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 receive callback at the above required timepoints will be deemed inevaluable. Patients with callback errors (e.g. patients who begin protocol therapy before callback form is verified) will be considered inevaluable and be taken off protocol. Additionally, patients with incomplete data (such as incomplete VXLD-Reinduction data) needed for risk stratification and callback will be considered 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 futher reference, please see the section on Performance Status Scales at http://www.cogmembers.org under Standard Sections for Protocols.

___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 ≥ 30,000/µl 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/µl 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 ≥ 27% by echocardiogram, or
  - Ejection fraction of ≥ 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 as long as 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 as long as 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. Please see the figure and description in Section 3.3.1 for classification of sites of disease.
Note: Group 2 and 3 patients with known non-hematopoietic, non-CNS/testicular extramedullary disease (i.e., chloromatous disease) are eligible provided that this is NOT the only site of relapsed disease. Please see the figure and table in Section 3.3.1 for classification of sites of 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.

Group 1

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 & BUN
d. CSF cell count and cytospin, obtain with each IT.
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 (if applicable)

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. 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 Central Flow Immunophenotyping and MRD. See Section 14.1 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. 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.
l. Testicular Exam.

*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.

TOXICITIES AND DOSAGE MODIFICATIONS:

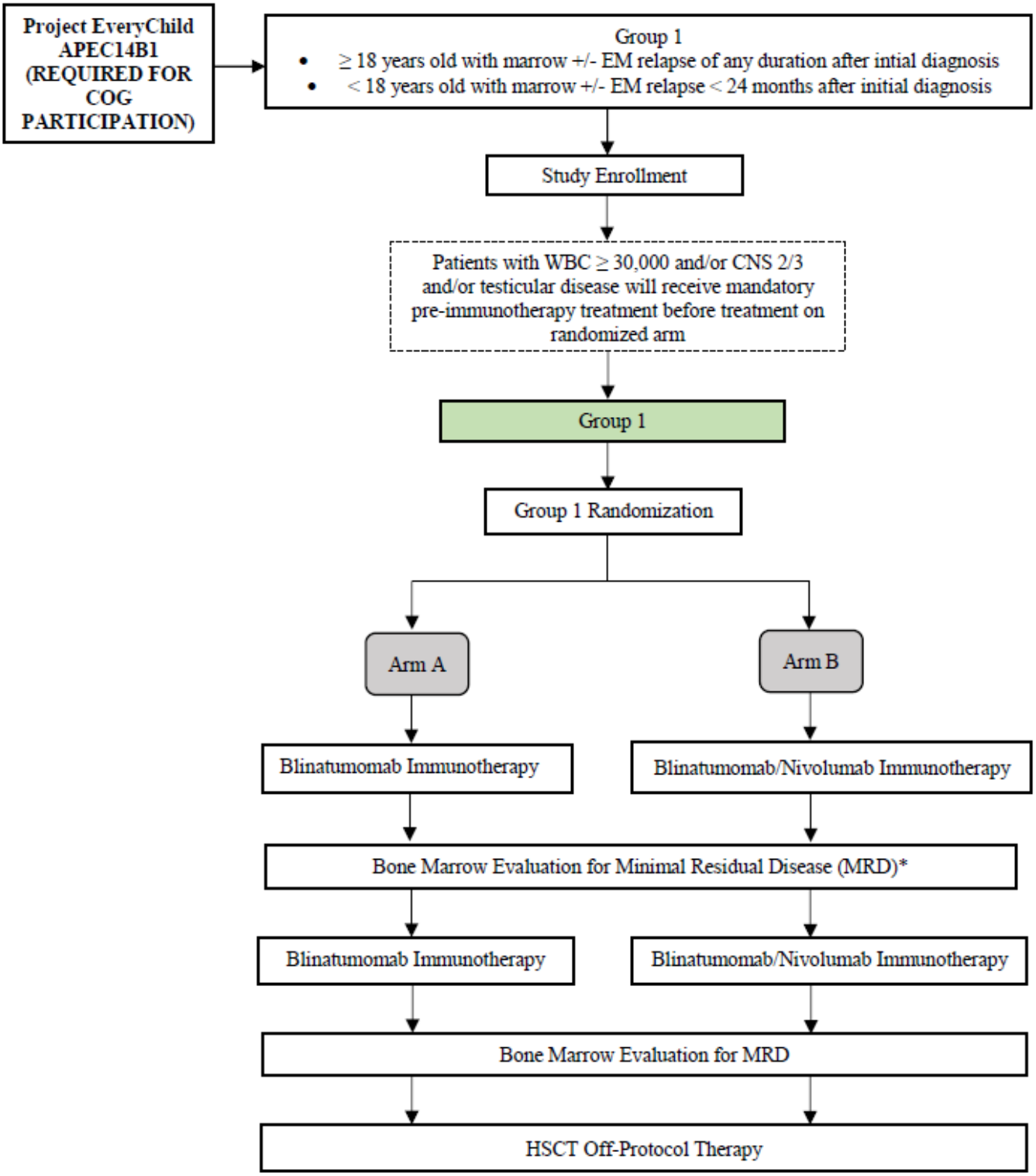
See Section 5

BIOLOGY REQUIREMENTS:

Per Section 14:

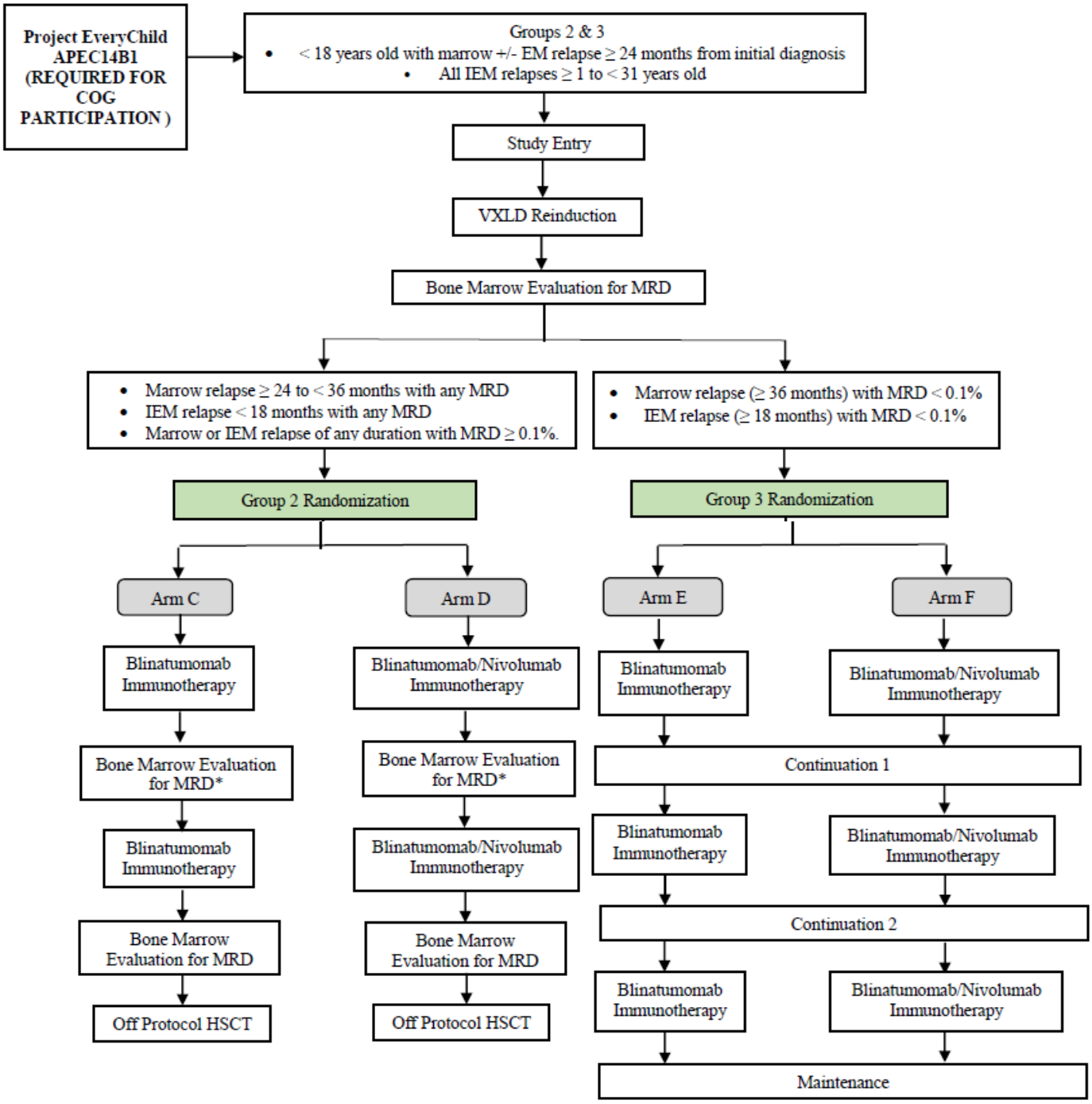
- Via APEC14B1, optional, 5cc of peripheral blood and bone marrow.
- Via AALL1821, required, bone marrow for Central Flow
    - 2-5cc media
    - 4-10 peripheral blood if no marrow and >1k absolute blast count
- Optional – Correlative Immunobiology Studies
    - Bone marrow and peripheral blood 3-5cc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

TREATMENT PLAN:
EXPERIMENTAL DESIGN SCHEMA: GROUP 1



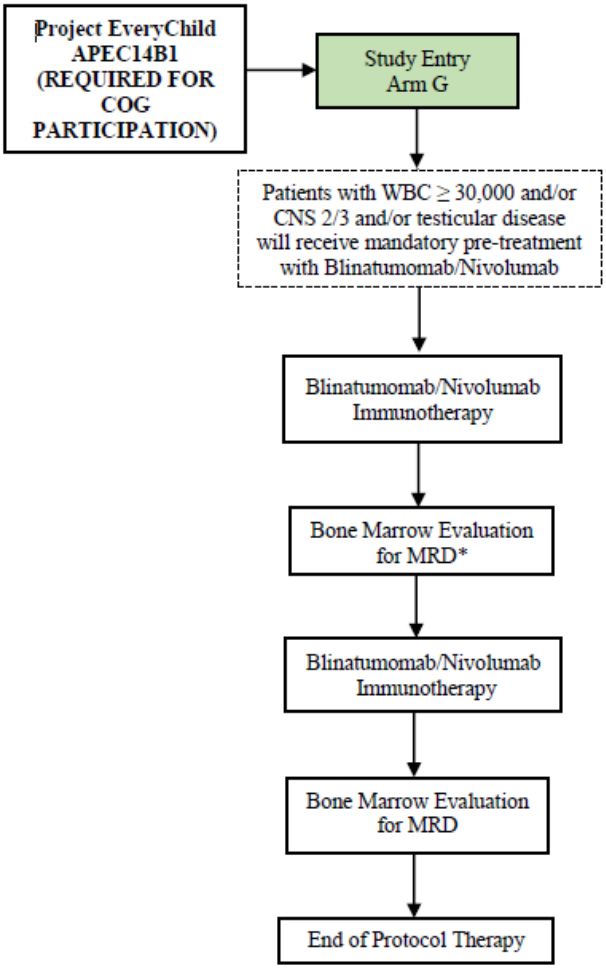
*Patients with MRD < 0.01% after Cycle 1 may choose to either go off protocol therapy (at physician's discretion) or proceed to Cycle 2 immunotherapy on assigned arm. Patients with MRD ≥ 0.01% will receive Cycle 2 immunotherapy on assigned arm.

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.

EXPERIMENTAL DESIGN SCHEMA: GROUP DOWN SYNDROME (DS)



*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.