AMC PROTOCOL #053:
Safety and Efficacy Pilot Trial of the Anti-Viral and Anti-
Tumor Activity of Velcade Combined with (R)ICE in Subjects
with Relapsed/Refractory AIDS-Associated Lymphoma

A Multi-Center Trial of the AIDS Malignancy
Clinical Trials Consortium

Sponsored by: National Cancer Institute
Office of HIV and AIDS Malignancy (OHAM)

Pharmaceutical Support Provided by: Millennium Pharmaceuticals, Inc.
Millennium Protocol # X05199

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5.0 STUDY POPULATION

5.1 Selection of Subjects

Enrollment is defined as the first day of Velcade treatment (i.e., Day 1 of Part A).

The pilot phase of the protocol will plan to enroll up to 18 subjects. Within the AMC, we expect to enroll eight subjects per year.

5.2 Inclusion Criteria

Each subject must meet all of the following inclusion criteria to be enrolled in the study:

5.2.1 Histologically or cytologically confirmed relapsed or refractory HIV-associated NHL or Hodgkin lymphoma; patients with clinical relapsed/refractory disease where biopsy is not feasible need to have had histologic or cytologic documentation of AIDS-associated NHL or Hodgkin lymphoma previously (i.e., at time of diagnosis). Subjects must have documented HIV seropositivity.

5.2.2 Subjects who are on antiretroviral therapy at the time of entry must be on a stable regimen for at least 12 weeks prior to study entry.

5.2.3 Demonstration of either ABC subtype of DLBCL (using Hans criteria) or EBV and or HHV-8 infection within the lymphoma (i.e. LMP-1 or LANA expression, positive Epstein-Barr–encoded RNAs (EBERs)). Documentation of this status may be from either initial lymphoma diagnosis or at relapse.

5.2.4 Age ≥18 years. Because no dosing or adverse event (AE) data are currently available on the use of Velcade in combination with ICE in subjects <18 years of age, children are excluded from this study, but will be eligible for future pediatric Phase 1 combination trials.

5.2.5 ECOG performance status 0, 1 or 2 or Karnofsky Performance Status ≥ 50% (See Appendix II).

5.2.6 Life expectancy > 2 months

5.2.7 Subjects must have adequate organ and marrow function as defined below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Requirement</th>
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<tbody>
<tr>
<td>ANC</td>
<td>≥1,000/mm³*</td>
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<tr>
<td>Hemoglobin</td>
<td>≥8.0 gm/dL.*</td>
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<tr>
<td>Platelets</td>
<td>≥100,000/mm³</td>
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<tr>
<td>Total bilirubin</td>
<td>≤1.5 mg/dL</td>
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<td>AST(SGOT) and ALT(SGPT)</td>
<td>≤2.5 X institutional upper limit of normal (ULN)</td>
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<tr>
<td>Serum creatinine</td>
<td>≤ institutional ULN</td>
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<tr>
<td>Creatinine clearance</td>
<td>≥50 mL/min/1.73 m² for subjects with creatinine levels above institutional normal</td>
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Subjects may be receiving growth factor support to meet these criteria. Subjects with lymphomatous involvement of the bone are eligible even if they do not meet the hematologic criteria listed above.

5.2.8 Female subjects must have a negative pregnancy test within 2 weeks of entering into the study and all subjects agree to use adequate birth control if conception is possible during the study. It is recommended that women avoid pregnancy and men avoid fathering children while in the study. Should a woman subject or partner of a male subject become pregnant or suspect she is pregnant while the subject is participating in this study, she should inform her treating physician immediately.

5.2.9 Ability to understand and the willingness to sign a written informed consent document. (See Velcade (R)ICE Protocol Consent).

5.3 Exclusion Criteria

5.3.1 Subjects meeting any of the following exclusion criteria are not to be enrolled in the study.

5.3.2 Subjects who have had chemotherapy within 3 weeks prior to entering the study, radiation therapy within 2 weeks or those who, in the opinion of the investigator, have not recovered sufficiently from AEs due to agents administered more than 3 weeks earlier. Glucocorticoid therapy within the last 3 weeks is allowed.

5.3.3 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. Subjects with opportunistic infections that are controlled by antimicrobial or suppressive therapy are eligible for participation unless the investigator judges the infection likely to become life-threatening in the setting of multi-agent chemotherapy.

5.3.4 Subjects must not require concurrent therapy with moderate to strong CYP3A4 inducers or inhibitors other than protease inhibitors due to interactions with bortezomib and ifosfamide metabolism. See Section 7.5 for a list of prohibited concurrent medications.

5.3.5 Pregnant women are excluded from this study because Velcade, ifosfamide, carboplatin and etoposide are agents with the potential for teratogenic or abortifacient effects. All of these drugs are known to be excreted in breast milk. Because there is an unknown but potential risk for AEs in nursing infants secondary to treatment of the mother with Velcade, ifosfamide, carboplatin or etoposide, breastfeeding should be discontinued if the mother is treated with Velcade, ifosfamide, carboplatin or etoposide. These potential risks may also apply to other agents used in this study.

5.3.6 Female subject is pregnant or breast-feeding. Confirmation that the subject is not pregnant must be established by a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test result obtained during screening. Pregnancy testing is not
required for post-menopausal or surgically sterilized women.

5.3.7 Subject has ≥ Grade 2 peripheral neuropathy within 14 days prior to enrollment.

5.3.8 Myocardial infarction within 6 months prior to enrollment or has New York Hospital Association (NYHA) Class III or IV heart failure (see Appendix V), uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any electrocardiogram (ECG) abnormality at Screening has to be documented by the Investigator as not medically relevant.

5.3.9 Subject has hypersensitivity to compounds of similar chemical or biologic composition to Velcade, boron, mannitol, ifosfamide, carboplatin, or etoposide.

5.3.10 Subject has received other investigational drugs within 14 days prior to enrollment.

5.3.11 Acute active HIV-associated opportunistic infection requiring antibiotic treatment. Subjects with Mycobacterium avium or candidiasis are not excluded when concurrent therapy with moderate to strong CYP3A4 inducers or inhibitors is required because of this infection. Chronic therapy with potentially myelosuppressive agents is allowed provided that entry hematologic criteria are met.

5.3.12 Concurrent malignancy excluding in situ cervical cancer, in situ anal cancer, or non-metastatic non-melanomatos skin cancer, or Kaposi’s sarcoma not requiring systemic chemotherapy.

5.3.13 Serious medical or psychiatric illness likely to interfere with participation in this clinical study.

5.3.14 Patients found to have an active hepatitis B infection (hepatitis B surface antigen +) are not eligible unless they meet ONE of the following criteria:
   • Patient is able to start dual anti-Hep B therapy prior to enrollment with adefovir and telbivudine.
   • Patient is already on dual anti-hepatitis B therapy; if either of the agents has activity against HIV (i.e., entecavir, tenofovir, lamivudine or emtricitabine) they must have been on this regimen for at least 12 weeks prior to study enrollment.

5.3.15 Consultation and co-management with a hepatitis expert regarding hepatitis B treatment is strongly encouraged before and during the trial.

5.3.16 Subjects previously treated with the ICE salvage chemotherapy regimen.

5.4 Recruitment Plan

Subjects seen in the inpatient or outpatient setting who meet eligibility criteria will be recruited to this study. Participation is voluntary. The subject will be made aware of his or her diagnosis and current nature of this treatment program. All subjects will be required to sign a statement of informed consent that conforms to FDA and Institutional Review Board