

**COG-AAML07P1: A Phase II Pilot Study of Bortezomib (PS-341, Velcade, IND #58,443)
Combined with Reinduction Chemotherapy in Children and Young Adults
with Recurrent, Refractory or Secondary Acute Myeloid Leukemia**

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. Reservations may be obtained 24-hours a day through the COG website. Please refer to the Reservation System eRDES User Guide that can be downloaded from:
https://members.childrensoncologygroup.org/files/Help/eRDES_ReservationSystem_UserGuide.pdf
- ___ 3. Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than 5 calendar days after the date of study enrollment. **Patients who are started on protocol therapy on a Phase II study prior to study enrollment will not be entered on study.** See Section 7.1 for timing of entry/eligibility studies.
- ___ 4. **Eligibility studies must be performed within 7 days prior to enrollment, with the exception of the bone marrow aspirate, which may be performed within 14 days prior to enrollment.**
- ___ 5. This study is in the efficacy phase and the first stage of Arm A, patients must be > 12 months and ≤ 21 years of age at the time of study enrollment.
- ___ 6. Patients must have a diagnosis of acute myelogenous leukemia (AML) according to WHO classification with ≥ 5% blasts in the bone marrow, with or without extramedullary disease (see Appendix VII).
- ___ 7. To be eligible for the **Efficacy Phase**:
Relapse patients:
 - Must have had a prior diagnosis of AML, with no restriction on prior cytogenetics
 - Must be in first relapse, and
 - Must not have received prior reinduction therapy.Refractory patients:
 - Must have had a prior diagnosis of AML, and
 - Must not have received more than one attempt at remission induction (which may consist of up to two therapy courses).Patients with treatment-related AML (t-AML):
 - Must be previously untreated for secondary AML
- ___ 8. Patients diagnosed with any of the following are **not** eligible:
 - Down syndrome
 - Fanconi anemia, Kostmann syndrome, Shwachman syndrome or any other known bone marrow failure syndrome
 - Juvenile Myelomonocytic Leukemia (JMML) and Acute Promyelocytic Leukemia (APL; FAB M3)
- ___ 9. CNS disease: Patients must have the status of CNS1 or CNS2, and no clinical signs of CNS leukemia, such as cranial nerve palsy. Patients with CNS3 disease are not eligible. See Section 3.2.10.1 for further details.
- ___ 10. Performance Level: Patients must have a Lansky or Karnofsky performance status score of ≥ 50, corresponding to ECOG categories 0, 1 or 2 (Appendix I). Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age.
- ___ 11. Prior Therapy: Patients must have recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study. All prior treatment-related toxicities must have resolved to ≤ Grade 2 prior to enrollment.
 - Cytotoxic therapy: Patients must not have received cytotoxic chemotherapy within 2 weeks of the first dose of study drug (4 weeks if prior nitrosourea) with the exception of hydroxyurea, which is allowed up to 24 hours prior to first dose of study drug, and intrathecal chemotherapy, which is allowed immediately up to administration of study drug (see Section 4.4.1). Steroids may have been given as clinically indicated for patients with asthma; hydrocortisone and methylprednisolone may be given as premedication in patients with a history of severe allergic reactions. All prior treatment-related toxicities must have resolved to ≤ Grade 2 prior to enrollment.

- **Biologic Anti-Neoplastic Agents:** At least 7 days since the completion of therapy with biologic agents such as steroids, retinoids, or DLI (donor lymphocyte infusion without conditioning). For agents that have known adverse events occurring beyond 7 days after administration (i.e. monoclonal antibodies), this period must be extended beyond the time during which acute adverse events are known to occur.
- **Radiation Therapy:** The following amounts of time must have elapsed prior to entering study:
 - 2 weeks must have elapsed for local palliative XRT (small port);
 - 8 weeks must have elapsed if prior craniospinal XRT or if $\geq 50\%$ radiation of pelvis;
 - 6 weeks must have elapsed if other bone marrow radiation has been administered.
 See Section 3.2.7.5 regarding exclusion criteria involving prior radiation therapy, including prior total body irradiation (TBI).
- **Stem Cell Transplant (SCT):** No evidence of active graft vs. host disease. At least 2 months must have elapsed from Stem Cell reinfusion. Patients must be off all graft vs. host disease medication.
- Patients must have not received prior treatment with bortezomib or other proteasome inhibitors.

12. **Organ Function Requirements**

All patients must have:

- Adequate renal function defined as:
- Creatinine clearance or radioisotope GFR $\geq 70\text{ml/min/1.73m}^2$ 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 $\leq 1.5 \times$ upper limit of normal (ULN) for age and institution, and
- SGPT (ALT) $< 3.0 \times$ upper limit of normal (ULN) for age and institution (unless elevation is related to leukemia involvement).

Adequate cardiac function defined as:

- Shortening fraction of $\geq 27\%$ by echocardiogram, or
- Ejection fraction of $\geq 50\%$ by gated radionuclide study.

Adequate pulmonary function, both criteria must be met:

- A respiratory rate that is within normal limits for age when measured when the patient is afebrile and at rest (for definitions see Section 4.5.6), and a pulse oximetry $> 94\%$ on room air. The respiratory rate must be measured for a full minute, and not calculated on the basis of an observation period of less than 1 minute. Every attempt should be made to ensure that the observation for respiratory rate is performed when the patient is afebrile and comfortable. Patients with a history of asthma or other obstructive pulmonary disease are allowed to use bronchodilators prior to measurement of respiratory rate.
- Normal pulmonary function tests ($> 80\%$ predicted FEV1 and FVC and DLCO $> 50\%$ corrected for hemoglobin) for those patients able to perform this examination. Patients with a history of asthma or other obstructive pulmonary disease are allowed to use bronchodilators prior to pulmonary function testing. Patients who are unable to perform PFTs (e.g. because of young age) will be excluded if they have a medical history of significant prior pulmonary events or chronic pulmonary disease (e.g. pneumonia requiring mechanical ventilation support, pulmonary GVHD, pneumonectomy, or pulmonary toxin exposure); children with histories of resolved

bronchiolitis, resolved viral pneumonias and well-controlled asthma are eligible, even if they are unable to perform PFTs.

Central Nervous System function defined as:

- Patients with seizure disorder may be enrolled if on a non-enzyme-inducing anticonvulsant (see Appendix II and Section 3.2.8.2) and if seizures are well-controlled.
- CNS toxicity \leq Grade 2.

13. Other restrictions

- Patients who are pregnant or breast-feeding are not eligible for this study as there is yet no available information regarding human fetal or teratogenic toxicities. Negative pregnancy tests must be obtained in girls who are post-menarchal (see Section 7.1). Males or females of reproductive potential may not participate unless they have agreed to use an effective birth control method.
- Investigational Drugs: Patients who are currently receiving any investigational drugs are **not** eligible.
- Patients who have an uncontrolled infection are **not** eligible.
- Patients who have a known allergy to idarubicin, cytarabine, etoposide, boron, mannitol or bortezomib are **not** eligible.
- Patients with a prior history of radiation therapy to more than 25% of the lung volume are **not** eligible.
- Patients who have received TBI as a part of a hematopoietic stem cell conditioning regimen are not eligible.

14. Concomitant Medications:

- Growth factor(s): Growth factors that support platelet or white cell number or function must not be administered within 4 days of study entry. The intention is to provide a period of at least 7 days from growth factor therapy to the beginning of study therapy.
- P450-interacting agents: Patients taking the anticonvulsant medications known to be potent inducers of the cytochrome P450 system, including phenytoin, carbamazepine, and phenobarbital are excluded from study participation (see Appendix II). Benzodiazepines and gabapentin are acceptable (see Appendix II). A list of other drugs with potential for interaction with P450 enzymes are listed in Appendix III. Attempts should be made to avoid the use of the drugs listed in Appendix III.

REQUIRED OBSERVATIONS:

Required and Recommended Clinical, Laboratory and Disease Evaluations

All baseline studies must be performed within 7 days of starting protocol therapy unless otherwise noted below. This table only includes evaluations necessary to answer the primary and secondary aims. Obtain other studies as indicated for good clinical care.

- History
- Physical Exam (including VS)
- Ht, Wt, BSA
- Neurologic Exam ¹
- Performance Status ²
- CBC, Differential, Platelets ³
- Urinalysis
- Electrolytes including Ca⁺⁺, PO₄, Mg⁺⁺
- Creatinine, SGPT, Bilirubin
- Total Protein/Albumin
- Transcutaneous O₂ Saturation & Respiratory Rate ⁴
- Bone Marrow Aspirate ⁵
- Immunophenotyping ⁶
- Lumbar Puncture ⁷
- Pregnancy Test ⁸
- ECHO or MUGA ⁹
- Pulmonary Function Test ¹⁰
- 24-h Cr Clearance or GFR ¹¹
- Chest X-Ray

1. Required at baseline and upon the development of neurologic abnormalities. Weekly neurologic exams are strongly encouraged during the first cycle, but are not required (see Appendix IV)
2. See Appendix I for performance scale status scores
3. If patient develops Grade 4 neutropenia, CBC should be checked every 3-4 days until recovery to Grade 3. Patients placed on G-CSF should have twice-weekly CBC.
4. Determine that O₂ saturation is > 94% on room air and that patient is not tachypneic at rest within 12 hours prior to bortezomib administration.
5. Perform baseline BMA within 14 days prior to the beginning of treatment. End of cycle BMA is performed on Days 28-33. For patients whose initial response assignment is not evaluable, bone marrow analysis should be repeated weekly until ANC \geq 1000 or through at least Day 49 for response determination. A bone marrow biopsy is acceptable if an aspirate is not obtainable.
6. Immunophenotype confirmation of disease, either at diagnosis or at relapse, is required. When available, please fax immunophenotype report to Dr Horton's lab (832) 825-4276 (Appendix V).
7. Lumbar puncture within 7 days of study entry. Those with CNS symptoms or CNS3 status are ineligible (see Section 3.2.10.1). An initial dose of intrathecal chemotherapy may be given during the pre-treatment lumbar puncture. Repeat lumbar puncture in subsequent cycles as clinically indicated.
8. Patients of childbearing potential require a negative pregnancy test prior to coming on study.
9. The same test (ECHO or MUGA) should be used for each evaluation.
10. Obtain FVC, FEV1 and DLCO (on children old enough to perform tests) per institutional guidelines. Patients prescribed bronchodilators, inhaled steroids or other inhaled medications should take their routine medications prior to performing the evaluation.
11. Baseline observation may fulfill Day 1 requirement. 24 hr Cr Clearance/GFR is only required if serum creatinine does not meet the guidelines in Section 3.2.6.1. During Cycle 1, if serum creatinine shows an increase of baseline serum creatinine by > 25% repeat 24 Hour Cr Clearance/GFR at end of cycle.

TREATMENT PLAN:

For patients below a threshold cumulative anthracycline dose (400 mg/m^2), bortezomib will be combined with a regimen containing idarubicin and cytarabine (Arm A; CIB).

See attached Experimental Design Schema.

TOXICITIES AND DOSAGE MODIFICATIONS:

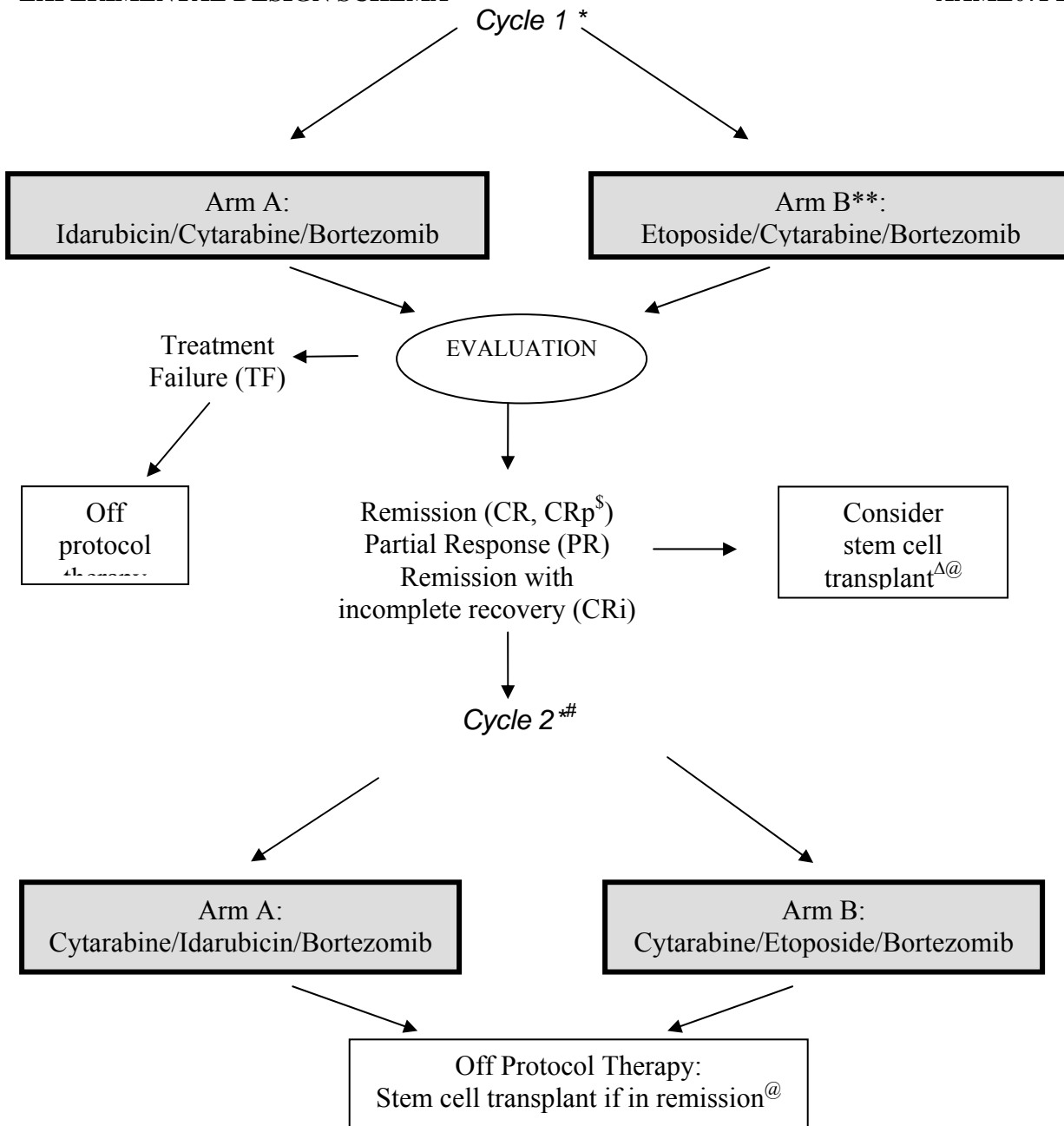
See Section 5.

SPECIMEN REQUIREMENTS:

See Appendixes V & VI

EXPERIMENTAL DESIGN SCHEMA

AAML07P1



*Each cycle is 28 days
 ** Initial Dose Escalation Phase for Arm B only: Starting dose of bortezomib 1 mg/m²; escalate to 1.3 mg/m² or deescalate to 0.7 mg/m² as tolerated. Efficacy phase in Arm B will use the dose of bortezomib determined to be the MTD in the initial Dose-Finding Phase. Arm A will open groupwide using bortezomib at 1.3 mg/m².
 # Patients can receive an additional cycle of therapy if they meet the criteria in Section 4.7. Patients in Arm A can receive an additional cycle of Arm A therapy IF they have received ≤ 400 mg/m² cumulative anthracycline dose. See Section 4.3 for anthracycline equivalence definitions. Patients in Arm B may receive an additional cycle of Arm B therapy.
 ^ Subjects may receive Cycle 2 while awaiting stem cell transplant if they meet criteria in Section 4.7.
 @ Enrollment on the current COG transplant protocol is strongly encouraged. However, investigators are permitted to use existing institutional high-dose chemotherapy preparative regimens prior to stem cell transplant. If therapy is unsuccessful, patients may be eligible for additional COG-sponsored salvage regimens (see COG priority list).
 \$ CR: Complete Remission; CRp: CR with partial recovery of platelets.