

**COG- AALL07P1: A Phase II Pilot Trial of Bortezomib (PS-341, Velcade, IND# 58,443)
in Combination with Intensive Re-Induction Therapy for Children with Relapsed
Acute Lymphoblastic Leukemia (ALL) and Lymphoblastic Lymphoma (LL)**

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. Prior to obtaining informed consent and enrolling a patient, a reservation must be made with the Statistical and Data Center through the eRDE system.
- ___ 2. Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than five calendar days after the date of study enrollment. **Patients who are started on protocol therapy prior to study enrollment are ineligible for study. The only exception to this is for intrathecal cytarabine, which can be given up to 72 hours prior to the start of systemic chemotherapy for patient convenience.**
- ___ 3. Patients must be ≥ 1 year of age and ≤ 31 years of age at the time of study enrollment.
- ___ 4. Diagnosis
 - Pre-B ALL in first early (< 36 months from diagnosis) isolated bone marrow (BM) or combined BM/extramedullary relapse; or
 - T-cell ALL in first isolated BM or combined relapse; or
 - T-LL in first relapse.
- ___ 5. Patients with leukemia must have had histologic verification of the malignancy at relapse, including immunophenotyping to confirm diagnosis.
- ___ 6. Patients with lymphoblastic lymphoma must have measurable disease documented by clinical, radiographic, or histologic criteria (see Section 3.3). Patients must have relapsed or become refractory to conventional therapy.
- ___ 7. 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.
- ___ 8. Patients who relapse while receiving standard ALL maintenance chemotherapy will not be required to have a waiting period before entry onto this study.
- ___ 9. Patients who relapse on therapy other than standard ALL maintenance therapy must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.
 - Cytotoxic therapy: At least 14 days since the completion of cytotoxic therapy with the exception of hydroxyurea, which is permitted up to 24 hours prior to the start of protocol therapy.
 - Biologic (anti-neoplastic) agent: At least 7 days since the completion of therapy with a biologic agent or donor lymphocyte infusions (DLI). For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur.
 - Stem cell transplant or rescue: No evidence of active graft-vs-host disease (GVHD) and ≥ 4 months must have elapsed. Must not be receiving GVHD prophylaxis.

10. Organ Function Requirements

All patients must have:

- 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 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
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 (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

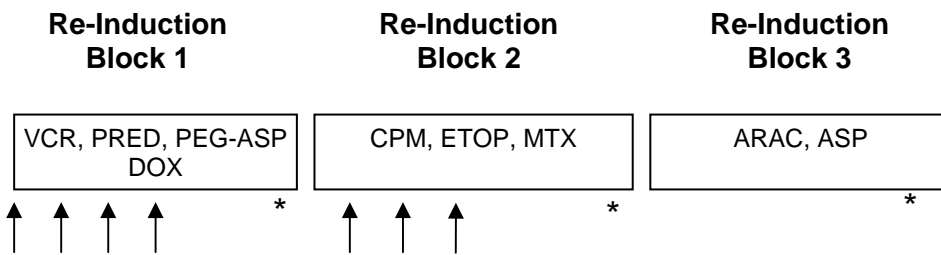
- Adequate Liver Function Defined As
 - Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
 - SGPT (ALT) < 3 x upper limit of normal (ULN) for age, unless elevation due to leukemia infiltration.
- Adequate Cardiac Function Defined As
 - Shortening fraction of $\geq 27\%$ by echocardiogram, or
 - Ejection fraction of $\geq 50\%$ by gated radionuclide study.
 - Please see Section 3.2.11.1 for prior anthracycline restrictions.
- Adequate Pulmonary Function Defined As
 - No evidence of dyspnea at rest, no exercise intolerance, and a pulse oximetry $\geq 94\%$ at sea level ($> 90\%$ if at high altitude).
 - No evidence of acute pulmonary infiltrates on chest radiograph.
- Central Nervous System Function Defined As
 - Patients with seizure disorder may be enrolled if on allowed anticonvulsants (see Section 3.2.11 and Appendix IIB) and well controlled. Benzodiazepines and gabapentin are acceptable.
 - CNS toxicity \leq Grade 2.

EXCLUSION CRITERIA:

1. Patients with Philadelphia chromosome positive ALL are **not** eligible unless refractory to at least one tyrosine kinase inhibitor (TKI) therapy. Patients that are unable to tolerate TKI therapy due to toxicity are eligible.
2. Patients with mature B-cell ALL, ie, leukemia with B-cell (sIg positive and kappa or lambda restricted positivity) ALL, with FAB L3 morphology and /or a myc translocation, are not eligible.
3. Extramedullary disease status: patients with isolated CNS disease or isolated testicular disease are **not** eligible.
4. Patients with known optic nerve and/or retinal involvement (because it may not be possible to safely delay irradiation) are **not** eligible. Patients presenting with visual disturbances should have an ophthalmological exam and, if indicated, an MRI to determine optic nerve or retinal involvement.
5. Patients with concomitant genetic syndrome: patients with Down syndrome, Fanconi anemia, Kostmann syndrome, Shwachman syndrome or any other known bone marrow failure syndrome are **not** eligible.
6. Cumulative prior anthracycline exposure must not exceed 400 mg/m² (each 10 mg/m² of idarubicin should be calculated as the isotoxic equivalent of 30 mg/m² of daunorubicin or doxorubicin).
7. Patients taking anticonvulsants known to activate the cytochrome p450 system, in particular anticonvulsants such as phenytoin, carbamazepine, and phenobarbital, are **not** eligible. Benzodiazepines and gabapentin are acceptable (see Appendix IIB). Please see Appendix II for a list of drugs known to be potent inducers/inhibitors of the cytochrome p450 system.
8. Patients who have previously received bortezomib or other proteasome inhibitors are **not** eligible.

- ___9. Patients who have a known allergy to doxorubicin, cytarabine, both etoposide and etopophos, boron, mannitol or bortezomib are **not** eligible.
- ___10. Patients who cannot receive asparaginase on this study (eg, due to prior severe pancreatitis, stroke or other toxicity) are not eligible. Patients who initially receive asparaginase, but must discontinue due to toxicity, remain eligible. Patients with clinically significant prior allergies to pegaspargase are eligible if *Erwinia L-asparaginase* can be substituted. (See guidelines in Section 5.2.)
- ___11. Pregnancy and Breast Feeding: patients who are pregnant or breast-feeding are not eligible for this study as there is as yet no available information regarding human fetal or teratogenic toxicities. Negative pregnancy tests must be obtained in girls who are post-menarchal. Males or females of reproductive potential may not participate unless they have agreed to use an effective birth control method.
- ___12. Patients must not have received any prior Re-Induction attempts and must not have received treatment for prior extramedullary relapse. Patients with primary induction failure are not eligible.

**TREATMENT PLAN:
EXPERIMENTAL DESIGN SCHEMA**



↑ Bortezomib on
Days 1, 4, 8 & 11 of Block 1
Days 1, 4, & 8 of Block 2

VCR = Vincristine
 PRED = Prednisone
 PEG-ASP = PEG-asparaginase
 DOX = Doxorubicin
 CPM = Cyclophosphamide
 ETOP = Etoposide
 MTX = Methotrexate
 ARAC = Cytarabine
 ASP = L-Asparaginase

* MRD at the completion of each block

TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5.0.

SPECIMEN REQUIREMENTS:

Required Observations and Optional Research Studies Pre-Study

All baseline studies must be performed within 1 week prior to study entry (unless otherwise specified).

- History
- Physical Exam with vital signs and complete neurologic exam ¹
- Height, weight, BSA
- Performance Status
- CBC, differential, platelets
- Urinalysis
- Electrolytes including glucose, Ca⁺⁺, PO₄, Mg⁺⁺
- BUN, Creatinine, uric acid, ALT, AST, bilirubin
- Total protein/albumin
- Chest x-ray
- Pulse oximetry
- Echocardiogram or gated radionuclide study
- Prothrombin, partial thromboplastin time and fibrinogen
- Bone marrow for FAB morphology, immunophenotyping and cytogenetic analysis ²
- Bone marrow for MRD (leukemia patients only, see Appendix V)
- CT and PET or gallium – lymphoma patients only ³
- Lumbar puncture with CSF cell count and cytopin cytology.
- Pregnancy Test ⁴
- Correlative Biology Studies ⁵

1. See Section 11.9 for information on submission of data via RDE for the baseline neurologic exam.
2. Bone marrow aspirate to confirm M3 bone marrow.
3. Gallium scan may be substituted for PET scan at sites where PET is not available. PET should not be used as a substitute for CT with contrast at diagnosis or at any required evaluation point. The same scanning modality (gallium or PET) should be used for all required evaluation points. Combined PET/CT is acceptable.
4. Female patients of childbearing potential require a negative pregnancy test prior to starting treatment and must use an acceptable method of birth control. Abstinence is an acceptable method of birth control.
5. See Section 7.2 for specifics of optional correlative biology studies in consenting patients.

BIOLOGY REQUIREMENTS:

Bone marrow for MRD testing is required prior to treatment and at the end of Block 1. Other blood and marrow submissions are optional.

CONCOMITANT AND PRIOR MEDICATIONS RESTRICTIONS:

1. Hydroxyurea (20-30 mg/kg/day; escalate as needed to 80-100 mg/kg/day) is permitted up to 24 hours prior to the start of protocol therapy.
2. No other cancer chemotherapy or immunomodulating agents will be used. Corticosteroid therapy is not permissible except as 1) treatment or prophylaxis for anaphylactic reactions, or 2) treatment for pulmonary toxicity. Steroids are not permitted as anti-emetic therapy.
3. Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary. (See COG Member website for supportive care guidelines.) NOTE: It is recommended that Ciprofloxacin **not** be used as a prophylactic antibiotic.
4. Of the drugs used in the protocol, the following are substrates or inhibitors of the cytochrome P450 (CYTP450) enzymes. For a list of interacting drugs, see Section 5.12. For a list of CYT P450 inhibitors and inducers see Appendix II.

Drug	Substrates of CYP450 enzymes					Inhibitors of CYP450 enzymes				
	2C9	2C19	2D6	3A4	other	2C9	2C19	2D6	3A4	other
Bortezomib	+	+++	+	+++	1A2 +	+	++	+	+	1A2 +
Cyclophosphamide	+	+		+++	2B6 +++ 2C9 +				+	
Doxorubicin			+++	+++				+	+	2B6 ++
Etoposide				+++	1A2 + 2E1 +	+			+	
Hydrocortisone				+						
Prednisone				+						
Vincristine				+++					+	

+ minor or weak

++ moderate

+++ major