

COG-AALL0232: High Risk B-Precursor Acute Lymphoblastic Leukemia

FAST FACTS

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.

PATIENT ELIGIBILITY:

- PATIENTS MUST BE ENROLLED ON COG AALL03B1 BEFORE TREATMENT BEGINS** (with the exception of the first dose of intrathecal chemotherapy or selected cases of steroid pretreatment). **PATIENTS THAT BEGIN PROTOCOL THERAPY ON THIS STUDY PRIOR TO ENROLLMENT ON AALL03B1 ARE INELIGIBLE FOR AALL0232.** Patients must be enrolled before systemic treatment begins. The only exceptions to this include previous treatment with corticosteroids. For patients who have received prior corticosteroids please see AALL03B1 eligibility criteria. Systemic chemotherapy must start within 72 hours of initial IT therapy. See Section 3.2.5 for previous treatment with intrathecal (IT) cytarabine.
- Patients must be eligible for and enrolled on AALL03B1.
- Patients must be between 1-30 years of age, inclusive.
- Patients must have newly diagnosed B-precursor ALL.
- WBC Criteria
 - Age 1.000-9.999 years: WBC \geq 50,000/ μ L
 - Age 10.000-30.999 years: Any WBC
 - Prior steroid therapy: Any WBC
 - Testicular disease: Any WBC
- Patients shall have had no prior cytotoxic chemotherapy with the exception of steroids and intrathecal cytarabine.
- Intrathecal chemotherapy with cytarabine is allowed prior to registration for patient convenience. This is usually done at the time of the diagnostic bone marrow or venous line placement to avoid a second lumbar puncture. Systemic chemotherapy must begin within 72 hours of this intrathecal therapy. Patients receiving prior steroid therapy (as described in AALL03B1) are eligible for study. The dose and duration of previous steroid therapy should be carefully documented.

RANDOMIZATIONS:

Both randomizations will take place at the time a patient is entered On Study via eRDE. Patients will be assigned to one of four arms: DC, DH, PC, or PH.

Exceptions to Randomization:

CNS 3: Assign to regimen DH with DDI, 2 extra Induction ITs and cranial XRT (1800 cGy) during second DI.

Testicular: Assign to regimen DH with DDI (except for patients who also have Down syndrome who will receive PC with SDI; see below). Those patients with clinical evidence of testicular disease at the end of Induction, as well as DS patients with testicular disease regardless of response to Induction therapy, will receive testicular XRT (2400 cGy) during Consolidation. A testicular biopsy should be performed if the clinical findings are equivocal.

MLL rearrangements: Randomize for Induction. Then RER patients with MLL rearrangements are nonrandomly assigned to receive augmented therapy with DDI (SER) and cranial XRT (1200 cGy). SER patients with MLL rearrangements are classified as VHR and not eligible to receive post-induction therapy on this trial but may be eligible for AALL0031.

Steroid pre-treatment: If a patient received < 48 hours of steroids during the week immediately prior to diagnosis – Randomize.

If a patient received > 48 hours of steroids during the week immediately prior to diagnosis - Assign to regimen DH with DDI and cranial XRT (1200 cGy).

Down Syndrome (DS): Patients will be non-randomly assigned to the PC arm, even in the presence of CNS3 or testicular disease. These patients will be assigned to regimen PC without IM-2 and DI-2 and, if CNS3 and/or SER, will receive cranial XRT (1800 cGy – note dose) during DI-1, rather than DI-2. Those patients with clinical evidence of testicular disease at diagnosis will receive testicular XRT (2400 cGy) during Consolidation, regardless as to response during Induction. In addition, patients with Down syndrome will receive modified leucovorin rescue (5mg/m² PO q12 hrs x 2 doses) starting 48 hours following each intrathecal methotrexate treatment during all stages of therapy **EXCEPT Maintenance**. Patients with DS will

also receive discontinuous dexamethasone during Delayed Intensification. Dexamethasone will be administered as follows: 10 mg/m² PO divided BID, days 1-7 and days 15-21 (14 days total: 7 days ON, 7 days OFF and 7 days ON), no taper.

Randomization must occur prior to any treatment. Intrathecal chemotherapy with cytarabine is allowed prior to registration for patient convenience. Systemic chemotherapy must begin within 72 hours of this intrathecal therapy.

See Section 3.3 for CNS Definitions.

REQUIRED OBSERVATIONS:

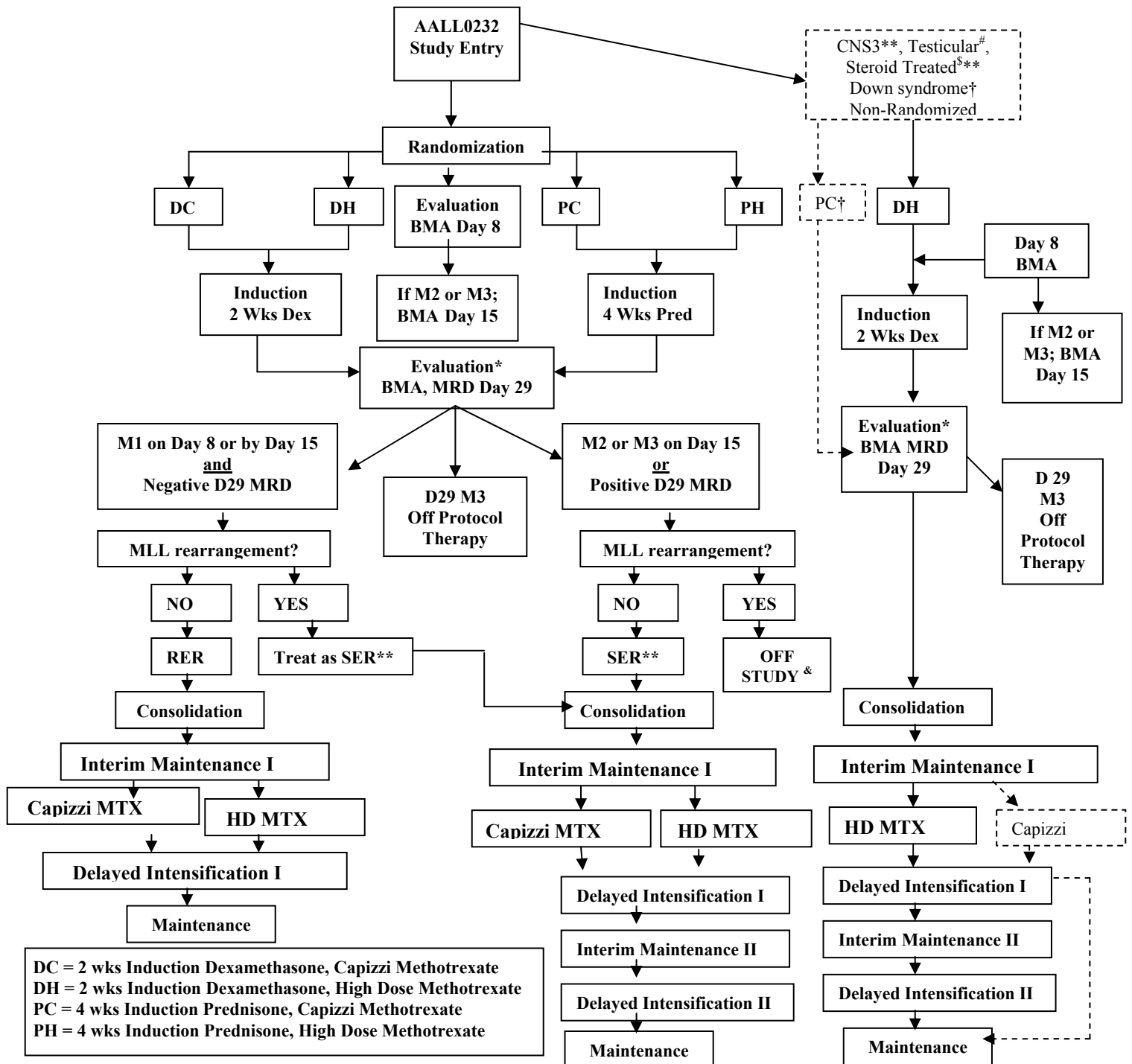
1. Hx/PE/Wt
2. CBC/diff/plts
3. LFTs (bilirubin, ALT)
4. Bun, Creatinine
5. Echo
6. Varicella titer

Note: Read clinical guidelines for management of patients during Induction Phase in Section 8.2.

For more information on this protocol, contact GRCOP at 616.391.1230

TREATMENT PLAN: A diagram of treatment can be seen below.

EXPERIMENTAL SCHEMA



* If Day 29 BM is M2 or M1 with MRD ≥ 1% patient receives 2 weeks of additional Induction followed by re-evaluation of BM morphology and MRD status. If marrow is M2 or M3 or MRD ≥ 1% on Day 43 patient is Off Study and may be eligible for AALL0031.

** Patients receive cranial XRT during DI-2, except for DS pts (receive during DI-1)

Patients receive testicular XRT during Consolidation only if they continue to have clinically evident testicular disease at end-Induction

§ Steroid Treated: Patients who received more than 48 hours of steroids during the week immediately prior to diagnosis.

& May be eligible for AALL0031.

† Note: Patients with Down syndrome (DS) will be non-randomly assigned to the PC arm, but without IM-2 and DI-2 (if SER). Patients with DS and either CNS3 and/or testicular involvement will also be non-randomly assigned to PC without IM-2 and DI-2 and will receive the appropriate radiation therapy. DS pts receiving cranial XRT: administer during DI-1.

TOXICITIES AND DOSAGE MODIFICATIONS

See Section 5.0.

SPECIMEN REQUIREMENTS:

Tests at Diagnosis for SR and HR B-Precursor ALL patients are listed on the Fast Facts for AALL03B1.

Tests on Day 8 for SR, HR B-Precursor and T-ALL Patients **

Specimen	Studies	Laboratory
Peripheral blood 5 ml*	<ul style="list-style-type: none"> MRD 	Flow Cytometry Lab

* This sample is optional and results will not be used for clinical decisions

** If a patient does not enroll on a therapeutic study, the Day 8 sample is NOT required, and should not be submitted to the Reference Laboratories.

Tests on Day 15 for SR and HR B-Precursor ALL Patients that are M2 or M3 at day 8 **

Specimen	Studies	Laboratory
Bone marrow 2 ml*	<ul style="list-style-type: none"> MRD 	Flow Cytometry Lab

* All patients that with an M2/M3 marrow at day 8 must have a day 15 bone marrow aspirate performed. When this is performed, patients that consent to optional research studies should have a sample sent to one of the COG ALL Flow Cytometry Reference Laboratories. The results of day 15 MRD assays will not be used for clinical decisions, and results will not be provided to treating physicians.

** If a patient does not enroll on a therapeutic study, the Day 15 sample is NOT required, and should not be submitted to the Reference Laboratories.

Tests on Day 29 for SR and HR B-Precursor ALL Patients

Specimen	Studies	Laboratory
Bone marrow 2 ml *	<ul style="list-style-type: none"> MRD 	Flow Cytometry Lab Molecular Lab
Peripheral blood 5 ml	<ul style="list-style-type: none"> Host polymorphisms 	Molecular Lab

* Required Samples - Note 2 ml of marrow should be sent to both the flow and Molecular laboratories.

PLEASE NOTE: Protocol-required fresh specimens must be sent directly at room temperature to the designated COG Reference Laboratory. **Follow AALL03B1 guidelines for specimen submissions.****Note: Registration on AALL03B1 is required for participation in this study.****Eastern Division**Elizabeth Raetz, MD, AALL03B1 Co-Chair
(212)-241-7022**Eastern Flow Cytometry Laboratory**Michael Borowitz, M.D., Ph.D.
Johns Hopkins Medical Institution
Flow Cytometry Lab
Weinberg Building - Room 2300
401 N. Broadway
Baltimore, MD 21231-2410
Tel: (410) 614-2968**Eastern Molecular Laboratory**Stephen Qualman, M.D.
Julie Gastier-Foster, Ph.D.
COG ALL Reference Laboratory
Columbus Children's Research Institute
700 Children's Drive, WA 1340
Columbus, OH 43205
Contact Person: Yvonne Moyer
Phone: (614) 722-2585
Fax: (614) 722-2897
Laboratory Phone: (614) 722-2866