COG-AALL1732: A Phase 3 Randomized Trial of Inotuzumab Ozogamicin (IND#:133494, NSC#: 772518) for Newly Diagnosed High-Risk B-ALL; Risk-Adapted Post-Induction Therapy for High-Risk B-ALL, Mixed Phenotype Acute Leukemia, and Disseminated B-LLy

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. **All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to the start of protocol-directed systemic therapy, unless otherwise indicated. Diagnostic biopsy for B-LLy must be performed within 28 days prior to enrollment. Imaging studies, if applicable, must be obtained within 14 days prior to enrollment (repeat the tumor imaging if necessary).**

___2. Timing

PATIENTS WITH B-ALL OR MPAL MUST CONSENT TO ELIGIBILITY SCREENING (PART A) AND BE ENROLLED ON PROJECT:EVERYCHILD (APEC14B1) AND OBTAIN A DIAGNOSTIC SAMPLE BEFORE RECEIVING ANY SYSTEMIC PROTOCOL THERAPY ON AALL1732. (For the purpose of this study, "systemic protocol therapy" does not include the first dose of intrathecal chemotherapy or selected cases of steroid pretreatment or cytoreduction). **PATIENTS THAT BEGIN SYSTEMIC PROTOCOL THERAPY PRIOR TO ENROLLMENT ON APEC14B1 ARE INELIGIBLE FOR AALL1732.**

___3. **PATIENTS WITH B-LLy ARE ELIGIBLE FOR PROJECT:EVERYCHILD (APEC14B1) BUT ENROLLMENT IS NOT AN ELIGIBILITY REQUIREMENT FOR AALL1732.**

___4. **Summary of Required Consents for AALL1732:**

Consent document	Time Point for Obtaining Consent	Population for Consent
APEC14B1 (Part A)	Prior to the start of protocol therapy	• NCI HR B-ALL • NCI SR B-ALL with CNS3, testicular leukemia, or steroid pretreatment • MPAL
		Disseminated B-LLy*
B-ALL and MPAL Induction & Consolidation	Prior to the start of Induction	• NCI HR B-ALL • NCI SR B-ALL with CNS3, testicular leukemia, or steroid pretreatment • Suspected MPAL
B-ALL Post-Consolidation	Prior to the start of the phase following Consolidation	• HR-Fav B-ALL (non-randomized) • surface CD22-positive HR B-ALL with EOC MRD < 0.01% for NCI HR and < 1% for NCI SR (randomized)
MPAL Post-Consolidation	Prior to the start of Interim Maintenance I	Centrally confirmed MPAL (non-randomized)
B-LLy (All phases of therapy)	Prior to the start of Induction	Disseminated B-LLy (non-randomized)

* Encouraged but not required

Consents for Optional Studies on AALL1732:

Consent document	Time Point for Obtaining Consent	Population for Consent
Adherence Study^	Prior to the start of the phase following Consolidation	HR B-ALL 10 years old or older and receiving treatment at a COG institution in the United States
Minimal Marrow Disease Study#	Prior to the start of Induction	Disseminated B-LLy and receiving treatment at a COG institution in the United States

^ Included in B-ALL post-Consolidation consent document
# Included in B-LLy consent document

___5. **All Patients:**
Study enrollment on AALL1732 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.
Patients must meet all eligibility criteria prior to the start of protocol therapy or enrollment, whichever occurs first. All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to the start of protocol-directed systemic therapy, unless otherwise indicated in the eligibility section below. Diagnostic biopsy for B-LLy must be performed within 28 days prior to enrollment and imaging studies for B-LLy must be performed within 14 days prior to enrollment.

___6. Initiation of systemic protocol therapy: Systemic Induction chemotherapy, with the exception of steroid pretreatment or cytoreduction as outlined below, must begin within 72 hours of the first dose of intrathecal chemotherapy.

___7. Eligibility Screening
B-ALL and MPAL patients must be enrolled on APEC14B1 and consented to Eligibility studies (Part A) prior to treatment and enrollment on AALL1732. Note that central confirmation of MPAL diagnosis must occur within 22 days of enrollment for suspected MPAL patients. If not performed within this time frame, patients will be taken off protocol. See Section 3.1.4 for timing details.
APEC14B1 is not a requirement for B-LLy patients but for institutional compliance every patient should be offered participation in APEC14B1. B-LLy patients may directly enroll on AALL1732.

___8. Age at diagnosis
Patients must be > 365 days and < 25 years of age

___9. White Blood Cell Count (WBC) Criteria
- White Blood Cell Count (WBC) Criteria for patients with B-ALL
  - Age 1-9.99 years: WBC ≥ 50,000/µL
  - Age 10-24.99 years: Any WBC
  - Age 1-9.99 years: WBC < 50,000/µL with:
    - Testicular leukemia
    - CNS leukemia (CNS3)
    - Steroid pretreatment (see Section 3.3.3)
- White Blood Cell Count (WBC) Criteria for patients with MPAL
  - Age 1-24.99 years: any WBC
    NOTE: Patients enrolled as suspected MPAL but found on central confirmatory testing to have B-ALL must meet the B-ALL criteria above (age, WBC, extramedullary disease, steroid pretreatment) to switch to the the B-ALL stratum before the end of Induction.

___10. Diagnosis
- Patient has newly diagnosed B-ALL or MPAL (by WHO2016 criteria) with >25% blasts on a bone marrow (BM) aspirate;
  OR If a BM aspirate is not obtained or is not diagnostic of acute leukemia, the diagnosis can be established by a pathologic diagnosis of acute leukemia on a BM biopsy;
  OR A complete blood count (CBC) documenting the presence of at least 1,000/µL circulating leukemic cells if a bone marrow aspirate or biopsy cannot be performed;
- OR Patient has newly diagnosed B-LLy Murphy Stages III or IV (See Appendix VII for staging);
- OR Patient has newly diagnosed B-LLy Murphy Stages I or II with steroid pretreatment (See Section 3.3.3 for steroid pretreatment details).

Note: For B-LLy patients with tissue available for flow cytometry, the criteria for diagnosis should be analogous to B-ALL. For tissue processed by other means (i.e., paraffin blocks), the methodology and criteria for immunophenotypic analysis to establish the diagnosis of B-LLy defined by the submitting institution will be accepted.

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

EXCLUSION CRITERIA:

___1. Patients with Down syndrome are not eligible (patients with Down syndrome and B-ALL are eligible for AALL1731, regardless of NCI risk group).

___2. Prior Therapy
With the exception of steroid pretreatment and steroid cytoreduction (defined in Section 3.3.3) or the administration of intrathecal cytarabine, patients must not have received any prior cytotoxic chemotherapy for the current diagnosis of B-ALL, MPAL, or B-LLy or for any cancer diagnosed prior to initiation of protocol therapy on AALL1732.

___3. Patients who have received > 72 hours of hydroxyurea within one week prior to start of systemic protocol therapy.

___4. Patients with B-ALL or MPAL who do not have sufficient diagnostic bone marrow submitted for APEC14B1 testing and who do not have a peripheral blood sample submitted containing >1,000/µL circulating leukemia cells.

___5. Patients with Acute Undifferentiated Leukemia (AUL) are not eligible.

___6. For Murphy Stage III/IV B-LLy patients, or Stage I/II patients with steroid pretreatment, the following additional exclusion criteria apply:
- T-Lymphoblastic Lymphoma.
- Morphologically unclassifiable lymphoma.
- Absence of both B-cell and T-cell phenotype markers in a case submitted as lymphoblastic lymphoma.

___7. Patients with known Charcot-Marie-Tooth disease.

___8. Patients with known MYC translocation associated with mature (Burkitt) B-cell ALL, regardless of blast immunophenotype.

___9. Patients requiring radiation at diagnosis.

___10. Female patients who are pregnant, since fetal toxicities and teratogenic effects have been noted for several of the study drugs. A pregnancy test is required for female patients of childbearing potential.

___11. Lactating women who plan to breastfeed their infants while on study and for 2 months after the last dose of inotuzumab ozogamicin.

___12. Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of study participation. For those patients randomized to inotuzumab ozogamicin, there is a minimum of 8 months after the last dose of inotuzumab ozogamicin for females and 5 months after the last dose of inotuzumab ozogamicin for males.

REQUIRED OBSERVATIONS:

Required Observations in Induction – B-ALL

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

a. Hx/PE/Wt /Ht/BSA. Note: Height/BSA is only required at the beginning of this course.
b. CBC/diff/platelets
c. Creatinine
d. Total bilirubin, ALT
e. CSF cell count and cytospin (Obtain only on days with IT administration)
f. Echocardiogram (MUGA is acceptable)
g. Pregnancy test
h. Performance status
i. TPMT and NUDT15 genotype (TPMT highly recommended for all subjects; NUDT15 is highly recommended for subjects of Hispanic/Native American or East Asian ancestry, and optional for all other subjects).
j. **REQUIRED** (done as part of APEC14B1)**:** Local assessment of surface CD22 expression (see Appendix XIII for best practice guidelines). A diagnostic BM sample must also be submitted to the COG Biopathology Center for central assessment of surface CD22 expression for patients with negative or unknown CD22 expression by local assessment.
k. **REQUIRED:** Submit baseline samples for required eligibility studies done as part of APEC14B1. See APEC14B1 Manual of Procedures for details.
l. Optional: for patients who consent on APEC14B1, send baseline PB and BM samples for banking. Done as part of APEC14B1, see APEC14B1 Manual of Procedures for details.
m. **REQUIRED:** Bone marrow evaluation to assess response by morphology (at local institution), and flow MRD (at COG-approved flow laboratory). See Section 14.1 for collection and shipping requirements. This sample should be drawn no more than two days early or late, with a preference for early rather than late to avoid potentially missing a high MRD level. **If Day 29 BM sample for MRD testing is not obtained and shipped to a COG-approved flow lab then the patient will not be eligible to continue on AALL1732 following completion of Consolidation therapy. These samples are essential.**
n. Optional: for patients who consent on APEC14B1, send Day 29 PB and BM samples for banking. Done as part of APEC14B1, see APEC14B1 Manual of Procedures for details.

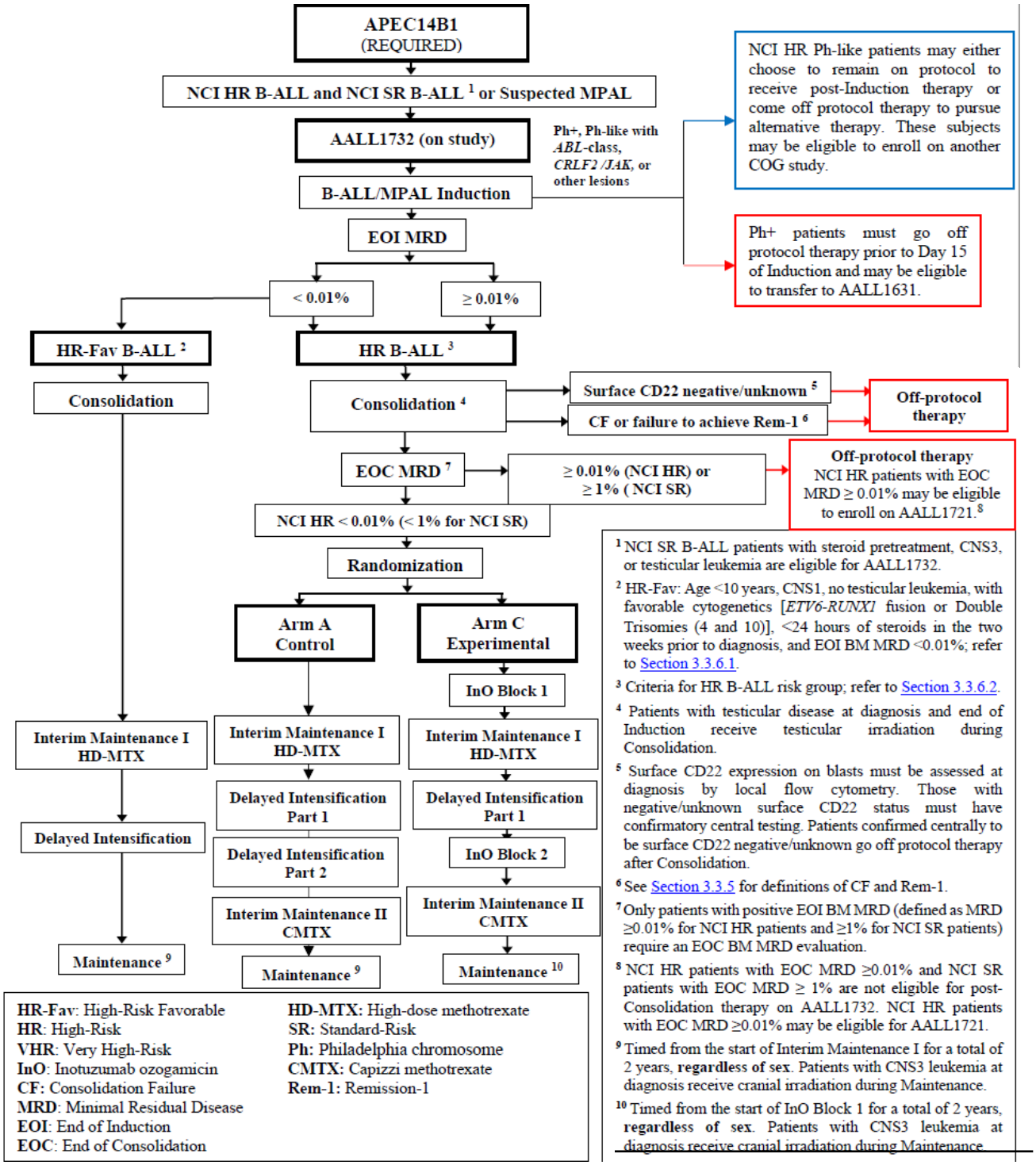
TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5.0.

SPECIMEN REQUIREMENTS:

Per APEC14B1 and Sections 13.0 and 14.0. Note: Blood and marrow must be sent to the ALL molecular reference lab for potential confirmatory testing. Bone Marrow – 7ml. Peripheral Blood – 5 ml in shipping media.

TREATMENT PLAN: – B-ALL Patients (Effective with Amendment #6B)
See Protocol for B-LLy and MPAL details



[1] NCI SR B-ALL patients with steroid pretreatment, CNS3, or testicular leukemia are eligible for AALL1732.

[2] HR-Fav: Age <10 years, CNS1, no testicular leukemia, with favorable cytogenetics [*ETV6-RUNX1* fusion or Double Trisomies (4 and 10)], <24 hours of steroids in the two weeks prior to diagnosis, and EOI BM MRD <0.01%; refer to Section 3.3.6.1.

[3] Criteria for HR B-ALL risk group; refer to Section 3.3.6.2.

[4] Patients with testicular disease at diagnosis and end of Induction receive testicular irradiation during Consolidation.

[5] Surface CD22 expression on blasts must be assessed at diagnosis by local flow cytometry. Those with negative/unknown surface CD22 status must have confirmatory central testing. Patients confirmed centrally to be surface CD22 negative/unknown go off protocol therapy after Consolidation.

[6] See Section 3.3.5 for definitions of CF and Rem-1.

[7] Only patients with positive EOI BM MRD (defined as MRD ≥0.01% for NCI HR patients and ≥1% for NCI SR patients) require an EOC BM MRD evaluation.

[8] NCI HR patients with EOC MRD ≥0.01% and NCI SR patients with EOC MRD ≥ 1% are not eligible for post-Consolidation therapy on AALL1732. NCI HR patients with EOC MRD ≥0.01% may be eligible for AALL1721.

[9] Timed from the start of Interim Maintenance I for a total of 2 years, **regardless of sex**. Patients with CNS3 leukemia at diagnosis receive cranial irradiation during Maintenance.

[10] Timed from the start of InO Block 1 for a total of 2 years, **regardless of sex**. Patients with CNS3 leukemia at diagnosis receive cranial irradiation during Maintenance.