



**AIDS MALIGNANCY
CLINICAL TRIALS CONSORTIUM**

**AMC PROTOCOL #047:
A Phase II Trial of Doxil, Rituximab, Cyclophosphamide,
Vincristine, and Prednisone (DR-COP) in Patients with Newly
Diagnosed AIDS-associated B-Cell Non-Hodgkin's Lymphoma**

**A Multi-Center Trial of the AIDS Malignancy
Clinical Trials Consortium (AMC)**

Sponsored by: National Cancer Institute
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AMC PROTOCOL SIGNATURE PAGE

I, _____, Principal Investigator at site _____, agree to conduct and follow this protocol: **AMC Protocol #047 - A Phase II Trial of Doxil, Rituximab, Cyclophosphamide, Vincristine, and Prednisone (DR-COP) in Patients with Newly Diagnosed AIDS-Associated B-Cell Non-Hodgkin's Lymphoma (Version 6.0, 01/21/2011)**, as written according to AMC, NCI and FDA guidelines. I understand that no deviations from the above protocol may be made without written permission from the Protocol Chair(s).

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PROTOCOL ROSTER

AMC-047

A Phase II Trial of Doxil, Rituximab, Cyclophosphamide, Vincristine, and Prednisone (DR-COP) in Patients with Newly Diagnosed AIDS-Associated B-Cell Non-Hodgkin's Lymphoma

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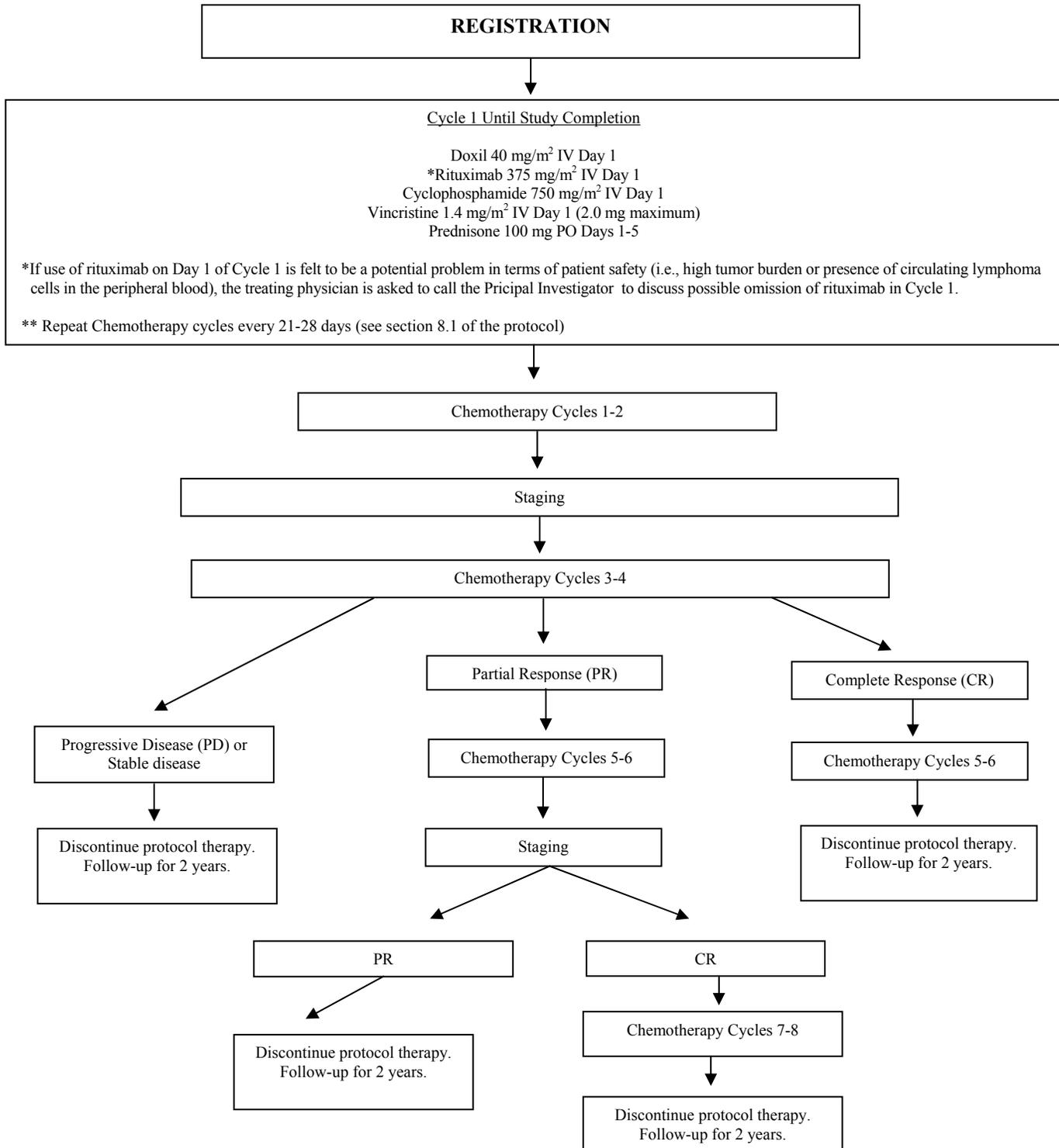
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STUDY SCHEMA

A Phase II Trial of Doxil, Rituximab, Cyclophosphamide, Vincristine, and Prednisone (DR-COP) in Patients with Newly-Diagnosed AIDS-Associated B-cell Non-Hodgkin's Lymphoma (NHL)



1.0 BACKGROUND AND RATIONALE

1.1 Role of Highly Active Anti-Retroviral Therapy (HAART) in Acquired Immune Deficiency Syndrome (AIDS)-Related Lymphoma

The use of HAART has been associated with a marked improvement in overall survival for patients with AIDS-related lymphoma, such that median survival times now approach those achieved in HIV-negative patients with de novo aggressive lymphoma.¹⁻⁶ Nonetheless, while HAART has clearly been associated with prolonged survival, it is currently unclear if HAART must be given concomitantly with chemotherapy or immediately thereafter.^{2,7}

1.2 Response to Therapy and MDR-1 Expression

It has been hypothesized that suboptimal responses to chemotherapy observed in some patients with AIDS-related lymphoma may be due to tumor cell resistance, mediated by the protein product of multi-drug resistance 1 (MDR-1), p-glycoprotein (P-gp). MDR-1 gene expression has been correlated with clinical resistance to chemotherapy, mediated through overexpression of P-gp, a 170-kd plasma glycoprotein, which acts as a unidirectional, drug efflux pump, resulting in decreased intracellular drug accumulation.⁸⁻¹⁰ In lymphoma that is unrelated to human immunodeficiency virus (HIV), the majority of studies have demonstrated MDR-1 expression in less than 20% of patients at the time of initial diagnosis, with an increase to more than 50% at the time of relapse.^{11,12} By contrast, in a population of 50 patients with newly-diagnosed AIDS-related lymphoma, Tulpule et al. demonstrated that tissues from 33 patients (66%) expressed MDR-1 at lymphoma diagnosis.¹³ Of importance, this group had a significantly lower complete remission (CR) rate when compared with MDR-1 negative patients. Thus, an abnormally high rate of MDR-1 expression in patients with AIDS-related lymphoma may serve as another explanation for the low response rates observed in these individuals. Of interest, protease inhibitors may serve as both substrates and inducers of MDR-1, thus providing a potential explanation for the divergence of MDR-1 expression profiles in patients with HIV-related or de novo aggressive lymphoma.^{14,15}

1.3 Addition of Rituximab to Combination Chemotherapy in Patients with AIDS-Related Lymphoma

Coiffier and colleagues demonstrated a significant advantage to the addition of rituximab to the cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) regimen in elderly patients (> 60 years) with newly-diagnosed diffuse large B-cell lymphoma (DLBCL), with a 20% improvement in CR rate, as well as median overall survival times.^{16,17} The improvements in overall survival seen with R-CHOP (rituximab-CHOP) have been verified with longer follow-up as well. These results have been confirmed by other groups, in both younger and older patients, and in population-based studies. In patients with AIDS-related lymphoma, the use of rituximab with chemotherapy has also resulted in improved outcomes in terms of higher CR rates, and decreased likelihood of death due to lymphoma.^{18,19} Thus, in a trial of CHOP versus R-CHOP conducted in approximately 200 subjects by the AIDS Malignancy Clinical Trials Consortium (AMC), while no statistically significant differences in CR rates were apparent between the two treatment groups, better tumor control was evident in the rituximab treated group in terms of CR rates, progression-free survival, and rate of death due to lymphoma. The failure of this AMC trial to document a statistically significant advantage in the rituximab-treated patients may be related to the fact that the

AMC trial was not adequately powered to detect differences at the 20% level, as were demonstrated by Coiffier and colleagues in their study of approximately 400 subjects, which clearly demonstrated a statistically significant advantage for rituximab-treated patients in terms of tumor control.^{17,19} The infusional cyclophosphamide/doxorubicin/etoposide (CDE) regimen with HAART has been studied in several sequential trials conducted in patients with newly-diagnosed AIDS-related lymphoma.²⁰ The addition of rituximab to CDE resulted in marked improvements in both CR rate and overall survival, when compared with patients treated with CDE and HAART alone.¹⁸ These data would, again, indicate an advantage to the use of rituximab along with chemotherapy in patients with AIDS-related lymphoma.

1.4 Occurrence of Infectious Death Among HIV-Infected Patients Treated with Rituximab-Containing Regimens

In the AMC trial of CHOP versus R-CHOP in patients with newly-diagnosed AIDS-related lymphoma, a statistically increased rate of infectious death was documented in patients treated in the R-CHOP arm.¹⁹ Nonetheless, the rates of Grade 4 neutropenia (<500/mm³), or febrile neutropenia were not statistically different in the two treatment groups, although the R-CHOP-treated patients tended to have more neutropenia. While full data were not available on the entire patient cohort, quantitative immunoglobulin levels also appeared similar in the two treatment arms. Of interest, the infectious deaths in the AMC trial occurred primarily among patients with CD4 cells <50/mm³, which is a known risk factor for infectious death in HIV-infected patients without underlying lymphoma.²¹ Thus, if patients with CD4 <50/mm³ were removed from the analysis, no difference in the rate of infectious death was apparent in the CHOP versus R-CHOP treated patients.¹⁹ The risk of infectious death after receipt of rituximab-containing chemotherapy thus remains somewhat controversial in patients with AIDS-related lymphoma, and additional data is clearly indicated to help to explain the findings to date. This would include a careful assessment of CD4 cell count, absolute neutrophil count (ANC), and quantitative immunoglobulin levels at baseline and throughout therapy, with an assessment of any relationship between these variables and the development of intercurrent infection. Additionally, based upon the AMC data, it would seem prudent to employ prophylactic antibiotics as well as hematopoietic growth factors (G-CSF or GM-CSF) in patients with AIDS-related lymphoma undergoing chemotherapy who have severe underlying immune deficiency.

1.5 Dose-Adjusted Etoposide, Vincristine Doxorubicin, Prednisone, Cyclophosphamide (EPOCH) Regimen

The dose-adjusted EPOCH regimen (da-EPOCH) was initially tested in a single center, Phase II study at the National Cancer Institute (NCI), in which 39 patients were accrued.⁷ In this study, HAART therapy was withheld until completion of the 6 months of chemotherapy. A CR rate of 74% was achieved. At a median follow-up of 53 months, disease-free survival was 92%, while overall survival was 60%. In patients with CD4 cell counts >100/mm³ at diagnosis, CR was achieved in 87%, while 53-month overall survival was 87%. In contrast, 56% of patients with CD4 cells <100/mm³ at diagnosis achieved CR, and 53-month survival was only 16%. During the course of chemotherapy, the median CD4 cells fell by 187 cells/mm³ (range +19-973 cells/mm³), while HIV-1 viral load increased a median of 0.83 log₁₀ (range -0.28-+4.12). While no patient experienced an opportunistic infection (OI) during EPOCH therapy, three patients developed OI at 5, 8 and 13 weeks after completion of chemotherapy.⁷

The EPOCH regimen was further tested in a multi-institutional clinical trial as part of the NCI-sponsored AMC. While full results are pending at this time, the preliminary results have recently been analyzed. In this trial (AMC #034), the AMC trial added rituximab to EPOCH, given either concomitantly (R-EPOCH) or sequentially (EPOCH followed by rituximab). Early data are as follows ²²:

| | Rituximab +EPOCH | EPOCH followed by Rituximab |
|--------------------------------|-------------------------|------------------------------------|
| Number | 40 | 40 |
| Median CD4 cell count | 198/uL | 188/Ul |
| Age adjusted IPI, score 2 to 3 | 54% | 60% |
| Stage III/IV | 85% | 73% |
| CR/CR u | 24 (60%) | 15 (37%) |
| 95% confidence intervals | (43%, 75%) | (23%,54%) |

While the outer limit of the confidence intervals for R-EPOCH include a CR rate of 75%, still, our multi-institutional data do not yet confirm the expected CR rate of 74% as originally described by Little et al from the NCI ⁷.

Additionally, the AMC data on R-CHOP versus CHOP (AMC protocol #010) did not confirm the potential of achieving a CR rate as high as 75%. Thus, with 99 patients randomized to R-CHOP and 50 to CHOP alone, the CR+ CRu rate for R-CHOP was 57.6%, while that for CHOP was 47% ¹⁹

While Levine et al demonstrated a 75% CR +CRu rate in 24 patients treated with liposomal anthracycline (Myocet) plus COP ²⁵, again, these data come from a small, single institutional trial (see Section 1.6, below), and have not been confirmed in a multi-center setting.

With these facts in mind, we believe it is appropriate to target a complete remission rate of 60% or more, as indicative of success for this currently proposed DR-COP regimen. We will also evaluate event-free survival at one year, looking for an increase in median EFS from 12 months to 18 months as a marker of success. Of interest, the current AMC #034 study (see table above) do indicate a potential superiority of concomitant rituximab as opposed to the sequential use of this agent along with EPOCH.²²

1.6 Use of Liposomal Preparations of Anthracycline with Standard Agents in AIDS-Related Lymphoma

Doxorubicin hydrochloride (doxorubicin) (MyocetTM, Caelyx[®], Doxil[®]) is one of the most active agents in the therapy of patients with aggressive lymphoma.¹⁶ However, doxorubicin is a substrate for P-gp, the protein product of MDR-1.^{12,14} In vitro studies have demonstrated that liposomal encapsulation of doxorubicin (e.g., Doxil) can overcome excessive drug efflux due to MDR-1 over-expression.^{23,24} Doxil is doxorubicin encapsulated in long-circulating STEALTH[®] liposomes. Liposomes are microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs. The STEALTH liposomes of Doxil are formulated with surface-bound methoxypolyethylene glycol (MPEG), a process often referred to as pegylation, to protect liposomes from detection by the mononuclear phagocyte system (MPS) and to increase blood circulation time.

A Phase I/II trial of liposomal doxorubicin in combination with standard agents vincristine, cyclophosphamide, and prednisone (COP) was recently reported by Levine and colleagues in a group of 24 patients with newly-diagnosed AIDS-related lymphoma.²⁵ Median CD4 count at study entry was 112/mm³, and median HIV-1 ribonucleic acid (RNA) level in plasma was 93,650 copies/cc in the 20 patients with detectable virus. A CR rate of 75% was achieved, with PR in 13% (overall response [OR] rate of 88%). The median duration of CR is in excess of 15.6 months (range 1.7-43.5+ months). At last follow-up, median survival had not been reached for the group as a whole, and overall survival was 58% at 1 year from start of chemotherapy. Effective HIV viral control during chemotherapy was associated with significantly improved survival, but CR rates were attained independent of HIV viral control. Of interest, the regimen was equally effective in both MDR-1 positive and negative cases, suggesting that the efficacy of the regimen was related to the ability of liposome encapsulated doxorubicin to overcome excessive drug efflux due to MDR-1 over-expression.²⁵ Additional use of liposomal doxorubicin

In a separate study by Zaja, et al.²⁶, thirty untreated patients, median age 69 years (range 60 - 75 years), with diffuse large B-cell lymphoma (B-DLCL) were treated with a pegylated liposomal doxorubicin (PL-doxorubicin) modified CHOP-rituximab regimen. PL-doxorubicin 30 mg/m², was given in combination with standard dosage of prednisone, vincristine, cyclophosphamide, rituximab (according to CHOP-R regimen) every 21 days for six courses. Cardiac toxicity was evaluated by mean of echocardiography for left ventricular ejection fraction (LVEF) evaluations and serum troponin-I levels. Overall response and complete response rates were 76% and 59%. Projected two year event free survival and overall survival are 65.5% and 68.5%. No treatment-related mortality was documented. WHO grade III-IV neutropenia and thrombocytopenia were 86% and 3%. Extra-hematological III-IV toxicity was represented, respectively, by a single case of infection, mucositis, and bleeding. LVEF evaluations and the troponin levels did not show significant changes over the course of the treatment. One patient with a previous history of atrial fibrillation experienced a single episode of arrhythmia. None of the patients developed palmar-plantar erythrodysesthesia. This regimen appears an active regimen for the treatment of elderly patients with B-DLCL. The replacement of conventional doxorubicin with PL-doxorubicin seems to be associated with a negligible incidence of extra-hematological toxicity, in particular cardiac and infectious complications.²⁶

In another trial by Visani et al.²⁷, subjects received a regimen consisting of Day 1: cyclophosphamide 750 mg/m², PL-doxorubicin, 40 mg/m², vincristine 1.4 mg/m², prednisone 100 mg p.o. (Days 1 – 5); rituximab 375 mg/m² on Day 15 of every cycle; granulocyte colony-stimulating factor (G-CSF) from Day 10 to Day 14. Therapy was repeated every 21 days for six cycles. Complete and partial remission were assessed as the overall response. Toxicity was evaluated according to the WHO criteria. Thirteen patients were treated; 12 (92%) completed the six courses and were assessable for response. A dose reduction (25%) was carried out in two cases (1 frail, 1 relapsed-refractory), due to their extremely altered clinical condition. Seven patients (53%) obtained complete remission, five (31%) partial remission, for an overall response rate of 84%. No major toxicity (WHO grade III/IV) occurred. Only one patient delayed therapy for grade II hematological toxicity. After a median follow-up of 18 months (range 8 – 22 months), seven patients are in continuous complete remission (53%), three (23%) in partial remission, one in stable disease, whereas only two patients progressed.²⁷

PL-Doxorubicin has also been associated with a lower risk of cardiotoxicity than conventional formulations of doxorubicin, allowing the use of higher cumulative doses.²⁸ In a recent Phase II study by Tsavaris, 25 patients aged over 70 years (median 79, range 75-82 years) with aggressive NHL (International Prognostic Index (IPI) -2, 12 (48%); IPI-3, 10 (40%); IPI-4, 3 (12%)) received CHOP with PL-doxorubicin. A complete response was achieved in 13 (52%) patients and a partial response in 12 (48%) patients, which was maintained for at least 12 months. The median time to progression was 26 months (range 14- >42) and median overall survival was 32 months (range 26-48). No Grades III/IV toxicity occurred; adverse events included neutropenia, anaemia, nausea and vomiting, diarrhoea and constipation in 16-29% of the cycles. Pegylated liposomal doxorubicin showed as an effective and well-tolerated component that may be substituted for doxorubicin in the CHOPC (cyclophosphamide, doxorubicin, vincristine, prednisolone) regimen for the treatment of aggressive NHL in elderly people.²⁸

A separate prospective, Phase II study for patients with DLBCL analyzed the feasibility of a regimen (CCOP) that includes pegylated liposomal doxorubicin (Caelyx) plus vincristine, cyclophosphamide and prednisone in patients with DLBCL above the age of 60 years. Thirty-three patients, with a median age of 74 years, were enrolled in the study. The overall response rate was 64% (49% complete remissions and 15% partial remissions). The estimated one-year overall and event-free survivals were 55% (95% CI, 38-72) and 45% (95%CI, 28-62), respectively. The only relevant toxicity was neutropenia, which reached Grades 3/4 in 21 cases (64%). These results suggest that CCOP appears to be an acceptable alternative for elderly patients with DLBCL, and randomized trials against a conventional doxorubicin-containing regimen are justified.²⁹

1.7 Rationale for Exploratory Use of Positron Emission Tomography (PET) Scans as Part of Staging and Response Evaluations

Over the years, there have been problems with the criteria that are currently in use for evaluating the response to lymphoma therapy.^{30,31} A designation of “complete remission unconfirmed” (CRu) has been suggested and employed in recent years. The designation of “CR” has been given when the following conditions were met at the conclusion of therapy: (a) all lymph nodes and nodal masses must have regressed to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes >1.5 cm before therapy); (b) previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to ≤ 1 cm in their greatest transverse diameter after treatment, or by $>75\%$ in the sum of the products of the greatest diameters (SPD); and (c) the spleen, if enlarged before therapy on the basis of a Computed Axial Tomography (CT) scan, must have decreased in size, and must not be palpable upon physical examination. In addition to these criteria, the designation of “Cru” has been made in the following circumstances: (a) a residual lymph node mass >1.5 cm in greatest transverse diameter present at the time of response evaluation, that has regressed by more than 75% in the SPD (individual nodes that were previously confluent must have regressed by $>75\%$ in their SPD compared with the size of the original mass); and (b) indeterminate bone marrow results at the time of re-biopsy, as indicated by increased number or size of lymphoid aggregates without cytologic or architectural atypia. Despite this definition, the designation of “Cru” has been unclear, with inconsistent definitions in various studies. Furthermore, “Cru” has not included definitions for response in extranodal sites, with the exception of the bone marrow. “Cru” has been used to describe

responses in the treatment of Hodgkin's disease, although it was really designed and tested for use in evaluating responses in DLBCL or aggressive lymphomas. Additionally, "Cru" depends upon technical mechanisms of staging that are outdated at the present time. For example, the CT scan, initially, was not considered a part of routine restaging, while single photon emission computed tomography (SPECT) gallium scan was. There are no data available on flow cytometry in bone marrow analysis that can more accurately identify isolated areas of marrow involvement.

For all of the reasons discussed above, a specific study group, International Harmonization project (IHP) of the Competence Network of Malignant Lymphoma, led by Bruce Cheson from the United States, was recently developed to assess the current criteria for staging and response criteria in patients with NHL.³⁰ This group has concluded that positron emission tomography (PET) scanning should be used to define response in DLBCL and NHL, and in all types of lymphomas, for studies in which response rate is the endpoint. If a patient was PET-positive for disease at baseline, and subsequently had negative findings on the CT scan at the end of therapy, or had a negative PET scan at the time of reevaluation, the patient was considered to be in CR. If, on the other hand, the patient was PET-negative at diagnosis or PET scanning was not done at time of diagnosis, and if the CT scan improved by 75%, but there is still residual disease, patients were regarded as having achieved a PR. Therefore, the category of "Cru" would cease to exist. There are multiple issues that need to be addressed in these new criteria, including the issue of when a restaging PET scan is to be performed. Furthermore, there are no data on the validity of PET restaging in patients with AIDS-related lymphoma. Since this area is currently one in which significant change is expected over the next few years, we will employ PET scanning as part of the current study, if feasible in terms of patient insurance coverage. Results of PET scanning will be used in an exploratory fashion to determine the validity and role of this procedure in assessing response of patients with AIDS-related aggressive lymphoma.

1.8 Rationale for Study of BCL-2 Expression in AIDS-Related Lymphoma

Mornier and colleagues have demonstrated that presence of BCL-2 expression in lymphoma tissue of de novo lymphoma, unassociated with HIV, was correlated with decreased likelihood of receiving benefit from the addition of rituximab along with the CHOP regimen.^{17,32-33} The precise prevalence of BCL-2 expression in AIDS-related lymphomas is not well studied, although Little et al. from NCI reported approximately 13% BCL-2 positivity in their study of 39 patients treated with EPOCH.⁷ It will be of interest to determine the prevalence of BCL-2 expression in larger numbers of patients with AIDS-related lymphoma to determine the role of this molecular marker, if any, in predicting outcome to therapy employing chemotherapy, with or without the addition of rituximab.

1.9 Rationale for Current Study

In this study, we wish to employ a regimen of HAART,³⁴ along with pegylated anthracycline (Doxil), Rituximab, and standard agents cyclophosphamide, vincristine, prednisone (DR-COP), using a Phase II design, in order to determine the potential efficacy and toxicity of the approach in a multi-institutional setting. In this regard, initial Phase II results of the EPOCH regimen, and of a liposomal anthracycline regimen with standard agents, have suggested similar outcomes, with CR rates of 74 and 75%, respectively.^{7,25} Nonetheless, while results of EPOCH when used in a multi-institutional setting are only preliminary at this time (see

Section 1.5 above), initial AMC data indicate that the CR rate of 75% will not be achieved with the back-bone EPOCH regimen.²² Furthermore, such confirmation has not yet been accomplished for use of conventional regimens in which doxorubicin has been replaced with a liposomal or pegylated anthracycline (Doxil). Nonetheless, early results do suggest possible equivalency with these two approaches. If Phase II results are found to be similar to those reported by AMC for R-EPOCH treated patients, AMC plans to move forward with a Phase III, randomized trial of DR-COP versus R-EPOCH in patients with newly-diagnosed AIDS-related lymphoma. Alternatively, if results from DR-COP are clearly inferior to those reported for EPOCH, the AMC will proceed forward with EPOCH as our platform for future study.

The importance of the question being addressed relates to practical aspects of therapy. While results from the EPOCH and R-EPOCH trials have been encouraging, the regimen is difficult to employ, requiring a 4-day continuous infusion, administered primarily in the hospital, monthly, and for as long as 6 months. If similar results could be achieved with a less complex regimen that did not require the continuous infusion of chemotherapeutic agents, the resulting regimen would clearly be more cost-effective, and easier, in a practical sense, for patients, healthcare providers, and the healthcare system in general. The current protocol seeks to obtain information on the results of DR-COP in patients with newly-diagnosed, CD20+, aggressive lymphoma. If results are acceptable (CR rate \geq 60%), the regimen will be carried forward in formal Phase III testing against R-EPOCH.

2.0 OBJECTIVES

2.1 Primary Endpoints

- 2.1.1 To determine the complete response rate (CR + Cru) to DR-COP in patients with newly-diagnosed AIDS-related lymphoma.
- 2.1.2 To determine the duration of response (DR) (relapse-free survival) of patients treated with DR-COP.
- 2.1.3 To determine the median survival time of patients treated with DR-COP.
- 2.1.4 To determine rate of bacterial, fungal and opportunistic infections in patients treated with DR-COP.

2.2 Secondary Endpoints

- 2.2.1 To determine, preliminarily, the relationship between MDR-1 expression in tumor tissue and response to therapy.
- 2.2.2 To determine, preliminarily, any relationship between response and survival, and BCL-2 expression in tumor tissue.
- 2.2.3 To determine any relationship between development of bacterial, fungal and/or opportunistic infections and baseline CD4 lymphocyte count, HIV-1 RNA level, and quantitative immunoglobulin levels, or with changes in quantitative immunoglobulin levels over time.
- 2.2.4 To examine, in exploratory fashion, the results of PET scanning when compared with traditional CT scans in predicting response to therapy in patients with AIDS-related lymphoma.
- 2.2.5 To examine the cause(s) of subject death.
- 2.2.6 To examine event-free survival (EFS) at one year.

3.0 STUDY DESIGN

3.1 Treatment Summary

This is a standard Phase II trial in which patients with newly-diagnosed AIDS-related lymphoma will receive DR-COP, given every 21 to 28 days. Data on tumor response will be collected, as well as serial data on CD4 cell counts, HIV-1 RNA levels, and quantitative immunoglobulin levels in an attempt to decipher those factors that may be operative in terms of prediction of intercurrent infection and/or death from infection.

Patients will be evaluated by physical examination, complete blood count (CBC), routine serum chemistries, lactate dehydrogenase (LDH), HIV viral RNA, T cell subsets, and immunoglobulin levels at Baseline, and after every two cycles of chemotherapy. CT scans will be performed at study entry, after Cycle 2, 4, and 6, and 1 month after completion of all therapy. Additionally, PET/CT, PET or gallium scans will be performed at the same time intervals, if feasible in terms of patient insurance coverage. Patients will be followed for immunologic and virologic parameters every 2 months during year 1 post chemotherapy, and every 6 months during years 2 and 3 post chemotherapy. Additionally, patients will be followed for survival and DR for 3 years posttherapy.

All patients will be on HAART (the specific agents are at the discretion of the treating investigator, but should be in accordance with the current International AIDS-Society guidelines). (See Section 7.5.6)

All eligible patients receiving at least one cycle of DR-COP chemotherapy will be evaluable for toxicity and response.

3.2 Treatment Regimen

DR-COP:

- Doxil 40 mg/m² intravenously (IV), Day 1.
- Rituximab 375 mg/m², slow IV infusion, Day 1, beginning with Cycle 1.
- Cyclophosphamide 750 mg/m² IV, Day 1.
- Vincristine 1.4 mg/m² IV (total dose not to exceed 2 mg), Day 1.
- Prednisone 100 mg orally (PO), Days 1-5 of each cycle.

BSA is to be recalculated at the start of each cycle. Doses of Doxil, rituximab, cyclophosphamide, and vincristine will be based upon the subject's BSA. With any change of weight within 10% of baseline, drug dosing will be maintained at the baseline level. Doses of chemotherapy are to be adjusted **only** if a subject's weight has changed more than 10% from baseline or prior dose.

Repeat DR-COP cycles every 21 to 28 days. One cycle is 21 to 28 days, depending upon recovery from any hematologic or non-hematologic toxicity, as specified in Section 8.1.

Central Nervous System (CNS) Prophylaxis:

Mandated per protocol in patients who meet the following criteria: lymphomatous involvement of bone marrow, testis, sinuses, or epidural regions; stage IV disease;

and/or two or more extra-nodal sites of disease. One of the following regimens will be required: intrathecal (IT) depocyt, IT cytarabine, or IT methotrexate. The specific regimen will be at the discretion of the primary oncologist.

Supportive Therapy:

Growth Factor (GF) therapy with G-CSF, GM-CSF, or pegfilgrastim will be used in all patients until post nadir of blood counts from each chemotherapy cycle, beginning on Day 3 of each cycle.

Use of erythropoietic factors is left up to the discretion of the Investigator.

Prophylaxis against *Pneumocystis carinii* is required, with the specific regimen at the discretion of the treating physician.

Prophylaxis against other common OI is encouraged, dependent upon the patient's CD4 cell count at study entry, and at the discretion of the treating physician.

Use of prophylactic oral quinalones is required for patients with CD4 cell counts $\leq 100/\text{mm}^3$ at study entry, for those whose CD4 counts fall to $\leq 100/\text{mm}^3$ during therapy, or for those patients who have experienced a fall in ANC to $<500/\text{mm}^3$ during treatment. In patients with CD4 counts $>100/\text{mm}^3$, use of prophylactic antibiotics is strongly encouraged at the discretion of the treating physician. Patients with active HBV (surface antigen positive) are strongly encouraged to receive anti-HBV therapy.

HAART Therapy:

All patients will be on HAART (the specific agents are at the discretion of the treating investigator, but should be in accordance with the current International AIDS-Society guidelines). Antiretroviral therapy that is currently available on an expanded access basis will be allowed during the treatment regimen, but use of experimental antiretroviral agents will not be allowed. Zidovudine and zidovudine-containing regimens (including Combivir[®] and Trizivir[®]) will be prohibited, due to known marrow suppressive effects of zidovudine.

3.3 Study Duration

The total duration of this trial includes 18 months for patient accrual, and 3 years for full therapy and follow-up.

4.0 STUDY POPULATION

4.1 Inclusion Criteria

- 4.1.1 Previously untreated, histologically or cytologically documented B-cell NHL. The following histologies are eligible: follicular large-cell (Grade 3), DLBCL, immunoblastic lymphoma, plasmablastic lymphoma, primary effusion lymphoma.
- 4.1.2 Lymphoma must be CD20+. Please note: If only a subset of tumor cells are CD20+, the subject will still be eligible for study entry.
- 4.1.3 Documented HIV infection. Documentation may be serologic (enzyme-linked immunosorbent assay [ELISA], western blot), culture, or quantitative polymerase chain reaction (Q-PCR) or Branched deoxyribonucleic acid (bdNA) assays. Prior documentation of HIV seropositivity is acceptable.
- 4.1.4 All stages of disease.
- 4.1.5 Measurable or non-measurable tumor parameter(s). Non-measurable tumor parameters are defined as not having bidimensional measurements (e.g., gastric or marrow involvement), but can be followed for response by other diagnostic tests such as gallium, PET imaging and/or bone marrow biopsy.
- 4.1.6 Age \geq 18 years.
- 4.1.7 Karnofsky Performance Status (KPS) \geq 50% (Eastern Cooperative Oncology Group [ECOG] Performance Score 0, 1, or 2).
- 4.1.8 Able to give signed informed consent.
- 4.1.9 Adequate hepatic function: bilirubin \leq 2.0 mg/dL (unless elevated secondary to lymphomatous involvement of liver or biliary system, or due to other HIV medications [e.g., indinavir, tenofavir, or atazanavir]. For patients whose bilirubin measures $>$ 3.0 mg/dL due to hepatic involvement, the initial dose of Doxil will be decreased by 50%, and the initial dose of vincristine will be omitted. Serum glutamic-oxaloacetic transaminase (SGOT) $<$ 5X upper limit of normal.
- 4.1.10 Adequate renal function: creatinine $<$ 2.0 mg/dL, or creatinine clearance \geq 60 ml/min, unless secondary to renal involvement by lymphoma.
- 4.1.11 Adequate hematologic function: granulocytes/ANC $>$ 1000/mm³, platelets $>$ 75,000/dL (unless these parameters are abnormal secondary to lymphomatous involvement of bone marrow, or due to HIV-related thrombocytopenia). All patients must cease colony-stimulating factor (CSF) therapy at least 24 hours prior to institution of Cycle 1 chemotherapy.
- 4.1.12 Left ventricular ejection fraction (LVEF) that is at or above the lower institutional limits of normal, as assessed by Multiple Gated Acquisition (MUGA) scan or echocardiogram within the 6 weeks prior to registration.

- 4.1.13 Concurrent radiation, with or without steroids, for emergency conditions secondary to lymphoma (i.e., CNS tumor, cord compression, etc.) will be permitted.
- 4.1.14 Female patients must have a negative pregnancy test within 72 hours of entering into the study. Both men and women will be included and, if of child bearing potential, must agree to use adequate methods of contraception for the duration of the treatment. Women must avoid pregnancy, and men must avoid fathering children while in the study, and for 6 months following the last study drug treatment.
- 4.1.15 Concurrent effective HAART treatment of HIV with any licensed agents, or any agent available on an expanded access program, is required at study entry. A specific level of HIV-1 RNA in plasma is not required for protocol entry. However, when the HIV-1 viral load analysis becomes clinically available, if the HIV viral load is \geq 50,000 copies/cc, the HAART regimen is to be modified to a patient-specific alternative regimen as decided by the primary treating physician. Concurrent therapy with zidovudine or a zidovudine-containing regimen (including combivir and Combivir and Trizivir) will be prohibited until 2 months following the completion of chemotherapy as part of this protocol.
- 4.1.16 Patients already receiving erythropoietin or G-CSF are eligible for participation, although GF therapy must be discontinued at least 24 hours prior to receiving chemotherapy.

4.2 Exclusion Criteria

- 4.2.1 Presence of second active tumor, other than non-melanomatous skin cancer, carcinoma in situ of the cervix, or Kaposi's sarcoma (KS) that does not require systemic therapy.
- 4.2.2 Primary CNS lymphoma, including parenchymal brain or spinal cord lymphoma.
- 4.2.3 Presence of leptomeningeal disease (positive cerebral spinal fluid [CSF] for lymphoma) or presence of metastatic disease to brain in terms of any mass lesion.
- 4.2.4 Pregnant women or nursing mothers.
- 4.2.5 KPS <50% (ECOG Performance Score > 3).
- 4.2.6 Expected survival < 2 months.
- 4.2.7 Unable to comply with the requirements of the protocol, or unable to provide adequate informed consent in the opinion of the Principal Investigator.
- 4.2.8 Serious, ongoing, non-malignant disease or infection, which, in the opinion of the Investigator and/or the sponsor, would compromise other protocol objectives.
- 4.2.9 Major surgery, other than diagnostic surgery, occurring 4 weeks prior to study entry.

- 4.2.10 Rituximab therapy within the 12 months prior to study entry. Patients treated with rituximab >12 months prior to study registration are eligible only if it was given for indications other than the treatment of aggressive lymphoma.
- 4.2.11 Prior cytotoxic chemotherapy or radiotherapy for this lymphoma, except as outlined in Section 4.1.13.
- 4.2.12 History of cutaneous or mucocutaneous reactions, or diseases in the past, due to any cause, severe enough to cause hospitalization or an inability to eat or drink for >2 days. This exclusion relates to the long-term possibility of severe cutaneous or mucocutaneous reactions to rituximab that might occur at increased frequency in patients who have had severe skin disease or reactions in the past.
- 4.2.13 Use of zidovudine as part of the HAART regimen.
- 4.2.14 Any acute, inter-current infection that may interfere with planned protocol treatment. Patients with mycobacterium avium will not be excluded from study entry.
- 4.2.15 Myocardial infarction (MI) within 6 months prior to study entry, New York Heart Association (NYHA) Class II or greater heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, clinically significant pericardial disease, or electrocardiographic evidence of acute ischemic or active conduction system abnormalities.
- 4.2.16 Inadequate hepatic function: Bilirubin >2.0 mg/dl (unless elevated secondary to lymphomatous involvement of liver or biliary system or due to other HIV medications such as indinavir, tenofovir, or atazanavir).
- 4.2.17 Inadequate renal function: Creatinine >2.0 mg/dl, or creatinine clearance <60 cc/min, unless secondary to renal involvement by lymphoma.
- 4.2.18 Inadequate cardiac function: Left ventricular cardiac ejection fraction that is less than the lower institutional limits of normal, as assessed by nuclear scan or echocardiogram obtained within 6 weeks prior to registration.
- 4.2.19 Inadequate pulmonary function: Presence of shortness of breath at rest, with arterial PO₂ of <70 or pulse oximeter derived O₂ saturation <94% on room air, unless due to lymphomatous involvement of the lungs.

4.3 Number of Patients to be Enrolled

A one-stage design will be employed, enrolling a total of 40 evaluable patients.

4.4 Patient Enrollment Procedure

This study will be available for enrollment at all AMC sites. Each site must have this protocol approved by their Institutional Review Board (IRB) and be registered with the AMC Operations Center before they may enroll patients.

After it has been determined that a patient is eligible and an informed consent has been signed by the patient, the patient must be registered on-line via the AMC AdvantageEDCSM Internet Data Entry System. Enrollment and data collection will occur via the AMC Internet Data Entry System.

The participating site will ensure the patient meets all eligibility criteria prior to completing the protocol-specific eligibility checklist. Patients will be enrolled on-line via the AMC Internet Data Entry System no more than one week prior to the initiation of treatment (enrollment one day prior to, or on the day of treatment is strongly encouraged). Once the eligibility checklist is submitted and eligibility is confirmed, a system generated confirmation email will be sent to the enroller upon successful completion of the patient enrollment. If the on-line system is inaccessible, the site should notify the AMC Operations Center (via e-mail at amcpm@emmes.com or phone at 301-251-1161) for further instructions.

5.0 STUDY PROCEDURES

(See Appendix I, Schedule of Evaluations)

5.1 Screening/Baseline Evaluations

Unless otherwise specified, the following evaluations must be performed within 4 weeks prior to patient registration:

- 5.1.1 Medical history, including history of nadir CD4 count, if available; history of current and past anti-retroviral regimens, if available; and history of any prior AIDS-defining conditions. Date of initial lymphoma diagnosis is required, with a copy of the pathology report in the medical record. Presence of systemic “B” symptoms should be noted, as well as other symptoms of NHL. History of drug allergies should be ascertained. Current concomitant medication list, including all anti-retroviral, anti-viral, antibiotics and opportunistic prophylaxis.
 - 5.1.1.1 A drug diary should be initiated and maintained, documenting all medications being taken by the study subject.
- 5.1.2 Physical examination, including performance status (see Appendix II; Performance Status Scale), vital signs (weight, height, body surface area), neurological examination, careful measurement of all palpable, peripheral lymph nodes and measurement of other sites of disease present.
- 5.1.3 CT scan or Magnetic Resonance Imaging (MRI) of chest, abdomen and pelvis.
- 5.1.4 PET, PET/CT or gallium scan to document active sites of lymphomatous disease. However, if the patient’s insurance or third party will not cover the costs for these tests, omission of these exams will not be considered a protocol violation. The PET/CT scan will substitute for separate CT and PET scans, if PET/CT is performed.
- 5.1.5 Electrocardiogram (ECG).
- 5.1.6 Laboratory tests, including:
 - 5.1.6.1 CBC with differential and platelet count (within 2 weeks prior to patient registration)
 - 5.1.6.2 Serum chemistries: glucose, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase (ALP), LDH, total protein, albumin, serum glutamic oxaloacetic transaminase and/or aspartate aminotransferase (SGOT and/or AST), serum glutamic pyruvic transaminase and/or alanine aminotransferase (SGPT and/or ALT) and calcium (within 2 weeks prior to patient registration)
 - 5.1.6.3 Serum pregnancy test for women of childbearing potential (within 72 hours prior to Cycle 1 chemotherapy).

- 5.1.1.4 Bone marrow biopsy or aspirate for histology and determination of percent bone marrow involvement (within 6 weeks prior to patient registration). Unilateral bone marrow biopsy/aspirate is allowed, with an aggregate core length of 2 cm, either from one site or bilateral sites. If feasible, a portion of the bone marrow biopsy and aspirate will be sent for cytogenetic analysis.
- 5.1.6.5 HIV-1 RNA viral load (evaluated at the local laboratory)
- 5.1.6.6 CD4 and CD8 cells
- 5.1.6.7 Quantitative serum immunoglobulin levels (IgG, IgA, IgM)
- 5.1.6.8 Assessment for Hepatitis C (hepatitis C virus [HCV] antibody) and Hepatitis B (hepatitis B surface antigen [HbSAg] and hepatitis B surface antibody [HbSAb]), in all patients.
- 5.1.7 Skin test (Delayed Cutaneous Hypersensitivity [DCH]) for Mycobacterium tuberculosis.
- 5.1.8 Determination of LVEF by MUGA scan or echocardiogram. Patients will not be enrolled if LVEF is below institutional lower limits.
- 5.1.9 Lumbar puncture with routine studies and cytology. IT chemotherapy may be injected at the time of initial staging lumbar puncture (see Section 7.4).
- 5.1.10 Central pathology review: All specimens will be reviewed by a panel of pathologists and must be submitted within 30 days of study enrollment.
- 5.1.11 Optional donation to the AIDS and Cancer Specimen Resource (ACSR). (See Appendix V for instruction on shipping samples).
- 5.1.12 MDR-1 determination on lymphoma tissue (to be sent to central laboratory for testing. [See Appendix VII for central laboratory information]).
- 5.1.13 Blood culture for Mycobacterium avium in all patients with fever at the time of presentation.

5.2 Evaluations During Treatment Period

- 5.2.1 Prior to each cycle of DR-COP chemotherapy:
 - 5.2.1.1 History, to include completion of drug diary.
 - 5.2.1.2 Physical examinations, including performance status and vital signs.
 - 5.2.1.3 Laboratory tests including:
 - CBC with differential and platelet count
 - Serum chemistries: glucose, BUN, creatinine, total bilirubin, ALP, LDH, total protein, albumin, SGOT, SGPT and calcium

Adverse events (AEs) are to be recorded on an ongoing basis and on appropriate source documents at the clinical site and in the patient's case report form (CRF). The onset of new AEs as defined in Section 10.0 will be documented in the patient's CRF. In addition, any transfusions of blood and/or blood products are to be recorded in the patient's CRF.

In the event that a Grade 3 or 4 hematologic toxicity occurs at any time, blood samplings for follow-up evaluations should be performed as clinically indicated until the abnormality is resolved.

5.2.2 After Cycles 2, 4 and 6 of DR-COP chemotherapy:

5.2.2.1 CD4 and CD8 cells.

5.2.2.2 HIV-1 viral load by Q-PCR or bDNA (evaluated at the local laboratory).

5.2.2.3 Quantitative immunoglobulins (IgG, IgA, IgM).

5.2.2.4 HBV and/or HCV viral load in patients with HBV surface antigen positivity, or HCV antibody positivity at baseline, respectively.

5.3 Evaluation of Response

5.3.1 After Cycles 2, 4 and 6 of DR-COP chemotherapy:

5.3.1.1 CT or MRI scan.

5.3.1.2 PET, PET/CT or gallium scan to document active sites of lymphomatous disease. However, if the patient's insurance or third party will not cover the costs for these tests, omission of these exams will not be considered a protocol violation. The PET/CT scan will substitute for separate CT and PET scans, if PET/CT is performed.

5.3.1.3 Repeat bone marrow biopsy after Cycle 4 if result of initial biopsy indicated that bone marrow is involved with lymphoma.

5.3.1.4 Repeat of any other test that demonstrated lymphomatous involvement at the Baseline evaluation.

5.3.1.5 History and physical examination.

5.3.2 One month after completion of chemotherapy:

5.3.2.1 CT or MRI scan.

5.3.2.2 PET, PET/CT or gallium scan to document active sites of lymphomatous disease. However, if the patient's insurance or third party will not cover the costs for these tests, omission of these exams will not be considered a

- protocol violation. The PET/CT scan will substitute for separate CT and PET scans, if PET/CT is performed.
- 5.3.2.3 Repeat bone marrow aspirate and biopsy if results of initial biopsy indicated that bone marrow is involved with lymphoma.
 - 5.3.2.4 Repeat of any other test that demonstrated lymphomatous involvement prior to protocol treatment.
 - 5.3.2.5 History and physical examination.

5.4 Follow-Up Evaluations (Month 3 and Beyond)

5.4.1 Post treatment Follow-up Period

The following will be performed/collected at 2-month intervals for 1 year post completion of protocol chemotherapy, and at 6-month intervals for an additional 2 years (total follow-up is 3 years). In those instances in which a third party payer denies payment for some or all of these laboratory analyses, absence of these test results will not be considered a protocol violation.

In participants who attain CR, laboratory and other evaluations will be performed in the manner outlined below in Sections 5.4.1.1-5.4.1.10.

Participants who attain PR after 6 cycles, or SD after 4 cycles will come off treatment at that point, and will be followed in the usual manner as outlined in Sections 5.4.1.1-5.4.1.10 until progression or an alternative anti-cancer therapy is begun. From that point on, the subject will be followed for survival alone.

- 5.4.1.1 Interim medical history.
- 5.4.1.2 Serious adverse events (SAEs), as well as any new or worsening drug-related AEs (see Section 10.0 and Appendix III, Common Terminology Criteria for Adverse Events [CTCAE]).
- 5.4.1.3 Quantitative serum immunoglobulins (IgG, IgA, IgM).
- 5.4.1.4 HIV-1 RNA levels.
- 5.4.1.5 CD4 and CD8 cells.
- 5.4.1.6 Physical examination, including performance status and vital signs.
- 5.4.1.7 Serum chemistries: glucose, BUN, creatinine, total bilirubin, ALP, LDH, total protein, albumin, SGOT, SGPT and calcium at Month 6 and Month 12 for the first year post treatment, and every 6 months thereafter during years 2 and 3 post treatment.
- 5.4.1.8 CBC with differential and platelet count.

- 5.4.1.9 Restaging of disease and Response Evaluation by physical examination. It is recommended that restaging of disease by CT scan or MRI be done every 6 months for the first year, and every 6 months for years 2 and 3 post-treatment.
- 5.4.1.10 In patients with HBV surface antigen positivity and/or HCV antibody positivity at baseline, HBV and/or HCV viral load will be determined at 2-month intervals after completion of therapy for a period of one year.

5.5 Disease Progression Evaluations/Off-Treatment

Patients who develop disease progression during the treatment period and who do not begin other anti-cancer therapy will continue to be followed for routine safety and efficacy for a total of 12 weeks following completion of protocol treatment and followed for vital status for 3 years post-treatment.

- 5.5.1 Tests to be Performed when a Patient is Determined to have Disease Progression or is Removed from Treatment for any Reason.

The following tests will be performed within 4 weeks after a patient has demonstrated clinical progression of disease. These tests do not have to be repeated if they were performed within 7 days prior to documentation of disease progression:

- 5.5.1.1 Tumor assessment (if patient is removed from the study for a cause other than progressive disease).
- 5.5.1.2 Interim medical history and physical examination, including performance status and vital signs.
- 5.5.1.3 CBC with differential and platelet count.
- 5.5.1.4 Quantitative serum immunoglobulins (IgG, IgA, IgM).
- 5.5.1.5 HIV-1 RNA levels.
- 5.5.1.6 CD4 and CD8 cells.
- 5.5.1.7 Serum chemistries: glucose, BUN, creatinine, total bilirubin, ALP, LDH, total protein, albumin, SGOT, SGPT and calcium.
- 5.5.1.8 Follow-up of all ongoing, related AEs until resolved or determined to be permanent.
- 5.5.1.9 In patients with HBV surface antigen positivity and/or HCV antibody positivity at baseline, HBV and/or HCV viral load.

6.0 PHARMACEUTICAL INFORMATION

6.1 Doxil

6.1.1 Description

Doxil is a formulation of doxorubicin, encapsulated in long-circulating STEALTH liposomes for IV administration.

Doxil was designed to enhance the efficacy and reduce the dose-limiting toxicities of doxorubicin by altering the plasma pharmacokinetics (PK) and tissue distribution of the drug. Preclinical results show that Doxil prolongs the systemic circulation of doxorubicin leading to higher concentrations of the drug in tumors and resulting in a reduction in tumor mass and prolonged survival.

6.1.2 Human Toxicology

The most extensive experience with Doxil to date has been reported in patients with AIDS-related KS. The most common AEs associated with Doxil in KS studies have been leukopenia, anemia, nausea, asthenia, thrombocytopenia, fever, alopecia, increased ALP, vomiting, diarrhea, and stomatitis.

6.1.3 Pharmacology

Several animal and human studies have been conducted to define the PK of Doxil. Plasma PK studies have been evaluated in 42 patients with AIDS-related KS who received single doses of 10 or 20 mg/m² IV Doxil administered over 30 minutes. Results from this study showed that Doxil displayed linear (dose proportional) PK. Disposition occurred in two phases after Doxil administration, with a relatively short first phase (5 hours) and a prolonged second phase (52 hours), that accounted for the majority of the area-under the curve (AUC).

6.1.4 Formulation

The vial contains 2.0 mg/mL doxorubicin hydrochloride, unless specified otherwise on the label. The volume of Doxil to be administered will be based upon the dose specified in the protocol.

Take the appropriate volume of Doxil up into a sterile syringe. Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in Doxil. Each vial is single-use only.

Dilute the Doxil in Dextrose 5% In Water for Injection, USP (D5W). For doses > 12 mg and < 90 mg, dilute in 250 mL of D5W. For doses > 90 mg, dilute in 500 mL D5W. Once Doxil has been diluted, it must be refrigerated at 2-8° C and administered within 8 hours of mixing. Ordinarily, the drug can be administered intravenously over 1 hour. However, because of occasional acute reactions to the first dose, the initial infusion can be administered more slowly if necessary (see Section 6.1.6).

6.1.5 Storage and Stability

Store Doxil in a refrigerator at 2-8° C. Avoid freezing. Doxil is supplied in vials as a liquid. Each vial contains 20 mg doxorubicin hydrochloride. Do not use if a precipitate or foreign matter is present. Do not use if vial seal is breached.

6.1.6 Administration

In patients with solid tumors and other malignancies, Doxil should be administered intravenously over 90 minutes. Rapid infusion may increase the risk of infusion-related reactions. In some patients, the reaction resolves by slowing the rate of infusion. To minimize the risk of infusion-related reactions, it is recommended that the first infusion of Doxil should be as follows:

- 10 mL over first 10 minutes
- 20 mL over next 10 minutes
- 40 mL over next 10 minutes

Then, complete the infusion over a total of 90 minutes.

If no infusion-related reactions are noted with the initial infusion, subsequent infusions will occur at a rate of 1 mg/minute.

Do not administer Doxil as a bolus injection or an undiluted solution. Doxil should be considered a vesicant and precautions should be taken to avoid extravasation. During IV administration of Doxil, extravasation may occur with or without an accompanying stinging or burning sensation, and even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the infusion should be immediately terminated and restarted in another vein. Doxil must not be given by intramuscular (IM) or subcutaneous (SC) route.

Parenteral drug products should be inspected visually for particular matter and discoloration prior to administration, whenever solution and container permit.

6.1.7 Supplier

Doxil will be provided by Ortho Biotech Clinical Affairs, LLC (Ortho Biotech), and will be free of charge.

Drug ordering and distribution procedures for Doxil will be posted on the AMC Operations Center web site (www.amcoperations.com) and are also listed in Appendix IX.

6.1.8 Handling and Disposal

Doxil should not be mixed with other drugs until specific compatibility data are available. The presence of any bacteriostatic agent, such as benzyl alcohol, may cause precipitation of Doxil.

Caution should be exercised in handling Doxil solution. The use of gloves is recommended. If Doxil comes into contact with skin or mucosa, immediately wash thoroughly with soap and water.

Doxil should be handled and disposed of in a manner consistent with other anti-cancer drugs.

6.2 Rituximab

6.2.1 Clinical Formulation

Rituximab is a mouse/human antibody. The antibody is produced by a Chinese hamster ovary transfectoma. Rituximab will be provided to the clinical sites packaged in 10 mL (100 mg) and 50 mL (500 mg) pharmaceutical grade glass vials at a concentration of 10 mg/mL.

Storage: Rituximab for clinical use should be stored in a secure refrigerator at 2-8° C.

6.2.2 Reconstitution and Dilution of Rituximab

The antibody should be diluted with normal saline (NS) to allow for a maximal concentration of rituximab to equal 1 mg/mL. The final preparation should be administered through a 0.22 micron in-line filter, although the specifics of administration will be left to the discretion of the individual Investigator, based upon the details required at each Institution. Caution should be taken during the preparation of the drug, as shaking can cause aggregation and precipitation of the antibody.

6.2.3 Product Administration

In calculating body surface area (BSA), actual height and weight should be used. There will be no downward adjustment to “ideal” weight. Dosage calculations for all treatments will be calculated using the patient’s body surface area as determined during the screening evaluation, with re-assessment on Day 1 of each new cycle.

6.2.4 Dose and Schedule

Rituximab will be administered as an IV infusion at 375 mg/m² based upon the patient’s BSA calculated during the baseline evaluation for cycle 1. BSA is to be recalculated at the start of each cycle. The dose of rituximab will be adjusted at the start of each cycle **only** if a subject’s weight has changed more than 10% from baseline or prior dose.

6.2.5 Method of Administration

CAUTION: DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.

Rituximab infusions will be administered to patients in either an outpatient or inpatient clinic setting, as clinically indicated. Oral premedication (acetaminophen and diphenhydramine hydrochloride) may be administered 30-60 minutes prior to starting each infusion of rituximab. A peripheral or central IV line will be established. The initial dose rate at the time of the first rituximab infusion should be 12.5 mg/hour. If no toxicity is seen, the dose rate may be escalated gradually (50 mg/hour increments at 30-minute intervals) to a maximum of 300 mg/hour. If the first dose of rituximab is well-tolerated, the starting flow rate for the administration of additional

doses will be 100 mg/hour and increased gradually (100 mg/hour increments at 30 minute intervals) not to exceed 400 mg/hour.

Patients may experience transient fever and rigors with infusion of chimeric anti-CD20 antibody. When these side effects are noted, the antibody infusion should be temporarily discontinued, the patient should be observed and the severity of the side effects should be evaluated. The patient should be treated according to the best available local practices and procedures. Following observation, when the patient's symptoms improve, the infusion should be continued, initially, at half of the previous rate (see table below). Upon resolution of all side effects, and in the judgment of the Investigator, the patient's dose may be gradually escalated (50 mg/hour increments at 30-minute intervals) to a maximum rate of 300 mg/hour. Following the antibody infusion, the IV line should be kept open for medications, as needed. If there are no complications, the IV line may be discontinued after one hour of observation. If complications occur during the rituximab infusion, the patient should be observed for two hours after the completion of the infusion, as per the recommendations at each individual Institution.

6.2.6 Human Antichimeric Antibody Response (HACA)

Both HACA and human antimouse antibody (HAMA) were monitored in the early trials of rituximab. None of the 67 patients tested developed a HAMA response. Of 355 patients in seven trials, three had a detectable HACA response (<0.9%). The HACA responses were transient and present at very low concentrations (<120 ng/mL). None of the three patients had clinical or laboratory abnormalities associated with a HACA response. The presence of a positive HACA response did not affect tolerability or preclude retreatment with rituximab.

6.2.7 Supplier

Rituximab is commercially available.

6.3 Cyclophosphamide (Cytosan[®]) (NSC-26271)

6.3.1 Description

2-[bis (2-chloroethyl) amino] tetrahydro-2H-1, 3, s-oxazophosphorine 2- oxide monohydrate. Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites which crosslink to tumor cell DNA. The active metabolite, hydroxycyclophosphamide, is produced by hepatic microsomal enzymes. It acts by substituting an alkyl group for the hydrogen atoms of certain organic compounds, primarily DNA, which produces breaks in the DNA molecule and cross-linking of its twin strands. These changes interfere with the DNA replication and the transcription of RNA.

6.3.2 Human Toxicology

Toxicity from cyclophosphamide includes bone marrow suppression which usually occurs 10 to 12 days after administration, nausea, vomiting, anorexia, abdominal discomfort, diarrhea, stomatitis, hemorrhagic colitis, jaundice, reversible alopecia, hemorrhagic cystitis which can frequently be prevented with increased hydration,

hematuria, ureteritis, tubular necrosis, fibrosis of the bladder, cardiac toxicity, which may potentiate doxorubicin-induced cardiotoxicity, rare anaphylactic reaction, skin rash, hyperpigmentation of the skin and nails, interstitial pulmonary fibrosis, and cross sensitivity with other alkylating agents. Treatment with cyclophosphamide may cause significant suppression of the immune system.

Second malignancies, most frequently of the urinary bladder and hematologic systems have been reported when cyclophosphamide is used alone or with other antineoplastic drugs. It may occur several years after treatment has been discontinued. It interferes with oogenesis and spermatogenesis and may cause sterility in both sexes which is dose- and duration-related. It has been found to be teratogenic, and women of childbearing potential should be advised to avoid becoming pregnant. Increased myelosuppression may be seen with chronic administration of high doses of phenobarbital. Cyclophosphamide inhibits cholinesterase activity and potentiates effect of succinylcholine chloride. If patient requires general anesthesia within 10 days after cyclophosphamide administration, the anesthesiologist should be alerted. Adrenal insufficiency may be worsened with cyclophosphamide. Cyclophosphamide is excreted in breast milk and it is advised that mothers discontinue nursing during cyclophosphamide administration. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

6.3.3 Pharmacology

Cyclophosphamide is activated principally in the liver by a mixed function microsomal oxidase system. PO administration is well-absorbed, with bioavailability >75%. Five to 25% of unchanged drug is excreted in the urine. Several active and inactive metabolites have been identified with variable plasma protein binding. There appears to be no evidence of clinical toxicity in patients with renal failure, although elevated levels of metabolites have been observed.

6.3.4 Formulation

Cyclophosphamide is supplied in 100 mg, 200 mg, 500 mg, 1 gram and 2 gram vials as a white powder. The drug should be reconstituted with Sterile Water for Injection, USP (SWI), and may be diluted in either NS or D5W.

6.3.5 Storage and Stability

The reconstituted drug is stable for 24 hours at room temperature and for 6 days under refrigeration. Tablets are stable at room temperature.

6.3.6 Administration

The drug should be diluted in approximately 150 cc of NS or D5W and infused intravenously. An added dose of IV fluids may help prevent bladder toxicity.

6.3.7 Supplier

The drug is commercially available for purchase through a third party.

6.4 Prednisone

6.4.1 Description

Prednisone is a glucocorticoid rapidly absorbed from the gastrointestinal (GI) tract.

6.4.2 Toxicology

Possible AEs associated with the use of prednisone are: fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, mood swings, depression, exacerbation of infection, exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer, dermatologic disturbances, convulsions, vertigo and headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some patients have experienced itching and other allergic anaphylactic or other hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia and arthralgia. Phenytoin, phenobarbital and phedrin enhance metabolic clearance of corticosteroids.

6.4.3 Pharmacology

Natural and synthetic glucocorticoids are readily and completely absorbed from the GI tract. Prednisone is very slightly soluble in water. Glucocorticoids have salt-retaining properties. The anti-inflammatory property of this drug is its ability to modify the body's immune system. On the other hand, glucocorticoids suppress the body's response to viral as well as bacterial infections. Equivalent doses are as follows:

| Dexamethasone | Prednisolone | Methyl-Prednisolone | Hydrocortisone | Cortisone |
|---------------|--------------|---------------------|----------------|-----------|
| 0.75 mg | 5 mg | 4 mg | 20 mg | 25 mg |

6.4.4 Formulation

Prednisone is available in 2.5 mg, 5 mg, 10 mg, 20 mg and 50 mg tablets.

6.4.5 Storage and Stability

Prednisone should be stored at room temperature.

6.4.6 Administration

Prednisone will be administered orally.

6.4.7 Supplier

Prednisone is commercially available and should be purchased by third party.

6.5 Vincristine

6.5.1 Chemistry

Vincristine is one of the vinca-alkaloids and is extracted from the plant *Cantharanthus roseus* (*Vinca rosea*). This drug appears to produce the arrest of mitosis in animal cells by interfering with microtubule function.

6.5.2 Human Toxicology

The primary toxic effects of vincristine are neurological with paresthesia, weakness, muscle wasting, motor difficulties, including difficulty walking and slapping gait, loss of deep tendon reflexes, sensory loss, neuritic pain, paralytic ileus, bladder atony, and constipation. Rarely, it produces myelosuppression. Other side effects may include alopecia, allergic reactions (including rare anaphylaxis, rash and edema), jaw pain, hypertension, hypotension, nausea, vomiting, diarrhea, fever, and headache.

6.5.3 Pharmacology

After IV administration, a triphasic serum decay pattern follows with half-lives of 5 minutes, 2-3 hours and 85 hours. The range of terminal half-life is 19-155 hours. Excretion is 80% in the feces and 10-20% in the urine. The liver is the major excretory organ in humans and animals, and biliary obstruction causes increased toxicity in man.

6.5.4 Formulation

The concentration of vincristine contained in all vials and disposable syringes is 1 mg/mL.

6.5.5 Drug Interactions

The simultaneous PO and IV administration of phenytoin and antineoplastic chemotherapy combination, that includes vincristine, has been reported to induce blood levels of the anticonvulsant and to increase seizure activity. Vincristine should not be diluted in solutions that raise or lower the pH outside the range of 3.5 to 5.5.

6.5.6 Storage and Stability

Vincristine should be stored under refrigeration. Once reconstituted, the drug should be used within 1 week if stored at room temperature, or 2 weeks if refrigerated. Protect from light. Depending on the manufacturer, the product may contain a preservative. If the product being used contains a preservative, the vial may be used longer than 1 or 2 weeks. Please refer to the individual manufacturer's package insert for more information. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

6.5.7 Administration

Vincristine should be administered through a freely-running IV. If vincristine extravasates, it produces a severe local reaction with skin slough.

CAUTION: FATAL IF GIVEN INTRATHECALLY. FOR IV USE ONLY.

6.5.8 Supplier

Vincristine is commercially available and should be purchased through a third party.

7.0 DRUG TREATMENT

7.1 Drug Administration

Cycles 1 through study completion

| | |
|------------------|---|
| Doxil | 40 mg/m ² IV Day 1 |
| Rituximab* | 375 mg/m ² IV Day 1 |
| Cyclophosphamide | 750 mg/m ² IV Day 1 |
| Vincristine | 1.4 mg/m ² IV Day 1 (2.0 mg maximum) |
| Prednisone | 100 mg PO Days 1-5 |

* If use of rituximab on Day 1 of Cycle 1 is felt to be a potential problem in terms of patient safety (i. e., high tumor burden or presence of circulating lymphoma cells in the peripheral blood), the treating physician is asked to call the Protocol Chair to discuss possible omission of rituximab in Cycle 1. Steroid pre-treatment for rituximab is allowed during Cycle 1.

BSA is to be recalculated at the start of each cycle. Doses of Doxil, rituximab, cyclophosphamide, and vincristine will be based upon the subject's BSA. With any change of weight within 10% of baseline, drug dosing will be maintained at the baseline level. Doses of chemotherapy are to be adjusted **only** if a subject's weight has changed more than 10% from baseline or prior dose.

7.2 Schedule

Chemotherapy cycles will be repeated every 21 to 28 days, depending upon blood counts and recovery from other toxicity (see Section 8.1). Chemotherapy cycles will be given every 21 days as long as the following criteria are met:

- ANC \geq 1000/mm³.
- Platelet count is \geq 75,000/mm³.
- Grade < 2 Hand Foot Syndrome (HFS), and absence of other severe skin reactions of grade 2 or more.
- Recovery to Grade \leq 1 non-hematologic toxicity.

If these criteria are not achieved by Day 21, the next cycle will begin on Day 28, as specified in Section 8.0. A minimum of six cycles, or two doses beyond documentation of CR (for a maximum of 8 cycles), will be administered.

7.3 Prevention of Tumor Lysis Syndrome

Specific methods to prevent or treat tumor lysis syndrome will be at the discretion of the investigator. Aggressive IV hydration and urinary alkalization are suggested, as is use of allopurinol, as follows:

- 7.3.1 Allopurinol, 600 mg (PO or IV, per Investigator discretion) should be given 24-48 hours prior to onset of chemotherapy, and thereafter, should be given at 300 mg/day, for at least 7 days following administration of the first cycle of chemotherapy.

- 7.3.2 Precautionary hospitalization is recommended for patients who have a high tumor burden, or who experience severe infusional reaction due to rituximab, that do not resolve after discontinuation or completion of the infusion.

7.4 CNS Prophylaxis

CNS Prophylaxis will be mandated per protocol for patients who meet the following criteria: lymphomatous involvement of bone marrow, testis, sinuses, or epidural regions; stage IV disease; ≥ 2 extra-nodal sites of lymphomatous disease. Specific regimen will be at the discretion of the primary oncologist. One of the following three regimens is recommended:

- 7.4.1 Cytarabine, 50 mg IT on Day 1 of each DR-COP cycle, for a total of 4 doses.
- 7.4.2 Methotrexate, 12 mg IT on Day 1 of each DR-COP cycle, for a total of 4 doses.
- 7.4.3 Depocyt, 50 mg IT, on Day 1 of each cycle of DR-COP, for a total of 4 doses.

7.5 Supportive Therapy

- 7.5.1 GF therapy with G-CSF, GM-CSF, or pegfilgrastim will be used in all patients, beginning on Day 3 of each cycle, until post nadir of blood counts from each chemotherapy cycle.
- 7.5.2 Use of erythropoietic factors is left up to the discretion of the individual Investigator.
- 7.5.3 Prophylaxis against *Pneumocystis carinii* is required. All patients will receive prophylaxis with either trimethoprim-sulfamethoxazole (160 mg/800mg, at least three times weekly), dapsone (100 mg daily), or inhaled pentamidine or alternative PCP prophylaxis (should the other methods not be feasible or are contraindicated).
- 7.5.4 Prophylaxis against other common opportunistic infections is encouraged, dependent upon the patient's CD4 cell count at study entry, and at the discretion of the treating physician.
- 7.5.5 Patients who meet the following criteria are required to receive oral quinolone prophylaxis during DR-COP chemotherapy, lasting throughout the period of neutropenia. Patients who do not meet these criteria may still receive antibiotic prophylaxis, at the discretion of the individual's physician.
- 7.5.1.1 A baseline CD4 count $\leq 100/\mu\text{L}$: prophylaxis should be given in all chemotherapy cycles.
- 7.5.1.2 A CD4 cell count that decreases to $\leq 100/\text{dL}$ during therapy: prophylaxis should be given in all subsequent cycles.
- 7.5.1.3 Nadir neutrophil count of $<500/\mu\text{L}$ occurring in a previous or current cycle: prophylaxis may begin immediately if the patient is severely neutropenic, and the prophylactic quinolone should be used in all subsequent cycles.

7.5.1.4 A nadir neutrophil count of <1000/uL associated with fever of at least 100.4° F, occurring in a previous cycle: prophylaxis should be given in all subsequent cycles. Patients with neutropenia and fever during a current cycle should be hospitalized and receive broad-spectrum antibiotic therapy.

7.5.6 **HAART Therapy:** All patients will be on HAART (the specific agents are at the discretion of the treating investigator, but should be in accordance with the current International AIDS-Society guidelines). Antiretroviral therapy available on an expanded access basis will be allowed, while experimental anti-retroviral agents will not be allowed. Zidovudine and zidovudine-containing regimens (including Combivir and Trizivir) will be prohibited, due to the known marrow suppressive effects of zidovudine.

7.5.7 Patients with active HBV infection (HBV surface antigen positive) are strongly encouraged to receive anti-HBV therapy.

7.6 Duration of Therapy

7.6.1 At the completion of Cycles 2, 4 and 6, and, if applicable, 8, all initially abnormal diagnostic tests should be repeated to document response to therapy.

7.6.1.1 If after four cycles of therapy, CR or PR has been documented, therapy will continue. If stable or progressive disease (PD) has been documented, the patient will be withdrawn from protocol therapy.

7.6.1.2 In patients who achieve a complete response after Cycle 4, two additional cycles of treatment will be administered for a maximum of six cycles. Chemotherapy will then be considered complete.

7.6.1.3 If PR has occurred after Cycle 4, treatment will be continued for a total of six cycles, at which time a restaging evaluation will be performed. If CR is then confirmed after Cycle 6, two additional cycles of DR-COP chemotherapy will be given, for a total of 8 cycles (see 7.6.1.2). If only stable disease persists after four cycles, or only PR persists after six cycles, the patient will come off treatment.

7.7 Criteria for Removal from Treatment

7.7.1 PD.

7.7.2 CR; six cycles of therapy for partial responders; or four cycles of therapy for patients with stable disease.

7.7.3 Severe toxicity, defined as grade 4 toxicity that is not resolved in a clinically satisfactory manner.

7.7.4 Patient request.

7.7.5 Investigator decision.

8.0 DOSE MODIFICATIONS

8.1 Decision to Re-Treat at Day 21 Versus Day 28 of the Cycle

8.1.1 The next planned cycle of DR-COP chemotherapy will be given on Day 21 of the cycle, provided that the following criteria are met:

- ANC \geq 1000/mm³
- Platelet count \geq 75,000/mm³
- HFS or other severe skin reactions recovered to < Grade 2
- Non-hematologic toxicity recovered to \leq Grade 1

8.1.2 If these criteria above are not met, the next planned cycle of DR-COP will be given on Day 28, unless toxicity has not yet recovered at that time (see section 8.2).

8.2 Hematologic Toxicity

8.2.1 Day 1 Counts

8.2.1.1 If ANC <1000/mm³ or platelets <75,000/mm³, delay up to 2 weeks (to Day 42) until ANC and platelets have increased above these levels. Treatment with G-CSF or pegfilgrastim is encouraged.

8.2.1.2 If by Day 42, ANC remains between 750-999/mm³, and/or the platelet count remains between 50,000/mm³-75,000/mm³, doses of cyclophosphamide and Doxil will be reduced by 25%.

8.2.1.3 If, by Day 42, ANC is <750/mm³, and/or the platelet count is <75,000/mm³, the patient will be removed from protocol.

8.2.1.4 Dose-reduction of 25% for cyclophosphamide and Doxil will be employed on the cycle following that in which the doses were initially reduced by 25%. However, if, ANC remains \geq 1000/mm³, and platelet count remains \geq 75,000/mm³ on Day 1 of the subsequent cycle, doses of cyclophosphamide and Doxil may be increased to 100% again.

8.2.1.4.1 If, in the discretion of the Investigator, the regimen is too toxic to the patient (e.g., ANC <1000/mm³ which has been prolonged, but resolved by Day 42; or intercurrent infection with ANC <1000/mm³ on more than one occasion while on protocol therapy; or more than one dose delay while on protocol therapy, the dose of liposomal doxorubicin may be decreased by 25% in subsequent cycles.

8.3 Non-Hematologic Toxicity

8.3.1 Neurological

| Neurotoxicity | Vincristine Dose |
|---|------------------|
| Moderate paresthesias (inability to button) | 50% dose |
| Inability to walk on heels or obstipation | No vincristine |
| Ambulation difficulties | No vincristine |

8.3.2 Renal

| Creatinine Clearance < 40 cc/min | |
|----------------------------------|--------|
| Drug | Reduce |
| Vincristine | 25% |

8.3.3 Hepatic

| If direct bilirubin >2.5 mg/ | |
|------------------------------|--------|
| Drug | Reduce |
| Vincristine | 25% |
| Doxil | 25% |

8.3.4 HFS Guidelines for Doxil Dose Adjustment:

| HAND FOOT SYNDROME (HFS) | | | |
|--|--|--|--|
| Toxicity Grade | Week after Dose | | |
| | 3 | 4 | 6 |
| 1 (mild erythema, swelling, or desquamation not interfering with daily activities) | Redose unless patient has experienced a previous Grade 3 or 4 skin toxicity in which case wait an additional week | Redose unless patient has experienced a previous Grade 3 or 4 skin toxicity in which case wait an additional week | Redose at 25% dose reduction; return to 4 week interval or withdraw patient per investigator's assessment |
| 2 (erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diam.) | Delay dosing up to 2 weeks or until resolved to Grade 0-1 | Delay dosing an additional week until resolved to Grade 0-1. If no prior Grade 3-4 HFS, continue treatment at previous dose and return to original dose interval. If patient experienced previous Grade 3-4 toxicity, continue treatment with a 25% dose reduction and return to original dose interval | Redose at 25% dose reduction; return to 4 week interval or withdraw patient per investigator's assessment |

| HAND FOOT SYNDROME (HFS) | | | |
|---|--|--|-------------------------|
| Toxicity Grade | Week after Dose | | |
| | 3 | 4 | 6 |
| 3 (blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing) | Delay dosing up to 2 weeks or until resolved to Grade 0-1 | Delay dosing an additional week until resolved to Grade 0-1. Decrease dose by 25% and return to original dose interval | Withdraw patient |
| 4 (diffuse or local process causing infectious complications, or a bed ridden state or hospitalization) | Delay dosing up to 2 weeks or until resolved to Grade 0-1 | Delay dosing an additional week until resolved to Grade 0-1. Decrease dose by 25% and return to original dose interval | Withdraw patient |

8.3.5 Stomatitis Guidelines for Doxil Dose Adjustment:

| STOMATITIS | | | |
|---|--|---|--|
| Toxicity Grade | Week after Dose | | |
| | 3 | 4 | 6 |
| 1 (painless ulcers, erythema, or mild soreness) | Redose unless patient has experienced a previous Grade 3 or 4 skin toxicity in which case wait an additional week | Redose unless patient has experienced a previous Grade 3 or 4 skin toxicity in which case wait an additional week | Redose at 25% dose reduction; return to 4 week interval or withdraw patient per investigator's assessment |
| 2 (painful erythema, edema, or ulcers, but can eat) | Delay dosing up to 2 weeks or until resolved to Grade 0-1 | Delay dosing an additional week until resolved to Grade 0-1. If no prior Grade 3-4 HFS, continue treatment at previous dose and return to original dose interval. If patient experienced previous Grade 3-4 toxicity, continue treatment with a 25% dose reduction and return to original dose interval | Redose at 25% dose reduction; return to 4 week interval or withdraw patient per investigator's assessment |

| STOMATITIS | | | |
|--|--|--|-------------------------|
| Toxicity Grade | Week after Dose | | |
| | 3 | 4 | 6 |
| 3 (painful erythema, edema, or ulcers, but cannot eat) | Delay dosing up to 2 weeks or until resolved to Grade 0-1 | Delay dosing an additional week until resolved to Grade 0-1. Decrease dose by 25% and return to original dose interval | Withdraw patient |
| 4 (requires parenteral or enteral support) | Delay dosing up to 2 weeks or until resolved to Grade 0-1 | Delay dosing an additional week until resolved to Grade 0-1. Decrease dose by 25% and return to original dose interval | Withdraw patient |

8.3.6 Bladder Toxicity

Cyclophosphamide-related cystitis, whether symptomatic or manifested only by otherwise unexplained microhematuria, will be treated by temporarily withholding the drug, vigorous hydration, and re-induction of cyclophosphamide when symptoms remit, or in 7 days in the case of asymptomatic microhematuria.

8.3.7 Skin Toxicity

Patients who have evidence of clinically significant skin rash, or oral/pharyngeal mucositis attributed to rituximab should have rituximab discontinued, with no further use of the agent. Please contact the Protocol Chair if this circumstance occurs.

9.0 CRITERIA FOR TREATMENT DISCONTINUATION

9.1 Permanent Withdrawal

After enrollment, the patient will be permanently withdrawn from study treatment for any of the following reasons:

- 9.1.1 Patients developing a life-threatening infection will have chemotherapy interrupted until the infectious process has cleared. The subject will be withdrawn from study treatment only if chemotherapy has been held for more than 6 weeks (Day 42).
- 9.1.2 Chemotherapy delays for more than 6 weeks (Day 42), for any reason.
- 9.1.3 Severe toxicities, defined as grade 4 toxicity that is not resolved in a satisfactory manner.
- 9.1.4 Progressive lymphoma at any time while on study.
- 9.1.5 Voluntary withdrawal.
- 9.1.6 The Investigator has the right to remove subjects from study for clinical reasons, which he or she believes to be life-threatening or resulting in significant morbidity to the subject

10.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

AE monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 10.1) and the characteristics of an observed AE (Section 10.2) will determine whether the event requires expedited reporting (via Adverse Event Expedited Reporting System [AdEERS] and to Ortho Biotech) in addition to routine reporting (via Clinical Trials Monitoring Service [CTMS] or Clinical Data Update System [CDUS]).

10.1 Adverse Event Characteristics

10.1.1 **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the NCI CTCAE will be utilized for AE reporting. CTCAE version 3.0 will be utilized for AE reporting until June 30, 2011. CTCAE version 4.0 will be utilized beginning July 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 3.0 and 4.0. A copy of the CTCAE version 3.0 and 4.0 can be downloaded from the CTEP web site (<http://ctep.cancer.gov>). The document “CTEP, NCI Guidelines: Adverse Event Reporting Requirements for NCI Investigational Agents” (sections 2 and 3) clearly outlines reporting criteria.

10.1.2 **ADVERSE EVENT (AE):** Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

10.1.3 **LIFE-THREATENING AE:** Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

10.1.4 **SERIOUS ADVERSE EVENT (SAE):** Any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization, or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Please note for **hospitalization** – All hospitalizations (or prolongation of existing hospitalization) for medical events equivalent to CTCAE Grade 3, 4, 5 must be reported regardless of the requirements for Phase of study, expected or unexpected, and attribution. For example, do not report an admission for PK sampling, but do report an admission for an MI. For this study, hospitalization for expedited AE reporting purposes is defined as an inpatient hospital stay equal to or greater than 24 hours. A hospital visit where a patient is admitted for observation or minor treatment (e.g., hydration) and released in less than 24 hours would not meet the requirements for hospitalization.

- 10.1.5 **TOXICITY:** Toxicity is a term NOT clearly defined by regulatory organizations. Toxicity has been described as an adverse event that has an attribution of possibly, probably or definitely related to investigational treatment. To minimize confusion the NCI would recommend that the term toxicity NOT be utilized for adverse event reporting purposes.
- 10.1.6 **UNEXPECTED AE:** Any AE that is not listed in available sources including the package insert, the Investigator's Brochure, or the protocol.
- 10.1.7 **Adverse Event Expedited Reporting System (AdEERS):** An electronic system for expedited submission of AE reports.
- 10.1.8 **ATTRIBUTION:** The determination of whether an AE is related to a medical treatment or procedure. Attribution categories:
- Definite – The AE is *clearly related* to the investigational agent(s).
 - Probable – The AE is *likely related* to the investigational agent(s).
 - Possible – The AE *may be related* to the investigational agent(s).
 - Unlikely – The AE *is doubtfully related* to the investigational agent(s).
 - Unrelated – The AE *is clearly NOT related* to the investigational agent(s).

10.2 Expedited AE Reporting

- 10.2.1 Expedited AE reporting for this study must use AdEERS, accessed via the CTEP home page (<http://ctep.cancer.gov>). The reporting procedures to be followed are presented in the CTEP, NCI Guidelines: Adverse Event Reporting Requirements which can be downloaded from the CTEP home page (<http://ctep.cancer.gov>). These requirements are briefly outlined in the table below (Section 10.3.3).

In the rare occurrence when internet connectivity is lost, an AE report may be submitted using CTEP's Adverse Event Expedited Report-Single Agent or Multiple Agent paper template (available at <http://ctep.cancer.gov>) and faxed to the AMC Operations Center at 240-238-2842. A 24-hour notification is to be made to AMC by telephone at 301-251-1161, only when internet connectivity is disrupted. Once internet connectivity is restored, an AE report submitted on a paper template, or a 24-hour notification phoned in, must be entered electronically into AdEERS by the original submitter at the site.

- 10.2.2 AdEERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. AdEERS provides a copy feature for other e-mail recipients.

10.2.3 Expedited Reporting Requirements for AEs that occur within 30 Days of Last Protocol Treatment

| | 1 | 2 | 2 | 3 | | 3 | | 4 & 5 | 4 & 5 ² |
|--|-------------------------|------------------|--------------|---------------------------------|------------------------------------|-------------------------------|----------------------------------|--------------------------|--------------------|
| | Unexpected and Expected | Unexpected | Expected | Unexpected with Hospitalization | Unexpected without Hospitalization | Expected with Hospitalization | Expected without Hospitalization | Unexpected | Expected |
| Unrelated Unlikely | Not Required | Not Required | Not Required | 10 Calendar Days | Not Required | 10 Calendar Days | Not Required | 10 Calendar Days | 10 Calendar Days |
| Possible Probable Definite | Not Required | 10 Calendar Days | Not Required | 10 Calendar Days | 10 Calendar Days | 10 Calendar Days | Not Required | 24-Hour; 5 Calendar Days | 10 Calendar Days |
| ¹ Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment require reporting as follows: 24-hour notification followed by complete report within 5 calendar days for: <ul style="list-style-type: none"> • Grade 4 and Grade 5 unexpected events Complete SAE report within 10 calendar days: <ul style="list-style-type: none"> • Grade 3 unexpected events with hospitalization or prolongation of hospitalization • Grade 5 expected events ² Although 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table. | | | | | | | | | |

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10.2.3.1 Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

10.2.3.2 Expedited AE reporting timelines defined:

“24 hours; 5 calendar days”– The investigator must initially report the AE via ADeERS, according to the procedures outlined in section 10.3.1, within 24 hours of learning of the event, and followed by a complete AE report submitted via ADeERS within 5 calendar days of the initial 24-hour report. Use the NCI protocol number and protocol-specific patient ID assigned during trial registration on all reports.

“10 calendar days”– A complete ADeERS report on the AE must be submitted within 10 calendar days of the Investigator learning of the event. Use the NCI protocol number and protocol-specific patient ID assigned during trial registration on all reports.

Any medical event equivalent to CTCAE Grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited AE reporting exclusions.

Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via ADeERS according to the guidelines as described above.

10.3 Expedited Reporting to Ortho Biotech

All SAEs regardless of relationship or severity must be reported to Ortho Biotech within 24 hours of the investigational staff's knowledge. Please fax all reports to the attention of Khalid Mamum at:

SAE Fax (Ortho Biotech Clinical Affairs, LLC): 908-541-4565

10.4 Routine Adverse Event Reporting

AEs reported through AdEERS must also be reported in routine study data submissions. Routine reporting of all AEs attributed to therapy, regardless of grade, should be reported.

10.5 Secondary AML/MDS

All cases of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and acute lymphocytic leukemia (ALL) that occur in patients on or following treatment on NCI-sponsored chemotherapy protocols must be reported to the AMC Operations Center using the NCI/CTEP Secondary AML/MDS Report Form. This form can be downloaded from the CTEP web site (<http://ctep.cancer.gov>). Refer to the CTEP, NCI Guidelines: Adverse Event Reporting Requirements (available at <http://ctep.cancer.gov>) for additional information about secondary AML/MDS reporting.

The following must be submitted within 30 days of an AML/MDS/ALL diagnosis occurring after treatment for cancer on an NCI-sponsored trial:

- A completed NCI/CTEP Secondary AML/MDS Report Form (do not use AdEERS);
- A copy of the pathology report confirming the AML/MDS/ALL; and
- A copy of the cytogenetics report (if available).
- The AMC Data Coordinator will forward copies to the Investigational Drug Branch (IDB) of the NCI CTEP.

11.0 EVALUATION OF RESPONSE

All patients will be evaluated for clinical response by physical examination following each chemotherapy cycle, and by imaging studies at the conclusion of the second cycle of chemotherapy, and every second cycle thereafter.

11.1 Response Assessment

Response is currently assessed on the basis of clinical, radiologic, and pathologic (e.g., bone marrow) criteria.

11.1.1 CT scans remain the standard for evaluation of nodal disease. Thoracic, abdominal, and pelvic CT scans will be performed for restaging even if those areas were not initially involved because of the unpredictable pattern of recurrence in NHL. MRI scans may be used instead of CT scans, at the discretion of the Investigator.

11.1.2 A bone marrow aspirate and biopsy should only be performed to confirm a CR if they were initially positive or if it is clinically indicated by new abnormalities in the peripheral blood counts or blood smear.

11.2 Definition of Response

11.2.1 CR requires the following:

11.2.1.1 Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalization of those biochemical abnormalities (e.g., LDH) definitely assignable to NHL.

11.2.1.2 All lymph nodes and nodal masses must have regressed to normal size (< 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy).

11.2.1.3 Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to <1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).

11.2.1.4 The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have decreased in size and must not be palpable on physical examination.

11.2.1.5 Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.

11.2.1.6 If the bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat bone marrow aspirate and biopsy of the same site.

- 11.2.1.7 For exploratory analyses alone, related to the use of PET scans: With residual nodal or extra-nodal masses on CT scan, greater than 1.5 cm in greatest transverse diameter that have regressed by more than 75% in the SPD; with individual nodes that were previously confluent, but have now regressed by more than 75% in their SPD compared with the size of the original mass on CT scan; or with indeterminate bone marrow biopsy, indicating increased number or size of lymphoid aggregates without cytologic or architectural atypia, a designation of CR will be made, if an initial PET, PET/CT or gallium scan was performed, was positive in these areas, and has now converted to negative at the time of assessment of tumor response.
- 11.2.2 CR unconfirmed (CRu) includes those patients who fulfill criteria 11.2.1.2 and 11.2.1.3 above, but with one or more of the following features:
 - 11.2.2.1 A residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the SPD. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD compared with the size of the original mass.
 - 11.2.2.2 Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia).
 - 11.2.2.3 For exploratory analyses alone, related to the use of PET scans: Patient has had staging and restaging with CT scans, but has not undergone PET scanning, PET/CT scanning or gallium scanning at Baseline, or underwent these studies, which were negative at baseline.
- 11.2.3 PR requires the following:
 - 11.2.3.1 $\geq 50\%$ decrease in SPD of the six largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following features: (a) they should be clearly measurable in at least two perpendicular dimensions, (b) they should be from as disparate regions of the body as possible, and (c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
 - 11.2.3.2 No increase in the size of the other nodes, the liver, or the spleen.
 - 11.2.3.3 Splenic and hepatic nodules must regress by at least 50% in the SPD.
 - 11.2.3.4 With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable, and not measurable, disease.
 - 11.2.3.5 Bone marrow assessment is irrelevant for determination of a PR because it is assessable, and not measurable, disease; however, if positive, the cell type should be specified in the report (e.g., large-cell lymphoma or low-grade lymphoma, [i.e., small, lymphocytic small cleaved, or mixed small and large cells]).
 - 11.2.3.6 No new sites of disease.

- 11.2.3.7 For exploratory analyses alone, related to the use of PET scans: If patient has had a Baseline PET, PET/CT scan or gallium scan which was positive, and has residual PET, PET/CT or gallium positivity in sites of prior disease, PR will be designated if the above size criteria are met in terms of CT scan findings, and CRu will be designated if PET, PET/CT or gallium scans have returned to normal (negative), and the above size criteria are met in terms of CT scan findings.
- 11.2.4 Stable disease is defined as less than a PR (see above) but is not a progressive disease (see below).
- 11.2.5 Progressive disease (PD, non-responders) requires the following:
- 11.2.5.1 50% increase from nadir in the SPD of any previously identified abnormal node for PRs or non-responders.
 - 11.2.5.2 Appearance of any new lesion during or at the end of therapy.
- 11.2.6 Recurrent disease is defined as the appearance of tumor following documentation of a complete remission.
- 11.2.7 Time to response is defined as time from the first dose of chemotherapy until documentation of first response.
- 11.2.8 Time to progression is defined as time from initiation of chemotherapy to documentation of first progression.
- 11.2.9 Response duration is defined as the time from first documentation of response to documentation of first progression.
- 11.2.10 Event free survival (EFS) is defined as time from initiation of chemotherapy to documentation of first progression or death.

12.0 STATISTICAL CONSIDERATIONS

12.1 Study Design

This will be a non-randomized, single arm, Phase II study.

12.2 Statistical Design

A sample size of 40 evaluable patients will be sufficient to test the null hypothesis that the complete response (CR + CRu) rate is 0.40 against the alternative hypothesis that it is 0.60 at the one-sided 0.10 significance level with power of 0.87.³⁵ It is anticipated that 44 patients will be enrolled to allow for a 10% drop-out rate.

12.3 Statistical Analysis Plan

Descriptive statistics will be used to summarize the patient population with respect to demographic features and baseline clinical characteristics.

Binomial proportions and their 95% confidence intervals will be used to describe the complete response (CR + CRu) rate and the overall response rate. The Kaplan-Meier method will be used to describe the duration of response, EFS and overall survival time. Binomial proportions will be used to estimate the proportion of patients who experience bacterial, fungal or opportunistic infections.

Fisher's exact rate will be used to evaluate the relationship between mdr-1 expression and BCL-2 expression with response. The Cox proportional hazards model will be used to evaluate the relationship between response and survival. The Wilcoxon rank sum test will be used to compare patients who develop a bacterial, fungal and/or opportunistic infection with those who do not with respect to baseline CD4 lymphocyte count, HIV-1 RNA level, quantitative immunoglobulin levels or changes in quantitative immunoglobulin levels.

To evaluate the role of PET scanning in predicting disease response, exploratory analyses will be done to evaluate the concordance between CT and PET for those patients and evaluations when both imaging modalities are used. Observations within a patient at different timepoints will be considered independent events for the purposes of the exploratory analyses. McNemar's chi-square test will be used to compare the two modalities with respect to whether or not response criteria have been met by each modality.

Causes of death for those patients who died will be summarized using a frequency table.

13.0 PATIENT CONSENT AND ETHICAL CONSIDERATIONS

All institutional and Federal regulations concerning informed consent will be fulfilled. A patient consent form will be used for this study, and must be approved by the IRB.

13.1 Institutional Review Board

This study must have the approval of a properly constituted Hospital Ethics Committee, Regional Ethics Committee or other IRB.

AEs must also be reported to the IRB by the investigator.

13.2 Informed Consent

The principles of informed consent described in Food and Drug Administration (FDA) regulations (21 CFR part 50) must be followed. IRB approval of the protocol and the informed consent form must be given in writing.

The AMC Operations Center must receive a copy of the letter of approval from the IRB, which specifically approves the protocol and informed consent, before patient enrollment. The IRB must also approve any significant changes to the protocol and documentation of this approval must be sent to the sponsor. Records of all study review and approval documents must be kept on file by the investigator and are subject to FDA inspection during or after completing of the study. Adverse events must be reported to the IRB. The IRB should receive notification of completion of the study. The investigator will maintain an accurate and complete record of all submissions made to the IRB, including a list of all reports and documents submitted.

13.3 Women and Minorities

This is a study being conducted by the NCI-sponsored AMC. Each participating site within the AMC and the AMC as a whole are required to assure that the participation of women and minority subjects reflects the percentage representation of these populations in their geographic region and, for the AMC, the United States as a whole. As such, it is expected that the representation of subjects on this trial will reflect the constitution of the respective populations.

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APPENDIX I: SCHEDULE OF ASSESSMENTS

| | Eligibility/ Screening ¹ | Prior to Cycle 1 | Prior to Cycle 2 | After Cycle 2 | Prior to Cycle 3 | Prior to Cycle 4 | After Cycle 4 | Prior to Cycle 5 | Prior to Cycle 6 | After Cycle 6 | 1 Month After Completion of all Therapy | Every 2 Months for 1 Year After Treatment Completion | Every 6 Months Thereafter for 2 Additional 1 Years | Treatment Discontinua tion ^{9,12} |
|---|--|---------------------------|---------------------------|---------------------|---------------------------|---------------------------|---------------------|---------------------------|---------------------------|---------------------|---|---|---|--|
| Clinical Studies: | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | |
| Lymphoma Documentation | X | | | | | | | | | | | | | |
| HIV Documentation | X | | | | | | | | | | | | | |
| Medical History | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Complete Physical Exam | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant Medication Review | X | | | | | | | | | | | | | |
| Laboratory Studies: | | | | | | | | | | | | | | |
| CBC with differential and platelets | X ² | X | X | | X | X | | X | X | | | X | X | X |
| Serum Chemistries | X ² | X | X | | X | X | | X | X | | | X ⁷ | X | X |
| HIV-1 RNA Viral load (local lab) | X | | | X | | | X | | | X | | X | X | X |
| HIV T-cell subsets (CD4, CD8) | X | | | X | | | X | | | X | | X | X | X |
| Quantitative Immunoglobulins (IgG, IgA, IgM) | X | | | X | | | X | | | X | | X | X | X |
| Serum pregnancy test | X ³ | X ³ | | | | | | | | | | | | |
| ACSR Donation | X | | | | | | | | | | | | | |
| Hepatitis B (HbSAg, HbSAb) and Hepatitis C (HCV antibody) | X | | | X | | | X | | | X | | X | | X |
| MDR-1 determination | X | | | | | | | | | | | | | |
| Staging Evaluation: | | | | | | | | | | | | | | |
| ECG | X | | | | | | | | | | | | | |
| CT or MRI scan: chest, abdomen, and pelvis | X | | | X | | | X | | | X | X | X ⁸ | X | X |
| PET scan, PET/CT, or Gallium scan ¹⁰ | X | | | X | | | X | | | X | X | | | |
| MUGA Scan or Echocardiogram | X | | | | | | | | | | | | | |
| Bone Marrow | X ⁴ | | | | | | X ⁶ | | | X ⁶ | X ⁶ | | | |

| | Eligibility/ Screening ¹ | Prior to Cycle 1 | Prior to Cycle 2 | After Cycle 2 | Prior to Cycle 3 | Prior to Cycle 4 | After Cycle 4 | Prior to Cycle 5 | Prior to Cycle 6 | After Cycle 6 | 1 Month After Completion of all Therapy | Every 2 Months for 1 Year After Treatment Completion | Every 6 Months Thereafter for 2 Additional 1 Years | Treatment Discontinua- tion ^{9,12} |
|-------------------------------|--|---------------------------|---------------------------|---------------------|---------------------------|---------------------------|---------------------|---------------------------|---------------------------|---------------------|---|---|---|---|
| Lumbar puncture ¹¹ | X | | | | | | | | | | | | | |
| Central Pathology Review | X ⁵ | | | | | | | | | | | | | |

¹ To be obtained within 4 weeks prior to patient registration, unless otherwise specified

² To be obtained within 2 weeks prior to patient registration

³ To be obtained within 72 hours prior to patient registration and again within 72 hours prior to cycle #1 chemotherapy

⁴ To be obtained within 6 weeks prior to patient registration

⁵ To be submitted within 30 days of study enrollment

⁶ Perform test if marrow was involved prior to treatment

⁷ To be performed at month 6 and 12 following treatment and every six months for years 2 and 3

⁸ Recommended every 6 months for the 1st year and every six months for years 2 and 3

⁹ To be performed within 4 weeks after a subject has demonstrated clinical progression of disease. These tests **do not** need to be repeated if they were performed within 7 days prior to documentation of disease progression.

¹⁰ If allowed by patients insurance company

¹¹ Intrathecal chemotherapy may be injected at the time of initial staging lumbar puncture.

¹² Tests are not required in participants who attain PR after 6 cycles or SD after 4 cycles **once** an alternative anti-cancer therapy is begun or disease progression has been documented. Patients will be followed for vital status only.

APPENDIX II: PERFORMANCE STATUS SCALE

| Karnofsky Performance Scale | | ECOG Performance Status Scale | |
|-----------------------------|--|-------------------------------|---|
| Percent | Description | Grade | Description |
| 100 | Normal, no complaints, no evidence of disease. | 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. |
| 90 | Able to carry on normal activity; minor signs or symptoms of disease. | | |
| 80 | Normal activity with effort; some signs or symptoms of disease. | 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work). |
| 70 | Cares for self, unable to carry on normal activity or to do active work. | | |
| 60 | Requires occasional assistance, but is able to care for most of his/her needs. | 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 50 | Requires considerable assistance and frequent medical care. | | |
| 40 | Disabled, requires special care and assistance. | 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 30 | Severely disabled, hospitalization indicated. Death not imminent. | | |
| 20 | Very sick, hospitalization indicated. Death not imminent. | 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 10 | Moribund, fatal processes progressing rapidly. | | |
| 0 | Dead. | 5 | Dead. |

APPENDIX III: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE)

CTCAE version 3.0 and 4.0 may be downloaded from the NCI CTEP website at:
<http://ctep.cancer.gov/reporting/ctc.html>.

APPENDIX IV: MODEL INFORMED CONSENT

A Phase II Trial of Doxil, Rituximab, Cyclophosphamide, Vincristine, and Prednisone (DR-COP) in Patients with Newly Diagnosed AIDS-Associated B-Cell Non-Hodgkin's Lymphoma

You are being invited to participate in a clinical research study. In order to decide whether you wish to be part of this research study, you should understand enough about the possible risks and benefits to make an informed decision. This process is known as informed consent. This form summarizes the specific information for this study. Your doctor will discuss the details of this study with you. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take an unsigned copy of this consent form home with you, to think about or to discuss with family or friends before making your decision. You should be satisfied that all your questions are answered before signing this consent form. You will be given a copy of this consent form to keep as a record.

WHY IS THIS STUDY BEING DONE?

You are being asked to take part in this research study because you have been diagnosed with non-Hodgkin's lymphoma (NHL), a cancer that begins in the lymph glands of the body, and then may spread to other areas of the body. Your lymphoma is related to your human immunodeficiency virus (HIV) infection.

The current standard treatment for NHL involves drugs called cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab used in a regimen called "R-CHOP." Using R-CHOP therapy, complete disappearance of disease is expected in over 50% of people. As part of this study, one of the active drugs in the R-CHOP regimen, doxorubicin, has been placed in a fatty bubble called a "liposome". The reason for placing the drug in the liposome is that there is evidence that the liposome is taken up better by the NHL cells, when compared to doxorubicin when it is given without the liposome. Liposomal doxorubicin (doxorubicin inside the liposome, also called Doxil) has shown similar or better anti-tumor activity against certain cancers, and has also been shown to have fewer side effects in some cancer patients.

- Liposomal doxorubicin is Food and Drug Administration (FDA) approved for ovarian cancer and also for patients with an acquired immune deficiency syndrome (AIDS)-related cancer called Kaposi's sarcoma. However, its use in NHL is still investigational. We hope that using liposomal doxorubicin (Doxil, the study drug) instead of doxorubicin in the R-CHOP regimen will be better at shrinking your tumor, and that you will have reduced side effects.
- Rituximab is a drug (called a "monoclonal antibody"), which works against certain types of lymphoma. Rituximab has been approved by the FDA for use in patients with NHL. Results from a recent study in individuals with lymphoma, but without HIV infection, suggested that chemotherapy given with rituximab was better than chemotherapy given alone, leading to better increased response rates and better increased overall survival.

The purpose of the current study is to see how well liposomal doxorubicin (Doxil) and rituximab work in combination with cyclophosphamide, vincristine, and prednisone (DR-COP) in shrinking tumors in patients with AIDS-related NHL. The combination of liposomal doxorubicin and rituximab

with cyclophosphamide, vincristine, and prednisone (all part of the standard R-CHOP treatment, in which only the doxorubicin is given in the liposome) is an experimental treatment, called “DR-COP”.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Approximately 40 people will take part in this study, nationwide. All people will receive the same chemotherapy treatment, DR-COP.

WHAT IS INVOLVED IN THE STUDY?

If you agree to participate and join in this study, the following will occur:

1. Screening Visit

You will need to have the following exams, tests, or procedures done to find out if you are eligible and can participate in the study. These exams, tests, or procedures are part of regular medical care for your lymphoma and may be done, even if you do not wish to join the study.

- Medical history and complete physical examination.
 - Vital signs (blood pressure, heart rate, breathing rate, and temperature) and height/weight will be measured.
 - Questions to see how much your lymphoma affects your daily life (called performance status evaluation).
 - Questions to see what medical problems or symptoms you may be having.
- Routine tests on your blood.
 - Blood (approximately 1 tablespoon) will be taken and will be used to check your blood cell numbers and blood chemicals that tell us how well your liver and kidneys are working, CD4 and CD8 numbers (the blood cells that are affected by HIV), and the amount of HIV in your blood (“viral load”).
 - Blood (approximately 2 teaspoons) will also be taken for tests for hepatitis C virus and hepatitis B virus.
 - A blood test (approximately 1 teaspoon) will be taken to determine if you are pregnant. This pregnancy test will be done if you are female, still having periods, and can become pregnant.
- Tests to measure where the lymphoma is in your body, and how big the lymphoma tumors may be:
 - CT scans (computed tomography, x-ray pictures of the inside of your body using a computer), and/or MRI scans (magnetic resonance imaging; pictures of the body which are made using magnetic rather than x-ray energy).
 - Gallium scan, PET/CT or PET scan (Positron Emission Tomography scan), which measure the lymphoma in your body using a small amount of radioactive material. Results of PET scanning will be used for research purposes only to determine how well this procedure can measure your response to therapy. All PET, PET/CT or gallium scans will be billed to your insurance company while you are taking part in this research study. If your insurance company does not agree to pay for these scans, you will not be excluded from other procedures included in the trial. All PET, PET/CT or gallium scans are optional.

- Bone marrow biopsy and aspiration (the removal of some cells from the inside of your pelvis bone, which is the factory where the cells in the blood are made) so that the doctors can look under the microscope to see if there is any lymphoma in the bone marrow. If there is lymphoma in your bone marrow when you start the study this test may be repeated again during the study to see if the treatment is working.
- Lumbar puncture (the removal of a small sample – about a teaspoon -of the fluid that surrounds your spinal cord and brain) to look for lymphoma cells.

The CT, MRI, Gallium, PET, PET/CT, lumbar puncture, and bone marrow biopsy tests will be more carefully explained to you by your doctor. You will be asked by your study doctor to sign a separate consent form for each of these tests.

- Tests to measure how well your heart is working.
 - Electrocardiogram (ECG or EKG– a painless test of how your heart is working).
 - MUGA (Multi Gated Acquisition) scan. A small amount of a short-lived radioactive material is injected into your vein to check the pumping action of your heart. You may be asked to sign a separate consent form for this.
 - Echocardiogram (ECHO) may also be done, instead of the MUGA scan. This is an ultrasound of the heart, which uses sound waves to check the pumping action of the heart).

At the screening visit, you will also be asked if you would donate blood or lymphoma tissue to the AIDS and Cancer Specimen Bank. You will be given a separate consent form to sign if you choose to donate.

2. Study Visits

If the exams, tests, and procedures show that you can be in the study, and you choose to be a part of the study, the study treatment will begin.

You will get chemotherapy with five drugs: liposomal doxorubicin (Doxil, the study drug), rituximab, cyclophosphamide, vincristine, and prednisone. Each course of treatment is called a cycle. Each cycle of therapy will be repeated every 21 to 28 days for a maximum of 8 cycles. The specific chemotherapy drugs will be given in the following way:

| | |
|--------------------------------|---|
| liposomal doxorubicin (doxil): | – will be given by vein (IV) over approximately 2 hours on Day 1 of each cycle |
| cyclophosphamide: | – will be given IV over approximately 1 hour on Day 1 of each cycle |
| vincristine: | – will be given IV over approximately 1 or 2 minutes on Day 1 of each cycle |
| prednisone: | – will be given by mouth as pills, taken in the morning on Days 1 through 5 of each cycle |
| rituximab: | – will be given by IV over approximately 5-7 hours on Day 1 of each cycle |

For each cycle, you will get the drugs at the clinic or outpatient center. The treatment will probably take all day, since the drugs must be given in order, one after the other. If you are sick due to the lymphoma, it is possible that the chemotherapy drugs will be given while you are in the hospital. It is unlikely that you would be admitted to the hospital for the only purpose of

getting the chemotherapy, but this may occur if you have any problems or side effects from the chemotherapy.

Before each cycle of treatment, you will:

- Have a complete physical examination.
 - Vital signs (blood pressure, heart rate, breathing rate, and temperature) and height/weight will be measured.
 - Questions to see how much your disease affects your daily life (performance status evaluation).
- Have routine blood laboratory tests (approximately 1 tablespoon) to check your blood cell numbers and blood chemicals.
- Be asked about any side effects you may be having and any medical illnesses or symptoms that you may have had since your last visit.

After every 2 cycles, you will *also* have:

- Blood tests related to your HIV (viral load, CD4 and CD8 cells).
- CT or MRI scans.
- Gallium, PET, or PET/CT scans (optional).
- Repeat of any of the tests done for the screening visit that showed lymphoma.

After cycle 4, you will *also* have:

- A bone marrow biopsy if your first biopsy showed lymphoma cells

3. End of Treatment Visit

The total length of time for treatment on this study is approximately 5 ½ to 7 ½ months. One month after your last chemotherapy, you will have the following tests to check how much lymphoma, if any, you have:

- CT or MRI scans.
- Gallium, PET, or PET/CT scans (optional).
- A bone marrow biopsy if your first biopsy showed lymphoma cells.
- Repeat of any of the tests done for the screening visit that showed lymphoma.

4. Follow-up Visits

You will be asked to come back to the clinic for follow-up visits. For the first year after the end of chemotherapy, you will have tests, exams, and procedures to check your cancer every 2 months. After one year, you will be asked to return every 6 months for a total of 3 years following the end of your chemotherapy. At these visits the following will be done:

- Complete physical examination, including:
 - Vital signs (blood pressure, heart rate, breathing rate, and temperature) and height/weight will be measured.

- Questions to see how much your disease affects your daily life (performance status evaluation).
- Assessment of any side effects you may be having, or any medical illnesses or symptoms that you may have had since your last visit.
- Routine laboratory blood testing to check your blood cell numbers, blood chemicals that tell us how well your liver and kidneys are working, CD4 and CD8 numbers (the blood cells that are affected by HIV), and HIV level.
- Tests to measure your lymphoma (every 6 months, even in the first year, for a total of 3 years from the end of your chemotherapy).
 - CT scans and/or MRI
 - Gallium scan, PET/CT or PET scans (optional)

5. Other Medications You May Need

You must take antiretroviral therapy (called HAART) in order to treat your HIV infection during the chemotherapy. However, you must not take HAART medicine containing zidovudine, such as Combivir[®] or Trizivir[®]. Your study doctor will discuss this with you.

You must receive prophylaxis (preventive treatment) for *Pneumocystis carinii* pneumonia (PCP), a common pneumonia in persons with immune deficiency).

You may get chemotherapy given directly into the central nervous system (CNS) as a preventive treatment. The drugs would be injected into the fluid surrounding the brain and spinal cord (called intrathecal chemotherapy). This is done to kill small numbers of cancer cells that may be in the brain and spinal cord, even though the numbers are so small that no cancer has actually been detected there. Your doctor will talk with you about whether or not you will need this preventive therapy given into the spinal fluid.

You must be given medicines to help increase your white blood cell number. Your doctor will discuss the specific treatments with you, which consist of injections given under the skin (subcutaneous) in an attempt to prevent the lowering of white blood cells, which commonly occurs with chemotherapy. If necessary, you may also be given medicines by injection under the skin to help increase your red blood cell number.

You may also be given antibiotics to help prevent infections, especially if your white blood cell number is low.

When chemotherapy is started you may be treated with the drug allopurinol to prevent “tumor lysis syndrome”. This syndrome may happen when the chemotherapy drugs kill lymphoma cells very quickly and cause them to release certain chemicals into the bloodstream, which may cause problems with the kidney. Allopurinol helps to reduce these chemical levels.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

While on study, you are at risk for the following side effects that you should discuss with the study doctor and/or your regular doctor. Other side effects that are less serious and uncomfortable may also

occur. Many side effects go away shortly after the chemotherapy is stopped, but in some cases side effects can be serious or long lasting or permanent.

1. Liposomal Doxorubicin

Common side effects are:

- Decreased white blood cell counts in the blood, which may increase the risk of fever and infection.
- Decreased red blood cells (anemia) which may increase the risk of tiredness, fatigue and shortness of breath.
- Decreased platelets (cells which help blood clotting) which may increase the risk of bleeding and/or bruising.
- Nausea (upset stomach)
- Hair loss (alopecia), or brittle hair
- Diarrhea
- Belly pain
- Mucositis (painful sores in your mouth, intestines and/or anus)
- Headache
- Vomiting
- Fever
- Constipation
- Weakness
- Skin rash, redness, peeling of the hands and feet

Less common:

- Acute infusion-related reaction, which may happen during the first drug infusion. Signs of this are flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat and a drop in blood pressure.

Rarely:

- There have been rare reports of death in patients who develop a body-wide infection as a result of decreased white blood cell number.
- There has been a report of heart failure and damage and death caused by liposomal doxorubicin.
- It is possible that liposomal doxorubicin may leak from your blood vessel and damage the nearby tissue. Signs of this are a burning sensation and swelling.
- Very severe skin reactions have been reported, consisting of redness, swelling, ulcers (skin breakdown) and/or pain of the skin, requiring immediate medical attention. Severe reactions in the mouth and other mucus membranes, with swelling, ulcerations and pain may occur (Stevens-Johnson syndrome), as well as painful rashes and ulcers on the skin (called erythema multiforme, or toxic epidermal necrolysis).

2. Cyclophosphamide

Just like liposomal doxorubicin, cyclophosphamide commonly causes belly pain, upset stomach, vomiting, diarrhea, hair loss, redness swelling and sores in the mouth, skin rash, and a drop in the numbers of white blood cells, red blood cells, and platelets.

Cyclophosphamide also causes:

- Loss of appetite (anorexia)
- Irritation of the large intestine with bloody stools
- Lung problems
- Yellow color of the skin and eyes (jaundice)
- Darkening of the skin and nails
- Heart damage; the combination of cyclophosphamide and liposomal doxorubicin may make this more likely or more severe
- Infertility in both men and women; if you are a woman of child bearing age your menstrual periods may stop either temporarily or permanently.
- Some people who have received cyclophosphamide developed other cancers of the urinary tract or bone marrow (like myelodysplasia or leukemia). This may happen years after the treatment has stopped.
- Kidney problems
- Irritation of the bladder and/or ducts connecting it with the kidneys (ureters) with bloody urine

3. Vincristine

In common with liposomal doxorubicin and/or cyclophosphamide, vincristine can cause nausea, vomiting, constipation, diarrhea, fever, headache, weakness and hair loss. Vincristine may also cause:

- Numbness and tingling in hands and feet
- Difficulty walking
- Muscle wasting
- Jaw pain
- Decreased bladder control
- High or low blood pressure
- Paralyzed bowel, which results in severe constipation.
- Rare allergic reaction (swelling of the face and breathing tube, rash, chills, drop in blood pressure, dizziness).
- Nerve pain
- Loss of normal reflexes
- Difficulty with balance
- Changes in taste sensation
- Change in the ability to see colors
- Hearing loss, ringing in the ears

4. Prednisone

- Difficulty sleeping
- Slow healing sores
- Weight gain (especially in the face, shoulders and belly)
- Dizziness
- Development of freckles on the skin
- Changes in personality
- Mood swings
- Severe mental disorder, craziness
- Spinal fractures
- Tendon rupture
- Clouding of the eyes (cataracts)
- Irritability, nervousness
- Electrolyte imbalance (abnormal amounts of various chemicals in your blood).
- Fluid retention, causing swelling of ankles or other areas
- Headache
- Increased risk of infections
- Feeling of extreme wellbeing
- Seizures
- Brittle bones
- Thin fragile skin
- Increase in blood pressure
- Increased eye pressure (glaucoma)

- Inflammation of the pancreas (a small gland that secretes substances such as insulin)
- If you are a diabetic, you may need to adjust (increase) the amount of insulin or diabetes pills you need to take.
- Decreased ability to tolerate carbohydrates (sugars and starches) and development of diabetes

Rare:

- Heart attack
- Stroke
- Blood vessel disease and other cardiac (heart) abnormalities.
- Allergic reaction (rash, itching, swelling, severe dizziness, trouble breathing), which could be severe and life-threatening

5. Rituximab

Some side effects occur in most individuals treated with rituximab. However, severe side effects occur in only 10-20% of people, and usually occur during the actual rituximab infusion (called infusion reaction complex).

Common side effects (*these effects occur in more than 9% of people taking rituximab*):

- Fever, chills
- Headache
- Low blood pressure
- Nausea (upset stomach)
- Weakness
- Angioedema (itchy rash and swelling of areas of the skin and mucous membranes, much like a serious allergic reaction)

Less common (*these effects occur in 3 – 9% of people taking rituximab*):

- Bronchospasm, which is an abnormal narrowing of the windpipe, which can cause coughing and wheezing, and difficulty in breathing.
- Vomiting
- Anemia (shortness of breath, weakness and fatigue)
- Belly (abdominal) pain
- Achy joints and muscles
- Dizziness
- Congestion

Rare (*these effects occur in less than 3% of subjects taking rituximab*):

- Weakening of certain parts of your immune system, resulting in a greater risk of infections.
- Life-threatening skin rashes (mucocutaneous reactions) that could occur many months after the end of the chemotherapy treatment. These reactions could occur on the skin, causing itching, and swelling, or in the mouth or other mucous membranes (such as the lining of the stomach, intestines and mouth), and could be very serious, leading to inability to eat or drink, the need to be hospitalized, or even death.
- Tumor lysis syndrome (where rapid destruction of lymphoma cells may cause chemical abnormalities in the body) has been reported within 12-24 hours after the first rituximab infusion.
- Infusion reactions (shortness of breath, rash, fever, chills, tightness in the chest and/or low blood pressure during the time that the rituximab is given by vein).

- Kidney failure.
- Death has been reported due to skin reaction, tumor lysis, infusion reaction complex, hepatitis B reactivation, and bowel obstruction and perforation.
- In patients with Waldenstrom's macroglobulinemia, rituximab therapy may cause an immediate reaction in your body that may result in the plasma (water part) of the blood becoming so thick that it cannot pass through small blood vessels. Blood cells then cannot deliver oxygen to where it is needed in your body. This side effect has only been reported in patients with a diagnosis of Waldenstrom's macroglobulinemia.

Rituximab Treatment Risks in Combination with Chemotherapy

Other events have occurred in patients receiving rituximab. The following have occurred in patients receiving rituximab in combination with chemotherapy:

- In some patients who have hepatitis B virus (HBV), rituximab has caused the infection to worsen by reactivating the virus. Severe and sudden hepatitis inflammation of the liver, very serious liver disease (including liver failure) and death can occur during, or within several months after rituximab treatment. HBV diagnosis in most patients has occurred approximately 4 months after their first dose of rituximab. Seek immediate medical attention if you develop persistent stomach/abdominal pain, dark urine, extreme fatigue, or yellowing eyes and/or skin. Treatment with antiviral medication is usually given to control HBV.
- There is a report of an increase in fatal infections in HIV-related lymphoma patients when rituximab was used in combination with CHOP chemotherapy.
- Other viral infections, including JC virus (a virus responsible for an infection of the brain and spinal cord), cytomegalovirus (a member of the herpesvirus group, which also includes herpes simplex virus and varicella-zoster virus [virus that causes chickenpox]), parvovirus B19 (a virus that can decrease or halt the body's production of red blood cells), West Nile virus (a virus causing an inflammation to the brain), and hepatitis C have been found in patients who have received rituximab in combination with chemotherapy.
- Patients have also experienced abdominal pain, bowel obstruction (blockage) and perforation (tearing), in some cases leading to death, after receiving rituximab in combination with chemotherapy for NHL and diffuse large B-cell lymphoma (DLBCL).

Rituximab Treatment Risks in Other Disease Areas

Rituximab is also used in studies to treat patients with rheumatoid arthritis (RA), a disease characterized by inflammation of the joints. Patients with RA are at increased risk for cardiovascular (heart) events compared with the general population. Three cardiovascular deaths have occurred in RA patients treated with rituximab.

Common side effects in RA studies. *(These effects occurred in 2% or more of people taking rituximab for RA compared to patients taking placebo, an inactive substance).*

- | | |
|---|--|
| • abdominal pain | • nausea (upset stomach) |
| • anxiety | • paresthesia (numbness, tingling of the skin) |
| • arthralgia (joint pain) | • pruritus (itching) |
| • asthenia (weakness, loss of strength) | • pyrexia (fever) |

- chills
- dyspepsia (indigestion, upset stomach)
- hypercholesterolemia (high blood cholesterol)
- hypertension (high blood pressure)
- migraine
- rhinitis (hayfever)
- throat irritation
- upper respiratory tract infection
- urticaria (hives)

6. CT-Scans

This research study involves being exposed to radiation from x-rays and CT scans. The amount of radiation you will receive from the scans is similar to that of an airline flight across the US. The risk from radiation exposure is too small to be measured directly, and is considered low when compared with other everyday risks. The study doctor will provide you with a contact person if you would like more information about radiation exposure.

7. Drawing Blood

There may be some pain, bleeding, bruising, or infection at the place where the blood tests were taken from the vein in your arm. There is also a possibility that you may feel faint when your blood is drawn.

8. Lumbar puncture (spinal tap) or bone marrow biopsy/aspirate.

There may be some pain and bleeding at the site of the biopsies, and infection may also occur.

9. Intrathecal (IT) chemotherapy to prevent lymphoma occurring in the brain and spinal cord and fluid.

Injection of chemotherapy into the spinal fluid may produce headache, stiff neck, or irritation of the lining of the brain.

WHAT ABOUT PREGNANCY?

If you are a woman who could become pregnant during this study, there may be risks to your unborn child and to you that are not now known. It is required that you practice birth control if you are capable of becoming pregnant during this study. If you are pregnant you may not participate in this study, and if you become pregnant you will be removed from the study. A blood or urine test will be done before you start this study to test for pregnancy. If you are a man, you and your female partner should use an effective method of birth control while you are participating in this study. Both men and women should continue to practice an effective method of birth control for at least 6 months after your last dose of study drug. Your study doctor will give you information on the ways in which you may keep from becoming pregnant.

WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART IN THIS STUDY?

If you agree to take part in this study, there may or may not be a direct medical benefit to you. One benefit could be that the treatment works and makes your lymphoma get smaller, or go away completely. We cannot promise that you will have a good response or any benefit from being in this

study, but we hope the information learned from this study will benefit other patients in the future, even if your own lymphoma does not shrink or go away completely.

WHAT OTHER OPTIONS ARE THERE?

If you do not want to join the study, there are other possibilities for treatment. You could receive treatment with other chemotherapy drugs, or other investigational (experimental) drugs. You can receive similar drugs (CHOP, using doxorubicin instead of the study drug, liposomal doxorubicin or Doxil) with or without rituximab without participating in this study. Another alternative is no further therapy. Your doctor can provide detailed information about your disease and the benefits of the various treatments available. You should feel free to discuss your disease and your prognosis (likely outcome) with the doctor.

WILL YOUR INFORMATION BE KEPT PRIVATE?

The Investigator and the Institutional Review Board (IRB) will keep your records private as far as the law allows. Officials of:

- The National Cancer Institute (NCI)
- The AIDS Malignancy Consortium Operations Center
- The EMMES Corporation (AMC Data Management Center)
- The Food and Drug Administration (FDA)
- The IRB may look at your research records and medical records. Unless otherwise required by law, your records will be kept confidential. Information collected will not identify you by name. A coded number called a “unique identifier” will be used. We may publish the information from this study in journals or present it at meetings. If we do, we will not use your name or any other information that could identify who you are.

Medical records that identify you and the consent form you signed will be looked at and/or copied for research or regulatory purposes by the sponsor and may be looked at and/or copied for research or regulatory purposes by:

- FDA
- Department of Health and Human Services (DHHS) agencies
- IRB

WHAT ARE THE COSTS?

If you take part in this study, your insurance company may not pay for some or all of the procedures, treatments, and tests. If that happens, you will need to pay for these procedures, treatments, and tests yourself. You will not be responsible for the cost of the drug, liposomal doxorubicin (Doxil), which will be provided free of charge by the drug manufacturer, Ortho Biotech Clinical Affairs, LLC (Ortho Biotech).

ARE THERE ANY PAYMENTS TO YOU FOR TAKING PART IN THE STUDY?

You will not be paid for taking part in this study.

WHAT HAPPENS IF YOU GET INJURED OR NEED EMERGENCY CARE?

If you get hurt or sick from taking part in the study, we will give you the medical care you need. You must pay for the care. You will not receive any compensation or payment if you get hurt or sick.

WILL YOU RECEIVE NEW INFORMATION ABOUT THIS STUDY?

During the study, we may learn new things about the risks or benefits of being in the study. If we do, we will share this information with you. You might change your mind about being in the study based on this information. If new information is provided to you, we will ask for your agreement to continue taking part in this study.

UNDER WHAT CIRCUMSTANCES CAN YOUR PARTICIPATION BE TERMINATED (STOPPED)?

You will be removed from the study for the following reasons:

- If you do not follow your doctor's (the Investigator's) instructions.
- If your disease gets worse.
- If you have unacceptable side effects.
- If you are unable to complete the necessary testing for the study.
- If the sponsor closes the study.
- If your chemotherapy treatment is delayed more than 6 weeks.
If this happens, your doctor (the Investigator) will discuss other options with you.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT AND WHAT WILL HAPPEN IF YOU DECIDE NOT TO PARTICIPATE?

Your participation in this study is voluntary. Your decision whether or not to take part will not affect your current or future care at this institution. You are not waiving any legal claims or rights. If you do decide to take part in this study, you are free to change your mind and stop being in the study at any time. However, if you decide to stop participating in the study, we encourage you to talk to the research doctor and your regular doctor first.

CERTIFICATE OF CONFIDENTIALITY

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the Federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

APPENDIX V: AIDS AND CANCER SPECIMEN RESOURCE (ACSR)

Specimen Preparation & Shipping Instructions

A. COLLECTION

Consent patient for ACSR donation. Collect 20 cc of whole blood in ACD tubes.

B. SHIPPING

To ship these specimens, use a diagnostic shipper approved for a volume of at least 30 cc. The use of the SAF-T-PAK STP-210 diagnostic cardboard shipper (for category B substances) is recommended. These shippers may be ordered at the SAF-T-PAK web site, www.saftpak.com. The instructions below are for use with the recommended STP-210 shipper. If using another federally approved diagnostic shipper, please follow instructions provided for that specific shipper.

To ship bloods, place the tubes into canister of a STP-210 SAF-T-PAK shipper for category B substances, wrapping each tube in bubble wrap and using the absorbent paper at the bottom of the canister. Each sample tube should be labeled using a sharpie pen (permanent marker) with the following information:

- AMC Protocol # **AMC-047**
- AMC Patient ID#
- Date and time of collection
- Specimen type, i.e., WB=Whole Blood, P=Plasma, S=Serum
- Specimen purpose: Donation

Place the lid on the canister and place it inside of the ambient SAF-T-PAK shipper. Fold and pack ACSR form inside shipping box. Seal the ambient shipper with cellophane shipping tape. Label the ambient shipper with the "UN 3373" diamond shaped label. On one side, in black marker write, your name or name of responsible person, date of collection and phone number of the person responsible for the package.

B.1 Specimen Shipment

Specimens are accepted MONDAY through THURSDAY. Specimens are not accepted on Friday. All specimens should be shipped by overnight express (AMC Operations Center FedEx account [REDACTED] at room temperature to:

ACSR Blood Receiving Lab
Johns Hopkins Oncology
1650 Orleans Street, CRB-384
Baltimore, MD 21231-1000
TEL: (410) 955-8721
FAX: (443) 287-3217

B.2 Instructions for Specimens Collected on Friday

PREPARATION OF PLASMA AND MONONUCLEAR CELLS

It is preferable that separation occurs as soon as possible. If necessary, whole blood in acid citrate dextrose (yellow top tube) can be held at room temperature for no more than 24 hours.

Materials:

- Lymphocyte Separation Medium (LSM Solution, Ficoll-Hypaque - sterile)
- 15 ml conical centrifuge tubes (sterile)
- PBS (sterile)
- 1, 5 ml and 10 ml serologic pipettes (sterile)
- NUNC tubes
- Alcohol-saturated, control rate freezer container
- DMSO freezing media:
 - 50% Cryoprotective Medium, Cambrex (catalog no.:12-132A)
 - 50% Heat Inactivated Fetal Bovine Serum

Preparation of Plasma Samples

- a. The 7 ml tube of whole blood in acid citrate dextrose should be rotated gently 2 or 3 times before being centrifuged. Do not transfer before centrifugation.
- b. The cells are separated by centrifugation at 500 g for 10 minutes.
- c. 0.5ml aliquots of plasma are removed and put into 1.5 ml screw top tubes and transferred to liquid nitrogen storage.

Peripheral Blood Mononuclear Cell Separation and Freezing

- a. The cells and plasma remaining from the previous step are transferred into a 15 ml conical tube, capped and re-suspended by gently tapping the bottom of the tube.
- b. Sterile PBS should be added to the suspended cells until the final volume is 8 ml; invert to mix.
- c. The 8 ml whole blood-PBS mixture should be carefully overlaid onto 4 ml of room temperature LSM or Ficoll-Hypaque solution in a sterile 15 ml conical tube. A sharp interface should exist between the LSM and the whole blood mixture. (If the layer of LSM gets mixed with the blood-PBS, the tube should be gently rotated to mix the blood, PBS, and LSM, and transfer to a 50 ml sterile conical tube. An equal volume of PBS is added, and the cells are separated at 600 g for 15 minutes. After removal of LSM-PBS supernatant, return to Step b).
- d. The 15 ml conical tube for 30 minutes at 900 g at room temperature. The mononuclear leukocytes (principally lymphocytes and monocytes) will band at plasma/LSM interface.
- e. The fluffy white layer just below the plasma layer should be aspirated off, along with approximately half of the LSM layer under it, and transferred to an appropriately labeled 15 ml sterile conical centrifuge tube. Mix by gentle rotation.
- f. Washed twice in sterile PBS - centrifuge at 500 g for 10 minutes.

- g. Cell pellet should be mixed well with a gentle finger-tapping action.
- h. Using a 1 ml pipette, the *DMSO freezing mixture should be added drop wise to the cell pellet suspension. Gently finger-tap between drops. If the cell pellet is small, only 0.5 ml of freezing media is added (and only one aliquot of cells is frozen). If the cell pellet is large, up to 2 ml of freezing media can be added in a drop wise fashion. (Cell densities of 1 - 10 million PBMC/ml are best for cryopreservation. If a hemocytometer is available, the optimal concentration is 5 million PBMC/ml).

*** Important-Do not put the DMSO containing media on the cell button all at once.**

Freeze the cell suspension in 0.5ml aliquots in sterile NUNC vials by placing the NUNC tubes in a room temperature, alcohol saturated, control rate freezer container and store in the -80°C freezer overnight. Transfer the cell suspension into the liquid nitrogen temperature freezer for long-term storage the next working day.

***PLEASE DOUBLE CHECK PACKAGING OF SHIPPER AND DO NOT DEVIATE FROM REQUESTED LABELING. ***Shipping frozen aliquots requires the use of packaging acceptable for dry ice and Class 9 label with weight of dry ice written on package.

Please Note: The shipper will be mailed back to the AMC site.

The STP-210 SAF-T-PAK shipper is a complete kit w/ all trappings, bubble wrap, absorbent paper, labels, everything (but to reuse the shipper, you will need new labels, wrap, etc).

B.3 Record of Specimens

This study will track specimens via GlobalTraceSM, a component of the AMC AdvantageEDCSM system. The GlobalTrace shipment manifest must accompany all specimen shipments.

APPENDIX VI: INFORMED CONSENT FORM RESEARCH STUDY AIDS AND CANCER SPECIMEN RESOURCE (ACSR)

A. INTRODUCTION

You are being asked to donate tissue for research. Before you decide to be a part of this research study, you need to understand the risks and benefits so that you can make an informed decision. This is known as informed consent.

This consent form provides information about the research study, which has been explained, to you. Once you understand the study and the tests it requires, you will be asked to sign this form if you want to take part in the study. Your decision to take part in the study is voluntary. This means that you are free to choose if you will take part in the study.

B. PURPOSE

The National Cancer Institute has set up a Bank for tissues and biological fluids from HIV-positive and HIV-negative individuals in order to have specimens available for scientists studying malignancies associated with HIV disease. Individuals who have had biopsies to determine a malignancy are being asked for permission to store some of the tissue in the Bank. Only tissue in excess of that required for decision making will be given to the Bank. If it turns out that your physician needs more of your tissue for additional studies, the Bank will release all of your tissue back to your doctor. No additional tissues will be taken from your body for the Bank.

In addition, you are requested to donate some of your blood to the Bank so that scientists will also be able to look for any deviation in these body fluids that may explain the malignancy.

C. PROCEDURES

You are being asked for consent to place some of the biopsy material in the ACSR. If you agree to allow the ACSR to have some of your tissue, we would also like to:

1. Confidentially obtain some clinical information from your medical records that could be useful to research investigators. The report of the information retrieved from your medical record that is given to research investigators will not have your name, or include any information which could personally identify you.
2. Obtain some blood for the Bank. Up to twenty (20) milliliters of blood will be obtained at your next visit to your physician.

If during the course of treatment by your physician, it is necessary to perform any of the following procedures for diagnostic reasons, you will be asked, at that time, to consent to having a portion of that specimen sent to the Bank. These requests will not require you to make any additional visits to your doctor or have any additional specimens taken just for the Bank. The Bank will only receive part of your specimen, and only what is in excess. No additional materials will be removed for the purposes of the Bank alone. Samples of interest would include, (but are not limited to):

1. Spinal fluid.
2. Airway washes.

3. Fluid around lungs and intestines.
4. Additional biopsy material.

You will not be asked to fill out any forms for any of these specimens.

D. POSSIBLE RISKS

There is a possibility of a bruise and slight pain at the time the blood samples are taken. There is also the possibility of fainting and infection at the site of the blood draw.

E. POSSIBLE BENEFITS

It may be that there will be no direct benefit to you by consenting to allow the Bank to have portions of your biopsies and biological fluids. However, there may be possible benefits to medical knowledge and HIV-infected individuals in the future.

F. COSTS

There will not be any additional costs to you for consenting to participate in the AIDS and Cancer Specimen Resource.

G. PAYMENT FOR INJURY OR HARM

As the lists of risks shows, taking part in this research study may result in injury or harm to you. In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. You or your insurance company will be charged for continuing medical care and/or hospitalization. (*Institution*) will not pay for the care. Likewise, (*Institution*) will not pay you for pain, worry, lost income, or non-medical care costs that might occur from taking part in this research study.

APPENDIX VII: HANDLING OF TISSUE

Handling of Tissues:

A paraffin block involved by lymphoma should be submitted to the following address:

Dr. Wayne Tam
Department of Pathology
The New York Presbyterian Hospital
525 E. 68th Street, ST-715
New York, NY 10021
Tel: (212) 746-2442
Fax: (212) 746-8173

The submitting Pathology laboratory is also asked to submit the tissue block from involved tissues; a total of three 1.0 mm tissue cores from the block will be taken by the Immunopathology Laboratory for inclusion in a tissue microarray. The block will be returned to the submitting laboratory within one month of receipt.

If the submitting Pathology Department does not agree to submitting the block, we will accept, instead, 15 blank tissue sections.

Specimen Accessioning and Tracking:

Upon receipt, each specimen from AMC will receive an Immunopathology Laboratory accession number which will be sequential with the other the specimens, including clinical specimens, received. This will avoid delays in processing. Specimens belonging to AMC will be so stated under “Clinical Information”, and therefore can be easily identified and tracked. A report will be issued by Dr. Chadburn within two days of receipt, with a description and preliminary diagnosis based on the microscopic review of H&E-stained sections. This will be followed by “procedure” reports describing the results of immunohistochemistry, in situ hybridization (EBER) and molecular analysis (if requested or considered informative for final diagnosis), as well as a final report correlating all the findings. Average turn-around time for routine immunohistochemistry and in situ hybridization is one week. All the reports will be sent by FAX to the Operations Center as well as to the submitting physician, and hard copies to both will follow. All information will also be entered into the EMMES tissue tracking system. An individual in the laboratory will be specifically designated as data coordinator for the AMC. This individual will be responsible for tracking AMC specimens received, logging the information in the appropriate data bases, and notifying AMC of specimen status. He/she will be the contact person in the laboratory for any questions AMC may have concerning the status of a specific specimen.

Tissue Microarrays:

Tissue microarrays will be constructed from formalin-fixed paraffin-embedded tissues from all the cases for which blocks are received. A Beecher tissue microarray instrument (Beecher instruments Inc., Sun Prairie, WI) will be used. Each case will be represented by three 1.0 mm tissue cores from neighboring areas on the same block. The test samples will be internal. The controls will consist of a lymphoma of known type, Tonsil, spleen and thymus. Once all the patients are recruited, and all the

specimens for the trial are received, the array blocks will be completed and sections will be made available to all AMC investigators.

Pathology Review:

Specimens received from AMC will undergo histopathologic diagnosis and classification, immunostaining and molecular analysis. Pathologic evaluation will be performed by Dr. Chadburn; all interesting, atypical and unusual cases will also be reviewed by Dr. Knowles. Molecular analysis will be performed in the Molecular Pathology Laboratory and reported upon by Dr. Cesarman. Specifically, cases will be processed as follows:

1. Histopathology- Process tissue, pathologist review of H&E and classification.
2. Immunohistochemistry for lymphoid, proliferation and differentiation antigens, including as needed: CD20, CD3, CD79a, CD10, bcl-6. If a lymphoma has histologic features of Hodgkin's lymphoma, immunohistochemistry will include CD45, CD20, CD3, CD30, and CD15. For DLBCLs we will evaluate germinal center B cell (GC) like vs non GCB-like (BCL-6, CD10, MUM1, FoxP1, CD138, IRF4).
3. Biological correlates. These will be done when the tissue arrays are completed, or using blank tissue sections for evaluation of cases not included in the arrays because a block was not received. They are as follows:
 - a. BCL-2- Immunohistochemistry will be performed, and cases will be classified as positive if more than 50% of the tumor cells are found to have clear positivity. BCL-2 is an anti-apoptotic gene that had been found to be a prognostic indicator of survival in some DLBL cohorts.
 - b. Ki67- This is an indicator of cellular proliferation, which will be included as it will provide the proliferation index. Cases will be divided into three categories: >90%, 60% to 90% and <60%.
 - c. MDR-1- Expression of MDR-1 will be evaluated by immunohistochemistry for P-glycoprotein, as this has been shown by some to be associated with a high probability of relapse and poor prognosis.

APPENDIX VIII: AMC DATA SAFETY MONITORING PLAN

Monitoring the Progress of Trials and the Safety of Participants

All AMC protocols follow the Cancer Therapy Evaluation Program (CTEP) guidelines for reporting of adverse events. All adverse events that meet the expedited reporting requirements of the National Cancer Institute (NCI) are reported to the Investigational Drug Branch (IDB) of the NCI via the Adverse Event Expedited Reporting System (AdEERS) web application. All expedited adverse event reports are also required to be submitted to the local Institutional Review Board (IRB) of the reporting institution. If NCI holds the IND or no IND is required for a study, the AMC sites report serious adverse events directly to the AMC Operations and Data Management Center (ODMC) via AdEERS. In some instances, the AMC sites may report serious adverse events directly to the commercial sponsor holding the IND who will then in turn report to the AMC ODMC. However, most AMC protocols require that sites report all serious adverse events via AdEERS with the AMC ODMC forwarding a copy of the report to the sponsor. Unless an AMC protocol specifies an alternate plan for the review and submission of serious adverse events, all serious adverse events received by the AMC ODMC will be reviewed by the AMC Medical Monitor at the AMC ODMC prior to submission to NCI and the sponsor. For protocols for which the IDB does not have an assigned drug monitor to review serious adverse event reports, in the event of disagreement between the reporting physician and the AMC Medical Monitor regarding the attribution of the event to the investigational agent(s) (i.e., determination of whether the relationship is unrelated, unlikely, possible, probable, or definite), the AMC Medical Monitor will provide the final determination of the relationship.

The AMC ODMC provides a listing of serious adverse events to the Protocol Chair and Co-chair(s) for review on a regular basis. The AMC ODMC compiles these events in a tabular format and posts them on the password-protected section of the AMC web site. The AMC web site is accessible to all AMC investigators, co-investigators, and their staff. Email notification that this information is available on the web site will be sent to all site PIs. It is the responsibility of each site to provide this information to their respective IRBs, if required by their IRB. For blinded studies, the serious adverse events are reviewed and tabulated without treatment assignment.

Accrual summaries for each AMC trial are updated nightly on the password-protected section of the AMC web site. The progress of each AMC trial is reviewed regularly by the Protocol Chair and also by the appropriate disease-oriented Working Group during scheduled conference calls. For phase I dose escalation trials, dose escalation (or dose de-escalation) is based on the rules in the protocol and the Protocol Chair and Group Statistician determine whether these criteria have been met. For phase II trials, stopping the trial for toxicity or efficacy, or suspending enrollment pending observation of responses in a multi-stage phase II trial, is based on meeting criteria stated in the protocol, and the Protocol Chair and Group Statistician determine whether these criteria have been met.

For phase III trials, the AMC has formed an independent Data Safety and Monitoring Committee (DSMC). Voting members of the DSMC are physicians, statisticians, and a patient advocate. All voting members are from outside the AMC. Non-voting members are the NCI scientific project officers and an NCI statistician. The AMC Data Safety and Monitoring Committee reviews AMC phase III studies in accordance with the National Cancer Institute's Policy for Data Safety and Monitoring. Confidential reports of all phase III trials are prepared by the AMC Group Statistician with support from the AMC ODMC. A written report containing the current status of each trial monitored, and when appropriate, any toxicity and outcome data, are sent to DSMC members by the

AMC ODMC allowing sufficient time for DSMC members to review the report prior to the meeting. This report addresses specific toxicity concerns as well as concerns about the conduct of the trial. The report may contain recommendations for consideration by the DSMC concerning whether to close the trial, report the results, or continue accrual or follow-up.

The results of each DSMC meeting are summarized in a formal report sent by the DSMC Chair to the Group Chair and AMC ODMC within 1 week of the meeting. The DSMC report contains recommendations on whether to close each study reviewed, whether to report the results, and whether to continue accrual or follow-up. A primary recommendation (e.g., continue with no change; recommended or required modification; stop) must be included in the document. The Group Chair is then responsible for notifying the Protocol Chair and relevant Disease-oriented Working Group Chair before the recommendations of the DSMC are carried out. In the unlikely event that the Protocol Chair does not concur with the DSMC, then the NCI Division Director or designee must be informed of the reason for the disagreement. The Study Chair, relevant Disease-oriented Working Group Chair, Group Chair, DSMC Chair and NCI Division Director or designee will be responsible for reaching a mutually acceptable decision about the study. CTEP approval of a formal amendment will be required prior to any implementation of a change to the study.

Following a DSMC meeting, a summary of the serious adverse events reported to the DSMC is posted to the AMC web site. It is each site's responsibility for conveying this information to its IRB.

Plans for Assuring Compliance with Requirements Regarding the Reporting of Adverse Events (AE)

For trials monitored by the NCI's Clinical Data Update System (CDUS), adverse event information is transmitted electronically to NCI on a quarterly basis. For trials monitored by NCI's Clinical Trials Monitoring Service (CTMS), adverse event information is transmitted electronically to NCI every two weeks.

Plans for Assuring that any Action Resulting in a Temporary or Permanent Suspension of an NCI-Funded Clinical Trial is Reported to the NCI Grant Program Director Responsible for the Grant

In the event that termination of the trial or major modification to the protocol is under consideration, the Protocol Chair will convene the AMC Data Coordinator and Disease-oriented Working Group Chair by conference call to discuss the options. For phase I and II trials, the Protocol Chair also has the option of asking the AMC DSMC to review the study. The AMC ODMC will inform the CTEP Protocol Information Office (PIO) when studies are temporarily or permanently closed. The Cancer Treatment and Evaluation Program (CTEP) of the National Cancer Institute (NCI) must approve all protocol amendments prior to distributing to the AMC sites.

Plans for Assuring Data Accuracy and Protocol Compliance

All study data for AMC clinical trials are entered directly by AMC site staff into AdvantageEDCSM (a web-based data entry and enrollment system). During data entry, the system performs validation checks on many fields and performs consistency checks between select fields. Range checks are placed on each field to eliminate entry of out-of-range values. Edit check programs are run on the database on a set schedule to identify and resolve inconsistencies between forms or data collected at different points in time. AMC ODMC staff routinely interacts with site staff to resolve any data problems.

In accordance with NCI guidelines, the AMC ODMC conducts monitoring visits at the AMC sites to evaluate compliance with regulatory issues, and to review data for specific cases by checking source documents. These reports are sent to the site Principal Investigator and to the NCI. In the event that major violations are identified, sites are asked to provide a plan to correct deficiencies within 30 days. If needed, a repeat site visit is conducted. In the event that a site does not correct deficiencies in a pre-determined time frame, the AMC Executive Committee has the option of taking action against the site. Possible actions include, but are not limited to, suspending enrollment of new patients to AMC trials until deficiencies are corrected; recommending a decrease in funding to the site; and requiring specific training for site investigators or staff members.

APPENDIX IX: DRUG DISTRIBUTION GUIDELINES

EMINENT Services Corporation INVESTIGATIONAL DRUG REPOSITORY

THE AIDS MALIGNANCY CLINICAL TRIALS CONSORTIUM - (Protocol# AMC 047)

DRUG DISTRIBUTION CENTER GUIDELINES

EMINENT Services Corporation is pleased to support the AMC in maintaining the Drug Distribution Center in compliance with current Good Manufacturing Practice regulations (21 CFR 211) as well as applicable other Federal, State and local regulations. The Drug Distribution Center's functions involve receiving, storing, packaging, labeling, and shipment of drug products, performing clinical study emergency procedures (to include drug recalls), and return drug processing and disposal.

In order to make it simple for the clinical sites to request or to return the study products for Protocol# AMC 047, we are providing the following information and guidelines. These guidelines also provide information relating to storage of the investigational drugs covered under this protocol as well as drug accountability procedures. If further information is needed please feel free to contact the pharmacist at (240) 629-1972.

Ordering

EMINENT hours are Monday through Friday, 8:00 AM to 5:00 PM EST. A pharmacist can be reached during normal business hours at (240) 629-1972.

EMINENT will be monitoring new as well as continuing patients and will attempt to ship medication to the clinic before they are needed. If it is necessary to order medications, the guidelines are as follows. To order drugs, please complete an Agent Request Form and FAX to (240) 629-3298.

Instructions: Type or clearly print all information except signature. Complete all sections except for box labeled **EMINENT Use**. Sign the form in the space provided. All requests received by 2:00 PM EST weekdays will be shipped to arrive 2nd business day by 4:30 pm. Requests pertaining to refrigerated drug products will be shipped by Overnight Service to arrive by next business day 10.00 am. If drug is needed overnight, check "Yes" in the Overnight field. If an overnight shipment is needed for Saturday and clinic personnel will be available to receive it, check "Yes" in the Saturday field.

Instructions for completing the Agent Request Form appear below. A master copy of the Agent Request Form is located in the Appendix A. This standard form should be photocopied and used for ordering agents from EMINENT Services Corporation (EMINENT).

Instructions for Completing an Agent Request Form

1. When completing an Agent Request Form, please type or clearly print all requested information. Data which remains the same from order to order, such as the clinical investigator's name, phone number and shipping address, should be typed on the original form prior to photocopying.
2. Enter the clinic number, clinical investigator's name, and other required information in the top, middle section of the Agent Request Form.
3. Each line of the order should contain only one item. Complete each line as follows:
 - a. Protocol number, (pre-printed Protocol# AMC 047)
 - b. current inventory, (at the site)
 - c. agent name, strength, and dosage form (pre-printed), and
 - d. quantity.

The following study products for Protocol# AMC 047 can be ordered using the *Agent Request Form*:

Doxil 2.0 mg/ml Inj. 10 ml vial

4. ONLY individuals authorized by the clinical investigator may sign and date the order form.
5. Initial orders must be approved by an AMC Operations Center representative. Requests for initial orders must be FAXed to the AMC Operations Center at (240) 238-2842.
6. The shipping address must be typewritten. Please avoid using a rubber stamp, since this usually does not yield a sharp image and does not photocopy or transmit well by FAX. To avoid errors in the address, it is better to add the address to the original you will keep for photocopying.
7. The completed Agent Request Forms may be FAXed to (240) 629-3298 or sent via express courier to the Eminent Services Corporation address at the top left corner of the form. Please retain a copy of the order; when study supplies arrive, you may want to verify what was received against what was ordered.

Receipt and Storage

When a drug order is received from EMINENT, it is important that it be inspected as soon as possible. Carefully check items against the packing slip, noting container sizes, quantities, and lot numbers. Complete the *Shipment Receipt Acknowledgment Form* that is sent along with the shipment and fax it back to EMINENT at (240) 629-3298. A copy of this form along with the

Packing Slip must be retained at the Clinical Site for audit purposes. EMINENT should be notified immediately if there are any discrepancies.

Please place study drugs in an appropriate storage areas.

Accountability

In order to comply with FDA regulations regarding investigational drugs, each site is required to keep a record of receipts and dispositions of all study drugs received from EMINENT. This can be accomplished by using the Investigational Drug Accountability Record or an equivalent computerized record. A copy of the Investigational Drug Accountability Record is included in the Appendix C. Please retain this form as an original and photocopy for future use.

This form is designed to be used for maintaining perpetual inventories. Each time a drug is dispensed to a patient, or received and/or returned to EMINENT, an appropriate entry should be made on the Investigational Drug Accountability Record for that drug and protocol. The inventory balance documented on this form should match the actual drug inventory on-hand at all times. It is suggested that a regular schedule be established for a physical inventory, the results of which should be noted on the Investigational Drug Accountability Record. When the recorded balance and the actual inventory are not equal, ascertain the reason and notify the EMINENT staff pharmacist via memo by FAX or mail. Attach a copy of the memo to the back of the Investigational Drug Accountability Record and retain.

FDA regulations require that drug accountability records must be retained for two years following the date that a New Drug Application (NDA) is approved or, if an NDA is not approved, until two years after the Investigational New Drug (IND) application or study is closed. These records shall be made available, upon request, for inspection and copying by a properly authorized employee, representative, or monitor of the FDA.

Returns

Study drugs, both used and unused, shall be returned to EMINENT for the following reasons:

- ◆ The study is completed or terminated,
- ◆ the drug has expired,
- ◆ the drug has been stored improperly or was received damaged, and/or
- ◆ the drug's return has been requested by EMINENT pharmacist.

A copy of the Agent Return Form is included in the Appendix B. This is a standard form that should be photocopied and used to return all study products of this protocol.

Instructions for Returning Study Supplies to EMINENT

1. Use a separate Agent Return Form for each site.
2. Complete all sections of the form, except the right-hand section with the heading FOR EMINENT USE ONLY (shaded area).
3. Print or type site address on the form.
4. Quantity: Enter the number of units being returned.
5. Sign and date the form. Please include the site phone number.
6. Enclose ONLY those items that EMINENT provided.
7. Include the completed Agent Return Form in the package. Make a copy of the completed form for your records.
8. **Pack the materials so that they will not break during transit!** Ship all items at room temperature, unless otherwise instructed.
9. The EMINENT address is also located in the upper right of the Agent Return Form.

The EMMES Corporation - AMC 047 (0058)
C/o EMINENT Services Corporation
7495 New Technology Way
Frederick, MD 21703

Tel: (240) 629-1972
Fax: (240) 629-3298

Email: service@emiserv.com

APPENDIX - A
AGENT REQUEST FORM

THE AIDS MALIGNANCY CLINICAL TRIALS CONSORTIUM - (Protocol # AMC 047)

AGENT REQUEST FORM

| | | | | | |
|---|--------------------------|--|---------------|--|-----------------|
| Instructions: Type or print clearly all information except signature. Complete all sections except for box labeled For EMINENT Use Only . Sign the form in the space provided. All requests received by 2:00 PM EST weekdays will be shipped to arrive 2nd business day by 4:30 pm. Requests pertaining to refrigerated drug products will be shipped by Overnight Service to arrive by next business day 10.00 am. If drug is needed overnight, check "Yes" in the Overnight field. If an overnight shipment is needed for Saturday and clinic personnel will be available to receive it, check "Yes" in the Saturday field. | | | | | |
| FAX or Express Mail to: EMINENT Services Corporation 7495 New Technology Way Frederick, MD 21703 Phone: (240) 629-1972 FAX: (240) 629-3298 | | Clinical Investigator's Name: _____ Ordered by: _____ Telephone number: _____ Site No.: _____ Date ordered: _____ Date needed by: _____ Overnight: () Yes Saturday: () Yes | | For EMINENT Use Only Order # _____ | |
| Protocol No. | Current Inventory | Agent Name | Unit | Quantity Required | Comments |
| AMC 047 | | Doxil 2.0 mg/ml Inj.10 ml vial | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| TYPE Pharmacy shipping address below: (No P.O. Box Numbers Please) | | | | | |
| <input type="checkbox"/> Initial Request <i>Please fax initial requests to AMC Operations Center at (240)238-2842.</i> | | | | | |
| <input type="checkbox"/> Subsequent Request | | | | | |
| _____ Authorized Signature (Clinical Site) | | | _____ Date | | |
| _____ Authorized Signature (Client) | | | _____ Date | | |

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APPENDIX - B
AGENT RETURN FORM

THE AIDS MALIGNANCY CLINICAL TRIALS CONSORTIUM - (Protocol # AMC 047)

AGENT RETURN FORM

RETURN ONLY AGENTS SUPPLIED BY EMINENT SERVICES CORPORATION

The Agents listed below were returned by: _____

Address: _____

Site: _____

INSTRUCTIONS FOR INVESTIGATOR

1. Type or print clearly all information-one item per line. Fill in all sections.
2. **DO NOT** mark in the shaded area.
3. Sign and date list.
4. Pack the agents well to minimize breakage and leakage.
5. Enclose the completed list with the agents and return to:

The EMMES Corporation-AMC 047 (0058)
c/o EMINENT Services Corporation
7495 New Technology Way
Frederick, MD 21703

| Protocol No. | Agent Name | Strength & Dosage Form | Quantity | Lot # | For EMINENT Use Only | |
|--------------|--------------------------------|------------------------|----------|-------|----------------------|--------------|
| | | | | | Rec. Code | Checked by: |
| AMC 047 | Doxil 2.0 mg/ml Inj.10 ml vial | | | | | |
| | | | | | | Verified by: |
| | | | | | | Date: |
| | | | | | | |

To be completed by site

Individual preparing this list:
(if other than the investigator)

Name

Title

Signature

Telephone No.

Comments: _____

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APPENDIX - C
INVESTIGATIONAL DRUG ACCOUNTABILITY RECORD

