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.**

3.3.1 Summary of Study Specific Population Categories

Treatment Group	Definition	Randomization
Group 4	• Patients ≥ 18 years of age with marrow relapse, regardless of duration between initial diagnosis and first relapse, with or without extramedullary disease • Patients < 18 years of age with marrow relapse < 36 months from initial diagnosis, regardless of bone marrow MRD after VXLD • Patients < 18 years of age with marrow relapse ≥ 36 months from initial diagnosis, with bone marrow MRD ≥ 0.1% after VXLD. • Patients ≥1-<31 years of age with IEM relapse < 18 months from initial diagnosis regardless of bone marrow MRD after VXLD • Patients ≥1-<31 years of age with IEM relapse ≥ 18 months from initial diagnosis with bone marrow MRD ≥ 0.1% after VXLD	Yes: Arm H (blinatumomab) vs. Arm I (blinatumomab with nivolumab)
Group 3	• Patients < 18 years of age with marrow relapse ≥ 36 months from initial diagnosis with bone marrow MRD < 0.1% after VXLD • Patients with IEM relapse ≥ 18 months from diagnosis with bone marrow MRD < 0.1% after VXLD	Yes: Arm E (blinatumomab) vs. Arm F (blinatumomab with nivolumab)
Down Syndrome (DS)	All patients with Down Syndrome and first marrow relapse, regardless of duration between initial diagnosis and first relapse, or presence of extramedullary disease	No: Arm G (blinatumomab with nivolumab)

For clarity, the term "CR1" has been retired in favor of the phrase "duration between initial diagnosis and first relapse" with Amendment #4E.

___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 5 - Down syndrome, will consent to the possibility of receiving pre-immunotherapy and immunotherapy	Prior to enrollment	DS
Consent 6 - Optional consent for any patient with suspected relapse who may later enroll on AALL1821. (new with Amendment #4E)	BM collection to confirm suspected relapse, prior to enrollment. See Section 14.1 for specimen collection requirements. NOTE: It's required that patients be informed of bone marrow collection for potential use in a research study. Use of a separate consent document per institutional guidelines is permitted in lieu of AALL1821 ICD #6	All potential AALL1821 patients
Consent 7 - Reinduction (VXLD) for Groups 3 and 4 (new with Amendment #4E)	Prior to enrollment	Groups 3 and 4
Consent 8 - Group 4 post-VXLD (new with Amendment #4E)	After post-VXLD evaluation	Group 4
Consent 9 - Group 3 post-VXLD (new with Amendment #4E)	After post-VXLD evaluation	Group 3

__5. Callback for Treatment Assignment/Randomization

Callback	Timing	Population	Purpose
Pre-VXLD Callback		Groups 4 and 3	Confirmation of eligibility to enroll on study.
*Post VXLD Callback	Post-VXLD evaluation	Group 3	Confirmation of eligibility and randomization: **Arm E** (blinatumomab)

		Group 4	or **Arm F** (blinatumomab with nivolumab) Confirmation of eligibility for immunotherapy and randomization: **Arm H** (blinatumomab) or **Arm I** (blinatumomab and nivolumab)
Down syndrome Pre-Immunotherapy Treatment Callback	After enrollment and prior to start of pre-immunotherapy treatment.	Patients with Down syndrome are required to receive pre-immunotherapy treatment	Confirmation of eligibility for pre-immunotherapy treatment.
Down syndrome Immu notherapy 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.	Patients with Down syndrome	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.

Requirements for Starting Protocol Therapy

Upon registration and enrollment on AALL1821 in OPEN, sites will need to complete the On Study form in Rave. Since there are questions on this form required for determination of Pre-immunotherapy treatment (for DS patients) and Stratum Assignment, it is imperative this form be completed prior to beginning protocol therapy.

Steps for Group 3 and Group 4 Patients

• The Pre-VXLD Callback form in OPEN will assign patients to VXLD Reinduction treatment. This step is required for all Group 3 and 4 patients and must be completed prior to beginning any protocol therapy.
This step is required for all Group 3 and 4 patients and must be completed prior to beginning any protocol therapy.

• Once the patient completes VXLD Reinduction Treatment, the corresponding Reporting Period CRF and the Day 36 VXLD Reinduction MRD CRF should be completed in Rave. When all the required information for stratum assignment has been entered into Rave, the New Stratum question on the Stratum Assignment Post VXLD Group 3/4 patients form will auto-populate and prompt the Study Chair to approve the form.

• Once the Study Chairs approve this form**, the site will then need to complete the Post-VXLD Callback form in OPEN**. This Callback randomizes and assigns patients to Arm H and I for Group 4 patients and Arm E and F for Group 3 patients.

• Please note that Group 4 and Group 3 patients who begin randomized immunotherapy without completing the Post-VXLD Callback in OPEN will be deemed inevaluable and the patient will be taken off protocol therapy.

Steps for Patients with DS

• For patients with DS, the New Stratum will be defaulted to Stratum 3 on the DS Stratum Assignment CRF in Rave.

• Once the Study Chair Stratum Assignment CRF is completed and approved, if Pre-immunotherapy treatment is required, sites must complete the Pre-immunotherapy Callback in OPEN. The purpose of this Callback is to assign patients to Pre-immunotherapy treatment and must be completed prior to beginning protocol therapy.

• Please note the Study Chair Stratum Assignment form will indicate whether Pre-immunotherapy is required for the patient. Therefore, sites should NOT begin pre-immunotherapy prior to Stratum Assignment and Callback completion.

• If Pre-immunotherapy treatment is not required, sites must complete the DS Callback in OPEN prior to beginning immunotherapy treatment. The DS Callback will assign patients to Arm G for DS immunotherapy.

If for any reason a patient is administered protocol treatment before the Callback is completed, please notify the Study Chair and Research Coordinator immediately.

___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.

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. Patients must not have had a prior hematopoietic stem cell transplant.
c. 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.
d. In the 28 days prior to enrollment, up to five days of post-relapse, preenrollment therapy (steroids and/or hydroxyurea only) is permissible.

• Patients with Down syndrome who received pre-enrollment therapy and have a WBC ≥ 30,000/µl at the time of enrollment still must receive protocol specified cytoreductive therapy with vincristine and dexamethasone per Section 4.1.2.4, and no "washout" is required

• Patients with Down syndrome 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/sex 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:

See section 3.2.4 for exclusions related to prior therapy.

___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.
___9. Patients with uncontrolled HIV, hepatitis B, or hepatitis C infection. 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.
___10. 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.
___11. Group 4 and patients with DS with known non-hematopoietic, nonCNS/testicular extramedullary disease (i.e., chloromatous disease) are not eligible.

Note: Group 3 patients with known non-hematopoietic, nonCNS/testicular extramedullary disease (i.e., chloromatous disease) are eligible if this is NOT the only site of relapsed disease.
___12. 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.

___13. <u>Pregnancy and Breastfeeding</u>
- 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.

- Lactating females are not eligible unless they agree to not 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 3 & 4
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, and creatinine.
d. IgG and absolute lymphocyte count (ALC).
e. Strongly recommended: absolute CD19 and CD3 count (peripheral blood), IgA and IgM
f. Strongly recommended: vaccine titers for varicella, measles, tetanus and Hemophilus influenza.
g. Echocardiogram
h. 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.
i. Testicular Exam for male patients. Patients with testicular involvement at relapse must have response to VXLD documented at the end of the cycle.
j. 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.
k. Local BM evaluation for morphology.
l. BM for baseline immunophenotyping at a COG-approved Flow Lab. Baseline BM assessment may be performed using flow cytometry or NGS. See Section 14.2 for details.
m. BM for post-VXLD MRD assessment. See Section 14.2 for details.
n. CSF cell count and cytospin. Obtain with each IT.
o. Peripheral Blood (PB) and BM for Banking for Future Research (optional). See Section 14.3 for details.
p. PB for Immunobiology Studies (optional). See Section 14.4 for details.
q. CSF for Immunobiology Studies (optional). See Section 14.4 for details.
r. BM for Immunobiology Studies (optional). See Section 14.4 for details

Group Down Syndrome

See 4.23.2 for Down syndrome ONLY Pre-Immunotherapy treatment for WBC ≥ 30,000

See 4.24.2 for Down syndrome ONLY Pre-Immunotherapy treatment for CNS 2/3 Disease

See 4.25.2 for Down syndrome ONLY Pre-Immunotherapy treatment for Testicular Disease

See 4.26.2 for Group DS, Arm G Immunotherapy Cycle 1

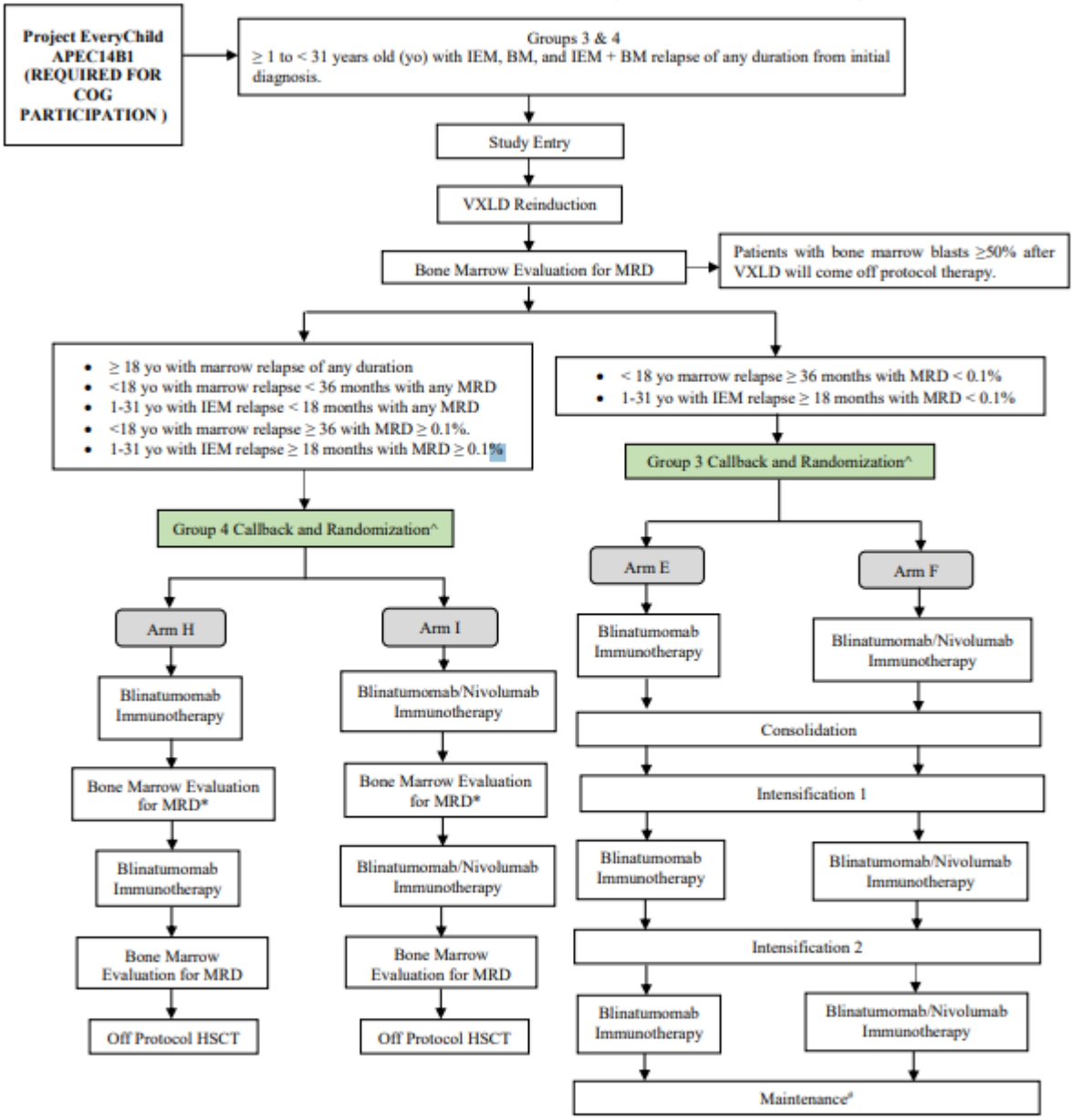
TOXICITIES AND DOSAGE MODIFICATIONS:
See Section 5

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

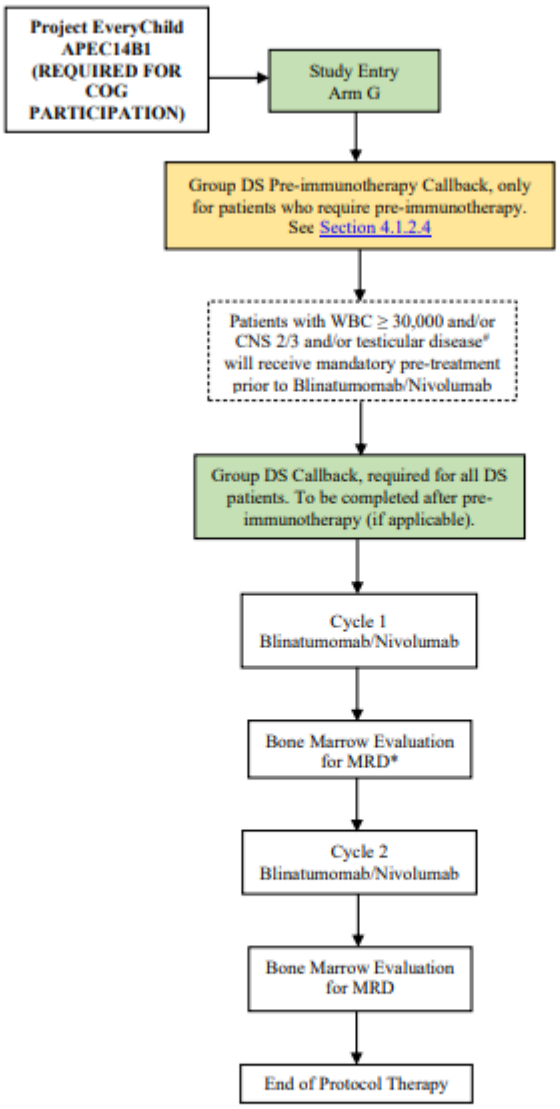
TREATMENT PLAN:

EXPERIMENTAL DESIGN SCHEMA: GROUPS 3 AND 4 (POST-AMENDMENT #4E)



EXPERIMENTAL DESIGN SCHEMA: GROUP DOWN SYNDROME (DS)

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.