THE UNIVERSITY OF TEXAS
M.D. ANDERSON CANCER CENTER

DIVISION OF MEDICINE

**TITLE:** A Phase II randomized Study of Rituxan-HCVAD alternating with Rituximab-methotrexate-cytarabine vs. standard Rituximab CHOP every 21 days for Patients with Newly Diagnosed with high risk aggressive B-cell non-Hodgkin's lymphomas in patients 60 year-old or younger

## 1.0 OBJECTIVES

1.1 To evaluate the Overall response rate (ORR), Complete Response (CR + Cru), Disease-free survival (DFS), and progression-free survival (PFS) rate following therapy with Rituxan-HCVAD alternating with Rituximab with high-dose methotrexate/ara-C and standard R-CHOP in patients with newly diagnosed B-cell aggressive non-Hodgkin's lymphomas younger than 60 years old and with adjusted IPI 2 or higher adverse prognostic features. Progression-free survival will be done for 3-years

1.2 Secondary objectives include: overall survival, toxicity profile.

## 2.0 BACKGROUND

2.1 Aggressive Non-Hodgkin's lymphomas

Aggressive NHL is the most common of the NHL diagnosed in the USA. Ninety to 95% of these will be of B-cell origin, and half of the patients will be younger than 60 years old. Many prognostic factors have been evaluated for patients with this condition, but the most commonly used is the International Prognostic Index (IPI). The IPI[1] has been adjusted in patients 60 years old or younger, and includes Stage I- II vs. III-IV, normal vs. elevated Lactic dehydrogenase (LDH), and Performance Status 0-1 vs. more than 1. For each one of these adverse prognostic features, patients received one adverse point; if none of these features are present, the score would be 0 and the patient would be at low risk for relapse. The disease-free survival and survival rates for the four groups of patients 60 years old or younger is summarized in the table below:

Age-Adjusted IPI index in patients 60 years old or younger:

| N=1274 | CR rate (%) | % 5-yr DFS | % 5-yr survival |
|---|---|---|---|
| 0 (22% of patients) | 92 | 86 | 83 |
| 1 (32% of patients) | 78 | 66 | 69 |
| 2 (32% of patients) | 57 | 53 | 46 |
| 3 (14% of patients) | 46 | 58 | 32 |

Therefore, almost half of the younger patients with aggressive lymphomas (FLCL, DLCL, Immunoblastic lymphomas) will present with poor prognostic features, and less than half of these will be alive at 5 year. The main cause of death is recurrent large cell lymphoma. This group of patients with two or more poor risk prognostic factors should be target for investigational therapies.

2.2. Rituximab-CHOP

Rituximab is a new chimeric antibody directed against CD20, a surface protein on B-cell lymphoma cells, and some normal B-lymphocytes. This drug has activity as a single agent in indolent and aggressive NHL.[2-5] In vitro studies showed an increase in sensitivity of different cell lines to chemotherapy agents, when Rituximab was added. Recently, investigators have reported overall responses values of more than 90% in treatment of follicular lymphomas by Czuczman et al (CHOP-R),[6] McLaughlin (FND-R),[7] Zinzani (FN-R),[8] in aggressive NHL by Julie

Vose et al (CHOP-R),[9] in mantle cell lymphoma by Romaguera et al (R-HCVAD),[10] and in Burkitt's and Burkitt's like lymphoma by Deborah Thomas et al (R-HCVAD)[11]. Coiffier et al also reported results from a randomized study in Diffuse Large B-cell Lymphoma (DLBCL) patients older than 60 year-old with Ann Arbor stage II or higher, comparing standard treatment with CHOP (cyclophosphamide, vincristine, doxorubicin, prednisone) versus CHOP + Rituximab (375 mg/m²). The patients treated in the R-CHOP arm had better response, complete response, disease-free survival, and overall survival rates than did those on the conventional arm, without any additional toxicity. For that reason, in most of the centers in USA, and according to NCCN recommendations, R-CHOP is considered an acceptable treatment for low-grade and aggressive NHL including DLBCL, follicular large cell lymphomas, and immunoblastic lymphomas. In this study, R-CHOP will be considered a standard treatment arm, and will be administered for a total of 6-8 cycles.[12]

2.3. Rituxan-HCVAD

The combination of Rituximab-HCVAD has been used at M.D. Anderson in more than 100 patients with mantle cell lymphoma. More than 90% of the patients treated with this protocol responded to the treatment with a mortality rate of 4%. Initially, HCVAD was designed for the treatment of Burkitt's lymphomas in pediatric patients. Subsequently, this protocol was adopted at M.D. Anderson Cancer Center for the treatment of acute lymphoblastic leukemias, lymphoblastic lymphomas, Burkitt's, and Burkitt's-like lymphoma-leukemia. In these studies, this combination chemotherapy produced responses in Burkitt's Lymphoma /leukemia, the results have been promising with an 81% CR rate, a 61% continuous CR rate, and a 3 year survival of 49%.[11] For mantle cell lymphoma, a similar regimen has resulted in a 92% CR rate and a failure-free survival of 80% at 2 years of follow-up for patients 65 years of age or younger.[10] In the same study patients over 65 years received a two-thirds dose reduction of Ara-C, achieving a CR rate of 90% and a median failure-free survival of 15 months. The R-HCVAD regimen consists in two alternating chemotherapy regimens. The first half of this regimen is HCVAD, which includes cyclophosphamide being given at a relatively higher dose and on a hyper fractionated schedule, doxorubicin, vincristine and dexamethasone. This regimen is alternated with high doses of methotrexate and Ara-C. For our study, our regimen will be Rituximab-HCVAD alternating with Rituximab-Methotrexate-Ara-C for a total of 6-8 cycles (3-4 cycles of each one).

2.3. CNS prophylaxis.

Prophylaxis for leptomeningeal disease will be given in patients considered at risk for CNS involvement. Guidelines are summarized below, unless the clinician decides otherwise: patients who will receive intrathecal prophylaxis for CNS disease will be those who have any of the following conditions:

a. Patients with involvement of the spinal canal.
b. Involvement of the bone marrow with aggressive lymphoma.
c. Testicular aggressive lymphoma.
d. Two or more extranodal sites involved,

e. Diffuse bone involvement.
f. Sinus or parasinus disease (or any risk for local extension)

CNS prophylaxis consists of intrathecal chemotherapy with every cycle of chemotherapy, alternating methotrexate 12 mg with ara-C 100 mg (if intrathecal chemotherapy is given by Ommaya reservoir, the dose of methotrexate will be reduced to 6 mg). The clinician may give variations of those doses and treatments according to patient's tolerance.

2.4. Radiation therapy to the involved field will be given to patients with stage I, and II if clinically appropriate, and stage III or IV if the investigator felt necessary.

## 3.0 BACKGROUND DRUG INFORMATION

### 3.1.1. Rituximab.

Rituximab (Rituxan®) is a humanized monoclonal antibody against CD20 a receptor in the surface of malignant B-cell lymphocytes. The drug has activity against aggressive and non-aggressive NHL of B-cell origin, and has been used in combination with chemotherapy. The drug is administered intravenously at doses of 375 mg to 500 mg/m². Side effects are as follows:

Hematologic Events: In clinical trials, Grade 3 and 4 cytopenias were reported in 48% of patients treated with RITUXAN; these include: lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1 to 588 days) and of neutropenia was 13 days (range, 2 to 116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following RITUXAN therapy were reported.

In addition, there have been a limited number of postmarketing reports of prolonged pancytopenia, marrow hypoplasia, and late onset neutropenia (defined as occurring 40 days after the last dose of RITUXAN) in patients with hematologic malignancies. In reported cases of late onset neutropenia (NCI-CTC Grade 3 and 4), the median duration of neutropenia was 10 days (range 3 to 148 days). Documented resolution of the neutropenia was described in approximately one-half of the reported cases; of those with documented recovery, approximately half received growth factor support. In the remaining cases, information on resolution was not provided. More than half of the reported cases of delayed onset neutropenia occurred in patients who had undergone a prior autologous bone marrow transplantation. In an adequately designed, controlled, clinical trial, the reported incidence of NCI-CTC Grade 3 and 4 neutropenia was higher in patients receiving RITUXAN in combination with fludarabine as compared to those receiving fludarabine alone (76% [39/51] vs. 39% [21/53]).

Administration: Dilute to an appropriate concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride USP or 5% dextrose in water USP. Gently invert the bag to mix the solution. Discard any unused portion left in the vial.
Dosage form: Injection: 100 mg (10 mL); 500 mg (50 mL).

**3.1.2. Cyclophosphamide:**

Cyclophosphamide is an alkylating agent. The usual dose goes from 50 mg/day to 60 mg/kg/day in transplant patients. Main side effects include cytopenias, nausea, vomiting, hemorrhagic cystitis, alopecia.
Administration: oral or intravenously. Intravenously, the drug is diluted in a concentration not higher than 20 mg/mL. Standard IVPB fluid: 250 mL. Maximum IVPB rate; 15 minutes; can be administered as IV push (2-5 minutes infusion) if ordered by physician. Room temperature stability is 48 hours (extrapolated stability policy considering % drug lost over time). Refrigerator stability: 28 days. Specials precautions: Keep the drug in refrigerator.
Dosage Forms:
Injections 100 mg, 200 mg, 500 mg, 1 g, 2 g.
Tablet: 25 mg, 50 mg.

**3.1.3. Vincristine.**

One of the vinca alkaloids. Used in lymphomas, leukemias, and other tumors. Main side effects include constipation, and peripheral neuropathy.
Usual dose is 1.4 mg/m² to a maximum of 2 mg (some protocols use higher doses).
Administration: intravenously. Maximum concentration 1 mg/mL. Standard IV dose is 50 mL administered IVPB over 15 minutes. Can be given IV push.
Room temperature stability: 21 days.
Refrigeration stability: 21 days.
Special precautions: Avoid extravasation.

Dosage forms: Injection: 1 mg/mL (1 mL).

**3.1.4. Doxorubicin Hydrochloride**

Anthracyclin, main side effects are nausea, vomiting, alopecia, cytopenias, cardiomyopathy.
Administration: intravenously, usual dose 25 mg/m² to 75 mg/m²
Maximum concentration 5 mg/mL
Standard IVPB fluid: 50 mL
Maximum IVPB rate: 15 minutes. Can be administered IV Push.
Avoid extravasation.
Dosage forms: Injection 10 mg, 50 mg, 150 mg, 200 mg.

**3.1.5. Dexamethasone:**

Dexamethasone is an steroid with multiple clinical applications and multiple ways of administration. Has activity against lymphoproliferative disorders among another malignancies. The usual dosage is 0.5 to 40 mg.
Administration: Oral or intravenously.
Dosage form: Injection, as sodium phosphate, 4 mg/mL (5mL), 24 mg (5 mL). Tablets 0.5 mg, 0.75 mg, 2 mg, 4 mg, and 10 mg.

**3.1.6. Methotrexate**

Antineoplastic drug, folic acid antagonist. Used for solid tumors, lymphomas, leukemias, autoimmune diseases. Main toxicity is mucositis, cytopenias, renal failure, liver toxicity.
Administration: Oral and intravenous.
Maximum concentration 25 mg/mL. Standard IVPB fluid: 50 mL. Maximum IVPB rate

is 15 minutes. Can be administered i.v. push. Room temperature stability 7 days. Refrigeration stability: 15 weeks.

Dosage Forms: 25 mg/mL (2 mL, 4 mL, 8 mL, and 10 mL).

### 3.1.7. Cytarabine Hydrochloride

Antineoplastic agent. Main side effects are myelosuppression, nausea, fever, ataxia, neurological problems as confusion. Used for lymphomas, leukemias.

Administration intravenously or intrathecal.
Dosage intrathecal is 5-100 mg intrathecal.
Intravenously, the dose varies from 100 mg/m²/day by continuous infusion x 7 days to 3 g/m² every 12 hours for 8 doses.

Administration: Maximum concentration: 100 mg/mL. Standard IVPB fluids 500 cc. Maximum IVPB rate 15 minutes. Can be given IV push. Dose more than 1 g/m² should be given in more than 2 hours.
Room temperature stability: 28 days.
Refrigeration stability: 25 days.
Dosage Forms: 100 mg, 500 mg, and 1 g.

### 3.1.8. Leucovorin calcium (Folinic Acid)

Antidote for folic acid antagonists, treatment of megaloblastic anemia.
Administration I.V., I.M., oral.
Maximum concentration 25 mg/mL
Maximum IVPB rate: 15 minutes. Can be given IV push.
Room temperature stability: 15 days.
Refrigeration stability: 15 days
Dosage forms: Injection 3 mg/mL (1 mL); 50 mg vial; 100 mg vial; 300 mg vial.
Tablet: 5 mg; 10 mg; 15 mg; and 25 mg.

### 3.1.9. Intrathecal Methotrexate and Intrathecal Ara-C

See 3.1.6. and 3.1.7. Intrathecal administration requires de use of preservative-free solution. Doses will be 6 mg-12 mg of methotrexate, and 50 mg-100 mg of intrathecal ara-c.

## 4.0 PATIENT ELIGIBILITY

**Inclusions**:

4.1 Confirmed diagnosis of previously untreated large B-cell Non Hodgkin's, Large Cell Lymphoma and B-Cell with high grade features. Other aggressive lymphomas such as Primary Mediastinal large B-cell Lymphomas will be also allowed to be included.

4.2 Patients with performance status of 0-2 (Zubrod Scale – see Appendix E).

4.3 Serum bilirubin <1.5 mg/dl and serum creatinine < 2.0 mg/dl unless due to lymphoma; ANC >1000/$mm^3$ and platelets >100,000/$mm^3$ unless due to lymphoma.

4.4 Cardiac ejection fraction 50% or greater.

4.5 Ages 16 – 60 (since CHOP-R is not studied enough in younger patients and is not considered standard of care.

4.6 Patients must be willing to receive transfusions of blood products.
4.7 Age adjusted International Prognostic Index Score of 2 or more
4.8 Previous steroids are allowed (if used to relieve some symptoms such as SVC, etc).

**Exclusions**:
4.9 Pregnancy, secondary to teratogenicity of the involved chemotherapy agents
4.10 Positive HIV serology secondary to poor tolerance to this intense chemotherapy regimen
4.11 Burkitt's lymphomas, and Mantle cell lymphoma, transformed follicular center cell lymphoma, follicular grade III.
4.12 Any clinical or cytological diagnosis of CNS involvement
4.13 Any co-morbid medical, such as Child's Class C liver cirrhosis, end-stage renal disease, and symptomatic congestive heart failure, or psychiatric illnesses that preclude treatment with intense dose chemotherapy as determined by the primary investigator.
4.14 Concurrent or previous malignancy whose prognosis is poor (< 90% probability of survival at 5 years)
4.10 Active Hepatitis B or C. Chronic carriers for Hepatitis B will be excluded.

## 5.0 PROTOCOL TREATMENT PLAN

(added 4/21/2009) A Bayesian adaptive algorithm (Berry, 1995) was originally used for this protocol. The trial is now redesigned as a single-arm phase II clinical trial to evaluate the efficacy of the combination regimen of Rituximab-HCVAD alternating with Rituximab-Methotrexate-Cytarabine in patients 60 years old or younger with newly diagnosed high risk aggressive B-cell non-hodgkin's lymphomas. Therefore patients will no longer be randomized and patients will no longer be randomized to receive R-CHOP.

The patients will now only receive treatment as in section 5.1 of the protocol, previously named ARM A:

General: All patients will be registered utilizing the MD Anderson Clinical Oncology Research System (CORe) system. Patients will be randomized utilizing the 'Clinical Trial Conduct Web Site." Cycles of R-HCVAD and Rituximab- Methotrexate/Ara-C will be alternated starting with R-HCVAD (in case of pleural effusion or ascitis, the methotrexate-ara-C cycle will be delayed until resolution of the effusion, and the patient will be receive another cycle of R-HCVAD again). The second arm (Arm –B) will be treated with standard Rituximab-CHOP every 21 days. (no longer applicable as of amendment dated 3/19/2009.)

5.1 CHEMOTHERAPY (Given every 21 days) See Section 5.2 for dose modifications.
ARM A: R-HCVAD/R-MTX-Ara-C

Cycle 1 (R-HCVAD)

A. Rituximab 375 mg/m² on day 1 (can be delayed up to day 8 in patients with leukemic phase of the lymphoma).

B. Cyclophosphamide 300 mg/$m^2$ IVPB over 3h Q12h x 6 doses. Cyclophosphamide may be started after the infusion of the Rituximab is finished.

C. Mesna 600 mg/$m^2$ IV daily over 24 hours by continuous infusion x 3 days. Begin 1 hour prior to cyclophosphamide and complete by 12 hours after last dose of cyclophosphamide

D. Doxorubicin 50 mg/$m^2$/day IV over 15 minutes (12 hours after last dose of cyclophosphamide). May be given IVPB over 15 minutes under RN supervision. In certain cases, if the primary physician considered necessary, doxorubicin can be given by continuous infusion over 48 hours.

E. Vincristine 1.4 mg/$m^2$ (maximum 2 mg) IVPB on Days 5 and on day 12.

F. Decadron 40 mg IV or P.O. daily x 4 on Days 2-5 and on days 12-15.

G. G-CSF (Neupogen) will be started 24 hours after finishing doxorubicin until recovery of the Neutrophils after nadir. Neulasta or Leukine (GM-CSF) can be used as alternatives. Patient may be taught to self administer the G-CSF and Neulasta injections.

H. Pre-med with Zofran 8- 32 mg IVPB daily days 2-5 (unless doxorubicin is given by continuous infusion)

I Prescriptions to start 24-48 hours after end of chemotherapy (recommended but alternative can be used on investigator discretion):

i) Ciprofloxacin 500 mg po BID X 10 days
ii) Fluconazole 100 mg po daily X 10 days
iii) Valacyclovir 500 mg po QD X 10 days
iv) Compazine 10 mg po Q 4-6 hours PRN n/v
v) If there is any contraindication to any of these antibiotics or anti-emetics, alternatives can be decided by the investigator.

Cycle 2 Chemotherapy (Mtx/Ara-c) **Must be administered in inpatient setting, and adjust according to 5.2.1. If Creatinine ≥2 patient will not receive this chemo and will go to R-HCVAD again.**

A. Rituximab 375 mg/m² on day 1

B. Methotrexate after finishing Rituximab, 200 mg/$m^2$ IV over 2 hours, then 800 mg/$m^2$ IV over 22 hours. Patients with a serum creatinine > 1.5 mg/dl will get 50% dose methotrexate (*adjust dose according to 5.2.1)

C. Patients will receive intravenous hydration containing sodium acetate for alkalinization as per discretion of primary physician.

D. Ara-C 3g/$m^2$ IV over 2 hours Q12 hours x 4 doses on Days 3-4. (Patients those with a serum creatinine > 1.5 mg/dl will get only 1 gram/m² of Ara-C per dose.

(**See section 5.2.1**).

E. Leucovorin rescue 50 mg po 12 hours after methotrexate infusion completed starting on Day 3 x 1 dose, followed by 15 mg p.o. Q6 hours until Methotrexate level is < 0.1.

F. Check serum creatinine. Check methotrexate levels at 24h and 48h post completion of methotrexate-if > 1 micromolar at 24 hrs or > 0.1 micromolar at 48 hours, increase citrovorum rescue to 50 mg IV Q6 hrs until methotrexate < 0.1 micromolar.

G G-CSF (Neupogen) will be started 24 hours after finishing last dose of ara-C and if methotrexate level is < 0.1 until recovery of the Neutrophils after nadir. Neulasta or Leukine (GM-CSF) can be used as alternatives.

H Additional prescriptions (recommended, variations may happen if clinically indicated). Prophylactic antibiotics should start 24-48 hours after end of chemotherapy.

I) Na bicarbonate 650 mg x 2 po BID x Days 2-6- of cycle
II) Ciprofloxacin 500 mg po BID – start 24 hours after end of chemotherapy
III) Fluconazole 100 mg po daily – start 24 hours after end of chemotherapy

IV) Pred forte 2 gtts each eye QID x 7 days (starting at Day 1 at discretion of physician)
V) Valacyclovir 500 mg po QD – start 24 hours after end of chemotherapy
VI) Other prophylactic antibiotics or anti-emetics can be used alternatively if clinically indicated.

INTRATHECAL CHEMOTHERAPY PROPHYLAXIS:

Intrathecal chemotherapy for prophylaxis of leptomeningeal recurrences, will be done in patients with parasinus or sinus disease, base of the skull, involvement of the testicle, bone marrow involved with aggressive lymphoma, epidural disease, or involvement of the spinal canal, or patients with two or more extranodal sites (at the discretion of the primary clinician).

Intrathecal chemotherapy at the discretion of M.D. and number of intrathecal chemotheraphy optional to M.D.

Dose of Methotrexate will be 6 mg if an Ommaya reservoir is used and 12 mg if lumbar puncture is performed.

Dose of Ara C will be 100 mg.

Changes in prophylaxis will be approved if toxicity happens or risk for serious toxicity is suspected.

**Radiation Therapy**:

Radiation therapy will be given in areas of involved field in patients with stage I.

### 5.2.1. Dose Adjustments for Different Regimens

Dose Modifications for Age and Special Circumstances

A. Age > 60 - change schedule of ARA-C to 1g/m² IV (if patient ages to > 60 during treatment) over 2 hours Q12h x 4 doses = 2 days (day 3 and 4).

B. Bilirubin
   a. 1.2-3.0 mg/dl- Reduce doxorubicin by 50%
   b. 3.1-5.0 mg/dl-Reduce doxorubicin by 75%
   c. >5.0 mg/dl-Do not use unless OK by Principal Investigator
   d. > 2.0 mg/dl-Reduce Vincristine by 50%

C. Serum creatinine > 1.5 mg/dl or clearance < 60 cc/min.- Decrease intravenous methotrexate dose by 50% and decrease intravenous Ara-C dose to 1 gm/$m^2$ per dose. Dose adjustment for elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) reduce Vincristine by 50 %.

D. Additional Methotrexate adjustment-
   i) If severe mucositis (grade 4) with previous dose, reduce MTX by 25% (1 dose level; see section 5.2.4)

   ii) If pleural effusion or ascites, hold MTX.

   iii) Check methotrexate levels at 24 and 48 hours: if > 1 micromolar at 24h or >0.1 micromolar at 48h respectively, give citrovorum rescue 50mg IV Q6h till methotrexate levels < 0.1 micromolar.

E. Additional Ara-C adjustment -
   If central nervous system toxicity with previous dose, decrease Ara-C (see section 5.2.4).

5.2.2 Dose Reduction For Hematologic Toxicity

| Toxicity | | Dose Modification |
|---|---|---|
| Day 21: | AGC>1000/$mm^3$ or Platelets>100,000/$mm^3$ | No Change |
| Day 21: | AGC 750-1000/$mm^3$ or Platelets 75-100,000/$mm^3$ | Delay therapy*until AGC > 1K, plat > 100K |
| Day 21: | AGC < 750/$mm^3$ or platelets < 75,000/$mm^3$ | Delay therapy*until AGC > 1K, plat > 100K and decrease 1 level |

*Unless BM extensively involvement by lymphoma cells

| | |
|---|---|
| Delay > 2 weeks | Discuss with Chairman |
| Neutropenic Fever | Decrease 1 level |

Serious Infection or Bleeding Discuss with Chairman

5.2.3 For Non-Hematologic Toxicity (Appendix B)

| Grade | Dose Modification |
|---|---|
| 0-2 | No change |
| 3 | Decrease 1 level |
| 4 | Remove from study after discussing with Chairman |

5.2.4 Dose Modification During Treatment

| Drug | -2 | -1 | 0 |
|---|---|---|---|
| Rituximab 375 mg/m² IV | 375 | 375 | 375 |
| Cytoxan* mg/m² IV over 3 hrs q 12 hrs x 6 | 150 | 240 | 300 |
| Vincristine* mg/m² IV days 5 and 12 | 0 | 1mg total dose | 1.4 (maximum 2 mg) |
| Doxorubicin* mg/m² IVPB over 1 hr on day 5 | 25 | 40 | 50 |
| Methotrexate* mg/m² as per instructions | 500 (100) (400) | 750 (150) (600) | 1000 (200) (800) |
| Ara-C* g/m² over 2 hrs q 12 hrs x 4 doses days 3 and 4 | 1 (or 33% dose) | 2 (or 66% dose) | 3 (or 100% dose) |
| Ara-C* 1g/m² over 2 hr q 12 hrs x 4 doses days 3 and 4 for patients with serum.creatinine > 1.5 to 2 mg/dl | .5 | .75 | 1 |

***See 5.2.1 for special instructions**

Adverse effects 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. In addition, any transfusions of blood and blood products are to be recorded in the patient's CRF.
In the event of grade 3 or 4 hematologic toxicity, blood samples for follow-up evaluations should be performed as clinically indicated until the abnormality is resolved.

5.2.5. ARM B: Rituximab-CHOP (no longer applicable as of amendment dated 3/19/2009.)

Chemotherapy will be given every 21 days with doses as follow

Rituximab 375 mg/m² day 1
Cyclophosphamide 750 mg/m² intravenously day 1
Doxorubicin 50 mg/m²/ day on day 1
Vincristine 1.4 mg/m² i.v. on day 1 (maximum dose of 2 mg)
Prednisone 100 mg P.O. daily for 5 days days 1-5

Note: Chemotherapy can be started in day 2 if clinically indicated, and doxorubicin can be done by continuous infusion over 48 hours in patients with history or risk for cardiac disease.

Dose Modifications: For toxicities as described in 5.2.2 and 5.2.3:

Level –1 reduction of the doxorubicin, cyclophosphamide by 20%
Level –2 reduction of doxorubicin, cyclophosphamide by 50%.

5.3 Treatment Plan and Response/Treatment Evaluation During Study
Staging after first 2 cycles (one R-HCVAD, one R-MTX/Ara-C) or R-CHOP:

- If complete response, continue X 4 more cycles
- If minor or partial response, continue X 2 more cycles and re-stage
- No change or progressive disease, off protocol

Staging after 4 cycles:

- If complete or partial response, and give 2 more cycles and restage
- If no change, biopsy positive, off protocol

Staging after 6 cycles:

- If complete response, give 2 more cycles and Re-stage

- If $\leq$ PR, biopsy proven, off protocol

Radiation Therapy: Patients with stage I will be consolidated with radiation therapy.

**5.4 CRITERIA FOR DISCONTINUATION OF TREATMENT:**

1. Patient refusal to continue to treatment
2. Progressive disease
3. Any reason that the primary investigator consider in best interest of the patient
4. Reactivation of hepatitis B or Active Hepatitis B infection.

**6.0 PRETREATMENT EVALUATION (See Appendix F)** (All x-rays should be done within 4-6 weeks of start of treatment.)

1. A complete history and physical.

2. Staging : CT chest, abdomen, pelvis, CXR, PET scan, bilateral bone marrow biopsies and aspirates, CXR, MUGA or Echo, EKG. Bone marrow aspirate will be sent for lymphoma markers. Gallium scan or PET scan is also recommended.

3. Laboratory studies shall include: CBC with differential and platelet count, Beta 2 microglobulin level, Serum albumin, alkaline phosphatase, bilirubin, BUN, calcium, creatinine, glucose, inorganic phosphorus, LDH, SGPT, T. protein, uric acid, sodium, potassium, chloride, CO2, HIV testing, and Quantitative Immunoglobulins.

4. Pregnancy test in female patients on childbearing potential.

5. Screening of patients at high risk of HBV infection to the recommended immunology evaluations. High-risk patients include: History of I.V. Drug abuse, persons born in high, men who have sex with men, endemic areas, dialysis patients, HIV patients, Family/household contacts of carriers/hepatitis B+ patients.

## 7.0 EVALUATION (Appendix F)

### 7.1 DURING STUDY

- Every cycle: CBC differential, platelets until ANC > 1,000/$mm^3$ and platelets > 20,000/$mm^3$. If clinically indicated, other studies may be performed, as determined by patients' primary oncologist.
- Every cycle: Total protein, albumin, calcium, inorganic phosphorus, glucose, BUN, creatinine, uric acid, bilirubin, alkaline phosphatase, LDH, SGPT, and electrolytes; History and physical exam.
- Every 2 cycles: In addition to above: unilateral BM biopsy and aspirate, if initially positive. BM aspirate and biopsies will be sent for lymphoma markers, if initially positive, until they become negative, after that they will be done if clinically indicated. PET scan will be performed, if initially positive, until becomes negative. Once is negative, repeat PET scan will be done at the investigator discretion. CT scans, neck, chest/abdomen/pelvis will be performed (if initially involved).
- Study treatment will be given on days specified in the protocol unless patient medical or logisitical problems arise. These changes to study treatment schedule will be discussed with the study chairman or co-chairman.

### 7.2 AFTER TREATMENT

- Full restaging of initially involved areas will be performed at least every 6 months during the first year from the start of treatment. After the 4th year follow up is yearly. Every 6 months during the 3rd, 4th year, then in one year for 5th year. After five years, patient will be followed yearly by survivorship clinic for observation. For patients with initially positive studies, BM aspiration and biopsies will also be done every other evaluation in the first 2 years and then yearly thereafter (if clinically indicated).

Serious adverse effects will be reported according to the MDACC Guidelines for SAE reporting (Appendix B). The following adverse effects are expected and will not be reported. They will be summarized in the updated and final results:

i) Myelosuppression and its associated complications are part of the successful treatment of aggressive lymphomas. Therefore, infections, bleeding and hospitalization due to this will not be reported as adverse drug reactions.

ii) Readmission day 0-30 post chemotherapy to receive parenteral narcotics for pain relief of mucositis for parenteral control of nausea/vomiting, to receive blood or platelet transfusions, or for supportive measures such as hydration and symptom control.

## 8.0 CRITERIA FOR RESPONSE

Response Definitions

Complete Response (CR): Assessed after cycles 2, 4, and 6. CR is defined as the disappearance of all clinical evidence of active tumor for a minimum of eight weeks. The patient must be free of all symptoms. Some patients with lymphoma remain with residual tumor masses that, upon biopsy, are composed of collagenous tissue. In view of this phenomenon, we consider 75% reduction in size of the mediastinum and/or abdominal mass with a negative fine-needle aspirate and a negative PET scan as CR. In these cases, biopsies are strongly recommended when feasible to confirm response status.

Complete Response unconfirmed (CRu): Assessed after cycles 2, 4, and 6. Some patients with lymphoma remain with residual tumor masses that, upon biopsy, are composed of collagenous tissue. In view of this phenomenon, we consider 75% reduction on size of the mediastinum and/or abdominal mass as CRu if no other definitive test (i.e. FNA with a negative PET scan or biopsy) is performed.

Partial Response (PR): Fifty percent or greater decrease in the sum of the products of all measured lesions persisting for at least four weeks. No lesion may increase in size and no new lesion may appear.

Minor Response (MR): More than 25% but less than 50% decrease in the sum of the products of all measured lesions persisting for at least four weeks. No lesion may increase in size and no new lesion may appear.

No Change: Steady state or response less than minor and no progression for at least 8 weeks. There may be no appearance of significant new lesions for this category.

Progressive Disease: Unequivocal increase in the size of any measurable lesion or appearance of significant new lesions will constitute progressive disease.

Failure: Any response less than a PR.

## 9.0 STATISTICAL CONSIDERATIONS

A Bayesian adaptive algorithm (Berry, 1995) was originally used for this protocol (2005-0054). The trial is now redesigned as a single-arm phase II clinical trial to evaluate the efficacy of the combination regimen of Rituximab-HCVAD alternating with Rituximab-Methotrexate-

Cytarabine in patients 60 years old or younger with newly diagnosed high risk aggressive B-cell non-hodgkin's lymphomas. This treatment was one of the two treatments in the original adaptive randomization design. As of February 24, 2009, sixteen patients have been enrolled to this treatment arm. Using the new design, the maximum sample size for the treatment of Rituximab-HCVAD alternating with Rituximab-Methotrexate-Cytarabine is 50.

## Study design:

The overall response at 4 months will be monitored using the Bayesian approach of Thall, Simon, Estey (1995, 1996) as extended by Thall and Sung (1998). Historical data on similar patients show an overall response rate (OR) of 60%. However, the information was down-weighted to reflect the same marginal OR in 2 patients. It is expected for the current trial that the combination drug will improve the OR to 80%. A sample size of 50 ensures that, if the trial is not terminated early, a posterior 90% credibility interval for overall response rate will have width of 0.18 at most, under the assumption of a 80% of OR. The probability of OR for the historical data is modeled by beta distribution (*Beta*(6, 4)). The prior probability of OR for the experimental regimen is also modeled by beta distribution (*Beta*(1.2, 0.8)), which has the same *a/b* (*a* and *b* denote the parameters for a *Beta* distribution) ratio as the beta distribution for the historical data. Denoting the historical probability of overall response rate by p(OR,H) the following decision rule will be applied:

Let E correspond to the experimental treatment, stop if
$\text{Prob}\{p(OR,H) + \delta_{OR} > p(OR,E) \mid \text{data}\} > 0.9$, where $\delta_{OR} = 0.20$

Patients will be monitored according to the following stopping boundaries for overall response.

| Number of patients evaluated | Recommend stopping if ≤ OR observed |
|---|---|
| 20 | 10 |
| 30 | 16 |
| 40 | 22 |
| 50 | 28 |

The operating characteristics are summarized in the following table (based on simulations from 10,000 trials).

| True OR Rate | Prob(stop the trial early) |
|---|---|
| 0.5 | 0.836 |
| 0.6 | 0.411 |
| 0.7 | 0.075 |
| 0.8 | 0.003 |
| 0.9 | <0.0001 |

**Analysis Plan**

Summary statistics will be provided for continuous variables such as age. Frequency tables will be used to summarize categorical variables including gender, stage, and response status. Logistic regression will be utilized to assess the effect of patient prognostic factors on the response rate. The distributions of time-to-event endpoints including overall survival and progression free survival will be estimated using the method of Kaplan and Meier. Comparison of time-to-event endpoints by important subgroups will be made using the log-rank test. Cox proportional hazard

regression will be employed for multivariate analysis on time-to-event outcomes.

## 10.0 DATA AND PROTOCOL MANAGEMENT

10.1 Data Entry: Patients must be registered on the Protocol Data Management System.

10.2 Accuracy of Data Collection: The chairman will be the final arbiter of response or toxicity should a difference of opinion exist.

10.3 The principal investigator is responsible for submitting AEs to the IRB per MDACC standard guidelines.

## 11.0 REPORT OF ADVERSE EVENTS

### 11.1 Adverse Event and Reporting Definitions

In the event of an adverse event, the first concern will be for the safety of the subject. Investigators are required to report to Genentech Drug Safety any **serious adverse event**, whether **expected** or **unexpected**, regardless of causality to rituximab. All events meeting these criteria will be reported for the time period beginning with any amount of exposure to rituximab through the protocol-defined follow-up period. Serious criteria, definitions, and guidance for reporting follow.

An **adverse event (AE)** is any untoward medical occurrence in a subject participating in an investigational trial or protocol regardless of causality assessment. An adverse event can be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, syndrome or disease associated with or occurring during the use of an investigational product whether or not considered related to the investigational product.

**Serious adverse events (SAE)** are adverse events occurring at any dose which meet one or more of the following **serious criteria**:

- Results in **death** (i.e. the AE caused or lead to death)
- Is **life-threatening** (i.e. the AE placed the subject at immediate risk of death; it does not apply to an AE which hypothetically might have caused the death if it were more severe)
- Requires or prolongs inpatient **hospitalization** (i.e. the AE required at least a 24-hour inpatient hospitalization or prolonged a hospitalization beyond the expected length of stay; hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not SAEs by this criterion)
- Is **disabling** (i.e. the AE resulted in a substantial disruption of the subject's ability to carry out normal life functions)

- Is a **congenital anomaly/birth defect** (i.e., an adverse outcome in a child or fetus of a subject exposed to the trial drug prior to conception or during pregnancy)

- It does not meet any of the above serious criteria but **may jeopardize the subject** and **may require medical or surgical intervention** to prevent one of the outcomes listed above

SAEs include any sign, symptom or medical condition that meets any of the above criteria and emerges during rituximab treatment or during a post-treatment follow-up period that (1) was not present at the start of treatment and is not a chronic condition that is part of the patient's medical history, OR (2) was present at the start of treatment or as part of the patient's medical history but worsened in severity and/or frequency during therapy.

**Expected** adverse events are those adverse events that are **listed** or characterized in the current Investigator Brochure.

**Unexpected** adverse events are those **not listed** in the current Investigator Brochure or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the Investigator Brochure. For example, under this definition, hepatic necrosis would be unexpected if the Investigator Brochure only referred to elevated hepatic enzymes or hepatitis.

### 11.2 Reporting of Serious Adverse Events Associated with Rituximab

All serious adverse events (SAEs) regardless of causality to rituximab (this applies to both expected and unexpected events) should be recorded on a MedWatch 3500 Form (Appendix H) and faxed to:

Genentech Drug Safety
Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4683

(Please use the safety reporting fax cover sheet attached to this document for your fax transmission.)

**AND:**

Dr. Luis Fayad
Ph: 713-792-2860
Fax: 713 794-4186

**AND:**
**Office of Protocol Research:**
**Phone: 713 792-2933**
**Fax: 713 794-4589**

**MedWatch 3500 Reporting Guidelines:**

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information

within the Event Description (section 5) of the MedWatch 3500 form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

**Follow-up information:**

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500 report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500 form
- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the subject for whom and adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above.

**Study Drug Relationship:**

The investigator will determine which events are associated with the use of the study drugs. For reporting purposes, an AE should be regarded as possibly related to the use of the investigational product if the investigator believes:

- There is a clinically plausible time sequence between onset of the AE and rituximab administration; and/or
- There is a biologically plausible mechanism for rituximab causing or contributing to the AE; and
- The AE cannot be attributed solely to concurrent/underlying illness, other drugs, or procedures.

## 11.3 Safety Reporting Requirements for IND Holders

**Expedited IND Safety Reports:**

For **Investigator Sponsored IND Studies**, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

***7 Calendar-Day Telephone or Fax Report*:**
The Sponsor-Investigator is required to notify the FDA of any **fatal or life-threatening** adverse event that is **unexpected** and assessed by the investigator to be **possibly related** to the use of rituximab. An unexpected adverse event is one that is not already described in the Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event. Each telephone call or fax transmission (see fax number below) should be directed to the FDA new drug review division in the Center for Drug Evaluation and Research or in the product review division for the Center for Biologics Evaluation and Research, whichever is responsible for the review of the IND.

***15 Calendar-Day Written Report*:**
The Sponsor-Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any **serious**, **unexpected** AE that is considered reasonably or **possibly related** to the use of rituximab and/or bevacizumab.

An **unexpected** adverse event is one that is not already described in the Investigator Brochure.

- Written IND Safety Reports should include an **Analysis of Similar Events** in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

- **Written IND safety reports with Analysis of Similar Events are to be submitted the FDA, Genentech Drug Safety, and all participating investigators within 15 calendar days of first learning of the event.** The FDA prefers these reports on a MedWatch 3500 Form but alternative formats are acceptable (e.g. summary letter).

**FDA fax number for IND Safety Reports:**

**1 (800) FDA 1078**

**All written IND Safety Reports submitted to the FDA by the Sponsor-Investigator must also be faxed to:**

Genentech Drug Safety
Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4683

(Please use the safety reporting fax cover sheet attached to this document for your fax transmission.)

**AND:**

Dr. Luis Fayad
Ph: 713-792-2860
Fax: 713 794-5656

**AND:**

Office of Protocol Research
Phone 713 792-2933
Fax 713 794 4589

For questions related to safety reporting, contact:
Genentech Drug Safety
Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4683

IND Annual Reports:

**In accordance with the regulation 21 CFR § 312.32, the Sponsor-Investigator shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the progress of the investigation. Please refer to Code of Federal Regulations, 21 CFR § 312.32 for a list of the elements required for the annual report. All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. Copies of such reports should be mailed to:**

Genentech, Inc.
ATTN: Brian King
IST Coordinator
1 DNA Way, Mailstop 88
South San Francisco, CA 94080-4990
Tel: (650) 225-6257

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