ≥ 50 mL/min/1.73 m^2

OR - a GFR ≥ 50 mL/min/1.73 m^2. GFR must be performed using direct measurement with a nuclear blood sampling method OR direct small molecule clearance method (iothalamate or other molecule per institutional standard).

Note: Estimated GFR (eGFR) from serum or plasma creatinine, cystatin C or other estimates are not acceptable for determining eligibility.

  - For adult patients (age 18 years or older):

Creatinine clearance ≥ 30 mL/min, as estimated by the Cockcroft and Gault formula or a 24-hour urine collection. The creatinine value used in the calculation must have been obtained **within 28 days** prior to registration. Estimated creatinine clearance is based on actual body weight.

$$\text{Estimated creatinine clearance} = \frac{(140 - \text{age}) \times \text{weight in kg}\ \dagger}{72 \times \text{creatinine*}\ (\text{mg/dl})}$$

Multiply this number by 0.85 if the participant is a female.

† The kilogram weight is the participant weight with an upper limit of 140% of the ideal body weight (IBW).
* Actual lab serum or plasma creatinine value with a minimum of 0.7 mg/dL.

- Adequate liver function* defined as:
  - Total bilirubin ≤ 2 x ULN, and
  - AST and ALT ≤ 3 x ULN
    * unless due to Gilbert's disease, lymphomatous involvement of liver or vanishing bile duct syndrome

- Adequate cardiac function defined as:
  - Shortening fraction of ≥ 27% by echocardiogram (ECHO), MUGA, or functional cardiac imaging scan
    or
  - Ejection fraction of ≥ 50% by radionuclide angiogram, ECHO, MUGA, or cardiac imaging scan.

- Adequate pulmonary function defined as:
  - DLCO ≥ 50% of predicted value as corrected for hemoglobin by pulmonary function test (PFT)
  - If unable to obtain PFTs, the criterion is: a pulse oximetry reading of > 92% on room air.

___11. HIV Status
Known HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

___12. HBV and HCV Status
For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

Assent: The CIRB has determined that assent of children age 14 and older is a necessary condition for proceeding with the research.

Note: This trial has a protocol supplied wallet card that is required to be provided to the patient. See Appendix XI.

EXCLUSION CRITERIA

___1. Patients with nodular lymphocyte predominant Hodgkin Lymphoma.

___2. Patients with a history of active interstitial pneumonitis or interstitial lung disease.

___3. Patients with a diagnosis of inherited or acquired immunodeficiency that is poorly controlled or requiring active medications, such as primary immunodeficiency syndromes or organ transplant recipients

___4. Patients with any known **uncontrolled** intercurrent illness that would jeopardize the patient's safety such as infection, autoimmune conditions, cardiac arrhythmias, angina pectoris, and gastrointestinal disorders affecting swallowing and/or absorption of pills.

___5. Patients with a condition requiring systemic treatment with either corticosteroids (defined as equivalent to > 10 mg daily prednisone for patients ≥ 18 years or > 0.5 mg/kg (up to 10 mg/day) for patients < 18 years) or other immunosuppressive medications within 14 days prior to enrollment.

Note: Replacement therapy such as thyroxine, insulin, or physiologic corticosteroid for adrenal or pituitary insufficiency is not considered a form of systemic treatment. Inhaled or topical steroids, and adrenal replacement doses (≤ 10 mg daily for patients ≥ 18 years or ≤ 0.5 mg/kg (up to 10 mg/day) prednisone equivalents are permitted in the absence of active autoimmune disease.

Note: Steroid use for the control of Hodgkin lymphoma symptoms is allowable, but must be discontinued by Cycle 1, Day 1.

___6. Patients with peripheral neuropathy > Grade 1 at the time of enrollment or patients with known Charcot-Marie-Tooth syndrome.

___7. Patients with a prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of the investigational regimen.

___8. Prior Therapy

- Administration of prior chemotherapy, radiation, or antibody-based treatment for cHL.
- Prior solid organ transplant.
- Prior allogeneic stem cell transplantation.
- Live vaccine within 30 days prior to planned Day 1 of protocol therapy (e.g., measles, mumps, rubella, varicella, yellow fever, rabies, BCG, oral polio vaccine, and oral typhoid). Administration of mRNA vaccines are permitted.

Please see Section 4.1 for the concomitant therapy restrictions for patients during treatment.

___9. Pregnancy and Breastfeeding,

- Female patients who are pregnant since fetal toxicities and teratogenic effects have been noted for several of the study drugs. A pregnancy test within 28 days prior to enrollment is required for female patients of childbearing potential.
- Lactating females who plan to breastfeed their infants starting with the first dose of study therapy and for at least 6 months after the last treatment.
- Sexually active patients of reproductive potential who have not agreed to use a highly effective contraceptive method (failure rate of < 1% per year when used consistently and correctly) for the duration of their study drug therapy. Following therapy, patients will be advised to use contraception as per institutional practice or as listed below for investigational agents, whichever is longer.

  Men and women of childbearing potential must continue contraception for a period of 6 months after last dose of brentuximab vedotin.

  Women of child-bearing potential (WOCBP) must continue contraception for a period of at least 5 months after the last dose of nivolumab.

REQUIRED OBSERVATIONS:

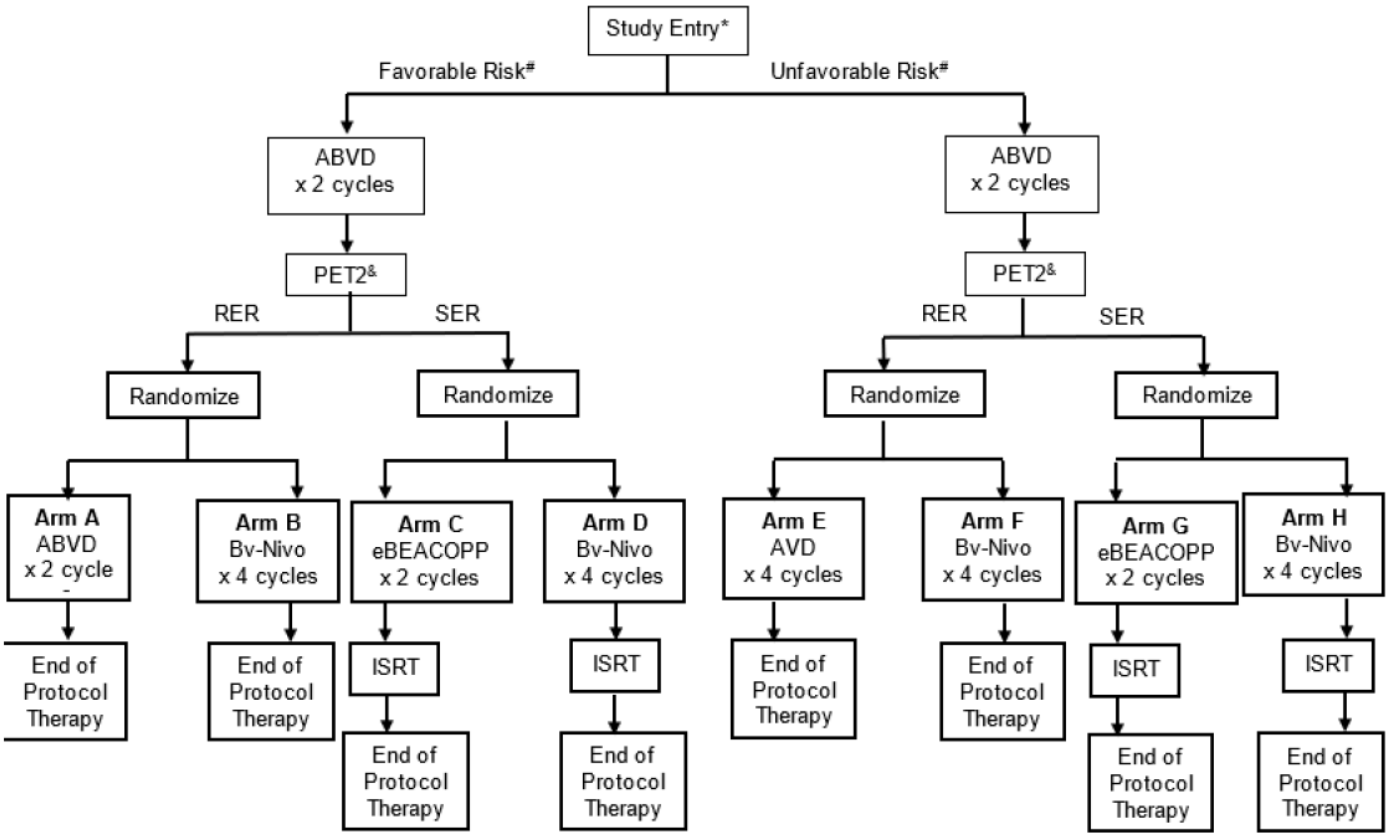
Required Observations – All Arms – ABVD, Cycles 1-2

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

a. Targeted history and physical with systems examined (including height and weight)
b. Performance status (see Appendix IV)
c. CBC, differential and platelets. Note: CBC with differential includes WBC count, hemoglobin, platelet count, absolute neutrophil count (ANC), and absolute lymphocyte count (ALC).
d. CMP. Note: CMP includes electrolytes (sodium, potassium, chloride, bicarbonate (CO_2)), albumin, serum or plasma creatinine or calculated creatinine clearance, and liver function tests (total bilirubin, SGOT [AST], SGPT [ALT], and alkaline phosphatase).
e. Erythrocyte sedimentation rate. Cycle 1 only.
f. Pregnancy test performed at baseline and then per institutional standards. Female patients only.
g. HIV viral load and CD4 count. Cycle 1 only. Note: Only if patient is known HIV positive.
h. HBV core antibody, and HBV surface antigen, and HCV antibody. If HBV core antibody or surface antigen positive, HBV viral load should be obtained. If HCV core antibody is positive, HCV viral load should be obtained. Cycle 1 only.
i. PRO-CTCAE or Ped PRO-CTCAE. See Section 14.1.
j. FACT-G item GP5. See Section 14.1.
k. FDG-PET. Prior to Cycle 1, and Cycle 2, Days 18-22. Note: Prior to Cycle 1, FDG-PET/CT scans are preferred; if PET-MRI obtained, a baseline IV contrast enhanced CT is also required. Imaging modalities should be consistent throughout all of treatment and follow up. See Section 16.0. Note: Images must be submitted for rapid central review. See Section 16.5.1 for instructions and Section 16.5.3 for timeline information.
l. ECHO, MUGA, or functional cardiac imaging scan. Prior to Cycle 1 and per institutional guidelines thereafter, if clinically indicated.
m. CXR (PA) for patients < 18 years; CXR or CT chest for patients ≥ 18 years. Prior to Cycle 1 only.
n. Pulmonary function test (or pulse oximetry if unable to get PFTs). Cycle 1 only.
o. PROMIS Health Status Profile + Cognition. See Section 14.1.
p. Self-reported Demographic & Baseline SDOH. Cycle 1 only. See Section 14.2.
q. Samples for banking (optional, consent required). See Section 15.0.

TREATMENT PLAN:
This is a randomized trial comparing an IO approach with or without radiation therapy to a standard chemotherapy approach with or without radiation therapy in early stage cHL. All patients will be stratified by favorable vs. unfavorable features at study enrollment. Patients are considered unfavorable if they have one or more of the following factors: (1) large mediastinal mass (> 10 cm by CT or 1/3 max chest diameter by CXR), (2) > 3 nodal sites, (3) B symptoms with ESR > 30, (4) ESR > 50 without B symptoms, and (5) age > 50 years.

EXPERIMENTAL DESIGN SCHEMA



*Eligible patients should complete a QoL contact information form at study entry to allow for the timely delivery of PRO/HRQoL assessments. See Section 3.1.5 for details.
#See Section 4.1 for details. Patients are considered to have unfavorable disease if they have one or more of the following factors: (1) large mediastinal mass (> 10 cm by CT or 1/3 max chest diameter by CXR), (2) > 3 nodal sites, (3) B symptoms with ESR > 30, (4) ESR > 50 without B symptoms, and (5) age > 50 years.
&Rapid central review will be performed on these scans. See Section 16.5.1.
ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine
AVD: doxorubicin, vinblastine, dacarbazine
Bv: Brentuximab vedotin
Nivo: Nivolumab
eBEACOPP: Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine
ISRT: Involved-site radiotherapy
RER: Rapid early response. See definition in Section 10.4.1.1.
SER: Slow early response. See definition in Section 10.4.1.1.
PET2: FDG-PET scans after 2 cycles of ABVD.

TOXICITIES AND DOSAGE MODIFICATIONS:
See Section 5.0

Central Review of Imaging Studies
Central review of images will be performed to confirm institutional reporting of staging and early response.

Rapid Central Review
Rapid (real time) central review to assess response will be done after the second cycle of ABVD chemotherapy for all patients and at the completion of chemotherapy or immunotherapy for patients who had a positive PET2.

Copies of all imaging studies at the following time points should be submitted as they are performed:

- Baseline (all patients; PET1)
- After 2 cycles of ABVD chemotherapy (all patients; PET2)
- After end of systemic therapy (SER patients only; PET-EST SER)

In this study, we will incorporate real-time central-review qualitative FDG PET using the 5-PS criteria into response-adapted treatment algorithms as an integral imaging biomarker for risk-stratification in cHL. All patients will undergo FDG PET at baseline (PET1), post cycle 2 (PET2), and for all SER patients after systemic treatment and prior to any external-beam radiation therapy (PET-EST). Visual PET review of interim scans (PET2) will be done in real-time with central-review using the 5-PS. Scores 1-3 will be considered PET-negative; scores 4 and 5 will be considered PET-positive.

Institutional imaging reports and the AHOD2131 Staging and Response Worksheet should be submitted with these scans. **Sites are encouraged to submit baseline scans directly after enrollment to confirm that all baseline scans required for the central imaging review are available and of adequate quality**.

Also see Section 16.5.4

RADIATION THERAPY TREATMENT PLAN SUBMISSION:
See Section 17.12

OPTIONAL BIOBANKING:
See Section 15.1 and Appendix VIII and IX