PATIENT ELIGIBILITY:

__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 14 days prior to enrollment. Imaging studies, if applicable, must be obtained within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary).__

___2. ___

___3. PATIENTS WITH B-ALL OR MPAL MUST CONSENT TO ELIGIBILITY SCREENING (PART A) AND BE ENROLLED ON PROJECT:EVERYCHILD (APEC14B1) AND SUBMIT 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). PATIENTS THAT BEGIN SYSTEMIC PROTOCOL THERAPY PRIOR TO ENROLLMENT ON APEC14B1 ARE INELIGIBLE FOR AALL1732.

___4. B-LLy PATIENTS MUST SUBMIT SAMPLES FOR CENTRAL RETROSPECTIVE PATHOLOGY REVIEW. SPECIFIC INSTRUCTIONS REGARDING REQUIRED TISSUE SUBMISSION ARE OUTLINED IN SECTION 13.0. EVERY EFFORT SHOULD BE MADE TO ACQUIRE AS MUCH TISSUE AS POSSIBLE.

___5. PATIENTS WITH B-LLy ARE ELIGIBLE FOR PROJECT:EVERYCHILD (APEC14B1) BUT ENROLLMENT IS NOT AN ELIGIBILITY REQUIREMENT FOR AALL1732.

___6. 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 14 days prior to enrollment.

___7. Initiation of systemic protocol therapy: Systemic Induction chemotherapy, with the exception of steroid pretreatment as outlined below, must begin within 72 hours of the first dose of intrathecal chemotherapy.

___8. 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 7 business days after enrollment for 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 and MUST submit eligibility studies as outlined in Section 13.0.

___9. Age at diagnosis

Patients must be > 365 days and < 25 years of age
10. **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

11. **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 criterion 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. Patients with known Charcot-Marie-Tooth disease.
3. **Prior Therapy**
   - With the exception of steroid pretreatment (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.
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. 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.
8. Lactating women who plan to breastfeed their infants while on study and for 2 months after the last dose of inotuzumab ozogamicin.
9. 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
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 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 CD22 expression for patients with negative or unknown CD22 expression by local assessment.


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:

EXPERIMENTAL DESIGN SCHEMA – B-ALL Patients

**APEC14B1 (REQUIRED)**

- **NCI HR B-ALL and NCI SR B-ALL ¹**
  - **AALL1732 (on study)**
    - **Induction**
      - **EOI MRD**
        - ≤ 0.01%
        - ≥ 0.01%
  - **Ph-like with ABL-1, CRLF2-1, or other lesion**
  - **Ph-like patients:** may either choose to remain on protocol to receive post-induction therapy or come off protocol therapy to pursue alternative therapy. These subjects may be eligible to enroll on another COG study.

**HR-Fav B-ALL ²**

- **Consolidation**

**HR B-ALL ³**

- **Consolidation ⁴**
  - **CD22 neoplastic/unknown ⁵**
    - **CF or failure to achieve Rem-1 ⁶**
      - ≥ 0.01% (NCI HR)
  - **EOC MRD ⁷**
    - NCI HR < 0.01% (< 1% for NCI SR)

**Randomization**

- **Arm A Control**
  - **Interim Maintenance I HD-MTX**
  - **Delayed Intensification**
    - **Interim Maintenance II CMTX**
    - **Maintenance ⁸**
- **Arm B Experimental**
  - **InO Block 1**
  - **Interim Maintenance I HD-MTX**
  - **Delayed Intensification**
    - **Interim Maintenance II CMTX**
    - **Maintenance ⁹**

**Criteria for HR B-ALL risk group:** refer to **Section 3.3.6.2**

1. 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 [Philadelphia chromosome, t(4;11) or Double Translocation (4 and 10)], ≤24 hours of steroid in the two weeks prior to diagnosis, and EOI BM MRD ≤0.01%; refer to **Section 3.3.6.1**

**References**

- [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 [Philadelphia chromosome, t(4;11) or Double Translocation (4 and 10)], ≤24 hours of steroid 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**
- [5] CD22 expression on blasts must be assessed at diagnosis by local flow cytometry. Those with negative/unknown CD22 status must have confirmatory central testing. Patients confirmed centrally to be 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%) require an EOI BM MRD evaluation.
- [8] NCI HR patients with EOC MRD ≥0.01% may be eligible to enroll on AALL1721 (NCI SR are not eligible for this study).
- [9] Tied 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] Tied 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.