**COG-AAML1331: A Phase III Study for Patients with Newly Diagnosed Acute Promyelocytic Leukemia (APL) using Arsenic Trioxide and All-Trans Retinoic Acid**

***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. 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.

___2. CLINICAL RQ-PCR Testing
Specimens for RQ-PCR of PML-RARα are required and must be obtained prior to Day 1 of protocol directed therapy (pre-treatment with ATRA allowed). These specimens must be sent to one of the approved labs for PML-RARα RQ-PCR testing but the cost is not covered by the study. It should be billed as a regular clinical lab through the institution/insurance/patient as appropriate. A list of approved labs is available on the protocol-specific web page of the COG website located at https://cogmembers.org/PROT/AAML1331/AAML1331ValidatedRQ-PCRLabsList.pdf

___3. Emergent Treatment

- A diagnosis of APL is a hematologic emergency and treatment with ATRA should be initiated without waiting for confirmatory genetic testing if there is a clinical suspicion of the diagnosis. Up to 5 days of ATRA pre-treatment, prior to start of protocol directed therapy, is allowed. Of note, if the patient is later determined to have non-APL AML they could remain eligible for the COG study of non-APL AML (AAML1031) since ATRA pre-treatment is also allowed on AAML1031.
- In patients with standard risk disease (WBC < 10,000/μL), ATRA should be started at time of first suspicion of APL diagnosis and then ATO given (when available) on Day 1 of protocol directed therapy.
- In patients with high risk disease (WBC ≥ 10,000/μL at diagnosis), ATRA should be started at time of first suspicion of APL diagnosis. Idarubicin and ATO should be given on Day 1 of protocol therapy. If an institution does not have ATO available on Day 1 when idarubicin is given, it will not be a protocol violation to start protocol directed therapy with idarubicin and ATRA as long as the ATO is started within 48 hours of the first idarubicin dose.

**___4. 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.**

___5. Patient must be ≥ 12 months and < 22 years of age at first diagnosis of APL.

___6. Diagnosis

- Patients must be newly diagnosed with a clinical diagnosis of APL (initially by morphology of bone marrow or peripheral blood).
  Bone marrow is highly preferred but in cases where marrow cannot be obtained at diagnosis, peripheral blood will be accepted.
- If the RQ-PCR results are known at the time of study enrollment, the patient must demonstrate the PML-RARα transcript by RQ-PCR to be eligible.

**NOTE: A lumbar puncture is not required in order to be enrolled on study nor are lumbar punctures recommended at the time of diagnosis.** If the diagnosis of APL is known or suspected, diagnostic lumbar punctures in patients with neurologic symptoms should be deferred until any coagulopathy is corrected. If CNS disease is suspected or proven, a CT or MRI should be considered to rule out the possibility of an associated chloroma. If CNS disease is documented, patients are still eligible and will receive protocol directed intrathecal treatments.

___7. Prior Therapy
- Patients may receive up to a maximum of 5 days of pre-treatment with ATRA prior to administration of protocol therapy.
- Treatment with hydroxyurea, corticosteroids (any route) and intrathecal cytarabine prior to beginning protocol directed therapy is allowed. However, it should be noted that lumbar puncture and intrathecal therapy at initial diagnosis of APL is not recommended due to the possible complications of coagulopathy.
- Please see Section 4.1.3 for concomitant therapy restrictions for patients during treatment.

___8. The CIRB has determined that assent of children 14 and older is a necessary condition for proceeding with the research.

**EXCLUSION CRITERIA:**

___1. Secondary APL
Patients with secondary APL are excluded. This includes all patients with APL that may have resulted from prior treatment (chemotherapy or radiation).

___2. Isolated Myeloid Sarcoma
Patients with isolated myeloid sarcoma (myeloblastoma, chloroma, including leukemia cutis) but without evidence of APL by bone marrow or peripheral blood morphology are excluded.

___3. EKG Abnormalities
- Patients with a pre-existing diagnosis of a prolonged QT syndrome (even if QTc is normal at the time of APL diagnosis) are excluded due to the use of arsenic trioxide, which can prolong the QT interval.
- Patients with a baseline QTc of > 450 msec are excluded. Bazett's formula is to be used for measurement of the corrected QT interval: the QT interval (msec) divided by the square root of the RR interval (msec).
- Patients with a history or presence of significant ventricular or atrial tachyarrhythmia are excluded.
- Patients with right bundle branch block plus left anterior hemiblock, bifascicular block are excluded.

___4. Renal Dysfunction
Patients with serum creatinine > 3.0 mg/dL and patients on active dialysis for renal dysfunction are excluded.

___5. Prior Chemotherapy
Patients who have received treatment with any other cytotoxic chemotherapy prior to beginning protocol therapy (other than allowed in Section 3.2.3) are excluded.

___6. Pregnancy and Breast Feeding
- Female patients who are pregnant are excluded. Treatment under this protocol would expose an unborn child to significant risks. Patients should not be pregnant or plan to become pregnant while on treatment. **There is an extremely high risk of fetal malformation if pregnancy occurs while on ATRA in any amount, even for short periods.**
  A pregnancy test prior to enrollment is required for female patients of childbearing potential.
- Lactating females who plan to breastfeed their infants are excluded.
- Sexually active patients of reproductive potential who have not agreed to be abstinent or use 2 forms of effective contraception during treatment through 1 month off therapy are excluded.

**REQUIRED OBSERVATIONS:**

Required Observations in Induction – Standard and High Risk APL

**All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.** Obtain other studies during Induction as indicated on the road map.

Prior to starting therapy

- History
- Physical Exam with VS
- Ht, Wt, BSA
- Performance status
- Pregnancy test: Female patients of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control.
- CBC, differential, platelets
- Urinalysis
- Electrolytes including Ca++, Mg++, K+ and creatinine
- Uric Acid
- AST, ALT, Total Bilirubin (and Direct Bilirubin if Total Bilirubin is >2 mg/dL)
- Cholesterol, triglycerides
- PT, PTT, fibrinogen, D-Dimer
- ECG for QTc monitoring
- Echocardiogram or MUGA
- BMA for morphology
- BMA for flow cytometry, cytogenetics & FISH
- BMA for clinical RQ-PCR of PML-RARα: At diagnosis. This clinical testing is separate from research samples submitted for the optional MRD study; this **mandatory** clinical testing is not free of charge (cost is not covered by the study), but the specimen must be sent to one of the approved labs for PML-RARα RQ-PCR testing; a list of approved labs is available on the protocol-specific web page of the COG website.
- FLT3*: bone marrow (or peripheral blood if bone marrow is unavailable) at diagnosis. See Section 15.1 for details.
- Research MRD (optional)*: bone marrow and peripheral blood at diagnosis and Day 29 of Induction. See Section 15.2 for details. Results of this research testing will not be returned to sites. This research testing does not take the place of the mandatory RQ-PCR clinical testing that must be done at the time of initial diagnosis (see observation "q" above).
- Coagulopathy*: peripheral blood at diagnosis (if available), Day 1, Day 8, Day 15 and Day 29 of Induction. See Section 15.3 for details.

*Only obtain in patients who have consented to participation in this component of the trial.

**TREATMENT PLAN:**

Treatment on this study will consist of an Induction course to achieve an hCR/hCRi, followed by 28 weeks of Consolidation. There is no randomization in this study. Patients will be stratified into risk groups based on WBC at diagnosis. The standard risk group includes patients with WBC < 10,000/μL, and the high risk group includes patients with WBC ≥ 10,000/μL.

Note: All doses of therapy on the protocol should be calculated using actual (not ideal or adjusted) body weight.

**TOXICITIES AND DOSAGE MODIFICATIONS:**

See Section 5.0.

**SPECIMEN REQUIREMENTS:**

See Section 15.0.