

COG-ANHL1931: A Randomized Phase 3 trial of Nivolumab (NSC#748726 IND#125462) in Combination with Chemo-immunotherapy for the Treatment of Newly Diagnosed Primary Mediastinal B-cell 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

Patients must be enrolled before ANHL1931 protocol 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 for patients starting protocol treatment with Cycle 1. Patients starting protocol treatment at Cycle 2 must start protocol therapy no later than **twenty-one (21)** calendar days after the date of study 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. Randomization

Randomization will take place only after a patient is enrolled via OPEN. The treatment will be randomly assigned based on the statistical design of the trial.

___ 3. Laboratory Studies

All laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Viral serologies must be performed within 21 days prior to enrollment.

Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy.

Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are greater than seven (7) days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) 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.

Clinical Studies

Clinical studies (eg cardiac imaging, pulmonary function tests), if applicable, must be obtained within 21 days prior to enrollment and start of protocol therapy (repeat if necessary). ECHO, if applicable, must be obtained within 28 days prior to enrollment and start of protocol therapy (repeat if necessary).

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

For patients who enroll after completion of one cycle of chemo-immunotherapy, clinical studies including imaging obtained before the start of chemo-immunotherapy will be acceptable.

___ 4. Age

Age \geq 2 years

___ 5. Diagnosis

Patient must have histologically confirmed primary mediastinal B-cell lymphoma (PMBCL) as defined by WHO criteria

___ 6. Performance Level

ECOG performance status of 0, 1, or 2 or ECOG performance status of 3 if poor performance is related to lymphoma

- COG Institutions: Use Karnofsky for patients \geq 17 and $<$ 18 years of age and Lansky for patients $<$ 17 years of age. See “Performance Status Scales Scoring.”

7. Organ Function Requirements

- Adequate renal function defined as:

Adults (age 18 or older):

- Creatinine clearance ≥ 30 mL/min, as estimated by the Cockcroft and Gault formula. 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.

$$\text{Estimated creatinine clearance} = \frac{(140 - \text{age}) \times \text{wt (kg)} \times 0.85 \text{ (if female)}}{72 \times \text{creatinine (mg/dl)}}$$

Pediatric Patients (age < 18 years):

The following must have been obtained **within 14 days** prior to registration:

- Measured or calculated (based on institutional standard) creatinine creatinine clearance or radioisotope GFR ≥ 70 ml/min/1.73 m², or
- Serum creatinine ≤ 1.5 x institutional upper limit of normal (IULN), 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 utilizing child length and stature data published by the CDC.

- Patients with abnormal liver function will be permitted if chemotherapy can still be delivered with standard dose reductions
- Adequate cardiac function defined as:
 - Age ≥ 18 years:**
 - Ejection fraction of $\geq 50\%$ by echocardiogram
 - Age <18 years:**
 - Shortening fraction of $\geq 27\%$ by echocardiogram, or
 - Ejection fraction of $\geq 50\%$ by radionuclide angiogram.
- Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.
- 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.

The required age of Assent is 14.

EXCLUSION CRITERIA:

- ___ 1. Prior Therapy
Administration of prior anti-cancer therapy except as outlined below:
 - a) A short course (≤ 2 weeks) of corticosteroids for the relief of lymphoma-related symptoms.
 - b) A single course of COP (cyclophosphamide, vincristine, and prednisone)
 - c) One cycle of chemo-immunotherapy including R-CHOP, DA-EPOCH-R, or a pediatric mature B-NHL induction therapy (such as ANHL1131) that has not started more than 21 days prior to enrollment.
- ___ 2. Active ischemic heart disease or heart failure.
- ___ 3. Active uncontrolled infection
- ___ 4. CNS involvement of lymphoma.
- ___ 5. Patients with a prior or concurrent malignancy whose natural history or treatment has the potential to interfere with safety or efficacy assessment of this trial.
- ___ 6. Active autoimmune disease that has required systemic treatment (such as disease modifying agents, corticosteroids, or immunosuppressive agents) in the past 2 years. Replacement therapy such as thyroxine, insulin or physiologic corticosteroid for adrenal or pituitary insufficiency is not considered a form of systemic treatment.
- ___ 7. In patients < 18 years of age Hepatitis B serologies consistent with past or current infections
- ___ 8. Pregnancy and Breastfeeding
 - a) Female patients who are pregnant since fetal toxicities and teratogenic effects have been noted for several of the study drugs. A pregnancy test is required for female patients of childbearing potential.
 - b) 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 participation.
 - c) Lactating females are not eligible unless they have agreed not to breastfeed their infants starting with the first dose of study therapy and for at least 6 months after the last dose of rituximab.

INDUCTION STRATIFICATION FACTORS:

Randomization will take place only after a patient is enrolled via OPEN. The treatment will be randomly assigned based on the statistical design of the trial.

CENTRAL MONITORING PLAN

Central monitoring will be required for the first patient enrolled at each site. All documents must be uploaded within 2 weeks of the corresponding time point or cycle.

REQUIRED OBSERVATIONS:

DA-EPOCH-R +/- Nivolumab

Required Observations: DA-EPOCH-R Cycles 1-6

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

- Physical exam with vital signs, height and weight. Note: Height is only required at the beginning of this cycle. If there is a >10% change in weight, BSA will be recalculated prior to each cycle.
- CBC, differential and platelets. Baseline and twice weekly three days apart until counts recover for Cycles 1-5.
- AST, ALT, bilirubin (total and direct). Baseline and prior to each cycle.
- Electrolytes, calcium, magnesium, phosphate. Baseline and prior to each cycle.
- Pregnancy test. Female patients of childbearing potential require a negative pregnancy test prior to starting each cycle.
- Hep B surface Ab, surface Ag, Core Ab; Hep C Ab. Baseline only.
- Performance status. Baseline only.
- LDH. Baseline only.
- HIV (optional). Baseline only.
- Echocardiogram and ECG. Baseline and per institutional guidelines thereafter, if clinically indicated
- Lumbar puncture, CSF cell count with cytospin. Optional at baseline only, not required.
- Unilateral bone marrow biopsy and aspirate. Optional at baseline. If performed at baseline and positive, this should be repeated after Cycle 2 and 6.
- CT-chest, abdomen, pelvis. Only performed if the following circumstances: at baseline if PET/CT not feasible; after cycle 2 if PET/CT not performed; **after cycle 2 and after Cycle 6 if response on PET/CT at these timepoints is categorized as Deauville score 4 or 5 (should be obtained within 7 business days of PET/CT but Cycle 3 should not be delayed).**
- PET/CT. Required at baseline and after Cycle 6. Optional PET/CT after cycle 2. Optional PET/CT after cycle 4 in patients for whom imaging after cycle 2 demonstrates increase in SUV from baseline without increase in tumor size by CT measurements (see [Section 10.5](#)).
- **If randomized to Nivolumab**: TSH. Baseline and prior to every cycle. If TSH is abnormal T3 and FT4 should be evaluated.

R-CHOP +/- Nivolumab

Required Observations: R-CHOP Cycles 1-6

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

- Physical exam with vital signs, height and weight. Note: Height is only required at the beginning of this cycle. If there is a >10% change in weight, BSA will be recalculated prior to each cycle.
- CBC, differential and platelets. Baseline and prior to each cycle.
- AST, ALT, bilirubin (total and direct). Baseline and prior to each cycle.
- Electrolytes, calcium, magnesium, phosphate. Baseline and prior to each cycle.
- Pregnancy test. Female patients of childbearing potential require a negative pregnancy test prior to starting each cycle.
- Hep B surface Ab, surface Ag, Core Ab; Hep C Ab. Baseline only.
- Performance status. Baseline only.
- LDH. Baseline only.
- HIV (optional). Baseline only.
- Echocardiogram and ECG. Baseline and per institutional guidelines thereafter, if clinically indicated
- Lumbar puncture, CSF cell count with cytospin. Optional at baseline only, not required.
- Unilateral bone marrow biopsy and aspirate. Optional at baseline. If performed at baseline and positive, this should be repeated after Cycle 2 and 6.
- CT-chest, abdomen, pelvis. Only performed if the following circumstances: at baseline if PET/CT not feasible; after cycle 2 if PET/CT not performed; **after cycle 2 and after Cycle 6 if response on PET/CT at these timepoints is categorized as Deauville score 4 or 5 (should be obtained within 7 business days of PET/CT but Cycle 3 should not be delayed).**
- PET/CT. Required at baseline and after Cycle 6. Optional PET/CT after cycle 2. Optional PET/CT after cycle 4 in patients for whom imaging after cycle 2 demonstrates increase in SUV from baseline without increase in tumor size by CT measurements (see [Section 10.5](#)).
- **If randomized to Nivolumab**: TSH. Baseline and prior to every cycle. If TSH is abnormal T3 and FT4 should be evaluated.

TREATMENT PLAN:

Note: It is strongly recommended that physicians choose DA-EPOCH-R for pediatric patients less than 18 years of age given the lack of data for R-CHOP in this age group.

Therapy will consist of 6 cycles of chemo-immunotherapy with or without nivolumab. Each cycle is 21 days. Radiation is permitted at the completion of cycle 6 if dictated by the protocol (see below). Prior to randomization +/- nivolumab, physicians will choose one of three treatment backbones: 1) DA-EPOCH-R, 2) R-CHOP with RT only in the setting of biopsy positive disease after 6 cycles, 3) R-CHOP with RT regardless of response at end of therapy. Patients will then be randomized 1:1 to receive chemo-immunotherapy alone or chemo-immunotherapy + nivolumab. Following randomization, the patient may potentially be on one of the following six treatment arms:

Arm A: DA-EPOCH-R

Arm B: DA-EPOCH-R + nivolumab

Arm C: R-CHOP

Arm D: R-CHOP + nivolumab

Arm E: R-CHOP + radiotherapy

Arm F: R-CHOP + radiotherapy + nivolumab

As of amendment #2, all patients less than 18 years of age who are enrolled and those currently receiving therapy will receive the updated Nivolumab dosing.

Patients with prior thoracic radiotherapy for a prior cancer (including breast cancer) should not be enrolled onto arms E and F.

TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5

SPECIMEN REQUIREMENTS:

Rationale

To maintain the integrity of the trial and to provide quality control of tissue for downstream correlatives, retrospective central pathology will be performed to confirm diagnosis and assess tissue quality tumor content. Pathology review results will not be returned to the site. A 5% discrepancy rate between central of local read is anticipated, potentially affecting final analysis of primary and secondary endpoints or power calculations.

Specimen requirements

- One H&E stained slide from each representative block from diagnostic biopsy
- One representative paraffin block of tissue or 10 unstained (4 micron thick) sections on charged slides
- Transmittal form
- Copy of all pathology reports for each case including the final pathology diagnosis report, immunophenotyping reports and any results of genomic studies, FISH studies or cytogenetic analysis

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

BIOLOGY REQUIREMENTS:

See Section 14.0.

- 40 mL green top Na Hep
- 20 mL cell free DNA Streck tubes