

COG AALL0434: Intensified Methotrexate, Nelarabine (Compound 506U78; IND#52611) and Augmented BFM Therapy for Children and Young Adults with Newly Diagnosed T-cell Acute Lymphoblastic Leukemia (ALL)

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 ON COG AALL03B1 BEFORE TREATMENT ON COG AALL0434 BEGINS** (with the exception of the first dose of intrathecal chemotherapy and/or selected cases for which there has been steroid pretreatment). **PATIENTS THAT BEGIN PROTOCOL THERAPY FOR LEUKEMIA, PRIOR TO ENROLLMENT ON AALL03B1, ARE INELIGIBLE FOR BOTH AALL03B1 AND COG ALL THERAPEUTIC TRIALS.** Study enrollment for AALL0434 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. Randomization will take place through the eRDE system after Day 29 T-ALL risk status has been assigned. There are four treatment arms in this study. They are identified as follows:
 - Arm A: Capizzi MTX without Nelarabine (CMTX);
 - Arm B: Capizzi MTX with Nelarabine (CMTX + Nel);
 - Arm C: High Dose MTX without Nelarabine (HDMTX); and
 - Arm D: High Dose MTX with Nelarabine (HDMTX + Nel).During the safety phase, ONLY high-risk patients will be randomized to receive Nelarabine. During the efficacy phase, both high and intermediate-risk patients will be included in the Nelarabine randomization. Low Risk patients do not receive Nelarabine on this protocol.
- ___ 3. Patients must be between 1-30 years of age, inclusive.
- ___ 4. Patients must have newly diagnosed T-cell acute lymphoblastic leukemia (T-ALL). A diagnosis of T-ALL is established when leukemic blasts lack myeloperoxidase or evidence of B-lineage derivation (CD19/CD22/CD20), and express either surface or cytoplasmic CD3 or two or more of the antigens CD8, CD7, CD5, CD4, CD2 or CD1a. If surface CD3 is expressed on all leukemic cells, additional markers of immaturity, including TdT, CD34 or CD99 will be assessed for expression. Cases with uncertain expression will receive additional review within the appropriate COG reference laboratory.
- ___ 5. Patients shall have had no prior cytotoxic chemotherapy with the exception of steroids and/or IT cytarabine. IT 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. (Note: **The CNS status must be determined based on a sample obtained prior to administration of any systemic or intrathecal chemotherapy, except for steroid pretreatment as discussed in Section 3.3.)** Systemic chemotherapy must begin within 72 hours of this IT therapy. Patients receiving prior steroid therapy are eligible for study. Steroid pretreatment may alter the risk group assessment (see Section 3.3.5). The dose and duration of previous steroid therapy should be carefully documented. For the management of airway compromise, patients who have received emergent chest irradiation up to 600 cGy will be eligible for this study.
- ___ 6. **Concomitant Medications Restrictions**
Patients with a prior seizure disorder requiring anti-convulsant therapy are not eligible to receive Nelarabine. In addition, patients with pre-existing Grade 2 (or greater) peripheral neurotoxicity, as determined prior to induction treatment by the treating physician or a neurologist, are not eligible to receive Nelarabine. These restrictions in eligibility are designed to prevent excessive Nelarabine-induced central and peripheral neurotoxicity in at-risk patients. For the purposes of this study, this includes any patient that has received **anticonvulsant therapy to prevent/treat seizures in the prior two years.**
- ___ 7. Pregnant or lactating females are ineligible. The medications used in this protocol may put the fetus at risk, and may cross into the breast milk and out the infant at risk.
- ___ 8. Patients with Down syndrome are ineligible to enroll onto this study.
- ___ 9. Hematological Parameters
INITIAL WBC: The first WBC at the treating COG institution. If prior therapy (i.e. steroids) or IV hydration has

been administered then the initial WBC prior to therapy and/or hydration should be used.

INITIAL PLATELET COUNT: The first platelet count at the treating COG institution, or the count before transfusion of platelets if transfused prior to arrival.

INITIAL HEMOGLOBIN: The first hemoglobin at the treating COG institution, or the hemoglobin prior to intravenous fluid or red cell transfusions, whichever occurred first.

ABSOLUTE NEUTROPHIL COUNT (ANC): Total WBC count multiplied by the percentage of (neutrophils + bands).

10. Definitions of Extramedullary Disease

CNS LEUKEMIA AT DIAGNOSIS:

CNS 1: In cerebral spinal fluid (CSF), absence of blasts on cytopsin preparation, regardless of the number of white blood cells (WBCs).

CNS 2: In CSF, presence of < 5/μL WBCs and cytopsin positive for blasts or ≥ 5 μL WBCs with negative Steinherz Bleyer algorithm.

CNS 2a: < 10/μL RBCs; < 5/μL WBCs and cytopsin positive for blasts;

CNS 2b: ≥ 10/μL RBCs; < 5/μL WBCs and cytopsin positive for blasts; and

CNS 2c: ≥ 10/μL RBCs; ≥ 5/μL WBCs and cytopsin positive for blasts but negative by Steinherz/Bleyer algorithm (see below).

CNS 3: In CSF, presence of ≥ 5/μL WBCs and cytopsin positive for blasts and/or clinical signs of CNS Leukemia. (Note: Clinical CNS criteria appear below in CNS 3c):

CNS 3a: < 10/μL RBCs; ≥ 5/μL WBCs and cytopsin positive for blasts;

CNS 3b: ≥ 10/μL RBCs; ≥ 5/μL WBCs and positive by Steinherz/Bleyer algorithm (see below); and

CNS 3c: Clinical signs of CNS leukemia (such as facial nerve palsy, brain/eye involvement or hypothalamic syndrome).

METHOD OF EVALUATING INITIAL TRAUMATIC LUMBAR PUNCTURES:

If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and contains ≥ 5 WBC/μL and blasts, the following algorithm should be used to distinguished between CNS2 and CNS3 disease:³⁹

$$\frac{\text{CSF WBC}}{\text{CSF RBC}} > 2X \frac{\text{Blood WBC}}{\text{Blood RBC}}$$

A patient with CSF WBC ≥ 5/μL blasts, whose CSF WBC/RBC is 2X greater than the blood WBC/RBC ratio, has CNS disease at diagnosis. Example: CSF WBC = 60/μL; CSF RBC = 1500/μL; blood WBC = 46000/μL; blood RBC = 3.0 X 10⁶ /μL:

$$\frac{60}{1500} = 0.04 > 2X \frac{46000}{3.0 \times 10^6} = 0.015$$

TESTICULAR LEUKEMIA AT DIAGNOSIS: Unilateral or bilateral testicular disease. Biopsy is required if clinical findings are equivocal or suggestive of hydrocele or a non-leukemic mass. NOTE: patients with Down syndrome AND testicular disease will receive testicular radiation regardless of response to Induction therapy.

REQUIRED OBSERVATIONS:

- Hx/PE
- BSA
- CBC/diff/plts
- Bone Marrow Cytomorphology ^{1,2}
- CSF cell count and cytospin
- Bilirubin, ALT creatinine, BUN
- Echo
- Varicella titer

1. If Day 8 BMA was M2 or M3 obtain additional bone marrow for morphology & MRD on Day 15.
2. Obtain bone marrow for morphology; send D15 BM and D8 PB samples to ALL Flow Cytometry Reference Lab ONLY for MRD; send D29 BM and D1 PB samples to ALL Molecular and Flow Cytometry Reference Labs for MRD (see AALL03B1 for shipping requirements and addresses) for patients that are High-Risk and Induction Failures.

TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5.

SPECIMEN REQUIREMENTS:

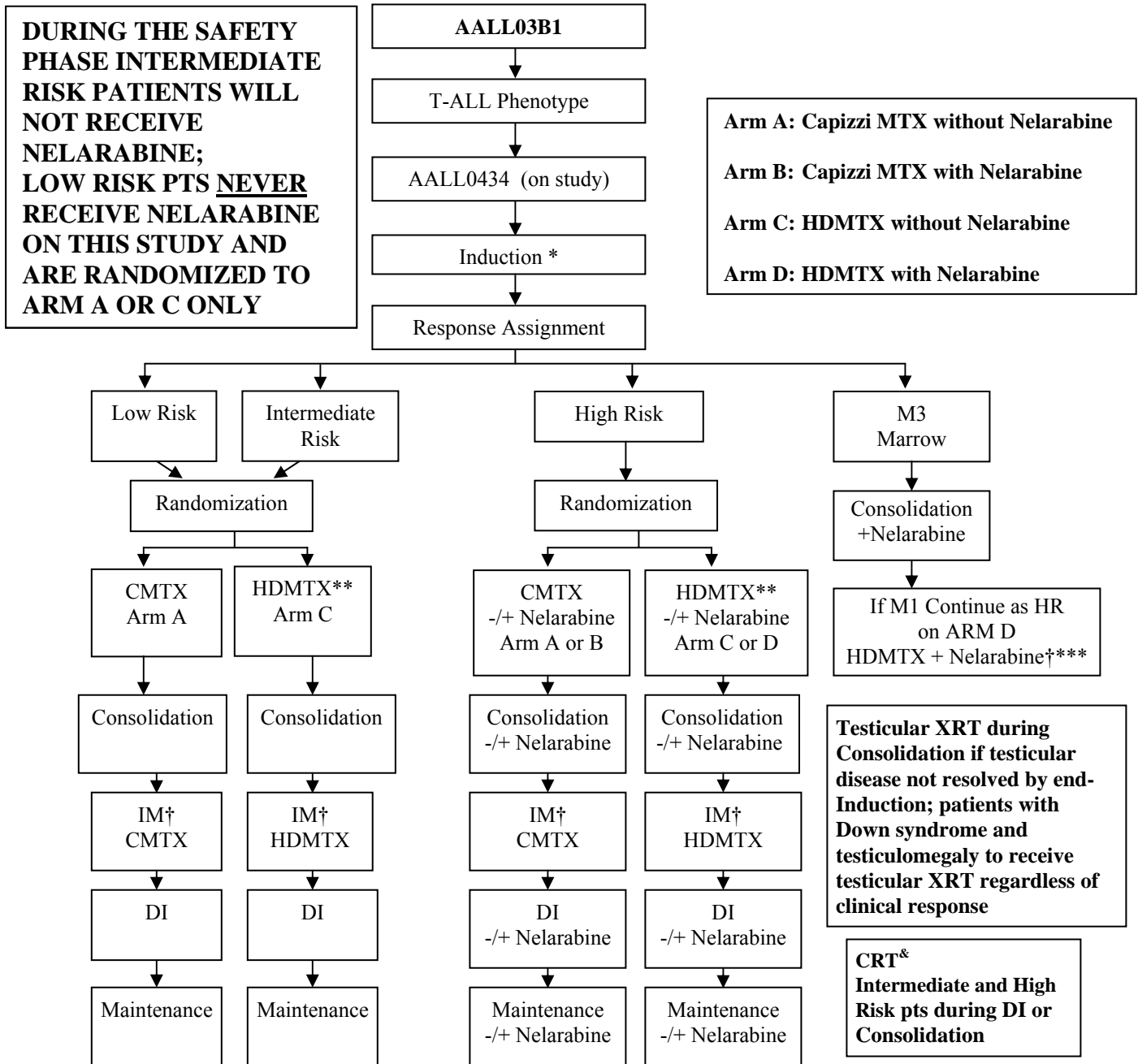
As per AALL03B1, consider optional pharmacokinetics.

See Section 7.1 for specimen requirements during consolidation.

BIOLOGY REQUIREMENTS:

As per AALL03B1.

EXPERIMENTAL DESIGN SCHEMA: SAFETY PHASE



* Induction evaluation = Day 8 BMA; if not M1 then repeat on Day 15.
 Evaluation of BMA and MRD on Day 29.
 ** Patients with CNS3 and/or testicular disease at Dx will be assigned to HDMTX arms
 ***Patient may also be taken off study for alternate therapy, including BMT
 †Patients must be M1 at end-Consolidation to continue on therapy
 RER = M1 marrow on Day 8 and < 0.1% MRD on Day 29 OR
 M2/M3 marrow on Day 8 and M1 marrow on Day 15 and < 0.1% MRD on Day 29.
 SER = M2/M3 on Day 15 OR positive MRD on Day 29.
 Low Risk = NCI SR by age & WBC count; RER, M1 on Day 15 and MRD < 0.1% on Day 29; CNS 1 status; and no testicular disease at diagnosis.
 Intermediate Risk = RER or SER with MRD < 1% on Day 29; any CNS status.
 High Risk = M2 at end of Induction or MRD ≥ 1% on Day 29; any CNS status.

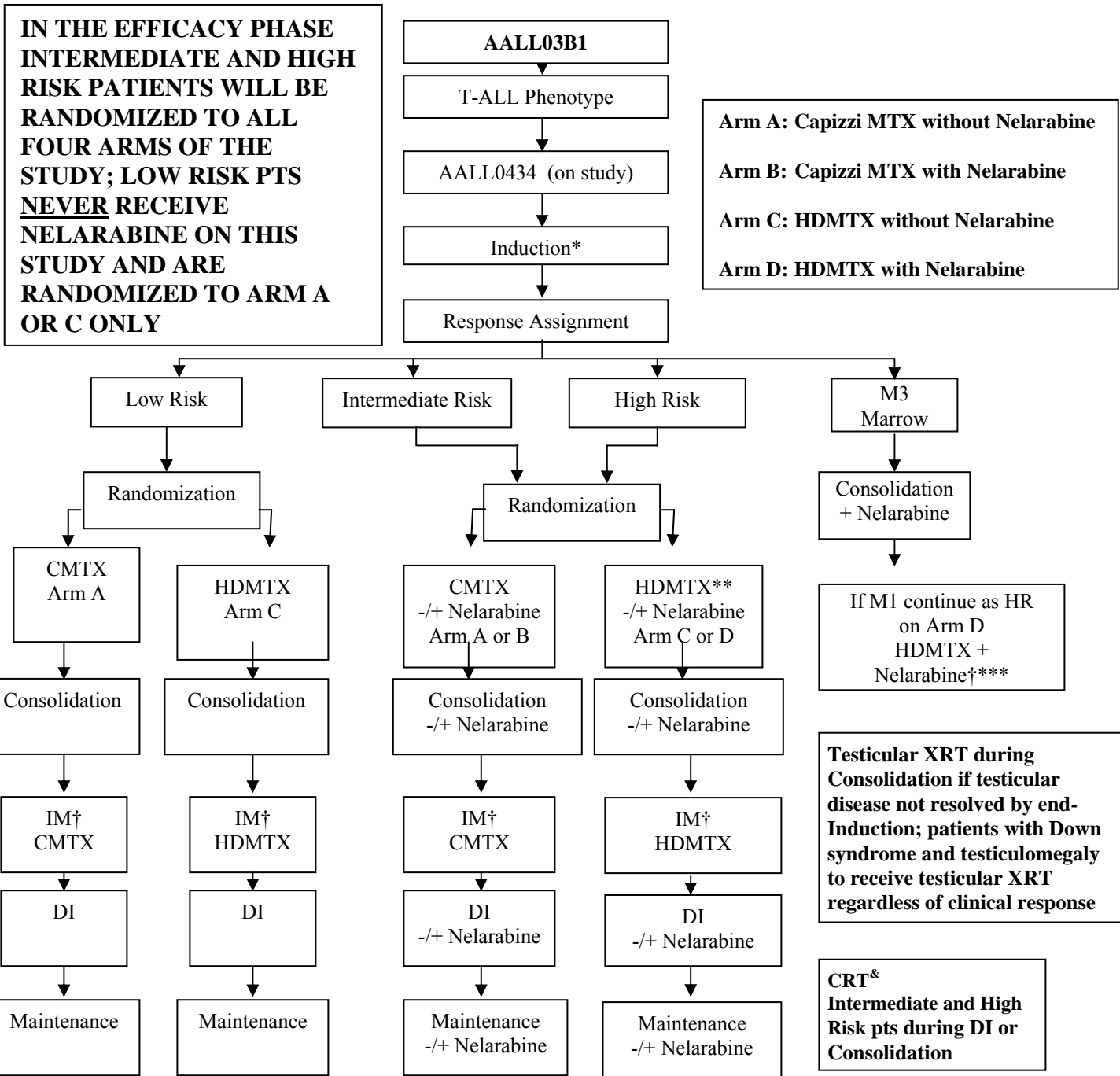
CMTX = Capizzi escalating MTX
 HDMTX = High dose MTX
 IM = Interim Maintenance
 DI = Delayed Intensification

Patients with Down Syndrome will not receive HDMTX or Nelarabine and will be non-randomly assigned to Arm A. Patients with a prior seizure disorder will not receive Nelarabine.

& CRT = cranial radiation (See Section 14.0 for details).

The safety phase ends when the 1st 20 High Risk pts to receive Nelarabine have been evaluated per Section 10.2.

EXPERIMENTAL DESIGN SCHEMA: EFFICACY PHASE



* Induction evaluation = Day 8 BMA; if not M1 then repeat on Day 15.
Evaluation of BMA and MRD on Day 29.

** Patients with CNS3 and/or testicular disease at Dx will be assigned to HDMTX arms

***Patient may also be taken off study for alternate therapy, including BMT

†Patients must be M1 at end-Consolidation to continue on therapy
RER = M1 marrow on Day 8 and < 0.1% MRD on Day 29 OR
M2/M3 marrow on Day 8 and M1 marrow on Day 15 and
< 0.1% MRD on Day 29.

SER = M2/M3 on Day 15 OR positive MRD on Day 29.

Low Risk = NCI SR by age & WBC count; RER, M1 on Day 15 and MRD < 0.1% on Day 29; CNS 1 status; and no testicular disease at diagnosis.

Intermediate Risk = RER or SER with MRD < 1% on Day 29; any CNS status.

High Risk = M2 at end of Induction or MRD ≥ 1% on Day 29; any CNS status.

CMTX = Capizzi escalating MTX
HDMTX = High dose MTX
IM = Interim Maintenance
DI = Delayed Intensification

Patients with Down Syndrome will not receive HDMTX or Nelarabine and will be non-randomly assigned to Arm A. Patients with a prior seizure disorder will not receive Nelarabine.

& CRT = cranial radiation (See Section 14.0 for details).