COG-AHOD1331: A Randomized Phase 3 Study of Brentuximab Vedotin (SGN-35, IND #117117) for Newly Diagnosed High-Risk Classical Hodgkin Lymphoma (cHL) in Children and Young Adults

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 - Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than five (5) calendar days after the date of study enrollment. All clinical and laboratory studies to determine eligibility must be performed within 14 days prior to enrollment unless otherwise indicated in the eligibility section below.

___2. Randomization - Randomization will take place at the time a patient is enrolled via OPEN. The patient will be randomly assigned 1:1 to Bv-AVEPC arm or ABVE-PC arm. Randomization will be stratified by clinical characteristics (Stage IIB with bulk vs. Stage IIIB vs. Stage IVA vs. Stage IVB).

___3. **All clinical and laboratory studies to determine eligibility must be performed within 14 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than fourteen (14) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within fourteen (14) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are > 14 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT), albumin and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies and bone marrow evaluations must be obtained within 21 days prior to start of protocol therapy. Repeat the tumor imaging if necessary (see Section 14.3). Histologic core bone marrow biopsy is required in children < 18 years of age regardless of FDG-PET results. Exceptions to the bone marrow requirement in cases of patients with airway compromise, can be applied if adequate documentation of contraindication to the procedure is noted. However, bone marrow can be obtained after the initiation of emergency steroid therapy in such cases as per Section 4.2 and Section 4.3.**

___4. Ages > 2 - < 22 years at the time of enrollment.

___5. Patients with newly diagnosed, pathologically confirmed cHL meeting one of the following Ann Arbor stages are eligible:

- Stage IIB with bulk*
- Stage IIIB
- Stage IVA
- Stage IVB

Bulk is defined in Appendix I. **If study eligibility by staging is uncertain, consultation with IROC RI may be obtained prior to study enrollment.**

___6. Organ Function Requirements

- Adequate Renal Function Defined As:
  - Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m^2 or
  - 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 (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

- Adequate Liver Function Defined As:
  - Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
  - SGOT (AST) or SGPT (ALT) < 2.5 x upper limit of normal (ULN) for age.
- Adequate Cardiac Function Defined As:
  - Shortening fraction of ≥ 27% by echocardiogram, or
  - Ejection fraction of ≥ 50% by radionuclide angiogram.
- Adequate Pulmonary Function Defined As:
  - FEV1/FVC > 60% by pulmonary function test (PFT), unless due to large mediastinal mass from HL.
  - For children who are unable to cooperate for PFTs, the criteria are: no evidence of dyspnea at rest, no exercise intolerance, and a pulse oximetry reading of > 92% on room air.

EXCLUSION CRITERIA

___1. Patients with nodular lymphocyte-predominant HL.
___2. Patients with an immunodeficiency that existed prior to diagnosis, such as primary immunodeficiency syndromes, organ transplant recipients and children on current systemic immunosuppressive agents are not eligible.
___3. Patients who are pregnant. (Since fetal toxicities and teratogenic effects have been noted for several of the study drugs, a negative pregnancy test is required for female patients of childbearing potential).
___4. Lactating females who plan to breastfeed.
___5. Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation and for 30 days after the last dose of chemotherapy.
___6. Patients known to be positive for HIV are not eligible.
___7. Patients who have received any previous chemotherapy or radiation therapy are not eligible.
___8. Patients who received systemic corticosteroids within 28 days of enrollment on this protocol, except as specified (See Section 4.2), are not eligible.

REQUIRED OBSERVATIONS:
Required Clinical, Laboratory and Disease Evaluations
STUDIES TO BE OBTAINED

- History and physical, including nodal exam **(Day 1 of cycle unless otherwise indicated)**
- CBC/differential, electrolytes, BUN, creatinine, AST or ALT, and bili.
- Albumin
- ESR (Erythrocyte Sedimentation Rate)
- Tumor biopsy/Pathology Report
- Bilateral bone marrow biopsy*
- ECG
- ECHO or MUGA
- PFTs [A], DLCO if > 5 years
- CXR (PA lateral)**
- CT with IV contrast **
- Flurodeoxyglocose Imaging** (FDG-PET) [B]
- Pregnancy test [C]
- Tissue for Correlative Biology
- Patient demographics @ (CIPN study)
- FACT-GOG-Ntx@ (CIPN study)
- CHRIS-Global@ (CIPN study)
- TNS-PV@ (Limited Institutions) CIPN
- Health Utility Index 2/3# (CEA)
- Stanford Healthcare Utilization# (CEA)
- Caregiver Work Limitation(CEA)

A. Pulmonary Function Tests (PFTs) to include Forced Vital Capacity (FVC); Total Lung Capacity (TLC); Functional Residual Capacity (FRC); Carbon Monoxide Diffusing Capacity (DLCO) corrected for anemia, Residual Volume (RV) and Peak Flows (PIF, PEF).
B. PET0 is baseline FDG-PET/CT. PET2 is interim FDG-PET/CT obtained between Days 18-22 of Cycle 2 of either therapy arm.
C. Women of childbearing potential require a negative pregnancy test prior to starting treatment; males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method during protocol therapy and for at least 30 days after the last dose of chemotherapy. Abstinence is an acceptable method of birth control.
@ See Appendix VII for CIPN and Quality of Life study Parent or patient reported outcomes (CIPN): **Baseline is prior to chemotherapy . Also obtain at Day 8 of Cycles 2 and 5.**
 # See Appendix VIII for Cost Effective Analysis (CEA) study. Baseline is prior to chemotherapy. Also obtain at Day 8 of cycles 2 and 5.
***** Baseline required for children < 18 years old; recommended (not required) in adults ≥ 18. After Cycles 2, 5: in any age patient if positive at previous biopsy.
** Baseline chest radiograph must be upright CXR with a PA view (portable AP is not acceptable). See Section 14.4 for imaging central review requirements. See Section 15.13 for quality assurance documentation that must be submitted prior to start of RT.
$ Tissue for patients who Consent to the Biology Studies should be submitted as per Section 13.0. Also see Section 7.2: if no block is available, 10 unstained slides and 2 H&E slides should be obtained for the Correlative Biology studies.

NOTE: This table only includes evaluations necessary to answer the primary and secondary aims. Obtain other studies as indicated for good clinical care.

TREATMENT PLAN:
Therapy will consist of **five** cycles of ABVE-PC or Bv-AVEPC. Each cycle is 21 days. After Cycle 2 (approximately Days 18-22), FDG-PET will be done to determine response. Upon central review, individual lesions will be defined as rapidly responding lesions (RRL) if the Cycle 2 FDG-PET is negative, defined as Deauville score less than or equal to 3 (less than or equal to that of liver). See Table 10.3.1

Experimental therapy consists of 5 cycles of Bv-AVEPC. Each cycle is 21 days in duration. Each cycle commences on Day 1 if the ANC ≥ 750/μL and platelets are ≥ 75,000/μL. **Response will be determined by central review.**

All doses will be based on actual body surface area or weight (where applicable). Only brentuximab vedotin, vincristine and colony stimulating factor doses will be capped.

Brentuximab vedotin*: IV over 30 minutes
Day 1 (prior to other chemotherapy)
Dose: 1.8 mg/**kg/dose.** (Maximum dose is 180 mg based on manufacturer prescribing information and 100 kg maximum weight)

***Brentuximab vedotin is supplied by the NCI and should not be dispensed from regular (commercial) pharmacy supply.**

Dosing is based on patient weight according to the institutional standard. Actual weight will be used except for patients weighing greater than 100 kg. The dose for patients with weight greater than 100 kg will be calculated based on 100 kg.

DOSAGE MODIFICATIONS:
See Section 5.0

SPECIMEN REQUIREMENTS:
For those consenting to tissue biology studies, the diagnostic/pre-treatment requirements are:

- 1 block or 10 unstained and 2 H&E stained slides
- 0.5 g frozen tumor
- No more than 40ml blood in green top heparin tubes

Also see Section 7.2.