

**COG-ANHL12P1: A Randomized Phase 2 Trial of Brentuximab Vedotin or Crizotinib
in Combination with Chemotherapy for Newly Diagnosed Patients
with Anaplastic Large Cell Lymphoma (ALCL)**

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. 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. **Patients who are started on protocol therapy on a phase II study prior to study enrollment will be considered ineligible.**
- ___2. **All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. 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 > 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. Imaging studies, if applicable, must be obtained within 2 weeks prior to start of protocol therapy (repeat the tumor imaging if necessary).**
- ___3. Patient must be < 22 years of age at the time of study enrollment.
- ___4. Diagnosis
 - Newly diagnosed patients with histologically proven ALCL (ICD-0 code: 9714/3).
 - Disease must be CD30 positive.
 - Disease must be ALK positive (defined by local institutional standards).
 - Patients must have Stage II, III, or IV disease (see [Appendix I](#) for staging).
- ___5. Patients must have a life expectancy of ≥ 8 weeks.
- ___6. Organ Function Requirements
 - Adequate Liver Function Defined As:
 - Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN) for age.
 - ALT (SGPT) $< 2.5 \times$ upper limit of normal (ULN) for age. For the purpose of this study, the ULN for ALT is 45 U/L.
 - If the lab abnormality is thought to be due to the lymphoma the patient is eligible and dose adjustments should be made ([See Section 5.0](#)).
 - Adequate Cardiac Function Defined As:
 - Shortening fraction of $\geq 27\%$ by echocardiogram, or
 - Ejection fraction of $\geq 50\%$ by radionuclide angiogram.
 - Adequate Pulmonary Function Defined As:
 - Patients with a history of pulmonary dysfunction must have no evidence of dyspnea at rest, no exercise intolerance due to pulmonary insufficiency, and a pulse oximetry $> 92\%$ while breathing room air unless current dysfunction is due to the lymphoma in which case the patient is eligible.

RANDOMIZATION FACTORS:

Randomization will take place at the time a patient is enrolled via OPEN. Eligible patients will be stratified as follows:

- **Stratum 1:** Patients with BSA ≥ 0.9 m²
- **Stratum 2:** Patients with BSA < 0.9 m²

Eligible patients in Stratum 1 will be randomized (1:1) to Arm BV or Arm CZ. Eligible patients in Stratum 2 will be non-randomly assigned to Arm BV because crizotinib is only available in certain strengths.

Two exceptions to randomization:

- 1) If one arm is temporarily closed, patients will be non-randomly assigned to the other arm.
- 2) If Arm BV is temporarily closed and the patient is < 0.9 m², then the patient is not eligible for the study.

EXCLUSION CRITERIA:

- ___1. Patients with CNS disease are not eligible.
- ___2. Patients with disease limited to the skin are not eligible, regardless of how wide-spread.
- ___3. Patients with Stage I disease are not eligible.
- ___4. Patients who have received any prior cytotoxic chemotherapy for the current diagnosis of ALCL or any cancer diagnosed previously are not eligible.
- ___5. Previous steroid treatment and/or radiation treatment is not allowed unless it is for the emergent management of a mediastinal mass. Emergent steroid treatment and/or radiation treatment should stop once protocol therapy is initiated.
- ___6. Intrathecal chemotherapy prior to enrollment is allowed for the current diagnosis of ALCL as long as adequate CSF is obtained prior to administration of the intrathecal chemotherapy and subsequently demonstrated to be negative for ALCL.
- ___7. Female patients who are pregnant are not eligible due to risks of fetal and teratogenic adverse events. Pregnancy tests must be obtained in girls who are post menarchal.
- ___8. Lactating females are not eligible unless they have agreed not to breastfeed their infants.
- ___9. Sexually active patients of reproductive potential are not eligible unless they agree to use an effective contraceptive method for the duration of treatment and for 3 months after stopping treatment.
- ___10. Patients with Down syndrome are not eligible due to the amount of methotrexate and potential for side effects.
- ___11. Patients with an immunodeficiency that existed prior to diagnosis such as primary immunodeficiency syndromes or organ transplant recipients are not eligible.
- ___12. CYP3A4 Substrates with Narrow Therapeutic Indices: Patients chronically receiving medications known to be metabolized by CYP3A4 and with narrow therapeutic indices including pimozone, aripiprazole, triazolam, ergotamine and halofantrine are not eligible. The topical use of these medications (if applicable) is allowed. [See Appendix IV.](#)
- ___13. CYP3A4 Inhibitors: Patients chronically receiving drugs that are known potent CYP3A4 inhibitors within 7 days prior to study enrollment, including but not limited to ketoconazole, itraconazole, clarithromycin, erythromycin, ritonavir, indinavir, nelfinavir, saquinavir, delavirdine, nefazodone, diltiazem, verapamil, and grapefruit juice are not eligible. The topical use of these medications (if applicable), e.g. 2% ketoconazole cream, is allowed. [See Appendix IV.](#)
- ___14. CYP3A4 Inducers: Patients chronically receiving drugs that are known potent CYP3A4 inducers within 12 days prior to study enrollment, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, ritonavir, and St. John's wort are not eligible. The topical use of these medications (if applicable) is allowed. [See Appendix IV.](#)
- ___15. Patients that are known to be positive for HIV are not eligible.
Note: Inclusion of HIV positive patients will be considered at a later date.
- ___16. Patients who weigh < 10 kg are not eligible.

REQUIRED OBSERVATIONS:

STUDIES TO BE OBTAINED

- History
- Physical Exam (Ht, Wt, BSA, Vital Signs)
- Pregnancy Test ¹; Uric Acid, LDH
- Performance Status
- CBC, differential, platelets
- Electrolytes including Ca⁺⁺, PO₄, Mg⁺⁺
- Cr, Bilirubin, AST (SGOT), ALT (SGPT)
- Total protein, Albumin
- Urinalysis
- Bone Marrow Aspirate/Biopsy (Bilateral)
- CSF
- Echocardiogram and EKG
- CXR (PA + Lateral)
- CT or MRI (primary site and neck/chest/abd/pelvis)
- Bone Scan (For patients with bone primary disease only)
- FDG-PET Scan (highly recommended - not mandatory)
- **Blood for MRD**
 - ^{1.} 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.

TREATMENT PLAN:

See Section 4.

Note: Prophylactic anticoagulation is required for patients on Arm CZ due to the potential risk of thromboembolic events (see Section 2.6).

Concomitant Therapy Restrictions

Strong inducers or inhibitors of CYP3A enzymes should be avoided. See Appendix IV for full list.

TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5

SPECIMEN REQUIREMENTS:

See Section 13.2 for Optional Central Pathology Review

BIOLOGY REQUIREMENTS:

Required MDD/MRD peripheral blood studies at baseline, Day 6 and End of Cycle 1: 15 mL in EDTA. Collect on weekdays for M-F delivery. Also see Section 13.4.