

**COG-AALL0433: Intensive Treatment for Intermediate-Risk Relapse of Childhood B-Precursor Acute Lymphoblastic Leukemia (ALL): A Randomized Trial of Vincristine Strategies**

**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 and within 7 days of obtaining required baseline studies (see Section 7.0). Please see Section 3.2.4 for details regarding an exception for intrathecal chemotherapy.
- \_\_\_ 2. Randomization will take place at the time a patient is entered On Study via RDE. Patients will be assigned to either Regimen A (standard vincristine) or Regimen B (intensive vincristine). Patients with a suitable HLA-matched family bone marrow donor are recommended to undergo HSCT after completion of the third Induction block as per companion COG protocol ASCT0431. Suitable HLA-matched donors are defined as genotypically matched siblings or single antigen mismatched family members (9/10 genotypic match for the following alleles: HLA A, B, C, DRB1, and DQB1). Patients who have a suitable HLA-match, but do not proceed to transplant because of family refusal, may continue to receive AALL0433 chemotherapy and remain on study.
- \_\_\_ 3. Patients between 1 year and 29.99 years of age (inclusive) at the time of relapse will be eligible.
- \_\_\_ 4. Patients with an initial intermediate-risk relapse of B-precursor ALL will be eligible.
- \_\_\_ 5. **Intermediate-risk** relapse is defined as:
  - Bone marrow relapse  $\geq$  36 months from initial diagnosis, **or**
  - Combined bone marrow & extramedullary (CNS and/or testicular) relapse  $\geq$  36 months from initial diagnosis, **or**
  - Isolated extramedullary (CNS and/or testicular) relapse  $<$  18 months from diagnosis.**Please refer to Section 3.3 for definitions of relapse.**
- \_\_\_ 6. Organ Function Requirements:
  - Adequate cardiac function defined as:
    - Shortening fraction of  $\geq$  27% by echocardiogram, or
    - Ejection fraction of  $\geq$  50% by radionuclide angiogram.
  - Adequate biliary excretion, defined as a direct bilirubin  $<$  3.0 mg/dL
- \_\_\_ 7. Prior Therapy
  - Intrathecal chemotherapy (as per Induction 1, Day 1) MAY be given before study enrollment to facilitate administration at the same time as diagnostic bone marrow evaluation (in order to allow single sedation/anesthesia if utilized), as intrathecal chemotherapy is considered an established part of re-induction chemotherapy. Systemic chemotherapy must begin within 5 calendar days of intrathecal chemotherapy.
  - Patients whose relapse is detected during frontline chemotherapy do not require a delay off chemotherapy ("washout period") before initiation of Induction 1. At least 5 days is strongly recommended between a prior vincristine dose and the onset of Induction 1 systemic therapy in order to reduce cumulative toxicity
  - Patients with prior hematopoietic stem cell or marrow transplantation are not eligible for AALL0433
  - CNS relapse patients with prior cranial radiotherapy of greater than 1200 cGy are not eligible for AALL0433

- \_\_\_8. Exclusion criteria:
- Relapsed T-lineage ALL
  - Relapsed mature B-cell (“Burkitt”) leukemia (defined as L3 morphology and/or evidence of *c-myc* translocation)
  - Patients with Down Syndrome (Trisomy 21) because of increased sensitivity to methotrexate
  - Patients with Philadelphia-chromosome positive disease (because of the availability of imatinib or other tyrosine kinase inhibitors)
  - Patients with a history of Grade III or higher toxicity (i.e. peripheral neuropathy) attributable to vincristine within 1 month prior to study entry
  - Patients with known optic nerve and or retinal involvement (because they are unable to delay XRT for 12 months). Patients presenting with visual disturbances should have an ophthalmologic exam and, if indicated, an MRI to determine optic nerve or retinal involvement.
- \_\_\_9. All patients and/or their parents or legal guardians must sign a current version of the written informed consent.

**REQUIRED OBSERVATIONS:**

**EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED**

All baseline studies must be performed within 7 days prior to starting protocol therapy unless otherwise noted below.

1. Hx/PE
2. CBC, diff, plat
3. Urinalysis
4. Bone Marrow (BM)
5. CSF
6. Bili T/D
7. ALT
8. Creatinine
9. Echocardiogram or MUGA
10. BM Immunophenotyping & Cytogenetics %
11. Abd/Pelvic CT, Testicular Ultrasound\*\* Recommended +
12. Testicular Biopsy\*\*

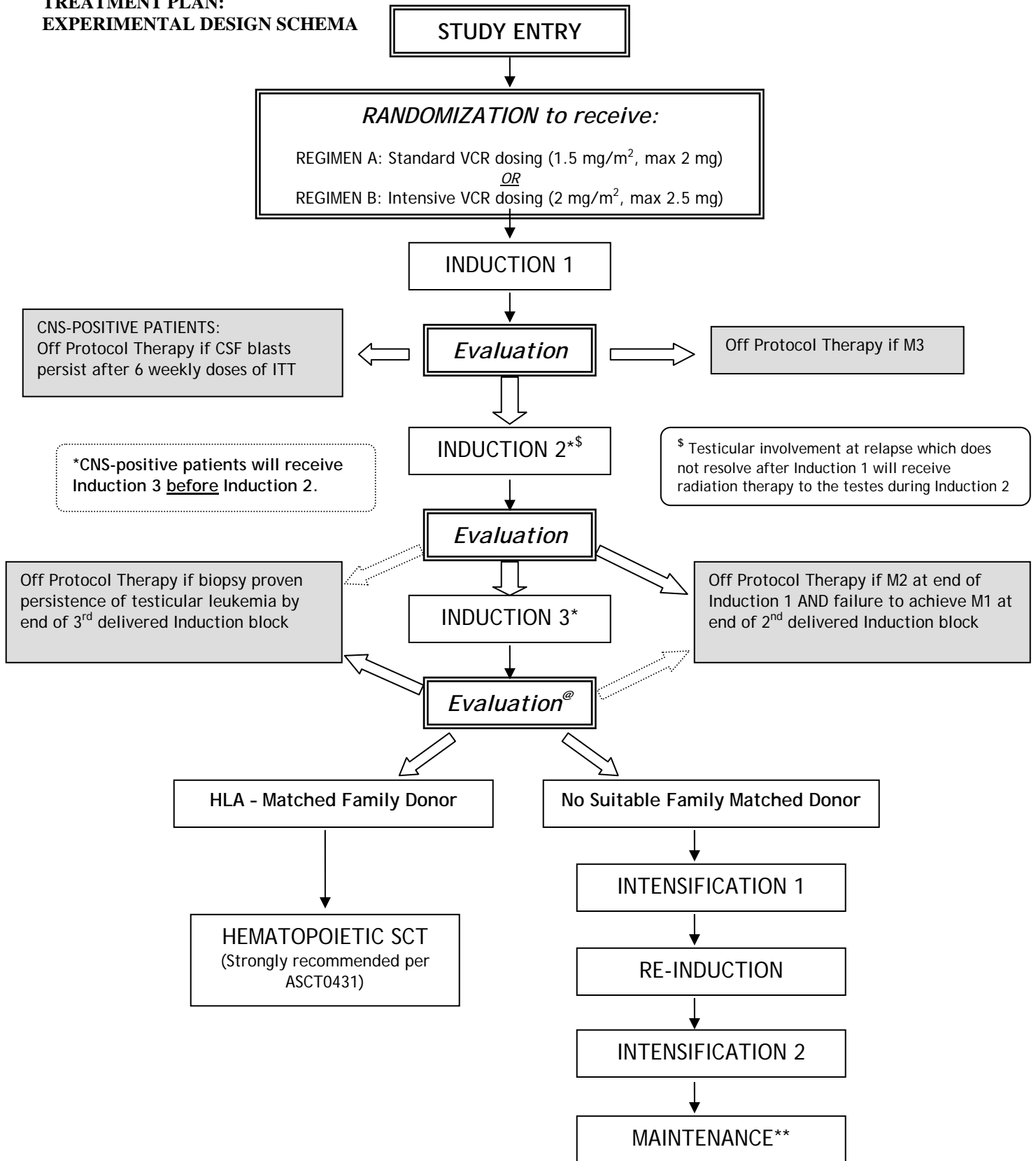
% See Section 15 for details.

\*\* Patients with suspected isolated testicular relapse or equivocal testiculomegaly with concurrent BM/CNS relapse must have biopsy performed at baseline. Patients with equivocal resolution of testiculomegaly require a repeat biopsy at

end of Induction 1 to document clearance (to determine whether XRT is to be given during Induction 2).

+ Only recommended if testicular involvement is suspected.

**TREATMENT PLAN:  
EXPERIMENTAL DESIGN SCHEMA**



@ This evaluation is after the third delivered block of Induction.

\*\* If CNS-positive at relapse, administer cranial radiotherapy at the beginning of Maintenance.

**TOXICITIES AND DOSAGE MODIFICATIONS:**

See Section 5.0.

**OPTIONAL BIOLOGY REQUIREMENTS:**

The following are optional correlative biology studies. Please see Sections 15 and 16 for specimen collection and shipping information. Patient consent is required.

	<b>Baseline</b>	<b>Induction 1</b>	<b>Induction 2</b>	<b>Induction 3</b>	<b>Relapse</b>
Cytogenetics central review	X				
MRD Studies	X	End of Phase	End of Phase@	End of Phase@	X
VCR Pharmacogenetics	X	End of Phase			
Cell banking & Gene Expression Profiling	X				X

- @ Only patients who are M2 at the end of Induction 1 should have MRD performed after completion of their 2nd delivered Induction block. **Please note:** For CNS-positive patients Induction 3 is the 2nd block of Induction delivered. All patients should have MRD performed after the 3rd block of Induction has been delivered