

**COG-AALL1821: A Phase 2 Study of Blinatumomab (NSC# 765986, IND# 125462)
in Combination with Nivolumab (NSC# 748726, IND# 125462), a Checkpoint Inhibitor of PD-1,
in B-ALL Patients Aged ≥ 1 to < 31 Years Old with First Relapse**

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. Project Every Child
Enrollment on APEC14B1 is required for COG participation in AALL1821.
- ___ 2. Timing
Patients must be enrolled before protocol therapy begins (including Pre- Immunotherapy treatment). The date protocol therapy is projected to start must be no later than **five (5)** calendar days after the date of study enrollment. **Patients who are started on systemic protocol therapy prior to study enrollment will be considered ineligible (with the exception of first dose of intrathecal chemotherapy and pre-enrollment steroids and/or hydroxyurea, per Section 3.2.4).**
- ___ 3. **Bone Marrow Evaluation must be within 14 days prior to enrollment. All other clinical and laboratory studies used to assess eligibility must be no older than 7 days at enrollment, with the exception of the enrollment CBC which must be obtained within 72 hours prior to enrollment.**
- ___ 4. Staged Consent
Informed consent will be obtained at critical stages of treatment for the different groups of patients on this study (see summary table).

Consent Form	Time Point to Obtain Consent	Population
Consent 1 - Group 1, will consent to the possibility of receiving pre-immunotherapy and immunotherapy	Prior to enrollment	Group 1
Consent 2 - Reinduction (VXLD) for Groups 2 and 3	Prior to enrollment	Groups 2 and 3
Consent 3 - Group 2 post-VXLD	After post-VXLD evaluation	Group 2
Consent 4 - Group 3 post-VXLD	After post-VXLD evaluation	Group 3
Consent 5 - Down syndrome, will consent to the possibility of receiving pre-immunotherapy and immunotherapy	Prior to enrollment	DS

5. Callback for Treatment Assignment/Randomization

Callback	Timing	Population	Purpose
Group 1 and DS Pre-Immunotherapy Treatment Callback	After enrollment and prior to start of pre-immunotherapy treatment.	Group 1 and DS patients required to receive pre-immunotherapy treatment	Confirmation of eligibility for pre-immunotherapy treatment and treatment assignment: Group 1 Pre-Immunotherapy Treatment or Down Syndrome Pre-Immunotherapy Treatment
*Group 1 Callback	If pre-immunotherapy treatment is needed, callback will occur after pre-immunotherapy treatment. If pre-immunotherapy treatment is not needed, callback will occur after enrollment.	Group 1	Confirmation of eligibility for immunotherapy and randomization: Arm A (blinatumomab) or Arm B (blinatumomab with nivolumab)
*Post VXLD Callback	Post-VXLD evaluation	Group 2 Group 3	Confirmation of eligibility and randomization: Arm C (blinatumomab) or Arm D (blinatumomab with nivolumab) Confirmation of eligibility and randomization: Arm E (blinatumomab) or Arm F (blinatumomab with nivolumab)
Down Syndrome Callback	If pre-immunotherapy treatment is needed, callback will occur pre-immunotherapy treatment; if pre-immunotherapy treatment not needed, callback will occur after enrollment.	DS patients	Confirmation of eligibility for immunotherapy and non-random assignment to Arm G (blinatumomab with nivolumab)

*Patients that do not correctly complete callback at the randomization timepoints will be deemed inevaluable and be taken off protocol.

6. Age

Patients must be ≥ 1 and < 31 years at time of enrollment.

7. Diagnosis

Patients must have first relapse of CD19+ B-ALL (relapse blasts must express CD19) as defined in [Section 3.3.3](#) in one of the following categories:

- Isolated bone marrow relapse
- Isolated CNS (excluding known optic nerve/retinal and CNS chloromas) and/or testicular relapse
- Combined bone marrow with extramedullary relapse in the CNS (excluding known optic nerve/retinal and CNS chloromas) and/or testes.

Patients with DS are eligible in the following categories:

- Isolated marrow relapse
- Combined bone bone marrow with CNS (excluding known optic nerve/retinal and CNS chloromas) and/or testicular relapse.

8. Performance Level

Patients must have a performance status corresponding to ECOG scores of 0, 1 or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age. For further reference, please see the section on Performance Status Scales at <http://www.cogmembers.org> under Standard Sections for Protocols.

Of note, for patients with developmental delay (e.g. Down syndrome) regardless of age, Lansky scale may be

substituted for Karnofsky scale. However, the requirement for ECOG 0-2 remains, regardless of known history of developmental delay.

9. Prior Therapy

Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.

- a. Patients with prior blinatumomab or CD19+ chimeric antigen receptor therapy in the upfront setting will be eligible, provided relapsed lymphoblasts retain CD19 expression.
- b. Radiation therapy (RT): ≥ 3 months must have elapsed if prior RT. This includes any patient requiring urgent radiation to any sites of extramedullary disease prior to enrollment (e.g. retinal/optic nerve involvement).
- c. Hematopoietic Stem Cell Transplant (HSCT): Patients must not have had a prior hematopoietic stem cell transplant.
- d. A single intrathecal chemotherapy at the time of relapse will be allowed. If < 7 days have elapsed between this IT and the start of protocol therapy, then the Day 1 intrathecal chemotherapy (i.e. methotrexate, cytarabine, or triple intrathecal) may be omitted.
- e. In the 28 days prior to enrollment, up to five days of post-relapse, pre-enrollment therapy (steroid and/or hydroxyurea only) is permissible.
 - Group 1 and Down Syndrome patients who received pre-enrollment therapy and have a WBC $\geq 30,000/\mu\text{l}$ at the time of enrollment must receive protocol specified cytoreductive therapy with vincristine and dexamethasone per [Section 4.1.1](#), and no “washout” is required.
 - Group 1 and Down Syndrome patients who received pre-enrollment therapy and have a WBC $< 30,000/\mu\text{l}$ at the time of enrollment must be given a 24 hour “washout” before starting immunotherapy.

Note: There is no waiting period or “washout” for patients who relapse while receiving upfront therapy.

10. Organ Function Requirements

- Adequate Renal Function Defined As:
 - Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m² OR
 - A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR utilizing child length and stature data published by the CDC.

- Adequate Cardiac Function Defined As:
 - Shortening fraction of $\geq 27\%$ by echocardiogram, or
 - Ejection fraction of $\geq 50\%$ by echocardiogram, cardiac MRI or radionuclide angiogram.
- Adequate Pulmonary Function Defined As:
 - No evidence of dyspnea at rest, no exercise intolerance, and a pulse oximetry $> 94\%$ if there is clinical indication for determination.

11. Assent of children age 14 and older is a necessary condition for proceeding with the research.

12. Note: This trial has a protocol supplied wallet card that is required to be provided to the patient. See Appendix VIII.

EXCLUSION CRITERIA:

In addition to the previously noted prior therapy restrictions.

- ___ 1. Patients with B-lymphoblastic lymphoma (B-LLy)
- ___ 2. Patients with Burkitt Leukemia/Lymphoma or mature B-cell leukemia
- ___ 3. Patients with Philadelphia chromosome positive (Ph+) B-ALL
- ___ 4. Patients with mixed phenotype acute leukemia (MPAL)
- ___ 5. Patients with known Charcot-Marie-Tooth disease
- ___ 6. Patients with known MYC translocation associated with mature (Burkitt) B-cell ALL, regardless of blast immunophenotype.
- ___ 7. Patients with active, uncontrolled infection defined as:
 - Positive bacterial blood culture within 48 hours of study enrollment
 - Receiving IV or PO antibiotics for an infection with continued signs or symptoms. Note: Patients may be receiving IV or oral antibiotics to complete a course of therapy for a prior documented infection if cultures have been negative for at least 48 hours and signs or symptoms of active infection have resolved. For patients with *C. difficile* diarrhea, at least 72 hours of antibacterial therapy must have elapsed and stools must have normalized to baseline.
 - Fever above 38.2°C within 48 hours of study enrollment with clinical signs of infection. Fever without clinical signs of infection that is attributed to tumor burden is allowed if blood cultures are negative for > 48 hours.
 - A positive fungal culture within 30 days of study enrollment or active therapy for presumed invasive fungal infection.
 - Active viral or protozoal infection requiring IV treatment
- ___ 8. Patients known to have one of the following concomitant genetic syndromes: Bloom syndrome, ataxia-telangiectasia, Fanconi anemia, Kostmann syndrome, Shwachman syndrome or any other known bone marrow failure syndrome are not eligible. Of note, patients with known HIV infection on effective anti-retroviral therapy with undetectable viral load for at least the last 6 months prior to enrollment are eligible. Similarly, hepatitis B and hepatitis C positive patients who have been treated and have no viral detectable burden are also eligible.
- ___ 9. Patients with significant central nervous system pathology that would preclude treatment with blinatumomab, including history of severe neurologic disorder or autoimmune disease with CNS involvement

Note: Patients with a history of seizures that are well controlled on stable doses of anti-epileptic drugs are eligible.

Patients with a history of cerebrovascular ischemia/hemorrhage with residual deficits are not eligible. Patients with a history of cerebrovascular ischemia/hemorrhage remain eligible provided all neurologic deficits have resolved.

- ___ 10. Patients with an active known/suspected autoimmune disease are not eligible. However, patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- ___ 11. Group 1 and DS patients with known non-hematopoietic, non-CNS/testicular extramedullary disease (i.e., chloromatous disease) are not eligible.
Note: Group 2 and 3 patients with known non-hematopoietic, non-CNS/testicular extramedullary disease (i.e., chloromatous disease) are eligible if this is NOT the only site of relapsed disease.
- ___ 12. Pregnancy and Breastfeeding
 - Female patients of childbearing potential are not eligible unless a negative pregnancy test result has been obtained within 7 days prior to enrollment. Patients who are sexually active and of reproductive potential are not eligible unless they agree to use an effective contraceptive method for the duration of this study. Men with female partners of childbearing potential should use effective contraception during the duration of their treatment.

The effect of blinatumomab on fertility has not been evaluated. Blinatumomab is not recommended for pregnant women or women of childbearing potential (WOCBP) not using contraception. Females of reproductive potential must use effective contraception during treatment and for at least 48 hours after the last dose of blinatumomab.

Studies in animal models have shown that nivolumab can adversely impair pregnancy. Thus, nivolumab is expected to cause fetal harm during pregnancy. WOCBP receiving nivolumab must continue contraception for a period of at least 5 months after the last dose of nivolumab. It is unknown whether nivolumab is present in breast milk, thus breastfeeding should be discontinued while a patient is receiving nivolumab. Men receiving nivolumab and who are sexually active with WOCBP must continue contraception for 7 months after the last dose of nivolumab.

- Lactating females are not eligible unless they agree not to breastfeed their infants.

It is unknown whether blinatumomab or its metabolites are excreted in human breast milk. Women are not permitted to breastfeed while receiving blinatumomab and for the last 48 hours after the last blinatumomab dose.

Due to the potential for serious adverse reactions in the breastfed infant, women are not permitted to breastfeed during treatment and for 5 months after the last nivolumab dose.

REQUIRED OBSERVATIONS:

Groups 2 & 3

Required Observations - VXLD Reinduction

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

- a. History/Physical Exam with Height & Weight (BSA).
- b. CBC, differential and platelets.
- c. Bilirubin, ALT, AST creatinine, BUN
- d. Local Bone Marrow (BM) Evaluation. BM evaluation should include morphology, immunophenotyping & cytogenetics/FISH. Cytogenetic/FISH analysis must be performed at a COG approved cytogenetics lab and cases will be reviewed retrospectively by the COG Cytogenetics Committee. See [Section 14.0](#) for details.
- e. BM for MRD by Flow Cytometry at COG-approved Flow Lab. See [Section 14.2](#) for details.*
- f. BM for Future Research/Banking. See [Section 14.3](#) for details.**
- g. CSF cell count and cytospin. Obtain with each IT.*
- h. Peripheral Blood (PB) for Immunophenotyping.*
- i. PB for Future Research/Banking. See [Section 14.3](#) for details.**
- j. Echocardiogram
- k. Pregnancy Test
- l. Testicular Exam. Patients with testicular involvement at relapse must have response to VXLD documented at the end of the cycle.

*BM for immunophenotyping, PB for immunophenotyping, and CSF tests are REQUIRED as part of standard of care, however, submission of these samples in accordance with [Section 14.4](#) is OPTIONAL.

**Submission of BM and PB samples for banking in accordance with [Section 14](#) is OPTIONAL.

Required Observations –Pre-immunotherapy Treatment

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

- a. History/Physical Exam with Height & Weight (BSA)
- b. CBC with differential.
- c. Bilirubin, ALT, AST, Creatinine, and BUN
- d. CSF cell count and cytospin, obtain with each IT.
- e. Echocardiogram
- f. Testicular Exam (if applicable)
- g. Bone marrow (BM) for cytogenetics/FISH at a COG approved cytogenetics lab. Cases will be reviewed retrospectively by the COG Cytogenetics Committee. See [Section 14.0](#) for details. NOTE: This baseline evaluation only needs to be completed once.
- h. Local BM Evaluation for morphology. NOTE: This baseline evaluation only needs to be completed once.
- i. BM for Central Flow Cytometry. See [Section 14.1](#) for details. NOTE: This baseline evaluation only needs to be completed once.
- j. Peripheral blood (PB) and BM for Banking for Future Research (optional). See [Section 14.3](#) for details. NOTE: This baseline evaluation only needs to be completed once.
- k. PB for Immunobiology Studies (optional). See [Section 14.4](#) for details.
- l. CSF for Immunobiology Studies (optional). See [Section 14.4](#) for details.
- m. BM for Immunobiology Studies (optional). See [Section 14.4](#) for details.

Required Observations – Group 1, Arm A, Immunotherapy Cycle 1

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

- a. History/Physical Exam with Height & Weight (BSA).
- b. CBC, differential, and platelets.
- c. Bilirubin, ALT, AST, Creatinine, and BUN
- d. Echocardiogram (not required if done prior to starting pre-immunotherapy treatment on AALL1821)
- e. Pregnancy test. Female patients of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control.
- f. Testicular Exam for male patients. Baseline testicular assessment not required if done after completion of pre-immunotherapy treatment to clear testicular disease on AALL1821.
- g. CSF cell count and cytospin. Obtain with each IT.
- h. Bone marrow (BM) for cytogenetics/FISH at a COG approved cytogenetics lab. Cases will be reviewed retrospectively by the COG Cytogenetics Committee. See [Section 14.0](#) for details. Baseline BM assessment on Day 0 is not required if done prior to beginning pre-immunotherapy treatment on AALL1821.
- i. Local BM Evaluation for morphology. Baseline BM assessment on Day 0 is not required if done prior to beginning pre-immunotherapy treatment on AALL1821.
- j. BM for Central Flow Cytometry. See [Section 14.1](#) for details. Baseline BM assessment on Day 0 is not required if done prior to beginning pre-immunotherapy treatment on AALL1821.
- k. Peripheral blood (PB) and BM for Banking for Future Research (optional). Baseline collection of PB and BM is not required if done prior to beginning pre-immunotherapy treatment on AALL1821. See [Section 14.3](#) for details.
- l. PB for Immunobiology Studies (optional). Day 0 PB should not be collected if obtained prior to beginning pre-immunotherapy treatment on AALL1821. See [Section 14.4](#) for details.
- m. CSF for Immunobiology Studies (optional). Day 0 CSF should not be collected if obtained prior to beginning pre-immunotherapy treatment on AALL1821. See [Section 14.4](#) for details.
- n. BM for Immunobiology Studies (optional). Day 0 BM should not be collected if obtained prior to beginning pre-immunotherapy treatment on AALL1821. See [Section 14.4](#) for details.

Group Down Syndrome

Required Observations – Group DS, Arm G Immunotherapy Cycle 1

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

- a. History/Physical Exam with Height & Weight (BSA)
- b. CBC, differential, and platelets.
- c. Bilirubin, ALT, AST, Creatinine & BUN
- d. Echocardiogram (not required if done prior to beginning pre-immunotherapy treatment on AALL1821)
- e. Pregnancy test. Female patients of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control.
- f. Testicular Exam for male patients. Baseline testicular assessment not required if done after completion of pre-immunotherapy treatment to clear testicular disease on AALL1821.
- g. CSF cell count and cytospin. Obtain with each IT.
- h. Bone marrow (BM) for cytogenetic/FISH analysis at a COG approved cytogenetics lab. Cases will be reviewed retrospectively by the COG Cytogenetics Committee. See [Section 14.0](#) for details. Baseline BM assessment on Day 0 is not required prior to beginning pre-immunotherapy treatment on AALL1821.
- i. Local BM Evaluation for morphology. Baseline BM assessment on Day 0 is not required if done prior to beginning pre-immunotherapy treatment on AALL1821.
- j. BM for Central Flow Cytometry. See [Section 14.1](#) for details. Baseline BM assessment on Day 0 is not required if done prior to beginning pre-immunotherapy treatment on AALL1821.
- k. Peripheral blood (PB) and BM for Banking for Future Research (optional). See [Section 14.3](#) for details. Baseline collection of PB and BM is not required if done prior to beginning pre-immunotherapy treatment on AALL1821.
- l. PB for Immunobiology Studies (optional). Day 0 PB should not be collected if done prior to beginning pre-immunotherapy treatment on AALL1821. See [Section 14.4](#) for details.
- m. CSF for Immunobiology Studies (optional). Day 0 CSF should not be collected if done prior to beginning pre-immunotherapy treatment on AALL1821. See [Section 14.4](#) for details.
- n. BM for Immunobiology Studies (optional). Day 0 BM should not be collected if done prior to beginning pre-immunotherapy treatment on AALL1821. See [Section 14.4](#) for details.

TOXICITIES AND DOSAGE MODIFICATIONS:

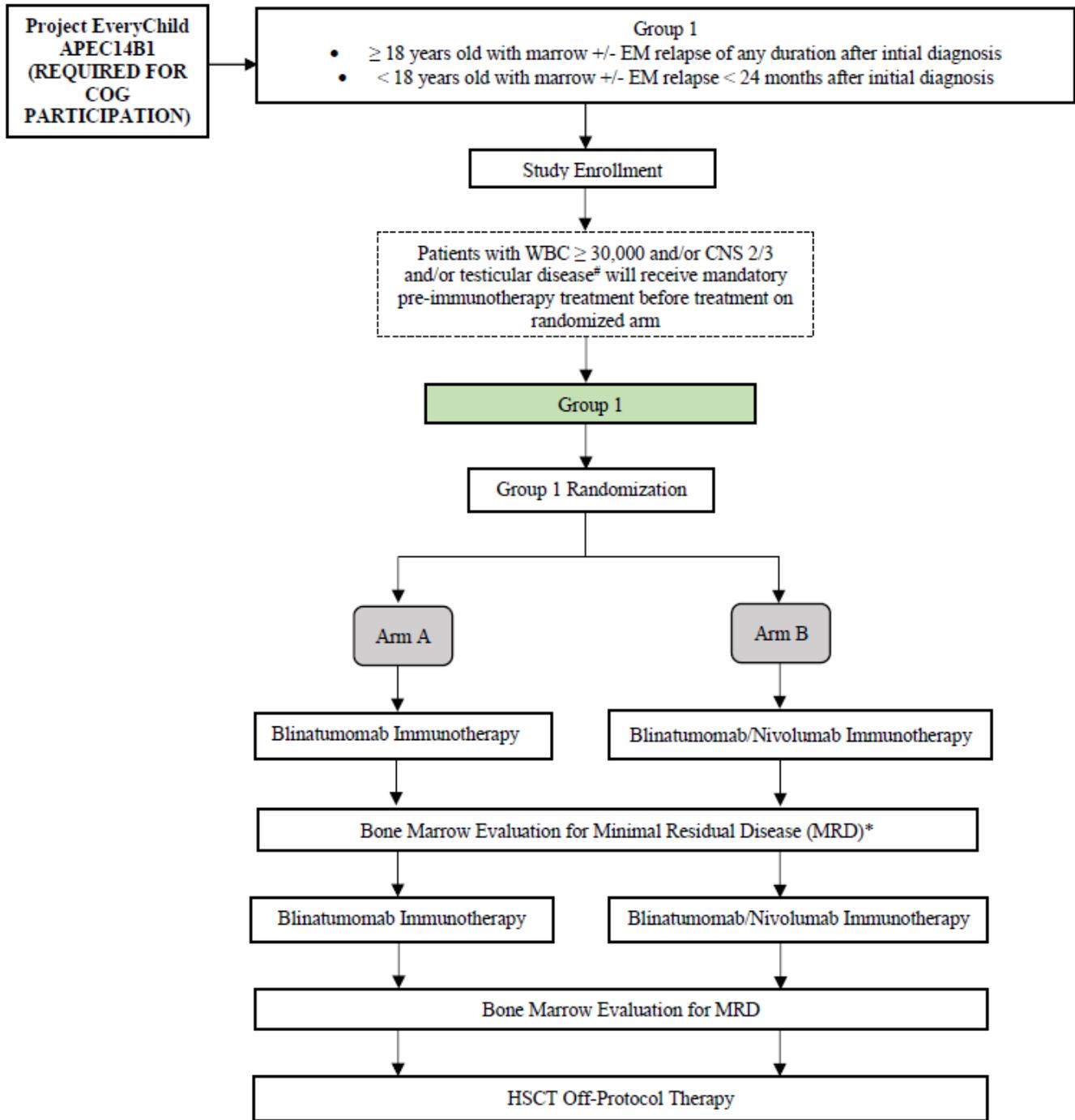
See Section 5

BIOLOGY REQUIREMENTS:

Per Section 14:

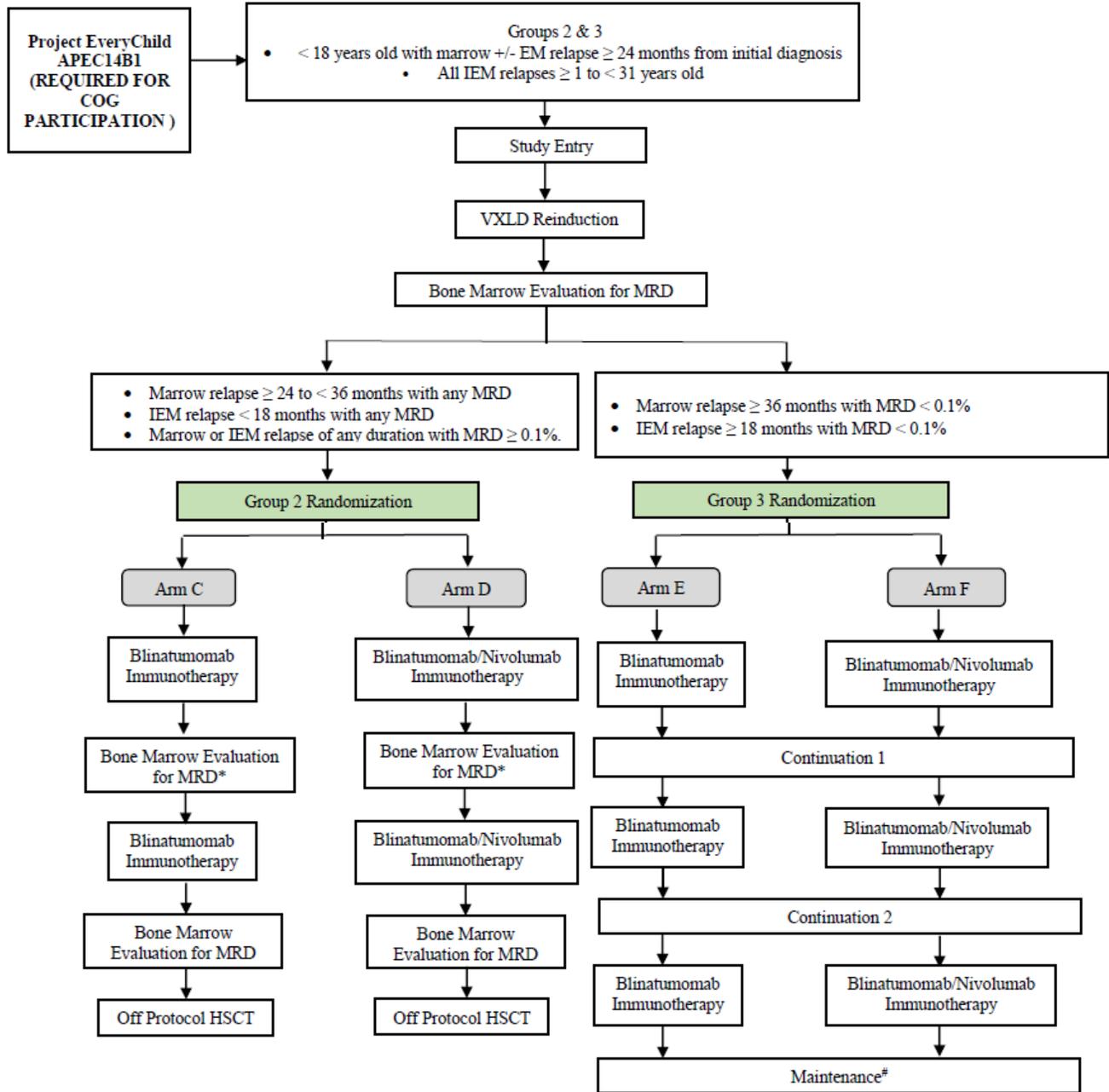
- Via APEC14B1, optional, 5cc of peripheral blood and bone marrow.
- Via AALL1821, required, bone marrow for Central Flow
 - o 2-5cc media
 - o 4-10 peripheral blood if no marrow and >1k absolute blast count
- Optional – Correlative Immunobiology Studies
 - o Bone marrow and peripheral blood 3-5cc in sodium heparin or lithium heparin
 - o CSF – 1cc in standard CSF tube

**TREATMENT PLAN:
EXPERIMENTAL DESIGN SCHEMA: GROUP 1**



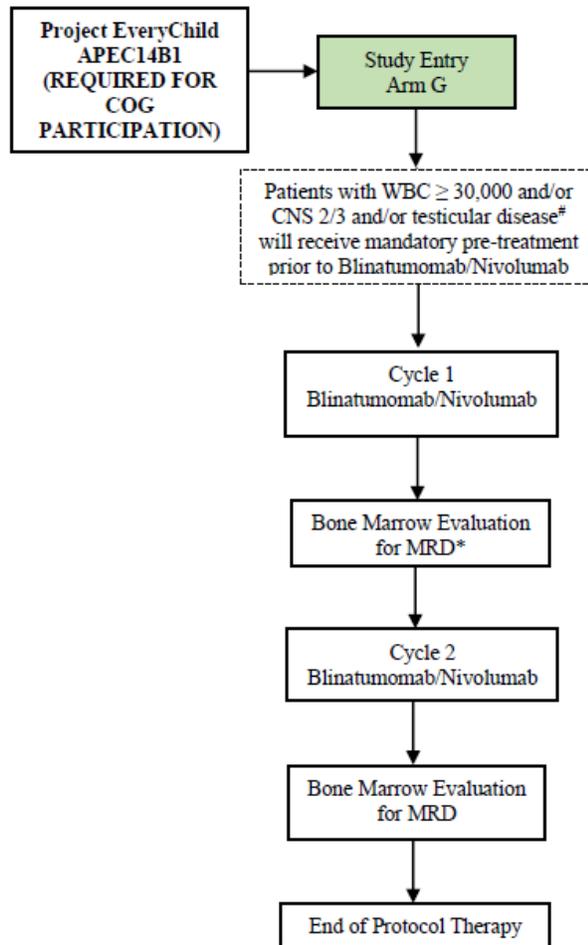
#Patients WBC ≥ 30,000 at enrollment will be treated with chemotherapy as pre-immunotherapy treatment; patients with CNS 2/3 at relapse will be treated with intrathecal chemotherapy as pre-immunotherapy treatment; patients with testicular disease at relapse will be treated with chemoradiation as pre-immunotherapy treatment. See [Section 4.1.1](#) for all possible pre-immunotherapy treatment regimens.
*Patients with MRD < 0.01% after Cycle 1 may choose to either go off protocol therapy (at physician's discretion) or proceed to Cycle 2 immunotherapy on assigned arm. Patients with MRD ≥ 0.01% will receive Cycle 2 immunotherapy on assigned arm.

EXPERIMENTAL DESIGN SCHEMA: GROUPS 2 AND 3



*Patients with MRD < 0.01% after Cycle 1 immunotherapy are eligible to come off protocol (at physician's discretion) without receiving Cycle 2 immunotherapy on assigned arm. Patients with MRD ≥ 0.01% after Cycle 1 of immunotherapy will receive Cycle 2 immunotherapy on assigned arm.
 #CNS 3 patients will receive chemoradiation treatment between the 1st and 2nd cycles of Maintenance.

EXPERIMENTAL DESIGN SCHEMA: GROUP DOWN SYNDROME (DS)



#Patients with WBC ≥ 30,000 at enrollment will be treated with chemotherapy as pre-immunotherapy treatment; patients with CNS 2/3 at relapse will be treated with intrathecal chemotherapy as pre-immunotherapy treatment, patients with testicular disease at relapse will receive mandatory chemoradiation as pre-immunotherapy treatment.
*Patients with MRD < 0.01% after Cycle 1 immunotherapy may choose to either go off protocol therapy (at physician's discretion) or proceed to Cycle 2 immunotherapy. Patients with MRD ≥ 0.01% will receive Cycle 2 immunotherapy.