# TABLE OF CONTENTS

**NEBRASKA LYMPHOMA STUDY GROUP** ................................................................. 3  
  Data Management ................................................................................................. 5  
  Triannual Meetings ............................................................................................... 6  
  Nebraska Lymphoma Study Group Oncologists ................................................. 7  

**Indolent Non-Hodgkin’s Lymphoma** ................................................................. 8  
  Clinical Trials ........................................................................................................ 10  
  Standard Therapy .................................................................................................. 35  
  Radiotherapy ......................................................................................................... 37  

**Aggressive B-cell Lymphoma** ......................................................................... 38  
  Clinical Trials ........................................................................................................ 39  
  Standard Therapy .................................................................................................. 54  
  Radiotherapy ......................................................................................................... 73  

**T-cell Lymphoma** ............................................................................................. 74  
  Clinical Trials ........................................................................................................ 75  
  Standard Therapy .................................................................................................. 85  
  Radiotherapy ......................................................................................................... 92  

**Hodgkin’s Lymphoma** ..................................................................................... 93  
  Clinical Trials ........................................................................................................ 94  
  Standard Therapy .................................................................................................. 104  
  Radiotherapy ......................................................................................................... 113  

**Non-Therapeutic Research** ............................................................................. 115  

**Appendices** ...................................................................................................... 122  

**HEMATOLOGIC MALIGNANCY NETWORK** ..................................................... 139  
  **ALL** .................................................................................................................. 140  
  **AML** ................................................................................................................ 141  
  **CLL** .................................................................................................................. 143  
  **CML** ................................................................................................................. 144  
  **GVHD** ............................................................................................................. 145  
  **MDS** ................................................................................................................. 146  
  **Mini Allogeneic Transplantation** .................................................................... 147  
  **Multiple Myeloma** ......................................................................................... 148
Nebraska Lymphoma Study Group Scheme for the Treatment of Non-Hodgkin’s Lymphoma and Hodgkin’s Lymphoma
December 2004 Edition

LYMPHOMA STUDY GROUP

Mailing Address:
University of Nebraska Medical Center
987680 Nebraska Medical Center
Omaha, Nebraska 68198-7680

REFERRAL PAGER: (402) 888-5615
PHONE: (402) 559-6203
FAX: (402) 559-7902
WEBSITE: www.unmc.edu/lymphoma

Physicians:
James O. Armitage, M.D. (402) 559-7290
Philip J. Bierman, M.D. (402) 559-5520
R. Greg Bociek, M.D. (402) 559-6313
Charles Enke, M.D. (402) 552-3844
Julie M. Vose, M.D. (402) 559-3848

Biostatistician:
James C. Lynch, Ph.D. (402) 559-8407

Clinical Nurse Coordinators:
Sue Daubman, R.N. (402) 559-9651
Kristin Griess, R.N. (402) 559-3201
Jane Kirk, R.N. (402) 559-9650

Transplant Nurse Coordinators:
Bettina Frappier, R.N. (402) 559-6268
Diane Hill-Polerecky, R.N. (402) 559-6268
Dawn Meisenger, R.N. (402) 559-7794
Joanne Torrey, R.N. (402) 559-7791

Clinical Trials Coordinators:
Susan Allen, R.N. (402) 559-8155
Susan Blumel, R.N. (402) 559-9183
Heather Brady, B.S. (402) 559-8570
Maribeth Hohenstein, R.N. (402) 559-9053
Jill Nienaber, R.N. (402) 559-4135
Beth Schreiner, M.S.N., R.N. (402) 559-6729

Data Management/Tissue Procurement:
Martin Bast, B.S. (402) 559-6203
Kim Klintobe, B.S. (402) 559-4508
Gene Sehi, M.S. (402) 559-3535

3
The Nebraska Lymphoma Study Group (NLSG), established in 1982 by James Armitage, M.D., is a unique collaborative effort between community oncologists and pathologists, and their counterparts at the University of Nebraska Medical Center. Through this collaborative effort, patients with Hodgkin’s disease, non-Hodgkin’s lymphoma, and other neoplastic hematologic disorders are treated according to standard, state-of-the-art therapies in the community setting, while being afforded the expertise and high technology of the University setting. The majority of the patients enrolled in the study group are previously untreated, and are the most likely to benefit from their therapy. In many cases, fresh tissues are shipped to the Department of Pathology and Microbiology at the University of Nebraska Medical Center for detailed histopathologic, immunologic, and molecular characterization. Cytogenetic studies are also performed.

The table below shows the number of cases of lymphoma which have been studied and treated by the NLSG. Dr. Armitage and Julie M. Vose, M.D., direct the NLSG, while Dennis Weisenburger, M.D., leads the Hematopathology Section which reviews all tissues submitted to the NLSG. The important work of the NLSG has lead to national and international recognition of the University of Nebraska Medical Center, as well as its collaborators in the state of Nebraska.

<table>
<thead>
<tr>
<th>Standard Therapy</th>
<th># of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hodgkin’s Lymphoma</td>
<td>3,078</td>
</tr>
<tr>
<td>Hodgkin’s Disease</td>
<td>577</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tissue Procurement Service</th>
<th># of Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic Review</td>
<td>36,930</td>
</tr>
<tr>
<td>Frozen Tissue</td>
<td>5,986</td>
</tr>
</tbody>
</table>

**UNMC Hematopathologists**

- Patricia Aoun, M.D. (402) 559-4593
- John Chan, M.D.  (402) 559-7684
- Kai Fu, M.D. (402) 559-7526
- Timothy Greiner, M.D. (402) 559-8707
- Dennis Weisenburger, M.D. (402) 559-7689
Data Management

Initially, an individual contract with the participating cancer group or designated site data manager (DM) needs to be signed before we can provide compensation (Appendix J) for completed data collection forms. A data collection manual is provided to participating sites. Data forms are available in the appendix for your perusal and copying if needed (Appendices G, H, I).

When an oncologist intends to place a patient on any standard therapy protocol (even if not indicated in this binder), the patient first needs to provide their consent. It is then necessary for the DM to call our office, or preferably fax, a Patient Registration Form (Appendix F) to secure an OHNO (patient registration number). Immediate registration is vital to our ability to capture and accurately report data on these protocols. Accrual must include every “intent to treat” case, as well as everyone who receives any part of one these regimens so we do not ‘lose’ those cases due to early death, patient withdrawal, change of protocols, etc. A stipend of $10.00 will be awarded for every registration form received within two weeks of day one, cycle one of a designated treatment plan.

The data forms are to be completed according to a time-line given at the top of each form. Original documentation needs to accompany these forms so we can review the data for quality control prior to computerization. Documentation includes pathology, staging, and therapeutic administration and toxicities, restaging, progression of disease, follow-up and death. A copy of all the data forms submitted to us should be kept on file at the participating site. Pathology materials on these “consented” patients will be secured and reviewed by our hematopathology research team, and specific queries for follow-up or other missing data on these patients will routinely come from our office for the DM to secure.
Triannual Meetings

The Nebraska Lymphoma Study Group/Leukemia Network (NLSG/LN) currently plans *three* dinner meetings per year (see table below). These comprise the principal educational activities for our participants. A nationally or internationally known expert is invited to provide the latest updates on a lymphoma or leukemia diagnostic or therapeutic topic. There may also be periodic brief research reports reviewing NLSG/LN protocols and corresponding data analysis.

<table>
<thead>
<tr>
<th>DATE</th>
<th>LOCATION</th>
<th>CITY</th>
<th>GUEST SPEAKER</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 21, 2005</td>
<td>Hilton Omaha</td>
<td>Omaha</td>
<td>Daniel DeAngelo, MD, PhD</td>
</tr>
<tr>
<td>April 22, 2005</td>
<td>Hilton Omaha</td>
<td>Omaha</td>
<td>Michael E. Williams, MD</td>
</tr>
<tr>
<td>TBA</td>
<td>TBA</td>
<td>TBA</td>
<td>TBA</td>
</tr>
</tbody>
</table>

Patient Consent

The NLSG Registry and Tissue Bank Consent Form, offered to new patients, must be approved by the participating institution’s Institutional Review Board (or equivalent regulatory body) and stamped by the NLSG. The NLSG Registry and Tissue Bank Protocol has been approved by the UNMC Institutional Review Board (IRB) and the UNMC Eppley Cancer Center Scientific Review Committee.

Once consent is obtained from the patient, the patient’s pathologic specimen(s) and clinical data will be available for research use by NLSG investigators.

A completed consent form would include the patient's signature, signature of person obtaining consent, and the date consent is signed. A copy of the consent form is submitted to the NLSG, and the original will be kept in the patient's medical record at each participating site. If the patient declines to participate in the protocol, this decision must be documented with the original documentation placed in the patient's medical record at the site. The consent information will be entered into a tracking database by the NLSG data manager in order to comply with regulatory guidelines regarding the use of patient data in research.
Nebraska Lymphoma Study Group Participating Oncologists

COUNCIL BLUFFS, IOWA
Heartland Oncology and Hematology LLP
Okerbloom, John, M.D. (712) 322-4136
Singh, Tejvir, M.D. (712) 322-4136
Tso, Elisa, M.D. (712) 322-4136
Warner, Robert, M.D. (712) 322-4136

GRAND ISLAND, NEBRASKA
St. Francis Cancer Treatment Center
Copur, Sitki, M.D. (308) 398-5450
Deshpande, Anita, M.D. (308) 398-5450

HASTINGS, NEBRASKA
Nebraska Cancer Care
Sengar, Ashvini, M.D. (402) 460-5899

KEARNEY, NEBRASKA
Heartland Hematology and Oncology
Lewis, Cindy, M.D. (308) 865-2303
Bascom, George, M.D. (308) 237-2263

LINCOLN, NEBRASKA
Nebraska Hematology-Oncology PC
Hansen, Susan, M.D. (402) 484-4900
Hutchins, Mark, M.D. (402) 484-4900
Moravec, Dan, M.D. (402) 484-4900
Tilford, Joni, M.D. (402) 484-4900
Prairie-View Clinic
Sorensen, Scot, M.D. (402) 489-1919

Southeast Nebraska Hematology Oncology
Berg, Alan, M.D. (402) 420-7000
Carlson, Mark, M.D. (402) 420-7000
Green, Nathan, M.D. (402) 420-7000
Peterson, Cary, M.D. (402) 420-7000

NORTH PLATTE, NEBRASKA
Callahan Cancer Center
Puray, Merla, M.D. (308) 534-8263

OMAHA, NEBRASKA
Internal Medicine Associates Hem/Onc
Kambhu, Susan, M.D. (402) 552-2177

Oncology Associates
Hartman, Herbert, M.D. (402) 354-5860
Lemon, Stephen, M.D. (402) 354-5860
Popa, Irena, M.D. (402) 354-5860

Oncology Hematology West
Block, Margaret, M.D. (402) 393-3110
Buddharaju, Laxmi, M.D. (402) 354-8124
Langdon, Robert, M.D. (402) 393-3110
Nordquist, Luke, M.D. (402) 393-3110
Silverberg, David, M.D. (402) 354-8124
Soori, Gamini, M.D. (402) 393-3110
Tarantolo, Stefano, M.D. (402) 393-3110
Townley, Peter, M.D. (402) 393-3110

UNMC Peggy D. Cowdery Cancer Center
Adults
Armitage, James, M.D. (402) 559-7290
Bierman, Philip, M.D. (402) 559-5520
Bociek, Greg, M.D. (402) 559-6313
Enke, Charles, M.D. (402) 559-3844
Vose, Julie, M.D. (402) 559-3848

UNMC Peggy D. Cowdery Cancer Center
Pediatrics
Abromowitz, Minnie, M.D. (402) 559-4296
Coccia, Peter, M.D. (402) 559-4062
Gordon, Bruce, M.D. (402) 559-7598
Grovas, Alfred, M.D. (402) 559-4925
Warkentin, Phyllis, M.D. (402) 559-7682

SCOTTSBLUFF, NEBRASKA
Scottsbluff Internal Medicine
Bjorling, Vince, M.D. (308) 632-3676
Packard, William, M.D. (308) 632-3676

SIOUX FALLS SOUTH DAKOTA
North Central Hematology and Oncology
McHale, Michael, M.D. (605) 339-4464
Indolent Non-Hodgkin’s Lymphoma

- Clinical Trials

Previously Untreated

IRB NO: 270-03 Prospective Collection of Data of Possible Prognostic Relevance in Patients with Follicular Lymphoma

IRB NO: 189-04 The National Lymphocare Study: An Observational Study of Treatment, Outcomes, and Prognosis in Patients with Follicular Non-Hodgkin’s Lymphoma

IRB NO: xxx-04 A Phase III Trial of CHOP + Rituximab vs. CHOP + Iodine-131-Labeled Monoclonal Anti-B1 Antibody (Tositumomab) for Treatment of Newly Diagnosed Follicular Non-Hodgkin’s Lymphomas (CALGB protocol S0016)

IRB NO: 353-04 A Phase II Study to Evaluate the Safety and Efficacy of Zevalin® Therapeutic Regimen in Patients with Transformed CD20+ B-cell Non-Hodgkin’s Lymphoma (CALGB protocol 50201)

Previously Treated – Non-Transplant

IRB NO: 535-00 A Phase I/II Study of IDEC-Y2B8 (Zevalin™) for Post Transplant Relapses of B-cell Non-Hodgkins Lymphoma

IRB NO: 039-03 A Phase II Study of PS-341 in Low–Grade Lymphoproliferative Disorders

IRB NO: 255-03 A Phase 2 Study to Evaluate Safety and Efficacy of Specific Immunotherapy, Recombinant Idiotype Conjugated to KLH (GTOP-99) Following the Anti-CD20 Antibody, Rituxan®, in Previously Treated Patients with Follicular Non-Hodgkin’s Lymphoma (Genitope 2002-09)

IRB NO: xxx-04 Zevalin for Transformed CD20+ B-cell NHL

IRB NO: 075-04 A Multi-Center, Open-Label, Dose-Escalation Study to Evaluate the Safety, Efficacy, and Exposure to TRM-1 (Fully Human Monoclonal Antibody to TRAIL-R1) in Subjects with Relapsed or Refractory Non-Hodgkin’s Lymphoma

IRB NO: 351-04 Pro 070769 (rhuMAb2h7)

IRB NO: 353-04 Bexxar Tellarium vs Fision

Previously Treated – Transplant

IRB NO: 260-00 A Pilot Trial to Evaluate Immune Response Using Idiotype Vaccines Following High-Dose Chemotherapy and Hematopoietic Stem Cell Transplantation for Follicular Lymphoma
• Clinical Trials

_Previously Treated – Transplant (continued)_

IRB NO: 389-00  Allogeneic Peripheral Blood Stem Cell Transplantation with a Minimally Myelosuppressive Regimen of Pentostatin and Low-Dose Total-Body Irradiation

IRB NO: 063-02  A Phase II Trial of BEAM/Rituximab/Autologous Hematopoietic Stem Cell Transplantation (AHSCT) for Patients with CD20 Positive Non-Hodgkin’s Lymphoma

IRB NO: 171-04  Autologous vs. Non-Myeloablative Hematopoietic Stem Cell Transplantation (HSCT) for Patients with Relapsed Follicular Non-Hodgkin’s Lymphoma

• Standard Therapy

_Treatment Schema for Indolent Non-Hodgkin’s Lymphoma_

• Radiotherapy
# Indolent Non-Hodgkin’s Lymphoma

## Referral Pager: (402) 888-5615

<table>
<thead>
<tr>
<th>Previously Untreated</th>
<th>Salvage Therapy</th>
<th>Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRB NO: 270-03</td>
<td>IRB NO: 535-00</td>
<td>IRB NO: 260-00</td>
</tr>
<tr>
<td>Prospective Collection of Data of Possible Prognostic Relevance in Patients with Follicular Lymphoma</td>
<td>A Phase I/II Study of IDEC-Y2B8 (Zevalin™) for Post Transplant Relapses of B-cell Non-Hodgkins Lymphoma</td>
<td>Vaccine Therapy Post-Transplant for Follicular NHL</td>
</tr>
<tr>
<td>IRB NO: 189-04</td>
<td>IRB NO: 039-03</td>
<td>IRB NO: 389-00</td>
</tr>
<tr>
<td>The National Lymphocare Study: An Observational Study of Treatment, Outcomes, and Prognosis in Patients with Follicular Non-Hodgkin’s Lymphoma</td>
<td>A Phase II Study of PS-341 In Low-Grade Lymphoproliferative Disorders</td>
<td>AlloPSCT with a Minimally Myelosuppressive Regimen: Pentostatin &amp; Low-dose TBI</td>
</tr>
<tr>
<td>IRB NO: xxx-04</td>
<td>IRB NO: 255-03</td>
<td>IRB NO: 063-02</td>
</tr>
<tr>
<td>A Phase III Trial of CHOP + Rituximab vs. CHOP + Iodine-131-Labeled Monoclonal Anti-B1 Antibody (Tositumomab) for treatment of Newly Diagnosed Follicular Non-Hodgkin’s Lymphomas (CALGB protocol S0016)</td>
<td>Rituxan+Vaccine for Vaccine Phase III Study Failures only</td>
<td>A Phase II Trial of BEAM/Rituximab/Autologous Hematopoietic Stem Cell Transplantation for Patients with CD20 Positive Non-Hodgkins Lymphoma</td>
</tr>
<tr>
<td>IRB NO: 353-04</td>
<td>IRB NO: xxx-04</td>
<td>IRB NO: 171-04</td>
</tr>
<tr>
<td>A Phase II Study to evaluate the Safety and Efficacy of Zevalin® Therapeutic Regimen in Patients with Transformed CD20+ B-Cell Non-Hodgkin’s Lymphoma (CALGB protocol 50201)</td>
<td>Zevalin for Transformed CD20+ B-cell NHL</td>
<td>Autologous vs. Non-Myeloablative Hematopoietic Stem Cell Transplantation (HSCT) for Patients with Relapsed Follicular Non-Hodgkin’s Lymphoma</td>
</tr>
<tr>
<td></td>
<td>IRB NO: 075-04</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A Multi-Center, Open-Label, Dose-Escalation Study to Evaluate the Safety, Efficacy, and Exposure to TRM-1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IRB NO: 351-04</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pro 070769 (rhuMAb2h7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IRB NO: 353-04</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bexxar Tellarium vs Fission</td>
<td></td>
</tr>
</tbody>
</table>
Prospective Collection of Data of Possible Prognostic Relevance in Patients with Follicular Lymphoma

Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

IRB No: 270-03

Title: Prospective Collection of Data of Possible Prognostic Relevance in Patients with Follicular Lymphoma

Principal Investigator: Julie M. Vose, MD

Planned Accrual Total: Approximately 6-10 eligible patients per year will be enrolled at UNMC over 3 years.

Clinical Coordinator/Data Manager: Telephone:
Heather Brady, B.A., M.P.H. (402) 559-8570

Purpose:
The purpose of the study is to validate the Follicular Lymphoma International Prognostic Index (FLIPI) and to verify whether a prospective collection of data would allow the development of a more accurate prognostic index.

Patient Eligibility:
Adult patients ages ≥19 years of age may enroll.
1. Patients with newly diagnosed follicular lymphoma
2. Patients with histologically confirmed diagnosis of follicular lymphoma according to REAL/WHO classification (any grade)
3. Written informed consent

Exclusion Criteria: None

Study Period:
There are no experimental procedures involved in this study. For patients that choose to participate, tissue from a clinically indicated lymph node biopsy to be or already performed on them will be sent to the laboratory at the University of Nebraska Medical Center (UNMC) so that a confirmation of follicular lymphoma diagnosis may be performed. The patient may choose to donate a small amount of blood and/or tissue from a lymph node biopsy for future research tests that have not yet been determined. Routine care may include regular physical examinations, biopsy, blood draws, CT scans or other evaluations as medically indicated. Patients will receive whatever form of treatment determined appropriate by their physician. Patients will be followed for five years for progression and survival.

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
The National Lymphocare Study: An Observational Study of Treatment, Outcomes, and Prognosis in Patients with Follicular Non-Hodgkin’s Lymphoma

Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

IRB No: 189-04

Title: The National Lymphocare Study: An Observational Study of Treatment, Outcomes, and Prognosis in Patients with Follicular Non-Hodgkin’s Lymphoma

Principal Investigator: Julie M. Vose, MD

Planned Accrual Total: Approximately 6 eligible patients per year will be enrolled at UNMC over 5 years.

Clinical Coordinator/Data Manager: Telephone:
Heather Brady, B.A., M.P.H. (402) 559-8570

Purpose: The purpose of the study is to define differences in outcome for patients with follicular non-Hodgkin’s lymphoma (NHL) by comparing the outcomes and safety of common front-line and subsequent therapeutic strategies.

Patient Eligibility:  
1. Adult patients ≥19 years of age may enroll.  
2. Patients with newly diagnosed follicular lymphoma (within 6 months prior to enrollment)  
3. Patients with histologically confirmed diagnosis of follicular lymphoma according to REAL classification, as assessed by the local pathologist and treating physician (composite follicular lymphomas are eligible, even minority percent follicular lymphoma)  
4. Written informed consent

Exclusion Criteria: None

Study Period: There are no experimental procedures involved in this study. Routine care may include regular physical examinations, biopsy, blood draws, CT scans or other evaluations as medically indicated. Patients will receive whatever form of treatment determined appropriate by their physician. Patients will be followed until death, withdrawal of consent, loss to follow-up or study termination for progression, subsequent treatments and survival.

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

IRB No: xxx-04

Title: A Phase III Trial of CHOP + Rituximab vs. CHOP + Iodine-131-Labeled Monoclonal Anti-B1 Antibody (Tositumomab) for treatment of Newly Diagnosed Follicular Non-Hodgkin’s Lymphomas  (CALGB protocol S0016)

Principal Investigator: Philip J. Bierman, M.D.

Clinical Coordinator/Data Manager: Susan Blumel, RN

Telephone: (402) 559-9183

Pager: (402) 888-5647

Purpose:
The primary purpose is to evaluate survival of patients with newly diagnosed follicular lymphoma treated with six cycles of CHOP chemotherapy with rituximab or six cycles of CHOP followed by anti-B1 antibody and Iodine-131 anti-B1 antibody. Toxicities, response rates, and molecular remission rates will also be evaluated.

Patient Eligibility:
1. Previously untreated follicular grade I, II, or III NHL.
2. CD20 antigen expression in tumor tissue.
3. Stage III, stage IV, or bulky stage II disease.
5. Adequate sections from diagnostic specimen must be available for central review.
6. Bilateral bone marrow biopsy and aspirate within 42 days prior to registration.
7. Pre-treatment heparinized marrow must be submitted for central review of t(14;18)/bcl-2.
8. CT scan of the chest, abdomen, and pelvis within 28 days prior to registration.
9. β2 microglobulin within 28 days prior to registration.
10. No CNS involvement by NHL.
11. No prior chemotherapy or antibody therapy may have been given for lymphoma.
12. No history of hypersensitivity to iodine.
13. Zubrod performance status of 0, 1, or 2.
14. 19 years of age or older.
15. ANC >1500/µl and platelets >100,000/µl within 28 days prior to registration.
16. Must have fewer than 5000 circulating lymphoid cells per µl on a WBC differential count within 28 days of registration.
17. No prior history of impaired cardiac status (CAD, cardiomyopathy, congestive heart failure, serious arrhythmia).
18. Patients known to be HIV-positive are not eligible.
19. Pregnant or nursing women are not eligible. Women or men of reproductive potential must use effective contraceptive from registration until 6 months after Iodine-131 Anti-B1 Antibody.
20. No prior malignancy except adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer for which the patient has been disease-free for five years.
21. Written informed consent must be obtained.
Study Period:
Patients are randomized to one of two arms:

Arm 1: The CHOP alone arm has been permanently closed.

Arm 2: Patients receive six cycles CHOP chemotherapy + rituximab according to the schedule described by Czuczman et al. Rituximab will be given on days 1, 6, 48, 90, 134, and 141. CHOP will be given at 21 day intervals on days 8, 29, 50, 71, 92, and 113.

Arm 3: Patients receive six cycles CHOP chemotherapy at 21 day intervals. Patients are re-evaluated 4 – 8 weeks after the last cycle of CHOP. Patients with adequate ANC, and platelet count, and less than 25% of the intratrabecular marrow space involved by lymphoma in bone marrow biopsy specimens, and no active obstructive hydronephrosis may proceed with I-131 tositumomab approximately 21 days after the last cycle of chemotherapy.

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
Zevalin for Transformed CD20+ B-cell NHL

Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

IRB No: 353-04

Title: A Phase II Study to evaluate the Safety and Efficacy of Zevalin® Therapeutic Regimen in Patients with Transformed CD20+ B-Cell Non-Hodgkin’s Lymphoma (CALGB protocol 50201)

Principal Investigator: Julie Vose, M.D.

Clinical Coordinator/Data Manager: Telephone: Pager:
Susan Blumel, RN (402) 559-9183 (402) 888-5647

Purpose:
The primary purpose is to evaluate safety and efficacy of Zevalin radioimmunotherapy for patients with transformed CD20+, B-cell NHL.

Patient Eligibility:
1. Transformed CD20+, B-cell NHL requiring treatment
2. Less than 25% bone marrow involvement with lymphoma
3. De novo transformed NHL are not eligible
4. No CNS disease
5. Measurable disease must be present
6. ANC ≥1,500/µL, lymphocyte count ≤5,000/µL, platelet count >150,000/µL, total bilirubin ≤2.0 mg/dL, serum creatinine ≤2.0 mg/dL
7. Patients with expected impairment in bone marrow reserve are not eligible
8. No anti-cancer tx for 3 weeks prior to registration (6 weeks for rituximab, nitrosourea, or Mitomycin C)
9. No prior myeloablative therapies
10. No prior radioimmunotherapy
11. No prior external beam radiation therapy to >25% of active bone marrow
12. No prior G-CSF or GM-CSF within two weeks prior to registration
13. No major surgery within 4 weeks of registration
14. No concurrent systemic corticosteroid therapy
15. HAMA reactivity testing will be run on those patients with prior exposure to murine antibodies
16. No HIV infection
17. Patients w/peritoneal or pleural effusion and/or ascites are eligible if effusion or ascites can be tapped dry
18. Performance status 0 – 2
19. Age 19 and older
20. No currently active second malignancy
21. Non-pregnant and non-lactating

Study Period: On day 1 patient receive an infusion of unlabeled rituximab 250 mg/m2 followed by In-111 Zevalin. Biodistribution is assessed at 2 to 3 timepoints over the next 2 – 120 hours after In-111 Zevalin. If biodistribution is acceptable, on day 8, patients receive unlabeled rituximab 250 mg/m2 followed by Y-90 Zevalin. The dose of Y-90 is 0.4 mCi/kg (maximum dose is 32 mCi).

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
Phase I/II Study of IDEC-Y2B8 (Zevalin™)

Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

IRB No: 535-00

Title: A Phase I/II Study of IDEC-Y2B8 (Zevalin™) for Post Transplant Relapses of B-cell Non-Hodgkins Lymphoma

Principal Investigator: Julie Vose, M.D.

Clinical Coordinator/Data Manager: Susan Blumel, RN
Telephone: (402) 559-9183
Pager: (402) 888-5647

Purpose:
To evaluate the safety and efficacy of Zevalin™ in patients with B-cell non-Hodgkin’s lymphoma (NHL) who have relapsed following autologous or mini-allogeneic transplantation.

Patient Eligibility:
1. Patients with a diagnosis of relapsed B-cell lymphoma following autologous stem cell transplantation or mini-allogeneic transplantation who meet one of the following criteria:
   A. any relapsed indolent non-Hodgkin’s lymphoma
   OR
   B. relapsed aggressive non-Hodgkin’s lymphoma with no lymph nodes >3cm in one dimension, and no more than three sites of disease.
2. Patients must have no other major medical problems and life expectancy must be at least 3 months, with a WHO performance status of 0, 1, or 2.
3. Evidence of CD20 antigen expression in tumor tissue within one year prior to enrollment, if clinically possible.
4. Adequate renal function (serum creatinine <2.0 mg/dL), hepatic function (total bilirubin <2.0 mg/dL) and SGOT and/or SGPT ≤2.5 times the upper limits of normal (unless due to lymphomatous infiltration of the liver) within seven days of study entry.
5. Written informed consent.
6. ANC >1500/mm³, Platelet count >150,000/mm³ within one week prior to enrollment.
7. Females of childbearing potential must have a negative serum pregnancy test. Males and females must agree to use effective contraception during the study and for 6 months following the therapeutic dose.
8. <25% bone marrow involvement with NHL within 6 weeks prior to study entry by unilateral or bilateral biopsy. Bone marrow biopsy should demonstrate at least 15-20% of the cellular space to be occupied by normal hematopoiesis.
9. Patients with measurable disease (>2cm in bi-dimensional measurement). Must have CT scan within 6 weeks prior to enrollment.
10. Patients ages ≥19 years of age may enroll.

Exclusion Criteria:
1. Patients who have received cytotoxic chemotherapy, biological therapy, radiation therapy or immunosuppressants within three weeks (or Rituxan within 6 weeks) prior to the radioimmunotherapy dose of Zevalin™, or who exhibit persistent clinical evidence of toxicity. Patients who have received prior treatment with nitrosourea must wait six weeks prior to study entry. The use of steroids must have been discontinued (except maintenance-dose steroids for non-cancerous disease).
Exclusion Criteria (continued):
2. Prior radioimmunotherapy or fludarabine therapy.
3. Prior pelvic radiation or radiation therapy to >25% of the estimated bone marrow reserve.
4. Active obstructive hydronephrosis.
5. Active infection requiring intravenous or oral antibiotics.
6. Active central nervous system lymphoma.
7. HIV or AIDS-related lymphoma.
8. Known HIV infection.
9. Positive baseline HAMA result.
10. Patients who are transfusion and/or hematopoietic growth factor (e.g., erythropoietin, IL-11, G-CSF, GM-CSF, etc) dependent. Patients who received growth factors within 4 weeks of study entry will be excluded.
11. Patients who are pregnant.
12. Patients who are on another protocol involving non-Food and Drug Administration (FDA) approved drugs or biologics.

Study period:
Phase I: Three patients will be treated at each dose level: 0.1 mCi/kg, 0.15 mCi/kg, 0.2 mCi/kg, 0.25 mCi/kg, until maximum tolerated dose is established.

Additional patients will be treated at dose levels where dose limiting toxicites are observed. Once the maximum tolerated dose (MTD) is established, enrollment into Phase II will begin.

On day 0 all patients receive an initial infusion of 250mg/m² Rituxan IV given according to package insert followed by In-Zevalin infusion for biodistribution. Gamma whole body scans are performed during the week following this first infusion.

On day 7, 8, or 9, patients receive another dose of Rituxan 250mg/m² IV followed by the dose of IDEC Y2B8 IV determined at enrollment. The exact dose of IDEC-Y2B8 will be based on the patient’s weight during the baseline evaluation. The maximum dose will not exceed 32mCi of ⁹⁰Y.

Response will be assessed by CT scans, CBC with differential, platelet count, and chemistries at 6 weeks and 12 weeks following the therapy dose and then subsequently at 3, 6, 9, and 12 months and then every 6 months for 2 years, then yearly until progression of the disease. Bone marrow biopsy would be performed in previously positive patients to confirm response if patient appears to have a complete remission based on CT scan. HAMA testing will be done periodically following treatment.

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

**IRB No:** 039-03

**Title:** A Phase II Study of PS-341 in Low–Grade Lymphoproliferative Disorders

**Principal Investigator:** Julie Vose, M.D.

**Planned Accrual Total:** Eighteen patients with follicular lymphoma, and eighteen patients with other low grade lymphomas will be enrolled. If at least 3 patients in a cohort respond, an additional 17 patients will be enrolled into that cohort for a total of 35 patients per cohort.

**Clinical Coordinator/Data Manager:** Susan Blumel, RN  
**Telephone:** (402) 559-9183  
**Pager:** (402) 888-5647

**Purpose:**
To determine frequency and duration of response rates, and to evaluate pharmacodynamics, response of minimal residual disease by PCR in bone marrow, time to progression and overall survival, and toxicities in patients with low-grade lymphoproliferative disorders treated with PS-341.

**Patient Eligibility:**
Adult patients ages ≥18 years of age may enroll.
1. Patients with relapsed or refractory low-grade non-Hodgkin’s lymphoma (CLL, small lymphocytic lymphoma, extranodal marginal zone B-cell, nodal marginal zone B-cell, follicular grade I, II, III, mantle cell, or Waldenstroms macroglobulinemia).
2. Measurable disease defined as at least one lesion with longest diameter ≥2cm with conventional techniques, or ≥1 cm by spiral CT scan. For CLL, patients must have absolute lymphocytosis >5 x 10^9/L with a B-cell phenotype (CD19, 20, or 23), with >30% bone marrow lymphocytes.
3. No more than 3 prior cytotoxic regimens.
4. Life expectancy 3 months or greater.
5. Karnofsky Performance Status >60%.
6. Absolute neutrophil count >1,500 (if bone marrow lymphoma involvement, then ANC >500), Platelet count >50,000/ml, total bilirubin <1.5 x ULN, AST/ALT ≤2.5 x ULN (4 x ULN if liver involvement), serum creatinine <1.5 x ULN.
7. No evidence active infection.
8. No pregnant or lactating females.
10. No signs of congestive heart failure according to the New York Heart Failure Guidelines Class III/IV.

**Exclusion Criteria:**
1. Chemotherapy or radiotherapy within 4 weeks of study entry or patients who have not recovered from adverse effects of prior therapy. Monoclonal antibody therapy within 3 months. Steroids within the last 7 days.
2. Patients receiving other investigational agents.
4. Major surgery within 4 weeks of study entry.
Exclusion Criteria (continued):
5. Uncontrolled intercurrent illness including ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
6. Patients with serious medical or psychiatric illness. Patients who have had a myocardial infarction, cerebrovascular accident or transient ischemic attack within 6 months prior to enrollment, or have a history of orthostatic hypotension. EKG evidence of acute ischemia or significant conduction abnormality. This determination will be made by a cardiologist, or the attending physician directly.
7. Uncontrolled hypertension requiring active manipulation of antihypertensive medications.
8. HIV – positive patients receiving combination anti-retroviral therapy. No known or active HIV infection.
9. No vulnerable subjects.

Study Period:
Treatment is outpatient. PS-341 is administered at a dose of 1.5 mg/m2 twice weekly for two weeks followed by a one week rest period. Cycles are repeated every 3 weeks. PS-341 is administered as an IV bolus over 3 – 5 seconds followed by IV normal saline infusion for 4 hours. Restaging will be done after every 2 cycles.

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

**IRB No:** 255-03

**Title:** A Phase 2 Study to Evaluate Safety and Efficacy of Specific Immunotherapy, Recombinant Idiotype Conjugated to KLH (GTOP-99) Following the Anti-CD20 Antibody, Rituxan®, in Previously Treated Patients with Follicular Non-Hodgkin’s Lymphoma (Genitope 2002-09)

**Principal Investigator:** Julie Vose, M.D.

**Planned Accrual Total:** Five patients will be registered at UNMC over a 2-year time period. The total sample size for this multicenter trial will be up to 140 patients.

**Clinical Coordinator/Data Manager:** Susan Blumel, RN  
**Telephone:** (402) 559-9183  
**Pager:** (402) 888-5647

**Purpose:**
The primary purpose is to describe time to tumor progression from the start of salvage treatment with Rituxan, followed by immunizations with recombinant Id-KLH (GTOP-99) and GM-CSF following a 26-week rest period (Arm I) or a 13-week rest period (Arm II) in patients with follicular NHL in first relapse.

**Patient Eligibility:**
1. Previously registered patients in Genitope study 2000-03 (IRB # 421-00) with CT scans of chest, abdomen, and pelvis (and neck if palpable disease) available for central radiographic review confirming they failed to achieve or maintain a CR, CRu, or PR at the 4 – 8 week visit or prior to or at the 22 week visit following last chemotherapy, and are ineligible for randomization on Genitope study 2000-03. The films must be performed within 60 days prior to registration in this protocol.
2. Follicular center cell NHL confirmed by central pathology review (IRB 421-00).
3. Stage III/IV disease at time of entry on IRB 421-00.
4. Completed all 8 cycles of CVP chemotherapy per Genitope study 2000-03.
5. At least one site of bidimensionally measurable disease (1.5 cm x 1.5 cm) by CT.

**Exclusion Criteria:**
1. Intervening therapy (antibody, corticosteroids, or cytotoxic therapies) between completion of CVP and entry onto this study. Previous radiation to < 2 sites at > 13 weeks prior to Rituxan therapy is permissible.
2. ECOG score of 2 or greater.
3. Prior malignancy other than non-basal cell carcinoma of the skin or in situ carcinoma of the cervix unless the tumor was treated with curative intent at least two years previously.
4. Known to be HIV positive.
5. Pregnant or lactating. Women or men of childbearing potential must agree to use effective contraception during the study and for at least 6 months after the last immunization series.
6. History of autoimmune disease or conditions requiring treatment with immunosuppressive agents including corticosteroids. Patients with chronic use of corticosteroids (including topical or inhaled steroids) are excluded. Transient use of corticosteroids (prior to CT imaging) or optical solutions is acceptable.
Exclusion Criteria (continued):
7. Evidence of transformation (e.g., rapid tumor growth, increasing LDH).
8. Central Nervous System involvement.

Study Period:
Patients will receive four doses of Rituxan 375 mg/m2 given every 7 days. The doses and dates of administration will be collected.

Eight weeks following the last dose of Rituxan patients will have restaging with CT scan and bone marrow biopsy if indicated to confirm response.

A rest interval between Rituxan and immunization with recombinant Id-KLH and GM-CSF is required. This period is 26 weeks from the last dose of Rituxan until the first immunization for the first 20 patients registered, and 13 weeks from the last dose of Rituxan until the first immunization for all subsequently registered patients. Patients with the 26-week rest period will have CT restaging 4 weeks prior to the first immunization.

Each patient will receive a series of eight immunizations administered, one every 2 weeks over a 14-week period.

Initial response assessment after immunizations will occur 8 weeks after the last immunization series. Followup continues every 12 weeks for a total of 4 follow-up assessments.

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
Antibody to TRAIL-R1 for Relapsed NHL

Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

IRB No: 075-04

Title: A Multi-Center, Open-Label, Dose-Escalation Study to Evaluate the Safety, Efficacy, and Exposure to TRM-1 (Fully Human Monoclonal Antibody to TRAIL-R1) in Subjects with Relapsed or Refractory Non-Hodgkin’s Lymphoma

Principal Investigator: Julie Vose, M.D.

Clinical Coordinator/Data Manager: Susan Blumel, RN
Telephone: (402) 559-9183    Pager: (402) 888-5647

Purpose: The primary purpose is to evaluate the safety of escalating doses of TRM-1 in subjects with relapsed or refractory non-Hodgkin’s lymphoma (NHL). Secondary purposes are to evaluate disease activity/tumor response in NHL, and to obtain specimens for the determination of plasma concentrations of TRM-1.

Patient Eligibility:
1. Histologically confirmed NHL.
2. Measurable disease ≥1.5 cm in the longest transverse diameter by CT scan.
3. Previously treated with at least 1 therapeutic regimen and have relapsed or progressed, or failed to achieve objective response after the last therapeutic regimen.
4. Hemoglobin ≥9.0 g/dL, ANC ≥1.0 x 10^9/L, Platelet count ≥75 x 10^9/L.
5. Bilirubin ≤1.5 fold upper limit of normal (ULN), AST and ALT ≤2.5 fold ULN, alkaline phosphatase ≤2.5 fold ULN, serum creatinine ≤1.5 fold ULN.
6. Performance status 0 to 2 on the ECOG Scale.
7. Expected survival of at least 6 months.
8. 19 years of age and older.
9. Ability to understand study requirements, provide written informed consent, including consent for the use and disclosure of research-related health information, and comply with the study and follow-up procedures.

Exclusion Criteria:
1. Any co-morbid condition at the judgment of the investigator that renders the subject at high risk of treatment complication or reduces the probability of assessing clinical effect.
2. Received cytotoxic chemotherapy, biological therapy (including hormonotherapy), radiation therapy or immunosuppressants within 3 weeks prior to day 1, cycle 1 or who exhibit persistent clinical evidence of toxicity.
3. Received monoclonal antibodies (eg. Rituximab) within 8 weeks prior to day 1, cycle 1.
4. Received investigational agents within 4 weeks prior to day 1, cycle 1.
5. Received radioimmunotherapy or nitrosourea within 8 weeks prior to day 1, cycle 1 or who exhibit persistent clinical evidence of toxicity.
6. The use of corticosteroids within 1 week prior to day 1, cycle 1(except maintenance dose for co-morbid conditions).
7. Subjects who are eligible for a hematopoietic stem cell transplant (HSCT) or who have had an autologous HSCT within the past 16 weeks.
Exclusion Criteria (continued):
8. Subjects with a prior history of allogeneic HSCT.
9. HIV infection, acquired immunodeficiency syndrome (AIDS)-related lymphoma, or central nervous
   system (CNS) lymphoma (primary or metastatic).
10. Grade 2 or greater neuropathy, graded by the National Cancer Institute-Common Terminology
    Criteria for Adverse Events (see full protocol, Appendix E).
11. Chronic or acute viral hepatitis.
12. Active infection requiring intravenous or oral antibiotics, or history of opportunistic infections
    within 4 weeks prior to day 1, cycle 1.
13. History of other cancers within 5 years of day 1, cycle 1 except for basal cell carcinoma of the skin
    and in situ cancers of the cervix.
14. Myocardial infarction (MI), cerebrovascular accident (CVA), or congestive heart failure (CHF)
    within the last 6 months.
15. Major surgical procedure or significant traumatic injury within 4 weeks of day 1, cycle 1.
16. Pregnant or breastfeeding women. Women with intact uterus (unless amenorrheic for the last 24
    months) must have a negative serum pregnancy test at screening. All non-sterile, non-menopausal
    females must agree to use medically approved method of contraception during the study and for 60
    days following the last dose.
17. Males who do not agree to use effective contraception during the study and for a period of 60 days
    following the last dose of TRM-1.

Study Period:
Subjects are dosed every 21 days for up to 6 cycles of treatment in the absence of dose limiting toxicity
or disease progression. Patients will be monitored for adverse events and will receive full supportive
care as medically necessary. Pharmacokinetic studies on blood and tumor tissue will also be performed.

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for
the complete checklist.
Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

IRB NO: 351-04

Title: An Open-label, Multi-center, Phase I/II Trial of the Safety of Escalating Doses and Accelerated Infusion Rates of PRO70769 (Humanized Anti-CD20) in Subjects with Relapsed Follicular Non-Hodgkin’s Lymphoma (ACT3133g)

Principal Investigator: Julie Vose, M.D.

Clinical Coordinator/Data Manager: Maribeth Hohenstein, R.N.  
Telphone: (402) 559-9053  
Pager: (402) 888-2717

Purpose: To evaluate the safety and tolerability of escalating intravenous doses and infusions rates of PRO70769 (rhuMAb 2H7) in subjects with Stage III or IV, CD20⁺ follicular NHL who have relapsed after a response of ≥6 months duration to a prior Rituximab-containing regimen, which must have been the last treatment given before enrollment.

Patient Eligibility:
1. Ability and willingness to provide written informed consent and to comply with the requirements of the study protocol.
2. Ages ≥19 years.
3. History of histologically confirmed Stage III or IV, CD20⁺ follicular NHL (any grade), according to the World Health Organization (WHO) classification system (Jaffe et al. 2002).
4. Histopathology will be reviewed at the study site to confirm diagnosis, and evaluation of CD20 expression will be based on the standard procedure used at each site.
5. Relapsed follicular NHL, with documented history of a response (CR, CRu, or PR) of ≥6 months duration to a prior Rituximab-containing regimen that was the last treatment given prior to enrollment.
6. There is no limit to the number of Rituximab-containing regimens that the subject may have previously received.
7. Bi-dimensionally measurable disease (at least one lesion ≥1.5 cm in its largest dimension) by CT scan. Note: All measurable and evaluable disease must be assessed and documented prior to initiation of treatment. Tumor response will be based on the status of all areas of disease.
8. Absolute B-cell count above the lower limit of normal (as determined by the central flow cytometry laboratory) measured within 28 days prior to enrollment.
9. Adequate marrow, hepatic, and renal function within 14 days prior to enrollment, using the following measures:
   - Platelets count ≥100,000/µL
   - Hemoglobin ≥10.0 g/dL
   - Neutrophils count ≥1.5 × 10³/µL
   - Lymphocytes count ≤5 × 10⁹/L
   - Serum creatinine ≤2 mg/dL
   - AST or ALT ≤2.5 × the upper limit of normal
   - ECOG performance status of 0 or 1 (see Appendix C)
Patient Eligibility (continued):

- Expected survival $\geq 6$ months.
- For subjects of reproductive potential (males and females), use of a reliable means of contraception (e.g., hormonal contraceptive, intrauterine device, physical barrier) during the study and for 1 year following the last dose of study treatment.
- For females of childbearing potential (including those who have had a tubal ligation), a negative serum pregnancy test within 14 days prior to enrollment.

Exclusion Criteria:

Subjects who meet any of the following criteria will be excluded from study participation:

1. Prior use of any monoclonal antibody therapy other than Rituximab, anti-cancer vaccine therapy, or prior radioimmunotherapy.
2. Central nervous system lymphoma.
3. History of cancer other than follicular NHL, including solid tumors and hematologic malignancies (except basal cell and squamous cell carcinoma of the skin that have been excised and resolved).
4. Evidence of significant uncontrolled concomitant diseases such as cardiovascular disease (including New York Heart Association Class III or IV cardiac disease or myocardial infarction within 6 months prior to enrollment, unstable arrhythmias, and unstable angina), nervous system, pulmonary (including obstructive pulmonary disease and history of symptomatic bronchospasm), renal, hepatic, endocrine, or gastrointestinal disorders.
5. Known active bacterial, viral, fungal, mycobacterial, other infection (including atypical mycobacterial disease, but excluding fungal infections of nail beds), or any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks of screening, or oral antibiotics within 2 weeks prior to screening.
6. History of recurrent significant infection or bacterial infections.
7. Major surgery within 4 weeks prior to enrollment, except for diagnostic surgery.
8. Positive hepatitis B or C serology.
10. History of severe allergic or anaphylactic reactions to humanized or murine products.
11. Pregnancy or lactation.

Treatment Plan:

This is an open-label, multicenter, Phase I/II study of the safety of escalating doses and infusion rates of single-agent PRO70769 in subjects with Stage III or IV, refractory or relapsed, CD20$^+$ follicular NHL. Subjects must have relapsed after a response (CR, CRu, PR of $\geq 6$ months duration to a prior Rituximab-containing regimen, which was the last treatment received prior to enrollment. Subjects may have received more than one prior Rituximab-containing regimen. Subjects may be refractory to prior chemotherapy, but must have responded to a prior Rituximab-containing regimen.

This study will enroll patients in 2 phases:

- The Phase I portion of the study will evaluate escalating doses and infusion rates (referred to as the escalation phase)
- The Phase II portion of the study will enroll additional subjects into the cohort selected for further study (referred to as the expanded cohort)
**Treatment Plan (continued):**

Escalation Phase: Subjects in each cohort will receive four weekly doses of PRO70769 at the assigned dose levels and infusion rates. Cohorts A-C (dose escalation cohorts) will evaluate the safety of escalating doses of PRO70769. Cohorts D and E (infusion rate escalation cohorts) will evaluate the safety of accelerated infusion rates for Infusions 2-4 (Days 8, 15, and 22). The PRO70769 dose for Cohort D and Infusions 2-4 of Cohort E will be the same as that for Cohort C. Cohort E will also evaluate the safety of administering a lower dose on Day 1 to deplete circulating B cells, using the minimum B-cell-depleting dose following Day 1 doses in either Cohort A or B.

Dose escalation to the next higher dose or infusion rate level (Cohorts B-D) will occur after review of safety data 7 days following Infusion 4 in the last subject in each dose level cohort. Cohort E will be enrolled sequentially, with no delay after the third subject is enrolled in Cohort D.

The second phase of the trial will enroll patients to expand the safety database and enable a preliminary assessment of activity. If escalation proceeds and all cohorts are enrolled, the final expanded cohort will be Cohort E, provided that adequate B-cell depletion occurs with Infusion 1 in this cohort. If escalation is halted as the result of DLTs, the expanded cohort will use the dose and infusion rate of the previous cohort.

All enrolled subjects will be followed for safety assessments to Day 50 after the last infusion. Unless withdrawn, all subjects will be followed for 48 weeks. Patients in the expanded cohort will be followed for an additional 48 weeks for progression-free survival.

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
Vaccine Therapy Post Transplant for Follicular NHL

Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

**IRB NO:** 260-00

**Title:** A Pilot Trial to Evaluate Immune Response Using Idiotype Vaccines Following High-Dose Chemotherapy and Hematopoietic Stem Cell Transplantation for Follicular Lymphoma

**Principal Investigator:** Julie Vose, M.D.

**Clinical Coordinator/Data Manager:** Maribeth Hohenstein, RN  
**Telephone:** (402) 559-9053  
**Pager:** (402) 888-2717

**Sponsor:** Genitope Corporation

**Purpose:** Using idiotype immunizations in the adjuvant setting of follicular non-Hodgkin’s lymphoma post hematopoietic stem cell transplantation, this trial will achieve the following objectives: Evaluate the humoral and cellular immune response to idiotype vaccine with KLH and GM-CSF adjuvant. Evaluate the safety and toxicity of the idiotype vaccine with KLH and GM-CSF adjuvant in the post-transplant setting. And evaluate changes in quantitative bcl-2 of the blood and bone marrow prior to and at various time points following the series of idiotype vaccines.

**Patient Eligibility:**
1. Histologic diagnosis from an open tissue biopsy of follicular lymphoma Grade I, II, or III.
2. Patients with one prior chemotherapy before initiation of salvage prior to transplant (excludes radiation).
3. Tumor sample safely accessible by biopsy, needle aspiration or phlebotomy. For tumor sampling by phlebotomy, circulating levels of lymphoma cells must be adequate for tumor harvest via blood sampling (absolute lymphoma counts of at least 5 x 10⁶ cells/ml by manual differential). Bone marrow with greater that 30% clonal involvement (as defined by flow analysis) may be adequate for collection via bone marrow aspirate.
4. Age >19 years.
5. Karnofsky Performance Status of >70%.
6. Adequate hepatic, renal and bone marrow function (measured within two weeks of study entry) to include:
   - Total bilirubin <2.0 mg/dL-unless due to lymphomatous involvement.
   - SGOT and SGPT <2x normal values-unless due to lymphomatous involvement.
   - Creatinine ≤2.0 mg/dL.
7. Patient comprehension of study risks and benefits with signed informed consent.
8. Patients should have received the BEAM transplant protocol at UNMC or other institution deemed appropriate.
9. Ability to manufacture vaccine.
Patient Eligibility (continued):
10. Patients will have maximal tumor reduction pre-transplant that can be achieved with salvage chemotherapy. Patients will have a PR, CR or CR(u) at Day +100 to 6 months post transplant.
11. ANC >1000/cmm and CD4+ count >200/ul at day +100, or if vaccine given at 6 months - no restrictions on ANC or CD4+ count.

Exclusion Criteria:
1. Any concomitant illness or condition which, in the opinion of the investigators, would interfere with any aspect of the planned protocol or add unacceptable risk for the patient.
2. Central nervous system lymphoma that is not in complete remission at the time of the transplant.
3. Any concomitant malignancy active within previous 5 years except basal or squamous cell carcinoma of the skin, or adequately treated cervical CIS.
4. Serology positive for HIV at time of transplant.

Schedule of Evaluations:
Baseline: Verification of entry criteria including H&P, hematology, serum chemistries, B and T cell subsets, HIV, and serum pregnancy test (if indicated). Tumor staging will be done prior to study entry and will included bone marrow biopsy (preferably bilateral), CT scanning, and other evaluations as indicated to measure extent of disease.

Treatment Plan:
1. Tissue biopsy will be obtained prior to any planned salvage regimen to prepare for transplant.
2. Autologous PSCT with BEAM chemotherapy at UNMC or other institution deemed appropriate.

Determination of Vaccine Eligibility:
1. Approximately day +100 or 6 months after transplantation, a repeat evaluation will be performed to determine eligibility for vaccination.

Vaccination:
1. To begin at day +100 or 6 months after hematopoietic stem cell transplantation.
2. The vaccine will be given every 4 weeks for 7 consecutive doses.
3. Evaluations at each vaccination will include physical exam, CBC, hepatic and renal profiles, CXR if indicated. Special procedures lab will also be collected for immune response immediately prior to vaccines #1, #5, #6, and #7 and two weeks following the administration of vaccine #7.
4. Three and one-half months following the last immunotherapy, the patient will have restaging evaluations completed including physical exam, CT, bone marrow biopsy and laboratory testing.
5. Followup will be conducted annually.
6. Patients will be followed until disease progression. At relapse, a FNA or open biopsy will be performed for any reasonably accessible node in order to assess for histologic change and idiotype expression or mutation.

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

IRB NO: 389-00

Title: Allogeneic Peripheral Blood Stem Cell Transplantation with a Minimally Myelosuppressive Regimen of Pentostatin and Low-Dose Total-Body Irradiation

Principal Investigator: R. Gregory Bociek, M.D.

Clinical Coordinator/Data Manager: Beth Schreiner, R.N., M.S.N.
Telephone: (402) 559-6729
Pager: (402) 888-3610

Purpose: To assess the safety and efficacy of a minimally myelosuppressive regimen with pentostatin and low-dose total body irradiation (TBI) followed by allogeneic peripheral blood stem cell transplantation (allo PSCT).

Patient Eligibility:
1. Age 19-75.
2. Patients who relapse after autologous stem cell transplantation.
3. Patients who are candidates for the autologous or conventional allogeneic stem cell transplantation from a disease standpoint but who do not qualify functionally (from the point of view of organ function, advanced age-related donor transplant >60 and unrelated donor transplant >50, or performance status) for a myeloablative protocol.
4. Identification of a matched related or unrelated stem cell donor.
5. Any patient where, in the opinion of the primary treating oncologist, nonmyeloablative therapy would be the treatment option in the patient’s best interest providing the patient fits all other eligibility criteria for this protocol.

One of the following diseases:
- AML
  - first complete remission (at high risk of relapse)
  - second complete remission
  - minimal residual disease (<10% blasts)
- ALL
  - first complete remission (at high risk of relapse)
  - second complete remission
  - minimal residual disease (<10% blasts)
- CML
  - first chronic phase
  - accelerated phase (<10% blasts)
  - blast phase with minimal residual disease (<10% blasts)
  - second chronic phase
- CLL
  - recurrence after the front line regimen (related donor transplant)
  - chemorefractory disease (unrelated donor transplant)
  - T-CLL in partial remission or any minimal residual disease
Patient Eligibility (continued):
One of the following diseases (continued):
- Myelodysplastic Syndromes
  - refractory anemia with or without ringed sideroblasts
  - RAEB, RAEB, and CMML (<10% blasts in blood and marrow)
- Small Lympho(plasma)cytic Lymphoma (B-SLL, B-LPL)
  - recurrence after a front line regimen (related donor transplant)
  - chemorefractory disease (related or unrelated donor transplant)
- Follicular Low-Grade Lymphoma, Marginal Zone Lymphomas (splenic, nodal, or extranodal/MALT type)
  - chemorefractory disease or >2 prior regimens
- Mantle Cell Lymphoma
  - first complete or partial remission
  - refractory disease
  - failed prior ASCT
- Diffuse Large B-Cell Lymphoma, Follicular Large cell Lymphoma, Peripheral T-cell Lymphoma, Anaplastic Large Cell Lymphoma
  - refractory disease
  - failed prior ASCT
- Burkitt or Acute Lymphoblastic Lymphoma
  - high risk disease in remission
  - chemosensitive persistent or recurrent disease
- Cutaneous T-Cell Lymphomas: (Mycosis Fungoides, Sezary Syndrome)
  - chemorefractory disease of >2 prior regimens
- Hodgkin’s Disease
  - refractory
  - persistent disease and not candidate for ASCT
  - failed prior ASCT
- Multiple Myeloma
  - after receiving at least one regimen of prior chemotherapy

Exclusion Criteria:
1. Progressive disease within 8 weeks of prior therapy or within 12 weeks after prior autologous stem cell transplantation.
2. Active CNS malignancy (patients with known positive CSF cytology or parenchymal lesions visible by CT or MRI).
3. Active uncontrolled infection, immediate life-threatening condition, or uncontrolled medical illness at the time of enrollment.

Study period:
Pentostatin 4 mg/m2/day IV QD x 3 days will be administered with 1000cc NS hydration 10 days prior to stem cell infusion (days -10, -9, -8). Total Body Irradiation will be given on day -1. This will be followed by infusion of donor stem cells on day 0. Patients with related donors will receive standard GVHD prophylaxis (unrelated donor recipients will have an extended GVHD prophylaxis).

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
BEAM/Rituximab/AHSCT for Patients with CD20 Positive NHL

Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

IRB NO: 063-02

Title: A Phase II Trial of BEAM/Rituximab/Autologous Hematopoietic Stem Cell Transplantation (AHSCT) for Patients with CD20 Positive non-Hodgkin’s Lymphoma

Principal Investigator:

Clinical Coordinator/Data Manager: Telephone: Pager:
Jill Nienaber, R.N., B.S.N. (402) 559-4135 (402) 888-0938

Purpose: To evaluate levels of soluble CD20 antigen in the blood of patients with NHL pre and post rituximab/BEAM/autologous hematopoietic stem cell transplantation, and to examine the effect of changes in levels of sCD20 with clinical outcomes. To confirm response rate, event-free survival, and toxicity profile.

Patient Eligibility:
1. Any B-cell, CD20 positive, non-Hodgkin’s lymphoma who is a primary induction failure, has chemotherapy refractory disease or has received ≥3 prior chemotherapy regimens or patients with mantle cell lymphoma, who are otherwise eligible for transplant.
2. Age ≥19 years.
3. Signed written informed consent.
4. Expected survival of ≥6 months.
5. Subjects without history of T-cell lymphoma.
7. Absolute Neutrophil Count ≥1.0 x 10³ /µL, platelet count >50K, and Hgb >8.0 unless this is due to lymphomatous involvement of the bone marrow.

Exclusion Criteria:
1. Patients with serious disease or condition that, in the opinion of the investigator, would compromise the patient’s ability to participate in the study.
2. Pregnant or lactating women.
3. Male or female subject of reproductive potential who is unwilling or unable to follow accepted birth control measures.

Treatment Plan:
Baseline PCR analysis of blood, bone marrow and stem cell product will be performed. Patients will receive two doses of Rituxan at 375mg/m² IV administered one week apart followed by standard hematopoietic stem cell or bone marrow harvesting.
BEAM/Rituximab/AHSCT for Patients with CD20 Positive NHL

Treatment Plan (continued):
After stem cells are collected patients will receive a third dose of Rituxan on Day -7 to -6 prior to Transplantation. The BEAM high-dose chemotherapy will be initiated on Day -6 with BCNU 300 mg/m² IV, followed by Etoposide 100mg/M² BID and Cytarabine 100 mg/m² daily on Days -5 to -2, and Melphalan 140 mg/m² IV on Day -1. Following the chemotherapy, on Day 0 of treatment, the previously stored hematopoietic stem cells will be reinfused via the central venous line and patients will be cared for per standard transplant protocol.

At Day 100 post-transplant, if response is less than a complete remission then rituximab is given weekly x four weeks.

Restaging will be done at day 100, one year and then yearly by CT scans, bone marrow biopsies, blood and bone marrow PCR analysis, and other tests as appropriate.

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

**IRB NO: 171-04**

**Title:** Autologous vs. Non-Myeloablative Hematopoietic Stem Cell Transplantation (HSCT) for Patients with Relapsed Follicular Non-Hodgkin’s Lymphoma

**Principal Investigator:** Julie Vose, M.D.

**Clinical Coordinator/Data Manager:** Jill Nienaber, R.N.  
**Telephone:** (402) 559-4135  
**Pager:** (402) 888-0938

**Purpose:** Compare progression-free survival at three years between the two treatment arms.

**Patient Eligibility:**
1. Patients with histologically confirmed recurrent REAL classification follicle center lymphoma, follicular grades I and II.
2. \( \leq \) 75 years.
3. Received \( \leq \) 3 prior regimens of chemotherapy. Monoclonal antibody therapy and involved field radiation therapy will NOT be counted as a prior therapy.
4. Either in 1st, 2nd, or 3rd relapse of disease AND demonstrate chemosensitive disease.
   Chemosensitive disease will be defined as \(<20\%\) bone marrow involvement with follicular lymphoma AND lymph node size in axial diameter of \(<3\ \text{cm}\) or a \(>75\%\) reduction in estimated lymph node volume to be measured as product of bi-dimensional measurements. Patients in 1st relapse are only eligible if the duration of the 1st complete remission was \(<12\ \text{months}\). PET scanning will not be used for staging or response purposes.
5. Adequate organ function as defined by LVF \(>45\%),\ \text{bilirubin} \(<2 \times \text{ULN},\ \text{ALT} \&\ \text{AST} \(<3 \times \text{ULN},\ \text{creatinine} \text{clearance} \geq 40 \text{ml/min, DLCO, FEV1, FVC} \geq 50\%\ \text{predicted.}}\)
6. Patients must be able to receive cyclophosphamide and rituximab mobilization chemotherapy no earlier than 3 weeks from the beginning of the most recent cycle of salvage chemotherapy and no later than 6 weeks from enrollment.

**Exclusion Criteria:**
- Karnofsky score \(<70\%
- Follicular lymphoma that show histologic evidence of transformation
- Uncontrolled hypertension
- Uncontrolled bacterial, viral or fungal infections
- Prior malignancies except resected basal cell carcinoma or treated cervical carcinoma in situ
- Pregnancy or HIV+
- Prior allograft or autograft
- Anaphylactic reaction to rituximab

In order to be eligible to continue on protocol and receive transplant, patients must collect an autologous or allogeneic graft of \(\geq 2.0 \times 10^6\ \text{CD34+ cells/kg}\) and blood count recovery defined as \(\text{ANC} \geq 1000/\text{mm}^3\) and platelets \(>100 \times 10^9/\text{L}\).
Treatment Plan:
Patients are biologically randomized. All patients will receive cyclophosphamide, rituximab, and G-CSF prior to collection as cytoreductive therapy and chemomobilization for patients without a matched sibling donor. Autologous patients will receive BCNU, VP-16, and cyclophosphamide as conditioning beginning on Day -6. Rituximab will be administered weekly x4 beginning on Day 42. If patient has a matched sibling donor, they will receive fludarabine and cyclophosphamide as mini-allo conditioning (beginning on Day -6), in addition to rituximab at days -13, -6, +1, and +8. GVHD prophylaxis will consist of tacrolimus and methotrexate.

The FACT-BMT and MOS SF-36 instruments will be used to describe the health-related quality of life (HQL) of patients.

Patients will be followed for at least 3 years.

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
## INDOLENT NHL – Standard Therapy

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Stage</th>
<th>Age</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-CLL/Small lymphocytic lymphoma</td>
<td>Hb ≥11 g/dl</td>
<td>any</td>
<td>Observation</td>
</tr>
<tr>
<td></td>
<td>Plt ≥100,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dbl. time &gt;12 mo.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hb &lt;11 g/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plt &lt;100,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Symptomatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dbl. time &lt;12 mo.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤60</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥60</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fludarabine, Fludarabine/Rituxan, or Fludarabine/Rituxan/Cytoxan x 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>At relapse:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>a) consider allogeneic or mini-allogeneic transplants after first or subsequent progression if the patient is a candidate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>b) CHOP-R, Campath, PCR, ESHAP, RICE</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>c) consider investigational study if appropriate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fludarabine, Fludarabine/Rituxan, or Fludarabine/Rituxan/Cytoxan x 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>At relapse:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>a) consider mini-allogeneic transplant if the patient is a candidate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>b) CHOP-R, Campath, PCR, ESHAP, RICE</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>c) consider investigational study if appropriate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## INDOLENT NHL – Standard Therapy

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age-Adjusted IPI Score *</th>
<th>Stage</th>
<th>Age</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular grade I, II</td>
<td>Any</td>
<td>I or minimal II</td>
<td>Any</td>
<td>Involved field (IF) radiotherapy only, or CVP-R or CHOP-R x 4 plus IF radiotherapy</td>
</tr>
<tr>
<td>Nodal marginal zone</td>
<td>Any</td>
<td>bulky II (≥5 cm), III, IV</td>
<td>≤ 60</td>
<td>Observation or CVP-R or CHOP-R x 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- if GPR/CR consider adjuvant Interferon (5,000,000 units 3 times/week) if follicular</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- if no CR, consider ABMT or AlloBMT or mini-allo (if possible) or at Progression/ relapse</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt; 60</td>
<td>Observation or Rituxan x 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>poor PS</td>
<td>No policy on maintenance Rituxan currently</td>
</tr>
<tr>
<td>Extranodal marginal zone, MALT type</td>
<td>Any</td>
<td>I non-gastric</td>
<td>Any</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>II-IV non-gastric</td>
<td>Any</td>
<td>Observation, Rituxan x 4, Chemotherapy +/- Rituxan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>gastric</td>
<td>Any</td>
<td>Two trials of antibiotics first (most appropriate if H.pylori positive) -&gt;if no response, Observation, Rituxan x 4, Local radiotherapy, Chemotherapy +/- Rituxan</td>
</tr>
</tbody>
</table>

* **Age-Adjusted IPI Score**

1) Stage III or IV
2) LDH greater than upper limits of normal
3) Karnofsky score ≤70
MALT Lymphomas

Radiation therapy is useful for definitive treatment of Stage I gastric and non-gastric MALT lymphomas. For gastric MALT lymphomas, radiation is considered when antibiotics have failed.

Radiation Therapy Techniques

Gastric MALT Lymphomas
AP/PA or AP/PA – lateral field techniques are used based on CT planning dosimetry with a distended stomach. The stomach and primary echelon lymph nodes are included.

Dose: Radiation doses are limited to 25 Gy in 15-17 fractions.

Non-gastric MALT Lymphomas
GI non-gastric primaries may require large fields to allow for the uncertainty in tumor location. Whole abdominal fields have been used, although blocking is used to limit the kidney and liver doses to 15-16 Gy.

Non-GI sites are treated with involved field techniques to 25 Gy. Conjunctival or orbital MALT lymphomas should be treated with techniques that limit the lens dose to 5-6 Gy.
Aggressive B-cell Lymphoma

- **Clinical Trials**

  *Previously Untreated*
  - IRB NO: 041-03  Microarray Analysis of Patients with Diffuse Large B-cell Lymphoma Treated with CHOP/Rituximab
  - IRB NO: 033-04  Phase I/II Trial of VELCADE + CHOP-Rituximab in Patients with Previously Untreated Diffuse Large B-cell or Mantle Cell Non-Hodgkin’s Lymphoma

  *Previously Treated – Non-Transplant*
  - IRB NO: 535-00  Zevalin for Post Transplant Relapse of B-cell NHL
  - IRB NO: 075-04  A Multi-center, Open label, Dose-Escalation Study to Evaluate the Safety, Efficacy, and Exposure of TRM-1 (Fully Human Monoclonal Antibody to the TRAIL-R1) in Subjects with Relapsed or Refractory Non-Hodgkins Lymphoma

  *Previously Treated – Transplant*
  - IRB NO: 051-00  BEAM + Iodine-131 Anti-B1 Antibody and Autologous Hematopoietic Stem Cell Transplantation for Treatment of Recurrent Diffuse Large B-cell Non-Hodgkin’s Lymphoma - **REVISED**
  - IRB NO: 389-00  Allogeneic Peripheral Blood Stem Cell Transplantation with a Minimally Myelosuppressive Regimen of Pentostatin and Low-Dose Total-Body Irradiation
  - IRB NO: 063-02  A Phase II Trial of BEAM/Rituximab/Autologous Hematopoietic Stem Cell Transplantation for Patients with CD20 Positive Non-Hodgkin’s Lymphoma – **REVISED**

- **Standard Therapy**

  *Treatment Schema for Aggressive B-cell Non-Hodgkin’s Lymphoma*
  - CHOP+Rituxan
  - CNOP+Rituxan
  - HyperCVAD+Rituxan
  - LBL 1
  - Magrath

- **Radiotherapy**
<table>
<thead>
<tr>
<th>Previously Untreated</th>
<th>Salvage Therapy</th>
<th>Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRB NO: 041-03</td>
<td>IRB NO: 535-00</td>
<td>IRB NO: 051-00</td>
</tr>
<tr>
<td>Microarray Analysis of Patients with Diffuse Large B-cell Lymphoma Treated with CHOP/Rituximab</td>
<td>Zevalin for Post Transplant Relapse of B-cell NHL</td>
<td>BEAM + Iodine-131 Anti-B1 Antibody and Autologous Hematopoietic Stem Cell Transplantation for Treatment of Recurrent Diffuse Large B-cell Non-Hodgkin’s Lymphoma</td>
</tr>
<tr>
<td>IRB NO: 033-04</td>
<td>IRB NO: 075-04</td>
<td>IRB NO: 389-00</td>
</tr>
<tr>
<td>Phase I/II Trial of VELCADE + CHOP-Rituximab in Patients with Previously Untreated Diffuse Large B-cell or Mantle Cell Non-Hodgkin’s Lymphoma</td>
<td>A Multi-center, Open label, Dose-Escalation Study to Evaluate the Safety, Efficacy, and Exposure of TRM-1 (Fully Human Monoclonal Antibody to the TRAIL-R1) in Subjects with Relapsed or Refractory Non-Hodgkins Lymphoma</td>
<td>Allogeneic Peripheral Blood Stem Cell Transplantation with a Minimally Myelosuppressive Regimen of Pentostatin and Low-Dose Total-Body Irradiation</td>
</tr>
<tr>
<td></td>
<td>IRB NO: 063-02</td>
<td>IRB NO: 041-03</td>
</tr>
<tr>
<td>Microarray Analysis of Patients with Diffuse Large B-cell Lymphoma Treated with CHOP/Rituximab</td>
<td>A Phase II Trial of BEAM/Rituximab/Autologous Hematopoietic Stem Cell Transplantation for Patients with CD20 Positive Non-Hodgkin’s Lymphoma</td>
<td></td>
</tr>
</tbody>
</table>
Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

IRB NO: 041-03

Title: Microarray Analysis of Patients with Diffuse Large B-cell Lymphoma Treated with CHOP/Rituximab

Principal Investigator: Julie Vose, M.D.

Clinical Coordinator/Data Manager: Paul Johnson, B.S.  Telephone: (402) 559-6745

Purpose: The primary purpose of this study is to evaluate the gene expression analysis of previously untreated patients with diffuse large B-cell lymphoma who are treated with CHOP/Rituximab.

Patient Eligibility:
1. Patients with a diagnosis of localized or advanced stage diffuse large B-cell non-Hodgkin’s lymphoma expressing the CD20 surface antigen (as measured by immunohistochemistry or flow cytometry on peripheral blood, marrow, or tumor tissue). Patients with composite histology that is >50% diffuse large B-cell NHL are also eligible.

OR

Patients with a suspected lymphoma in which an initial diagnostic biopsy is planned.

2. Patients with stage I or non-bulky stage II will be treated as localized disease. Patients with bulky stage II (at least one tumor mass ≥ 5 cm), or stage III or stage IV disease will be treated as advanced disease.

3. Adequate lymph node tissue for gene expression analysis.

Exclusion Criteria:
1. Patients with known HIV infection.
2. Patients who are on another protocol involving non-FDA approved biologics or drugs.
3. Vulnerable subjects.
4. Subject unable to give informed consent.

Study Period: Prior to initiation of chemotherapy, a lymph node biopsy will be collected and sent to UNMC for analysis. Patients will then be treated with standard CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy in combination with Rituximab (Rituxan). Patients will receive three to four cycles of therapy if they have localized lymphoma or six to eight consecutive cycles of Rituximab in combination with CHOP chemotherapy if they have advanced stage lymphoma. Each cycle is 21 days apart.
Study Period (continued):
After completion of therapy and documentation of response to therapy, patients would be followed every 3 months for the first year, every 4 months for the second year, every 6 months for the third and fourth years, and once yearly after that time by the oncologist with physical exam and standard bloodwork.

Note: This is an abbreviated description. Please contact the coordinator listed for complete information.
Phase I/II Trial of VELCADE + CHOP-Rituximab in Patients with Previously Untreated Diffuse Large B-cell or Mantle Cell Non-Hodgkin’s Lymphoma (NHL)

Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

IRB NO: 033-04

Title: Phase I/II Trial of VELCADE + CHOP-Rituximab in Patients with Previously Untreated Diffuse Large B-cell or Mantle Cell Non-Hodgkin’s Lymphoma (NHL)

Principal Investigator: Julie Vose, M.D.

Clinical Coordinator/Data Manager: Maribeth Hohenstein, R.N.  Telephone: (402) 559-9053  Pager: (402) 888-2717

Purpose:
To determine the toxicity profile and maximum tolerated dose (MTD) of VELCADE when administered in combination with CHOP + Rituximab to patients with previously untreated diffuse large B-cell or mantle cell non-Hodgkin’s lymphoma (NHL). And to assess the response rate (overall and complete), event-free survival and overall survival with VELCADE and CHOP-R in patients with previously untreated diffuse large B-cell or mantle cell lymphoma (phase II component).

Patient Eligibility:
- Histologically confirmed diagnosis of diffuse large B-cell or mantle cell non-Hodgkin’s lymphoma with characteristic immunophenotypic profiles. For mantle cell: CD5(+), CD19(+) or CD20(+), cyclin D1(+), CD23(-) and CD10(-).
- Patient has not received any prior anti-cancer therapy for lymphoma.
- Tumor tissue confirmed to express the CD20 antigen by flow cytometry or immunohistochemistry.
- Available tumor tissue for correlative analyses (rebiopsy to be performed if needed).
- Patient has at least one tumor mass \( \geq 1.5 \) cm in one dimension.
- Patient has Stage II (abdominal – not XRT appropriate), III, or IV disease.
- Age \( \geq 19 \) years with KPS \( \geq 50\% \).
- Laboratory parameters: (unless considered by investigator to be due to lymphoma).
  - Absolute granulocyte count \( \geq 1000 \) cells/mm\(^3\).
  - Platelet count \( \geq 50,000 \) cells/mm\(^3\).
  - Creatinine \( \leq 2.0 \) x ULN.
  - Total bilirubin \( \leq 2.0 \) x ULN.
- Patient has signed IRB-approved informed consent and agrees to use birth control.

Exclusion Criteria:
- Known central nervous system (CNS) involvement by lymphoma.
- Known HIV disease.
- Known hypersensitivity to boron, mannitol, bortezomib, or murine products.
- Patient is pregnant or nursing.
- Patient has had major surgery within the last 3 weeks.
- Patient is receiving other investigational drugs.
- Known peripheral neuropathy Grade \( \geq 2 \).
Treatment Plan:
Standard CHOP chemotherapy administered every 21 days (full dose) for six cycles.
Rituximab administered (375 mg/m²) day 1 of each cycle (with usual premedications).

VELCADE is administered prior to rituximab and CHOP on day 1 of each cycle. Schedule will vary depending on when patient enrolls, and may include additional doses on Day 4 or 8 of each cycle.

VELCADE doses will be assigned in a sequential manner: the first patient will receive VELCADE at 0.7 mg/m²; subsequent patients (up to 18) will receive a dose/schedule that is estimated to be the MTD based on the most recent updates of all currently enrolled patients. For the Phase II portion of the study 60 additional patients will be treated at the MTD for efficacy evaluation.

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
Zevalin for Post-Transplant Relapse of B-cell NHL

Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

IRB NO: 535-00

Title: A Phase I/II Study of IDEC-Y2B8 (Zevalin™) for Post Transplant Relapses of B-cell Non-Hodgkin’s Lymphoma

Principal Investigator: Julie Vose, M.D.

Clinical Coordinator/Data Manager: Telephone: Pager:
Susan Blumel, RN (402) 559-9183 (402) 888-5647

Purpose:
To evaluate the safety and efficacy of Zevalin in patients with B-cell non-Hodgkin’s Lymphoma (NHL) who have relapsed following high-dose chemotherapy and autologous hematopoietic stem cell transplantation.

Patient Eligibility:
1. Patients with a diagnosis of relapsed B-cell lymphoma following autologous stem cell transplantation.
2. Patients must have no other major medical problems and specifically, life expectancy must be at least 3 months, with a WHO performance status of 0, 1, or 2.
3. Evidence of CD20 antigen expression in tumor tissue within one year prior to enrollment, if clinically possible.
4. Adequate renal function (serum creatinine <2.0 mg/dL) and hepatic function (total bilirubin <2.0 mg/dL) and SGOT and/or SGPT to be ≤2.5 times the upper limits of normal (unless due to lymphomatous infiltration of the liver) within seven days of study entry.
5. Written informed consent.
6. Patients without anti-cancer therapy for four weeks prior to radioimmunotherapy dose.
7. ANC >1500/mm³, Platelet count >150,000/mm³.
8. Females of childbearing potential must have a negative serum pregnancy test prior to enrollment to the study. Males and females must agree to use effective contraception during the study and must continue effective contraception for 6 months following the therapeutic dose.
9. <25% bone marrow involvement with NHL within 6 weeks prior to study entry by unilateral or bilateral biopsy. Bone marrow biopsy should demonstrate at least 15-20% of the cellular space to be occupied by normal hematopoiesis.
10. Patients with measurable disease (>2cm in bi-dimensional measurement). Must have CT scan within 6 weeks prior to enrollment.
11. Patients ages 19-70 years of age may enroll.
Zevalin for Post-Transplant Relapse of B-cell NHL

Exclusion Criteria:
1. Patients who have received cytotoxic chemotherapy, biological therapy, radiation therapy or immunosuppressants within FOUR weeks prior to study entry (or two weeks prior to the radioimmunotherapy dose) or who exhibit persistent clinical evidence of toxicity. Patients who have received prior treatment with nitrosourea must wait six weeks prior to study entry. The use of steroids must have been discontinued (except maintenance-dose steroids for non-cancerous disease).
2. Active obstructive hydronephrosis.
3. Active infection requiring intravenous antibiotics at the time of study enrollment.
4. Active central nervous system lymphoma.
5. HIV or AIDS-related lymphoma.
6. Known HIV infection.
7. Positive baseline HAMA result.
8. Patients who are pregnant.
9. Prior radioimmunotherapy or prior fludarabine therapy.
10. Patients who are on another protocol involving non-Food and Drug Administration (FDA) approved drugs or biologics.
11. Prior pelvic radiation or radiation therapy to >25% of the estimated bone marrow reserve.
12. Patients who are transfusion and/or hematopoietic growth factor (e.g., erythropoietin, IL-11, G-CSF, GM-CSF, etc) dependent. Patients who received growth factors within 4 weeks of study entry will be excluded.

Study period:
Three patients will be treated on each of four dose levels. The maximum tolerated dose (MTD) will be determined by hematologic toxicity and an additional 10 patients will be treated at the MTD for the phase II portion.

Patients receive an initial infusion of 250mg/m² Rituxan by intravenous infusion, given according to package insert. Standard premedications include Benadryl, Tylenol, and hydration if clinically indicated.

One week later, patients receive another dose of Rituxan 250mg/m² IV followed by one of the following doses of IDEC Y2B8 by intravenous infusion: 0.15, 0.20, 0.25 or 0.30mCi/kg, dependent on when the patient enters the study. The exact dose of IDEC-Y2B8 will be based on the patient’s weight during the baseline evaluation. The maximum dose is not to exceed 32mCi of ⁹⁰Y.

Response will be assessed by CT scans, CBC with differential, platelet count, and chemistries at 6 weeks following the therapy dose and then subsequently at 3, 6, 9, and 12 months and then every 6 months for 2 years, then yearly until progression of the disease. Bone marrow biopsies would be repeated at those time points if the patient appears to have a complete remission based on CT scan findings to confirm the CR. HAMA testing will be done periodically following treatment. Response criteria will follow the International Workshop guidelines.

Note: This is an abbreviated inclusion/checklist. Please contact the coordinator listed for the complete checklist.
Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

**IRB No: 075-04**

**Title:** A Multi-Center, Open-Label, Dose-Escalation Study to Evaluate the Safety, Efficacy, and Exposure to TRM-1 (Fully Human Monoclonal Antibody to TRAIL-R1) in Subjects with Relapsed or Refractory Non-Hodgkin’s Lymphoma

**Principal Investigator:** Julie Vose, M.D.

**Clinical Coordinator/Data Manager:** Susan Blumel, RN  
**Telephone:** (402) 559-9183  
**Pager:** (402) 888-5647

**Purpose:**
The primary purpose is to evaluate the safety of escalating doses of TRM-1 in subjects with relapsed or refractory non-Hodgkin’s lymphoma (NHL). Secondary purposes are to evaluate disease activity/tumor response in NHL, and to obtain specimens for the determination of plasma concentrations of TRM-1.

**Patient Eligibility:**
1. Histologically confirmed NHL.
2. Measurable disease ≥1.5 cm in the longest transverse diameter by CT scan.
3. Previously treated with at least 1 therapeutic regimen and have relapsed or progressed, or failed to achieve objective response after the last therapeutic regimen.
4. Hemoglobin ≥9.0 g/dL, ANC ≥1.0 x 10⁹/L, Platelet count ≥75 x 10⁹/L.
5. Bilirubin ≤1.5 fold upper limit of normal (ULN), AST and ALT ≤2.5 fold ULN, alkaline phosphatase ≤2.5 fold ULN, serum creatinine ≤1.5 fold ULN.
6. Performance status 0 to 2 on the ECOG Scale.
7. Expected survival of at least 6 months.
8. 19 years of age and older.
9. Ability to understand study requirements, provide written informed consent, including consent for the use and disclosure of research-related health information, and comply with the study and follow-up procedures.

**Exclusion Criteria:**
1. Any co-morbid condition at the judgment of the investigator that renders the subject at high risk of treatment complication or reduces the probability of assessing clinical effect.
2. Received cytotoxic chemotherapy, biological therapy (including hormonotherapy), radiation therapy or immunosuppressants within 3 weeks prior to day 1, cycle 1 or who exhibit persistent clinical evidence of toxicity.
3. Received monoclonal antibodies (eg. Rituximab) within 8 weeks prior to day 1, cycle 1.
4. Received investigational agents within 4 weeks prior to day 1, cycle 1.
5. Received radioimmunotherapy or nitrosourea within 8 weeks prior to day 1, cycle 1 or who exhibit persistent clinical evidence of toxicity.
6. The use of corticosteroids within 1 week prior to day 1, cycle 1(except maintenance dose for co-morbid conditions).
Exclusion Criteria (continued):
7. Subjects who are eligible for a hematopoietic stem cell transplant (HSCT) or who have had an autologous HSCT within the past 16 weeks.
8. Subjects with a prior history of allogeneic HSCT.
9. HIV infection, acquired immunodeficiency syndrome (AIDS)-related lymphoma, or central nervous system (CNS) lymphoma (primary or metastatic).
10. Grade 2 or greater neuropathy, graded by the National Cancer Institute-Common Terminology Criteria for Adverse Events (see full protocol, appendix E).
11. Chronic or acute viral hepatitis.
12. Active infection requiring intravenous or oral antibiotics, or history of opportunistic infections within 4 weeks prior to day 1, cycle 1.
13. History of other cancers within 5 years of day 1, cycle 1 except for basal cell carcinoma of the skin and in situ cancers of the cervix.
14. Myocardial infarction (MI), cerebrovascular accident (CVA), or congestive heart failure (CHF) within the last 6 months.
15. Major surgical procedure or significant traumatic injury within 4 weeks of day 1, cycle 1.
16. Pregnant or breastfeeding women. Women with intact uterus (unless ammenorrheic for the last 24 months) must have a negative serum pregnancy test at screening. All non-sterile, nonmenopausal females must agree to use medically approved method of contraception during the study and for 60 days following the last dose.
17. Males who do not agree to use effective contraception during the study and for a period of 60 days following the last dose of TRM-1.

Study Period:
Cohorts will be treated in sequence with TRM-1 at planned dose levels of 3 mg/kg (cohort 1, 6 subjects) and 10 mg/kg (cohort 2, up to 30 subjects). Each subject will receive a dose on Day 1 followed by the same dose every 21 days (+/- 2 days) up to 6 treatment cycles in the absence of disease progression or dose limiting toxicity (DLT). Patients will be monitored for adverse events, and will receive supportive care as needed. Pharmacokinetic studies on blood and tumor will be performed throughout the study according to the full protocol. Disease evaluation will be performed after cycles 3 and 6, or during any other cycle if there is evidence of possible progression. Responding patients will be followed every 3 months until progression. All patients are followed for 28 days after last dose for safety.

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
BEAM/B1/PSCT for NHL (DLC)

Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

IRB NO: 051-00

Title: BEAM + Iodine-131 Anti-B1 Antibody and Autologous Hematopoietic Stem Cell Transplantation for Treatment of Recurrent Diffuse Large B-cell Non-Hodgkin's Lymphoma

Principal Investigator: Julie Vose, M.D.

Clinical Coordinator/Data Manager: Telephone: Pager:
Susan Allen, RN (402) 559-8155 (402) 888-2537

Purpose:
1. To evaluate response rates and time to treatment failure with Iodine-131 Anti-B1 Antibody/BEAM/autologous hematopoietic stem cell transplantation (AHSCT) as compared with historical control patients receiving high-dose BEAM or BEAC chemotherapy/AHSCT.
2. To assess the safety of Iodine-131 Anti-B1 Antibody in combination with high-dose BEAM chemotherapy/AHSCT.

Patient Eligibility:
1. Adult patients ages 19-70 years of age may enroll.
2. Patients with a diagnosis of diffuse large B-cell lymphoma, composite lymphomas (those with ≥50% of tumor showing diffuse histology), diffuse mixed, or immunoblastic NHL who had a CR or CRu with induction therapy and now have relapsed disease which is sensitive to subsequent conventional therapy (defined as the attainment of at least a PR) OR, are receiving a stem cell transplantation for high risk disease in first remission (CR1). Patients must be otherwise eligible for high-dose therapy with the BEAM protocol and ABMT or PSCT.
3. No evidence of severe organ dysfunction.
4. No other major medical problems and specifically life expectancy must be at least 4 months post transplant, with a performance status Karnofsky score of ≥70.
5. Tumor tissue must express the CD20 antigen. Testing of tumor tissue from any time in the course of the patient's disease is acceptable.
6. Normal renal function (creatinine less than 2.0 mg/dL) and hepatic function (bilirubin less than 2.0 mg/dL) within seven days of study entry.
7. DLCO ≥50% of predicted.
8. If patient is ≥60 years or has a significant cardiac history (MI or CHF) or has received >350 mg/m² of Adriamycin, ejection fraction must be ≥40%.
9. Patients must give written informed consent.
10. Females of childbearing potential must have a negative serum pregnancy test. Males and females must agree to use effective contraception during the study and for 6 months following the therapeutic dose.

Exclusion Criteria:
1. Cytotoxic chemotherapy, radiation therapy or immunosuppressants within FOUR weeks prior to the radioimmunoconjugate dose or persistent clinical evidence of toxicity. The use of steroids must have been discontinued (except maintenance-dose steroids).
Exclusion Criteria (continued):
2. Obstructive hydronephrosis.
3. Evidence of active infection requiring intravenous antibiotics at the time of study entry.
4. New York Heart Association class 3 or 4 heart disease or other serious illness that would preclude evaluation.
5. Prior malignancy other than lymphoma, except for adequately treated skin cancer, in situ cervical cancer, or other cancer for which patient has been disease-free for five years.
6. Known HIV infection.
7. Known brain or leptomeningeal metastases.
8. Patients who are pregnant.
9. Progressive disease in a field that has been irradiated with more than 3500 cGy within the past year.
10. Patients who are on another protocol involving non-FDA approved drugs or biologics.
11. No vulnerable subjects will be entered into this study.
12. Positive HAMA test at baseline.
13. Patients who have not harvested a minimum CD34+ count of $1.5 \times 10^6$/kg body weight or CFU-GM count of $\geq 2.5 \times 10^4$/kg may not continue on to receive the study treatment.
14. Prior hematopoietic stem cell transplant following high-dose chemotherapy or chemo/radiotherapy.

Harvest:
Autologous peripheral blood progenitors are harvested per standard methods. Patients will have one apheresis procedure daily until at least $1.5 \times 10^6$/kg of CD34+ cells or $\geq 2.5 \times 10^4$/kg of CFU-GM count have been collected. The cells will be cryopreserved and stored until they are needed. All patients will have a central venous catheter placed as deemed appropriate by the physician.

Study period:
There will be two outpatient administrations of Iodine-131 Anti-B1 Antibody, the "dosimetric" dose and the "therapeutic" dose, followed by high-dose BEAM chemotherapy and autologous peripheral stem cell transplant. The dosimetric dose will consist of a diagnostic activity of 5 mCi of Iodine-131 Anti-B1 Antibody and will be administered at Day -19 prior to transplant. The dosimetric dose is given to determine the absorbed dose in the whole body so the whole-body radiation dose can be calculated. The radioimmunotherapy dose is then given at Day -12 followed by high dose BEAM chemotherapy on Day -6 and PSCT on Day 0. The patients will then be cared for as standard bone marrow transplant patients.

Follow-up will include hematology labwork until stable count recovery has occurred. Tumor response (physical exam and radiographic studies, such as CT scans and other x-rays or scans as indicated) will be assessed throughout the therapy as appropriate and then at day 100 and yearly post-transplant. Patients will be followed for acute toxicity for 12 weeks after the therapeutic dose. Long-term follow-up for time to treatment failure and toxicities will continue indefinitely.

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

**IRB NO: 389-00**

**Title:** Allogeneic Peripheral Blood Stem Cell Transplantation with a Minimally Myelosuppressive Regimen of Pentostatin and Low-Dose Total-Body Irradiation

**Principal Investigator:** Julie Vose, M.D.

**Planned Accrual Total:** Anticipated accrual will be 40 patients

**Clinical Coordinator/Data Manager:** Beth Schreiner, R.N., M.S.N.  
**Telephone:** (402) 559-6729  
**Pager:** (402) 888-3610

**Purpose:**  
To assess the safety and efficacy of a minimally myelosuppressive regimen with pentostatin and low-dose total body irradiation (TBI) followed by allogeneic peripheral blood stem cell transplantation (allo PSCT). Secondary objective is to assess GM-CSF (cytokine therapy) toxicity and potential therapeutic efficacy. Patients with persistent or progressive disease who fail or do not qualify for the cytokine therapy portion of the study will become candidates for donor leukocyte infusions.

**Patient Eligibility:**
1. Age 19-75 years.
2. Patients who relapse after autologous stem cell transplant.
3. Patients who are candidates for autologous or conventional allogeneic stem cell transplant, but who do not qualify functionally (from the point of view of organ function or performance status) for a myeloablative protocol.
4. Any patient, where in the opinion of the primary treating oncologist, non-myleoablative therapy would be the treatment option in the patient’s best interest providing the patient fits all other eligibility.
5. Available related or unrelated allogeneic stem cell donor matched at HLA-A, B and DR loci (6 antigen match). One antigen mismatch related or unrelated donor will also be acceptable, molecular typing needs to be used at each HLA-A, B, or DR loci in case of mismatched unrelated donor.
6. **Diseases:**
   A. Acute myelogenous leukemia or acute lymphocytic leukemia:
      - first complete remission at high risk of relapse
      - second complete remission
      - minimal residual disease (<10% blasts*)
   B. Chronic myelogenous leukemia:
      - first chronic phase
      - accelerated phase (<10% blasts*)
      - blast phase with minimal residual disease (<10% blasts*)
      - second chronic phase
Patient Eligibility (continued):

C. Chronic lymphocytic leukemia:
   recurrence after the front line regimen (related donor transplant)
   chemorefractory disease (unrelated donor transplant)
   T-CLL in partial remission or any minimal residual disease

D. Myelodysplastic syndromes:
   refractory anemia with or without ringed sideroblasts
   RAEB, RAEB-T, and CMML (<10% blasts [*both in PB and BM])

E. Multiple myeloma - after receiving at least one regimen of prior chemotherapy

F. Non-Hodgkin’s Lymphomas:
   - Small Lympho(plasma)cytic Lymphoma (B-SLL, B-LPL): recurrence after a front line regimen (related donor transplant), chemorefractory disease (related or unrelated donor transplant)
   - Follicular Low-Grade Lymphoma, Marginal Zone Lymphomas (splenic, nodal, or extranodal/MALT type): chemorefractory disease or >2 prior regimens
   - Mantle Cell Lymphoma: first complete or partial remission, refractory disease, failed prior ASCT
   - Diffuse Large B-cell Lymphoma, Follicular Large cell Lymphoma, Peripheral T-cell Lymphoma, Anaplastic Large Cell Lymphoma: refractory disease, failed prior ASCT
   - Burkitt or Acute Lymphoblastic Lymphomas: high-risk disease in remission, chemosensitive persistent or recurrent disease
   - Cutaneous T-cell lymphomas: (Mycosis Fungoides, Sezary Syndrome): chemorefractory disease or >2 prior regimens

G. Hodgkin’s Disease: refractory or persistent disease and not candidate for ASCT, failed prior ASCT

H. Agnogenic myeloid metaplasia with myelofibrosis: hemoglobin 4,000 or >30,000 circulating blood or marrow blasts or clonal abnormality

Exclusion Criteria:
1. Progressive disease within 8 weeks of prior therapy or within 12 weeks after prior autologous stem cell transplantation.
2. Active CNS malignancy or Patients who are HIV seropositive.
3. Active, uncontrolled infection or immediate life-threatening condition at the time of enrollment or significant organ dysfunction.

Study Period:
Pentostatin 4 mg/m2/d IV QD x 3 days will be administered with 1000 cc NS hydration before and after pentostatin three weeks prior to stem cell infusion (days -21, -20, and -19). Total Body Irradiation will be given on Day -1. This will be followed by infusion of donor stem cells on Day 0. Patients will receive standard GVHD prophylaxis.

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

**IRB NO: 063-02**

**Title:** A Phase II Trial of BEAM/Rituximab/Autologous Hematopoietic Stem Cell Transplantation (AHSCT) for Patients with CD20 Positive non-Hodgkin’s Lymphoma

**Principal Investigator:** R. Gregory Bociek, M.D.

**Contact:**
Maribeth Hohenstein, R.N., B.S.N.  
(402) 559-9053  
(402) 888-2717

**Purpose:**
To evaluate levels of soluble CD20 antigen in the blood of patients with NHL pre- and post-rituximab/BEAM/autologous hematopoietic stem cell transplantation, and to examine the effect of changes in levels of sCD20 with clinical outcomes. To confirm response rate, event-free survival, and toxicity profile.

**Patient Eligibility:**
1. Any B-cell, CD20 positive, non-Hodgkin’s lymphoma who is a primary induction failure, has chemotherapy refractory disease or has received \( \geq 3 \) prior chemotherapy regimens or patients with mantle cell lymphoma, who are otherwise eligible for transplant.
2. Age \( \geq 19 \) years.
3. Signed written informed consent.
4. Expected survival of \( \geq 6 \) months.
5. Subjects without history of T-cell lymphoma.
6. WHO Performance Status \( \leq 2 \).
7. Absolute Neutrophil Count \( \geq 1.0 \times 10^3/L \), platelet count \( >50k \), and Hgb \( >8.0 \) unless this is due to lymphomatous involvement of the bone marrow.

**Exclusion Criteria:**
1. Patients with serious disease or condition that, in the opinion of the investigator, would compromise the patient’s ability to participate in the study.
2. Pregnant or lactating women.
3. Male or female subject of reproductive potential who is unwilling or unable to follow accepted birth control measures.

**Treatment Plan:**
Baseline PCR analysis of blood, bone marrow and stem cell product will be performed. Patients will receive two doses of Rituxan at 375mg/m² IV administered one week apart followed by standard hematopoietic stem cell or bone marrow harvesting.
BEAM/RITUXIMAB/AHSCT For Patients With CD20 Positive NHL

Treatment Plan (continued):
After stem cells are collected patients will receive a third dose of Rituxan on Day -7 to -6 prior to Transplantation. The BEAM high-dose chemotherapy will be initiated on day -6 with BCNU 300 mg/m² IV, followed by Etoposide 100mg/M² BID and Cytarabine 100 mg/m² daily on days -5 to -2, and Melphalan 140 mg/m² IV on day -1. Following the chemotherapy, on day 0 of treatment, the previously stored hematopoietic stem cells will be reinfused via the central venous line and patients will be cared for per standard transplant protocol.

At Day 100 post-transplant, if response is less than a complete remission then rituximab is given weekly x four weeks.

Restaging will be done at day 100, one year and then yearly by CT scans, bone marrow biopsies, blood and bone marrow PCR analysis, and other tests as appropriate.

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
# AGGRESSIVE B-CELL NHL – Standard Therapy

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age Adjusted IPI Score *</th>
<th>Tumor Bulk</th>
<th>Stage</th>
<th>Age</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD20+</td>
<td>0 – 1</td>
<td>non-bulky</td>
<td>I – II</td>
<td>&lt;60</td>
<td>CHOP-R x (3-4) + 40 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥60</td>
<td>CHOP-R or CNOP-R (if low ejection fraction) x (3-4) + 40 Gy</td>
</tr>
<tr>
<td>Follicular large cell (grade III)</td>
<td></td>
<td></td>
<td>II – IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥60</td>
<td>CHOP-R or CNOP-R (if low ejection fraction) x 6-8</td>
</tr>
<tr>
<td>Diffuse large B-cell</td>
<td>≥ 2</td>
<td>non-bulky</td>
<td>III - IV</td>
<td>&lt;60</td>
<td>CHOP-R x (6-8) + 40 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥60</td>
<td>CHOP-R or CNOP-R (if low ejection fraction) x 6-8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>bulbly ≥ 5 cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mantle cell</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;60</td>
<td>R-HyperCVAD x 2-3 full cycles (if young and good PS), or CHOP-R → best response → AlloBMT (if possible) → or ABMT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥60</td>
<td>CHOP-R</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>best response → ABMT (if transplant candidate)</td>
</tr>
<tr>
<td>Lymphoblastic</td>
<td>No risk factors</td>
<td></td>
<td></td>
<td></td>
<td>LBL 1</td>
</tr>
<tr>
<td></td>
<td>Any of the following risk factors:</td>
<td></td>
<td></td>
<td></td>
<td>LBL 1 → Early transplant</td>
</tr>
<tr>
<td></td>
<td>CNS +, marrow +, high LDH, bulky tumor, or Stage IV</td>
<td></td>
<td></td>
<td></td>
<td>AlloBMT if &lt;40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥60</td>
<td>AutoBMT ≥40</td>
</tr>
<tr>
<td>Burkitt’s</td>
<td>Any Age Adjusted IPI Score</td>
<td></td>
<td></td>
<td></td>
<td>Magrath regimen x 2 full cycles</td>
</tr>
</tbody>
</table>

* **Age Adjusted IPI Score**

Stage III, IV
LDH > upper limits of normal
Karnofsky score ≤ 70
Systemic Therapy for Non-Hodgkin’s Lymphoma Using
Cyclophosphamide, Doxorubicin, Vincristine, Prednisone and Rituxan

**CHOP + Rituxan**

Effective January 1, 2001

**I. ELIGIBILITY**
Any biopsy proven non-Hodgkin’s lymphoma with the following WHO classification subtypes: Follicular large cell grade III, Diffuse large B-cell, or Mantle cell. CD20+ on immunophenotype of pathology.

**II. STANDARD STAGING EVALUATION**
Modify as needed to document all initial disease sites adequately for follow-up evaluation.

A. History and physical examination.
B. Chest x-ray.
C. Laboratory:
   - CBC, differential, platelet count, Serum LDH, AST (SGOT), alkaline phosphatase, bilirubin, creatinine, uric acid, calcium, beta-2-microglobulin (if available).
D. Bone marrow aspiration and biopsy.
E. Evaluation of intra-abdominal and retroperitoneal disease. This usually includes abdominal and pelvic CT and/or possible abdominal ultrasound.
F. Thoracic CT, if necessary, to document the extent of chest or mediastinal disease.
G. Whenever possible, PET scan should be done as part of the initial evaluation.
H. Additional scans and biopsy as needed to unequivocally document the extent of disease especially sites of extra-nodal involvement.
I. MUGA scan or ECHO cardiogram to document ejection fraction, if appropriate.
J. CSF examination for lymphomatous involvement will be done if the lymphoma involves the sinuses, orbit, testes, or paraspinous areas. A dose of 12 mg of IT Methotrexate will be administered at this time.
A. SCHEDULE AND DOSES

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>ROUTE</th>
<th>DAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituxan *</td>
<td>375 mg/M²</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>750 mg/M²</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>50 mg/M²</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.4 mg/M²/\text{day} (max. 2.0 mg)</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>Prednisone</td>
<td>100 mg</td>
<td>PO</td>
<td>1 – 5</td>
</tr>
</tbody>
</table>

Repeat sequence at 21 days unless counts are not acceptable, then repeat at 28 day intervals.

*On cycle 1 Rituxan may be given on day 1 and CHOP on day 2 due to prolonged duration of infusion.

CENTRAL NERVOUS SYSTEM THERAPY FOR PATIENTS WITH POSITIVE CSF CYTOLOGY

Patients with positive CSF cytology at diagnosis will receive intrathecal Methotrexate at a dose of 12 mg plus Ara-C at a dose of 50 mg two times a week until the CSF is clear and then once a week for 2 doses, and continue with one dose at the start of each remaining CHOP cycle. The CHOP therapy will be followed with 2400 cGy of cranial/spinal radiotherapy to be initiated after recovery of counts from the last cycle of CHOP.

PROPHYLACTIC THERAPY FOR PATIENTS WITH LYMPHOMA INVOLVING THE SINUSES, ORBIT, TESTES, OR PARASPINOUS AREAS

Patients with aggressive NHL with sites of involvement mentioned above will receive prophylactic CSF treatment starting with cycle 1 of CHOP. They should receive intrathecal Methotrexate at a dose of 12 mg with each cycle of CHOP.

GROWTH FACTORS

Hematopoietic growth factors may be used at physician’s discretion.

PROPHYLACTIC ANTIBIOTICS

Sulfamethoxazole/trimethoprin (Bactrim DS or Septra DS) at a dose of one tablet twice a day on two days every week.
B. TOXICITY

1. Hematologic Toxicity: If absolute granulocyte count is <1500/cmm or platelet count is <100,000/cmm on day 22 then delay one week; if still low one week later, proceed with the doses outlined below (no other drug doses are reduced regardless of blood counts):

<table>
<thead>
<tr>
<th>Absolute granulocyte count</th>
<th>Platelet Count</th>
<th>Percent dose of Cyclophosphamide and Doxorubicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000 – 1499</td>
<td>75,000 – 100,000</td>
<td>50%</td>
</tr>
<tr>
<td>&lt;1000</td>
<td>&lt;75,000</td>
<td>0%</td>
</tr>
</tbody>
</table>

Vincristine and Prednisone are not reduced regardless of blood counts.

DOSE ATTENUATION SCHEDULE FOR AGE

No adjustment will be made for age.

2. Neurotoxicity: If muscle weakness sufficient to interfere with normal self care or debilitating ileus occurs, reduce or eliminate vincristine doses as needed to prevent worsening. The vincristine dose should not be reduced solely because of dysesthesia and parasthesias.

3. Hyperglycemia: Prednisone induced hyperglycemia should be managed with oral hypoglycemics, or dietary alteration, and if necessary daily subcutaneous insulin as needed to keep patients from having polyruia or sustained blood glucose above 300 mg/dl.

4. RITUXIMAB (Rituxan)
   a. Infusion-Related Reactions: Rituximab is associated with infusion-related reactions that may respond to adjustments in the infusion rate. Hypotension, bronchospasm, and angioedema have occurred in association with Rituximab infusion as part of an infusion-related symptom complex. Rituximab infusion should be interrupted for severe reactions and can be resumed at a 50% reduction rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Treatment of these symptoms with diphenhydramine and acetaminophen is recommended; additional treatment with bronchodilators or TV saline may be indicated. In most cases, patients who have experienced non-life-threatening reactions have been able to complete the full course of therapy. Medications for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines, and corticosteroids should be available for immediate use in the event of a reaction during administration. (See package insert for more detailed information.)
   b. Cardiovascular: In some cases patients with pre-existing cardiac conditions, including arrhythmias and angina, had recurrences of these events during Rituximab therapy. Accordingly, patients with pre-existing cardiac conditions should be monitored throughout the infusion and immediate post-infusion period.
Systemic Therapy for Non-Hodgkin’s Lymphoma Using
Cyclophosphamide, Mitoxantrone, Vincristine, Prednisone and Rituxan

**CNOP + Rituxan**

Effective: January 1, 2001

I. **ELIGIBILITY**  
Any biopsy proven non-Hodgkin’s lymphoma with the following WHO classification subtypes: Follicular large cell grade III, Diffuse large B-cell, Burkitt-like, or Mantle cell. CD20+ on immunophenotype of pathology.

II. **STANDARD STAGING EVALUATION**  
Modify as needed to document all initial disease sites adequately for follow-up evaluation.

A. History and physical examination.
B. Chest x-ray.
C. Laboratory:  
   CBC, differential, platelet count, Serum LDH, AST (SGOT), alkaline phosphatase, bilirubin, creatinine, uric acid, calcium, beta-2-microglobulin (if available).
D. Bone marrow aspiration and biopsy.
E. Evaluation of intra-abdominal and retroperitoneal disease. This usually includes abdominal and pelvic CT and/or possible abdominal ultrasound.
F. Thoracic CT, if necessary, to document the extent of chest or mediastinal disease.
G. Whenever possible, PET scan should be done as part of the initial evaluation.
H. Additional scans and biopsy as needed to unequivocally document the extent of disease especially sites of extra-nodal involvement.
I. CSF examination for lymphomatous involvement will be done if the lymphoma involves the sinuses, orbit, testes, or paraspinous areas. A dose of 12 mg of IT Methotrexate will be administered at this time.
A. SCHEDULE AND DOSES

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>ROUTE</th>
<th>DAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituxan *</td>
<td>375 mg/M²</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>750 mg/M²</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>12 mg/M²</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.4 mg/M²/day (max. 2.0 mg)</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>Prednisone</td>
<td>100 mg (total dose)</td>
<td>PO</td>
<td>1 – 5</td>
</tr>
</tbody>
</table>

Repeat sequence at 21 days unless counts are not acceptable, then repeat at 28 day intervals.

*On cycle 1 Rituxan may be given on day 1 and CNOP on day 2 due to prolonged duration of infusion.

CENTRAL NERVOUS SYSTEM THERAPY FOR PATIENTS WITH POSITIVE CSF CYTOLOGY
Patients with positive CSF cytology at diagnosis will receive intrathecal Methotrexate at a dose of 12 mg plus Ara-C at a dose of 50 mg two times a week until the CSF is clear and then once a week for 2 doses, and continue with one dose at the start of each remaining CNOP cycle. The CNOP therapy will be followed with 2400 cGy of cranial/spinal radiotherapy to be initiated after recovery of counts from the last cycle of CNOP.

PROPHYLACTIC THERAPY FOR PATIENTS WITH LYMPHOMA INVOLVING THE SINUSES, ORBIT, TESTES, OR PARASPINOUS AREAS
Patients with aggressive NHL with sites of involvement mentioned above will receive prophylactic CSF treatment starting with cycle 1 of CNOP. They should receive intrathecal Methotrexate at a dose of 12 mg with each cycle of CNOP.

GROWTH FACTORS
Hematopoietic growth factors may be used at physician’s discretion.

PROPHYLACTIC ANTIBIOTICS
Sulfamethoxazole/trimethoprin (Bactrim DS or Septra DS) at a dose of one tablet twice a day on two days every week.
B. TOXICITY

1. **Hematologic Toxicity**: If absolute granulocyte count is <1500/cmm or platelet count is <100,000/cmm on day 22 then delay one week; if still low one week later, proceed with the doses outlined below (no other drug doses are reduced regardless of blood counts):

<table>
<thead>
<tr>
<th>Absolute granulocyte count</th>
<th>Platelet Count</th>
<th>Percent dose of Cyclophosphamide and Mitoxantrone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000 – 1499</td>
<td>75,000 – 100,000</td>
<td>50%</td>
</tr>
<tr>
<td>&lt;1000</td>
<td>&lt;75,000</td>
<td>0%</td>
</tr>
</tbody>
</table>

Vincristine and Prednisone are not reduced regardless of blood counts.

**DOSE ATTENUATION SCHEDULE FOR AGE**

NO adjustment will be made for age.

2. **Neurotoxicity**: If muscle weakness sufficient to interfere with normal self care or debilitating ileus occurs, reduce or eliminate vincristine doses as needed to prevent worsening. The vincristine dose should not be reduced solely because of dysesthesia and paraesthesias.

3. **Hyperglycemia**: Prednisone induced hyperglycemia should be managed with oral hypoglycemics, or dietary alteration, and if necessary daily subcutaneous insulin as needed to keep patients from having polyuria or sustained blood glucose above 300 mg/dl.

4. **RITUXIMAB (Rituxan)**
   a. **Infusion-Related Reactions**: Rituximab is associated with infusion-related reactions that may respond to adjustments in the infusion rate. Hypotension, bronchospasm, and angioedema have occurred in association with Rituximab infusion as part of an infusion-related symptom complex. Rituximab infusion should be interrupted for severe reactions and can be resumed at a 50% reduction rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Treatment of these symptoms with diphenhydramine and acetaminophen is recommended; additional treatment with bronchodilators or TV saline may be indicated. In most cases, patients who have experienced non-life-threatening reactions have been able to complete the full course of therapy. Medications for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines, and corticosteroids should be available for immediate use in the event of a reaction during administration. (See package insert for more detailed information.)
   b. **Cardiovascular**: In some cases, patients with pre-existing cardiac conditions including arrhythmias and angina had recurrences of these events during Rituximab therapy. Accordingly, patients with pre-existing cardiac conditions should be monitored throughout the infusion and immediate post-infusion period.
I. ELIGIBILITY
Any biopsy proven non-Hodgkin’s lymphoma with the following WHO classification subtype: Mantle Cell

II. STANDARD STAGING EVALUATION
Modify as needed to document all initial disease sites adequately for follow-up evaluation.
A. History and physical examination.
B. Chest x-ray.
C. Laboratory:
   CBC, differential, platelet count, Serum LDH, AST (SGOT), alkaline phosphatase, bilirubin,
   creatinine, uric acid, calcium, beta-2-microglobulin (if available).
D. Bone marrow aspiration and biopsy.
E. Evaluation of intra-abdominal and retroperitoneal disease. This usually includes abdominal and pelvic CT and/or possibly abdominal ultrasound.
F. Thoracic CT, if necessary, to document the extent of chest or mediastinal disease.
G. Whenever possible, PET scan should be done as part of the initial evaluation.
H. Additional scans and biopsy as needed to unequivocally document the extent of the disease, especially sites of extra-nodal involvement.
I. CSF examination for lymphomatous involvement will be done if the lymphoma involves the sinuses, orbit, testes or paraspinous areas. A dose of 12 mg of IT Methotrexate will be administered at this time.
A. SCHEDULE AND DOSES

Cycle A

<table>
<thead>
<tr>
<th>DAY</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>7</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab 375 mg/m² IV (Day 1)</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytoxan 300 mg/m² Every 12 hrs x 6 doses (Days 1-3)</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesna 600 mg/m² each 24 hours by CI (Days 1-4)</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Doxorubicin 25 mg/m²/day By CI over 24 hours x 2 (Days 4 and 5)</td>
<td></td>
<td></td>
<td></td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Vincristine 1.4 mg/m² Max 2.0 mg (Days 4 and 11)</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone 40 mg PO or IV (Days 1-4 and 11-14)</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>G-CSF 5 ug/kg (Starts on Day 7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>*------until ANC &gt;1500</td>
</tr>
</tbody>
</table>

Prescriptions:
Cipro, Valacyclovir, Fluconazole - optional
Add Bactrim DS 1 tablet PO BID twice per week for PCP prophylaxis.
**Cycle B** – on or before day 21 (when ANC >1500 off G-CSF)

<table>
<thead>
<tr>
<th>DAY</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab 375 mg/m² IV</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Day 1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate 200 mg/m²</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over 2 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Day 1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Then MTX 800 mg/m²</td>
<td>****</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over the next 22 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Day 1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leucovorin 50 mg PO 12 hours</td>
<td></td>
<td></td>
<td>****</td>
<td></td>
</tr>
<tr>
<td>After MTX infusion and</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 mg PO every 6 hrs x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 until MTX level &lt;0.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Days 3+)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARA-C 3 gms/m² over 2 hrs</td>
<td>**</td>
<td>**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV q 12 hours x 4 doses,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 gm/m² if age &gt;65</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>or creatinine is &gt;1.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Days 2 and 3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| G-CSF 5 ug/kg or Neulasta 6mg | | | | *

**Prescriptions:**
- Leucovorin 15 mg q 6 hrs x 8
- Pred-Forte Poth Drops – 2 gtts QID x 7 days after ARA-C
- Cipro, Fluconazole, Valacyclovir - optional

Start cycle A again at day 21 or when ANC >1500 off G-CSF

**Dose Reductions:**
1. For a delay of more than 7 days (>28 days between cycles) reduce cytoxan and doxorubicin doses by 20% and Methotrexate and Ara-C by 25%.
2. For severe mucositis reduce Methotrexate by 25% and for pleural, pericardial effusion or ascites reduce the Methotrexate by 50%.

Restage after 2 of each cycles (A+B). Maximum for non-transplant patients would be 3 cycles of each cycle A and B.
CENTRAL NERVOUS SYSTEM THERAPY FOR PATIENTS WITH POSITIVE CSF CYTOLOGY
Patients with positive CSF cytology at diagnosis will receive intrathecal Methotrexate at a dose of 12 mg plus Ara-C at a dose of 50 mg two times a week until the CSF is clear and then once a week for 2 doses, and continue with one dose at the start of each remaining HyperCVAD cycle. The HyperCVAD therapy will be followed with 2400 cGy of cranial/spinal radiotherapy to be initiated after recovery of counts from the last cycle of HyperCVAD.

PROPHYLACTIC THERAPY FOR PATIENTS WITH LYMPHOMA INVOLVING THE SINUSES, ORBIT, TESTES, OR PARASPINOUS AREAS
Patients with Mantle cell lymphoma will receive prophylactic CSF treatment starting with cycle 1 of HyperCVAD. They should receive intrathecal Methotrexate at a dose of 12 mg with each cycle (A+B) of HyperCVAD.

B. TOXICITY

1. Neurotoxicity: If muscle weakness sufficient to interfere with normal self care or debilitating ileus occurs, reduce or eliminate vincristine doses as needed to prevent worsening. The vincristine dose should not be reduced solely because of dysesthesia and parasthesias.

2. Hyperglycemia: Prednisone induced hyperglycemia should be managed with oral hypoglycemics, or dietary alteration, and if necessary daily subcutaneous insulin as needed to keep patients from having polyuria or sustained blood glucose above 300 mg/dl.

DOSE ATTENUATION SCHEDULE FOR AGE
Age ≥ 65 years: Reduce Ara-C to 1 gm/M²
Systemic Therapy for Lymphoblastic Lymphoma Using Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone, L-Asparaginase, Methotrexate, 6-Mercaptopurine, Interthecal Methotrexate and Whole Brain Radiotherapy for Adult Patients

LBL 1 Treatment Plan

Effective: May 3, 1991
Revised: March 20, 1995
Revised: March 20, 1996
Revised: January 1, 2000

I. ELIGIBILITY
A. Required:
   1. Biopsy proven Lymphoblastic Lymphoma.
   2. Age ≥16 years of age.

II. STANDARD STAGING EVALUATION
A. History and physical examination.
B. Chest x-ray.
C. Laboratory:
   CBC, differential, platelet count, Serum LDH, AST (SGOT), alkaline phosphatase, bilirubin, creatinine, uric acid, calcium, beta-2-microglobulin (if available).
D. Bone marrow aspiration and biopsy.
E. Evaluation of intra-abdominal and retroperitoneal disease. This usually includes abdominal and pelvic CT and/or possibly abdominal ultrasound.
F. Thoracic CT, if necessary, to document the extent of chest or mediastinal disease.
G. Whenever possible, PET should be done as part of the initial evaluation.
H. Additional scans and biopsy as needed to unequivocally document the extent of the disease, especially sites of extra-nodal involvement.
I. CSF Fluid examination for lymphomatous involvement will be done if the lymphoma involves the sinuses, orbit, testes or paraspinous areas. A dose of 12 mg of IT Methotrexate will be administered at this time.

III. TREATMENT AND DOSE ALTERATIONS
It is very important that treatment be given on time finishing in the planned number of cycles. All drugs should be given in FULL doses on time unless SPECIFIC toxicity requires dose reduction.

A. SCHEDULE AND DOSES
Prior to the initiation of systemic therapy, a lumbar puncture for cytology should be performed and the initial dose of IT Methotrexate (12 mg) administered. The therapeutic plan is in five phases; pre-systemic, induction, CNS prophylaxis, consolidation, and maintenance.

PRE-SYSTEMIC
IT Methotrexate (12 mg) is administered at the time of the lumbar puncture for cytologic studies.
INDUCTION
The following drugs are given: cyclophosphamide (1.0 Gm/m² IV) and doxorubicin (50 mg/m² IV) on
days 1 and 22, vincristine (2.0 mg IV) on days 1, 8, 15, 22, 28 and 35, Prednisone (40 mg/m² PO) given
daily on days 1 through 21 with a dose taper from day 22 to day 28 and L-Asparaginase 6,000 units/m²
IM or IV (max 10,000 units) with 5 doses during week 4 (days 22-28). One dose of IT Methotrexate (12
mg) is administered during week 3 and a total of 5 doses during weeks 5, 6, and 7.

CNS PROPHYLAXIS
CNS prophylaxis consists of 5 doses of IT methotrexate (12 mg) during weeks 5 through 7. Also given
is 2400 cGy of radiotherapy in 12 fractions to the whole brain.

CONSOLIDATION
Four cycles of the following drugs are given in weeks 9, 12, 15, and 18: cyclophosphamide (1.0 Gm/m²
IV) on day 1, doxorubicin (50 mg/m² IV) on day 1, vincristine (2.0 mg IV) on day 1 and Prednisone (40
mg/m² PO) given daily on days 1 through 5.

MAINTENANCE
Maintenance therapy consists of Methotrexate (30 mg/m² /week PO) and Mercaptopurine (75mg/m² /day
PO) during weeks 22 through 52. Bone marrow transplantation will be considered INSTEAD of
maintenance therapy for patients with unfavorable prognostic factors at diagnosis (CNS or bone marrow
involvement and/or LDH >2 times normal, bulky tumor, or stage IV). Allogeneic bone marrow
transplantation will be used for patients less than 40 years of age with an appropriately matched donor.
Autologous transplantation will be used for patients greater than or equal to 40 years of age.
### SCHEMA OF SCHEDULE OF DOSES:

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pre</th>
<th>Induction</th>
<th>CNS Prophylaxis</th>
<th>Consolidation</th>
<th>Maintenance or BMT/PSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide 1.0 Gm/M² IV</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Doxorubicin 50 mg/M² IV</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vincristine 2.0 mg IV</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Prednisone 40 mg/M² PO</td>
<td></td>
<td>------------</td>
<td>Taper</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-Asparaginase 6000 units/M² IM or IV</td>
<td></td>
<td>5 doses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate 12 mg IT</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole Brain XRT 2400 cGy in 12 fractions</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate 30 mg/M² PO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Weekly</td>
</tr>
<tr>
<td>Mercaptopurine 75 mg/M² PO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Daily</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Agent</th>
<th></th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12-21</th>
<th>22-52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide 1.0 Gm/M² IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin 50 mg/M² IV</td>
<td></td>
<td>Repeat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vincristine 2.0 mg IV</td>
<td></td>
<td>9-12 x 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone 40 mg/M² PO</td>
<td></td>
<td>5 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate 12 mg IT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate 30 mg/M² PO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mercaptopurine 75 mg/M² PO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### TOXICITY

1. **Hematologic Toxicity:** If absolute granulocyte count is <1500/cmm or platelet count is <100,000/cmm on day 22 then delay one week; if still low one week later, proceed with the doses outlined below (no other drug doses are reduced regardless of blood counts):

#### DOSE ATTENUATION SCHEDULE FOR COUNTS

<table>
<thead>
<tr>
<th>Absolute granulocyte count</th>
<th>Platelet Count</th>
<th>Percent dose of Cyclophosphamide</th>
<th>Percent dose of Doxorubicin and mercaptopurine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000 – 1499</td>
<td>75,000 – 100,000</td>
<td>50%</td>
<td>0%</td>
</tr>
<tr>
<td>&lt;1000</td>
<td>&lt;75,000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Vincristine and Prednisone are not reduced regardless of blood counts.

#### DOSE ATTENUATION SCHEDULE FOR AGE

NO adjustment will be made for age.
B. **TOXICITY (continued):**

2. **Neurotoxicity:** If muscle weakness sufficient to interfere with normal self care or debilitating ileus occurs, reduce or eliminate vincristine doses as needed to prevent worsening. The vincristine dose should not be reduced solely because of dysesthesia and parasthesias.

3. **Hyperglycemia:** Prednisone induced hyperglycemia should be managed with oral hypoglycemics, or dietary alteration, and if necessary daily subcutaneous insulin as needed to keep patients from having polyuria or sustained blood glucose above 300 mg/dl.

4. **GI:** L-Asparaginase has been shown to cause pancreatitis.

5. **Allergic:** L-Asparaginase has been reported to cause anaphylactic shock.

6. **Renal:** Allopurinol will NOT be used while patient is receiving Mercaptopurine.
Systemic Therapy for Non-Hodgkin’s Lymphoma Using
Cytarabine, Vincristine, Doxorubicin, Methotrexate, Leucovorin, and Cyclophosphamide
Alternating with Cytarabine, Methotrexate, Ifosfamide, and Etoposide

Magrath Hybrid Protocol

(for Burkitt’s NHL)

Effective: January 1, 2000

I. ELIGIBILITY
Any biopsy proven non-Hodgkin’s lymphoma with the following WHO classification subtype: Burkitt’s

II. STANDARD STAGING EVALUATION
A. History and physical examination.
B. Chest x-ray.
C. Laboratory:
   CBC, differential, platelet count, Serum LDH, AST (SGOT), alkaline phosphatase, bilirubin, creatinine, uric acid, calcium, beta-2-microglobulin (if available).
D. Bone marrow aspiration and biopsy.
E. Evaluation of intra-abdominal and retroperitoneal disease. This usually includes abdominal and pelvic CT and/or possibly abdominal ultrasound.
F. Thoracic CT, if necessary, to document the extent of chest or mediastinal disease.
G. Whenever possible, PET scanning should be done as part of the initial evaluation.
H. Additional scans and biopsy as needed to unequivocally document the extent of the disease, especially sites of extra-nodal involvement.
I. CSF Fluid examination for lymphomatous involvement will be done regardless of disease sites. A dose of 12 mg of IT Methotrexate will be administered at this time.
III. TREATMENT AND DOSE ALTERATIONS
It is very important that treatment be given on time finishing in the planned number of cycles. All drugs should be given in FULL doses on time unless SPECIFIC toxicity requires dose reduction.

A. SCHEDULE AND DOSES

*ALTERNATE CYCLES OF CYCLES A and B (following page) for a total of four cycles.*

**Cycle A: CODOX-M**

|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| × |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|   | ☐ | ☐ |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| ∈ |   |   | ∈ |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   | 9 | 9 | 9 | 9 | 9 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| + | + | + | + | + | + |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 |

✘ Rituxan 375 mg/m²
☐ IT Cytarabine, 70 mg
♠ IV Vincristine, 1.5 mg/m² (no cap)

Φ The day 15 dose of VCR is not given on cycle 1 and only if no neuropathy in cycle 2A

☐ IV Doxorubicin, 40 mg/m²

~ IT Methotrexate, 12 mg
† IV Cyclophosphamide, 800 mg/m² day 1, then 200 mg/m² days 2-5
≡ Methotrexate, 1200 mg/m² over 1 hour, then 240 mg/m² each hour for 23 hours (IV infusion)

Leucovorin, 200 mg/m² IV at hour 36, then 12 mg/m² every 6 hours until MTX level <5 \(10^{-8}\) mol/L

9G-CSF or GM-CSF, until ANC >1000/cu mm, or Neulasta 6 mg
### Cycle B: IVAC

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **×** Rituxan 375 mg/m²
- **☐** IV Cytarabine, 2 Gm/m² every 12 hours (4 doses), Pred-Forte ophthalmic drops × 7 days post Cytarabine
- **~** IT Methotrexate, 12 mg
- **[ ]** IV Mesna, 1500 mg/m²/day by CI day 1-5 1° prior to Ifosfamide and continue for 12 hours after Ifosfamide
- **[ ]** IV Ifosfamide, 1500 mg/m²/IV/day on days 1-5
- **[ ]** IV Etoposide, 60 mg/m²/day on days 1-5

- **9** G-CSF or GM-CSF, until ANC >1000/cu mm, or Neulasta 6 mg

Repeat sequence at 21 days if ANC ≥ 1000 and platelet count ≥ 50,000/µL, if not repeat at 28 day intervals. Complete a total of 2 cycles of A + B.

**IF CNS DISEASE at presentation add:**

- **CODOX-M (1 and 2 A):** IT Ara-C 70 mg on day 5 and IT Methotrexate 12 mg on day 17
- **IVAC (1 + 2 B):** IT Ara-C 70 mg on day 7 and 9
DOSE ATTENUATION SCHEDULE FOR COUNTS (at Day 28)

**CYCLE A**

<table>
<thead>
<tr>
<th>Absolute granulocyte count</th>
<th>Platelet Count</th>
<th>Percent dose attenuation of Cyclophosphamide and Doxorubicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1,000</td>
<td>&lt;50,000</td>
<td>25%</td>
</tr>
</tbody>
</table>

**CYCLE B**

<table>
<thead>
<tr>
<th>Absolute granulocyte count</th>
<th>Platelet Count</th>
<th>Percent dose attenuation of Cytarabine, Ifosfamide, and Etoposide</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1,000</td>
<td>&lt;50,000</td>
<td>25%</td>
</tr>
</tbody>
</table>

**DOSE ATTENUATION SCHEDULE FOR AGE**

NO adjustment will be made for age.
Involved field radiation therapy will be recommended following completion of chemotherapy to those groups so indicated in the Aggressive B-cell NHL - Standard Therapy Schema.

**Radiation Fields**

Radiotherapy will include the prechemotherapy target volume plus a 2 cm margin around the planning volume. No attempt will be made to cover contiguous nodal sites prophylactically. In the case of pre-chemotherapy, bulky sites (ex: mediastinal adenopathy), the target volume may be modified to include the post chemotherapy target volume, in order to decrease the risk of toxicity (ex: interstitial pneumonitis).

CT – based treatment planning dosimetry is recommended. Dose uniformity of +/- 5% is the goal. Tissue compensators, wedged field within a field boost, 3-D conformal (including IMRT) techniques are encouraged to achieve the uniformity goal.

**Radiation Doses**

A dose of 40 Gy (39.6 Gy – 40.5 Gy) delivered over 20 – 27 fractions. The dose fraction size will be adjusted to patient tolerance.

Weekly CBC with differential is recommended during radiation therapy.
T-cell Lymphoma

• **Clinical Trials**

*Previously Treated – Non-Transplant*

IRB NO: xxx-04  
Phase II Trial of Depsipeptide in Patients with Cutaneous T-cell Lymphoma and Relapsed Peripheral T-cell Lymphoma

IRB NO: 289-04  
A Phase II, Multi-Center-Label, Repeat-Dose Study of BCX-1777 Infusion in Patients with Advanced T-cell Leukemia with an Option of Long-Term BCX-1777 Use

IRB NO: 075-04  
A Multi-center, Open label, Dose-Escalation Study to Evaluate the Safety, Efficacy, and Exposure of TRM-1 (Fully Human Monoclonal Antibody to the TRAIL-R1) in Subjects with Relapsed or Refractory Non-Hodgkins Lymphoma

*Previously Treated – Transplant*

IRB NO: 389-00  
Allogeneic Peripheral Blood Stem Cell Transplantation with a Minimally Myelosuppressive Regimen of Pentostatin and Low-Dose Total-Body Irradiation

• **Standard Therapy**

*Treatment Schema for T-cell Lymphoma*

- CHOP
- CNOP

• **Radiotherapy**
# T-cell Lymphoma

**Referral Pager:** (402) 888-5615

<table>
<thead>
<tr>
<th>Previously Untreated</th>
<th>Salvage Therapy</th>
<th>Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRB NO: xxx-04</td>
<td>Phase II Trial of Depsipeptide in Patients with Cutaneous T-cell Lymphoma and Relapsed Peripheral T-cell Lymphoma</td>
<td>IRB NO: 389-00 AlloPSCT with a Minimally Myelosuppressive Regimen: Pentostatin &amp; Low-dose TBI</td>
</tr>
<tr>
<td>IRB NO: 289-04</td>
<td>A Phase II, Multi-Center-Label, Repeat-Dose Study of BCX-1777 Infusion in Patients with Advanced T-cell Leukemia with an Option of Long-Term BCX-1777 Use.</td>
<td></td>
</tr>
<tr>
<td>IRB NO: 075-04</td>
<td>A Multi-Center, Open-Label, Dose-Escalation Study to Evaluate the Safety, Efficacy, and Exposure to TRM-1</td>
<td></td>
</tr>
</tbody>
</table>
Phase II Trial of Depsipeptide in Patients with Cutaneous T-cell Lymphoma and Relapsed Peripheral T-cell Lymphoma

Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

IRB NO: xxx-04

Title: Phase II Trial of Depsipeptide in Patients with Cutaneous T-cell Lymphoma and Relapsed Peripheral T-cell Lymphoma

Principal Investigator: Julie Vose, M.D.

Clinical Coordinator/Data Manager: Maribeth Hohenstein, R.N.
Telephone: (402) 559-9053
Pager: (402) 888-2717

Purpose - Primary:
1. In patients with cutaneous T-cell lymphoma, the primary end points to be examined are overall response rate, complete response rate and duration of response. To evaluate the event-free survival in this patient group.
2. In patients with relapsed peripheral T-cell lymphoma, the endpoints to be examined are overall response rate and complete response rate.

Purpose - Secondary:
1. In patients with cutaneous T-cell lymphoma, the primary end points to be examined are overall response rate, complete response rate and duration of response. To evaluate the event-free survival in this patient group.
2. In patients with relapsed peripheral T-cell lymphoma, the endpoints to be examined are overall response rate and complete response rate.

Patient Eligibility:
1. Patients with cutaneous T-cell lymphoma (mycosis fungoides or Sézary syndrome) stage IA to IVB. Patients with stage IA, IB, IIA should be refractory to, intolerant to, or have reached a six-month or longer response plateau on at least two prior therapies from the following list: PUVA, UVB, EBT, photophoresis, interferon, systemic cytotoxic chemotherapy, topical nitrogen mustard, or topical Carmustine (BCNU). One qualifying prior treatment must have been topical nitrogen mustard, topical Carmustine or a phototherapy (UVB, PUVA or EBT). Topical steroids, systemic retinoids or biologicals do not qualify. Patients with stage IA, IB, IIA who are ineligible for topical nitrogen mustard, topical Carmustine or phototherapy (UVB, PUVA or EBT). Patients with stage IIB-IVB who have had no more than 2 prior systemic cytotoxic chemotherapy regimens are eligible. There is no restriction regarding prior topical therapies, skin irradiation, or non-cytotoxic systemic therapies (i.e. PUVA, retinoids or biologicals, with the exception of radiolabeled monoclonal antibody therapy). After 24 patients have been enrolled in this arm, the arm will close, and a replicate arm constituted of this patient population will be opened.
2. Patients with peripheral T-cell lymphoma, unspecified, or anaplastic large cell lymphoma, T and null cell, primary cutaneous type, as defined by the REAL/WHO classification (16-18), who have experienced disease progression after receiving prior standard treatment and who have had no more than 2 prior systemic cytotoxic chemotherapeutic regimens are eligible.
Phase II Trial of Depsipeptide in Patients with Cutaneous T-cell Lymphoma and Relapsed Peripheral T-cell Lymphoma

Patient Eligibility (continued):

3. Patients with cutaneous T-cell lymphoma (Myosis fungoides or Sezary Syndrome) or peripheral T-cell lymphoma as defined above who have received more than 2 prior systemic therapies and who have experienced disease progression will be included in a third and independent arm.

4. Patients with mature T-cell lymphomas not included above will be enrolled in a fourth arm. These include but are not exclusively limited to: Enteropathy-type T-cell lymphoma; Hepatosplenic T-cell lymphoma; Subcutaneous panniculitis-like T-cell lymphoma; Angioimmunoblastic T-cell lymphoma; Anaplastic large cell lymphoma. Patients must have experienced disease progression after receiving prior standard treatment. There will be no limit on the number of prior regimens. Primitive T-cell neoplasms and T-cell leukemias will not be enrolled.

5. Disease that is measurable by radiographic imaging, assessing skin lesions, or by quantitating Sézary cell count.

6. Patients must:
   - be age ≥ 18 years
   - have a performance status of ECOG 0-2
   - have no serious or intercurrent illness and have a life expectancy of >12 weeks
   - give written informed consent
   - female patients of childbearing potential must have a negative pregnancy test within 4 weeks and must use effective contraception
   - sexually active males must use effective contraception

7. Laboratory values (performed ≤ 14 days prior to registration):
   - absolute neutrophil count ≥ 1000/µL, platelets ≥ 100,000/µL, bilirubin (total and direct) ≤ 1.5x upper limit of normal, and AST ≤ 3x upper limit of normal, unless impairment is due to organ involvement by lymphoma, creatinine ≤ 1.5x upper limit of normal, or documented creatinine clearance of ≥ 60mL/min.

8. Cardiac studies (performed within 4 weeks of registration): Ejection fraction of > 50% by echocardiogram or cardiac MRI, or ≥ 45% by MUGA scan.

9. A stable dose (> 1 month) of corticosteroids administered for symptom management will not preclude enrollment. Tapering will be initiated following administration of depsipeptide.

Exclusion Criteria:

1. Patients with an unconfirmed diagnosis, or with B-cell lymphomas will be excluded.

2. Prior or concurrent malignancies that have not been curatively treated.


4. Chemotherapy within 4 weeks, 6 weeks for nitrosoureas or mitomycin C.

5. Biologics, Immunotherapy within 2 weeks.

6. HIV seropositivity (see section 6.1.3).

7. Pregnant or breast-feeding patients (see section 6.1.3).

8. Major surgery within 21 days.

9. Uncontrolled infection.

10. Patients with MI within previous 6 months, EF < 45%, (by MUGA) or (< 50% by echocardiogram or cardiac MRI), QTc > 500 ms, unstable angina, or with third degree, or Mobitz II second degree heart block that do not have a pacemaker. Patients with first degree or Mobitz I second degree heart block require consultation with cardiology. Patients with other cardiac disease may be excluded at the discretion of the PI following consultation with cardiology.
**Treatment Plan:**
During Treatment Period 1, blood samples will be obtained prior to infusion on Day 1 of each cycle, Day 2 of Cycle 1, after the fourth infusion of Treatment Cycles 1–5, and after the last infusion of Cycle 6. During the long-term, follow-up treatment period, blood samples will be obtained prior to the first infusion of each cycle for BCX-1777 levels and prior to the first infusion of Cycles 1, 3, and 6 for dGuo plasma levels and PNP activity.

The samples for BCX-1777, dGuo and PNP analysis will be sent to BioCryst Pharmaceuticals, Inc. (BioCryst). These results will be available to Investigators, DSMB, and Study Medical Monitor to assist with continuous safety and efficacy evaluation.

**NOTE:** This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

**IRB NO: 289-04**

**Title:** A Phase II, Multi-Center, Open-Label, Repeat-Dose Study of BCX-1777 Infusion in Patients with Advanced T-cell Leukemia with an Option of Long-Term BCX-1777 Use

**Principal Investigator:** Lori Maness, M.D.

**Clinical Coordinator/Data Manager:** Beth Schreiner, M.S.N., R.N.  
**Telephone:** (402) 559-6729  
**Pager:** (402) 888-3610

**Purpose - Primary:**
To determine the sustained effectiveness (for a minimum of 28 days) of intravenous (IV) BCX-1777 infusions in patients with advanced T-cell leukemia (T-cell acute lymphoblastic leukemia [T-ALL], T-cell prolymphocytic leukemia [T-PLL], or T-cell lymphoma with circulating blasts) as evidenced by peripheral blood evaluations and confirmatory bone marrow evaluation.

**Purpose - Secondary:**
1. To assess the safety and tolerability of multiple infusion cycles of BCX-1777 in this patient population.
2. To evaluate the effects of BCX-1777 on plasma levels of 2′-deoxyguanosine (dGuo) and red blood cell (RBC) purine nucleoside phosphorylase (PNP) activity and to correlate levels with efficacy parameters.
3. To describe the steady-state pharmacokinetics (PK) and pharmacodynamics (PD) of BCX-1777 following repeat administration.

**Patient Eligibility:**
1. Documented T-cell leukemia (T-ALL, T-PLL, or T-cell lymphoma with circulating blasts).
2. Failure to have responded to previous treatment or relapse after initial response to previous treatment.
3. Performance status of ≤2 by Eastern Cooperative Oncology Group (ECOG) criteria (see Appendix A).
4. All ages are eligible.
5. Life expectancy of at least 3 months.
6. Adequate liver function (aspartate transaminase [AST] and/or alanine transaminase [ALT] not >3 times upper limits of normal [ULN]).
7. Adequate kidney function (calculated creatinine clearance >50 mL/min).
8. Negative urine pregnancy test within 2 to 7 days prior to the start of study treatment in females of childbearing potential.
9. Signed informed consent/assent form (ICF) prior to start of any study specific procedures.
Exclusion Criteria:
1. Infrequent subsets of T-cell leukemias and natural killer leukemias (including large granular lymphocyte).
2. Active serious infection not controlled by oral or IV antibiotics.
3. Treatment with any investigational antileukemic agent or chemotherapy agent within 7 days prior to study entry, unless full recovery from side effects has occurred.
4. Rapidly progressive disease with compensated organ function judged to be life-threatening by the Investigator.
5. Concurrent treatment with other anticancer agents (corticosteroid use will not be excluded, but patient must remain on a stable dose).
6. Pregnant and/or lactating female.
7. Subjects not willing to use contraception (not required for postmenopausal women).

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
Antibody to TRAIL-R1 for Relapsed NHL

Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

IRB No: 075-04

Title: A Multi-Center, Open-Label, Dose-Escalation Study to Evaluate the Safety, Efficacy, and Exposure to TRM-1 (Fully Human Monoclonal Antibody to TRAIL-R1) in Subjects with Relapsed or Refractory Non-Hodgkin’s Lymphoma

Principal Investigator: Julie Vose, M.D.

Clinical Coordinator/Data Manager: Susan Blumel, RN  Telephone: (402) 559-9183  Pager: (402) 888-5647

Purpose: The primary purpose is to evaluate the safety of escalating doses of TRM-1 in subjects with relapsed or refractory non-Hodgkin’s lymphoma (NHL). Secondary purposes are to evaluate disease activity/tumor response in NHL, and to obtain specimens for the determination of plasma concentrations of TRM-1.

Patient Eligibility:
1. Histologically confirmed NHL.
2. Measurable disease ≥1.5 cm in the longest transverse diameter by CT scan.
3. Previously treated with at least 1 therapeutic regimen and have relapsed or progressed, or failed to achieve objective response after the last therapeutic regimen.
4. Hemoglobin ≥9.0 g/dL, ANC ≥1.0 x 10^9/L, Platelet count ≥75 x 10^9/L.
5. Bilirubin ≤1.5 fold upper limit of normal (ULN), AST and ALT ≤2.5 fold ULN, alkaline phosphatase ≤2.5 fold ULN, serum creatinine ≤1.5 fold ULN.
6. Performance status 0 to 2 on the ECOG Scale.
7. Expected survival of at least 6 months.
8. 19 years of age and older.
9. Ability to understand study requirements, provide written informed consent, including consent for the use and disclosure of research-related health information, and comply with the study and follow-up procedures.

Exclusion Criteria:
1. Any co-morbid condition at the judgment of the investigator that renders the subject at high risk of treatment complication or reduces the probability of assessing clinical effect.
2. Received cytotoxic chemotherapy, biological therapy (including hormonotherapy), radiation therapy or immunosuppressants within 3 weeks prior to day 1, cycle 1 or who exhibit persistent clinical evidence of toxicity.
3. Received monoclonal antibodies (eg. Rituximab) within 8 weeks prior to day 1, cycle 1.
4. Received investigational agents within 4 weeks prior to day 1, cycle 1.
5. Received radioimmunotherapy or nitrosourea within 8 weeks prior to day 1, cycle 1 or who exhibit persistent clinical evidence of toxicity.
6. The use of corticosteroids within 1 week prior to day 1, cycle 1(except maintenance dose for co-morbid conditions).
7. Subjects who are eligible for a hematopoietic stem cell transplant (HSCT) or who have had an autologous HSCT within the past 16 weeks.
Exclusion Criteria (continued):
8. Subjects with a prior history of allogeneic HSCT.
9. HIV infection, acquired immunodeficiency syndrome (AIDS)-related lymphoma, or central nervous system (CNS) lymphoma (primary or metastatic).
10. Grade 2 or greater neuropathy, graded by the National Cancer Institute-Common Terminology Criteria for Adverse Events (see full protocol, Appendix E).
11. Chronic or acute viral hepatitis.
12. Active infection requiring intravenous or oral antibiotics, or history of opportunistic infections within 4 weeks prior to day 1, cycle 1.
13. History of other cancers within 5 years of day 1, cycle 1 except for basal cell carcinoma of the skin and in situ cancers of the cervix.
14. Myocardial infarction (MI), cerebrovascular accident (CVA), or congestive heart failure (CHF) within the last 6 months.
15. Major surgical procedure or significant traumatic injury within 4 weeks of day 1, cycle 1.
16. Pregnant or breastfeeding women. Women with intact uterus (unless amenorrheic for the last 24 months) must have a negative serum pregnancy test at screening. All non-sterile, nonmenopausal females must agree to use medically approved method of contraception during the study and for 60 days following the last dose.
17. Males who do not agree to use effective contraception during the study and for a period of 60 days following the last dose of TRM-1.

Study Period:
Subjects are dosed every 21 days for up to 6 cycles of treatment in the absence of dose limiting toxicity or disease progression. Patients will be monitored for adverse events and will receive full supportive care as medically necessary. Pharmacokinetic studies on blood and tumor tissue will also be performed.

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

**IRB NO: 389-00**

**Title:** Allogeneic Peripheral Blood Stem Cell Transplantation with a Minimally Myelosuppressive Regimen of Pentostatin and Low-Dose Total-Body Irradiation

**Principal Investigator:** R. Gregory Bociek, M.D.

**Clinical Coordinator/Data Manager:** Beth Schreiner, R.N., M.S.N.  
**Telephone:** (402) 559-6729  
**Pager:** (402) 888-3610

**Purpose:** To assess the safety and efficacy of a minimally myelosuppressive regimen with pentostatin and low-dose total body irradiation (TBI) followed by allogeneic peripheral blood stem cell transplantation (allo PSCT).

**Patient Eligibility:**
1. Age 19-75.
2. Patients who relapse after autologous stem cell transplantation.
3. Patients who are candidates for the autologous or conventional allogeneic stem cell transplantation from a disease standpoint but who do not qualify functionally (from the point of view of organ function, advanced age-related donor transplant >60 and unrelated donor transplant >50, or performance status) for a myeloablative protocol.
4. Identification of a matched related or unrelated stem cell donor.
5. Any patient where, in the opinion of the primary treating oncologist, nonmyeloablative therapy would be the treatment option in the patient’s best interest providing the patient fits all other eligibility criteria for this protocol.

One of the following diseases:

**AML**
- first complete remission (at high risk of relapse)
- second complete remission
- minimal residual disease (<10% blasts)

**ALL**
- first complete remission (at high risk of relapse)
- second complete remission
- minimal residual disease (<10% blasts)

**CML**
- first chronic phase
- accelerated phase (<10% blasts)
- blast phase with minimal residual disease (<10% blasts)
- second chronic phase

**CLL**
- recurrence after the front line regimen (related donor transplant)
- chemorefractory disease (unrelated donor transplant)
- T-CLL in partial remission or any minimal residual disease
Patient Eligibility (continued):
One of the following diseases (continued):

Myelodysplastic Syndromes
- refractory anemia with or without ringed sideroblasts
- RAEB, RAEB, and CMML (<10% blasts in blood and marrow)

Small Lympho(plasma)cytic Lymphoma (B-SLL, B-LPL)
- recurrence after a front line regimen (related donor transplant)
- chemorefractory disease (related or unrelated donor transplant)

Follicular Low-Grade Lymphoma, Marginal Zone Lymphomas (splenic, nodal, or extranodal/MALT type)
- chemorefractory disease or >2 prior regimens

Mantle Cell Lymphoma
- first complete or partial remission
- refractory disease
- failed prior ASCT

Diffuse Large B-Cell Lymphoma, Follicular Large cell Lymphoma, Peripheral T-cell Lymphoma, Anaplastic Large Cell Lymphoma
- refractory disease
- failed prior ASCT

Burkitt or Acute Lymphoblastic Lymphoma
- high risk disease in remission
- chemosensitive persistent or recurrent disease

Cutaneous T-Cell Lymphomas: (Mycosis Fungoides, Sezary Syndrome)
- chemorefractory disease of >2 prior regimens

Hodgkin’s Disease
- refractory
- persistent disease and not candidate for ASCT
- failed prior ASCT

Multiple Myeloma
- after receiving at least one regimen of prior chemotherapy

Exclusion Criteria:
1. Progressive disease within 8 weeks of prior therapy or within 12 weeks after prior autologous stem cell transplantation.
2. Active CNS malignancy (patients with known positive CSF cytology or parenchymal lesions visible by CT or MRI).
3. Active uncontrolled infection, immediate life-threatening condition, or uncontrolled medical illness at the time of enrollment.

Study period:
Pentostatin 4 mg/m2/day IV QD x 3 days will be administered with 1000cc NS hydration 10 days prior to stem cell infusion (days -10, -9, -8). Total Body Irradiation will be given on day -1. This will be followed by infusion of donor stem cells on day 0. Patients with related donors will receive standard GVHD prophylaxis (unrelated donor recipients will have an extended GVHD prophylaxis).

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
## T-CELL LYMPHOMA – Standard Therapy

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age Adjusted IPI Score *</th>
<th>Tumor Bulk</th>
<th>Stage</th>
<th>Age</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO Classification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaplastic T-cell</td>
<td>0 – 1</td>
<td>non-bulky</td>
<td>I – II</td>
<td>&lt;60</td>
<td>CHOP x (3-4) + 40 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>III - IV</td>
<td></td>
<td>≥60</td>
<td>CHOP or CNOP (if low ejection fraction) x (3-4) + 40 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>bulky ≥ 5 cm</td>
<td></td>
<td>&lt;60</td>
<td>CHOP x (6-8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥60</td>
<td>CHOP or CNOP (if low ejection fraction) x (6-8)</td>
</tr>
<tr>
<td></td>
<td>≥ 2</td>
<td>non-bulky</td>
<td>Any</td>
<td>&lt;60</td>
<td>CHOP x 6 good PR or CR → ABMT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any</td>
<td></td>
<td>≥60</td>
<td>CHOP x or CNOP (if low ejection fraction) x 6 good PR or CR → ABMT (if transplant candidate)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>bulky ≥ 5 cm</td>
<td>Any</td>
<td>&lt;60</td>
<td>CHOP x 6 + 40 Gy good PR or CR → ABMT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥60</td>
<td>CHOP or CNOP (if low ejection fraction) x 6 + 40 Gy good PR or CR → ABMT (if transplant candidate)</td>
</tr>
<tr>
<td>Peripheral T-cell</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
<td>&lt;60</td>
<td>CHOP x 6 good PR or CR → ABMT</td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell</td>
<td></td>
<td></td>
<td></td>
<td>≥60</td>
<td>CHOP or CNOP x 6 good PR or CR → ABMT (if transplant candidate)</td>
</tr>
</tbody>
</table>

* Age Adjusted IPI Score

- Stage III, IV
- LDH > upper limits of normal
- Karnofsky score ≤ 70
Systemic Therapy for T-cell Lymphoma Using Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone

CHOP

Effective: January 1, 2000

I. ELIGIBILITY
Any biopsy proven non-Hodgkin’s lymphoma with the following WHO classification subtypes: Peripheral T-cell, Angioimmunoblastic T-cell, and Anaplastic T-cell. (See T-cell Lymphoma - Standard Therapy Schema.)

II. STANDARD STAGING EVALUATION
Modify as needed to document all initial disease sites adequately for follow-up evaluation.
A. History and physical examination.
B. Chest x-ray.
C. Laboratory:
   CBC, differential, platelet count, Serum LDH, AST (SGOT), alkaline phosphatase, bilirubin, creatinine, uric acid, calcium, beta-2-microglobulin (if available).
D. Bone marrow aspiration and biopsy.
E. Evaluation of intra-abdominal and retroperitoneal disease. This usually includes abdominal and pelvic CT and/or possible abdominal ultrasound.
F. Thoracic CT, if necessary, to document the extent of chest or mediastinal disease.
G. Whenever possible, PET scan should be done as part of the initial evaluation.
H. Additional scans and biopsy as needed to unequivocally document the extent of disease especially sites of extra-nodal involvement.
I. MUGA scan or ECHO cardiogram to document ejection fraction, if appropriate.
J. CSF Fluid Examination for lymphomatous involvement will be done if the lymphoma involves the sinuses, orbit, testes, or paraspinous areas. A dose of 12 mg of IT Methotrexate will be administered at this time.
III. TREATMENT AND DOSE ALTERATIONS
It is very important that treatment be given on time finishing in the planned number of cycles. All drugs should be given in FULL doses on time unless SPECIFIC toxicity requires dose reduction.

A. SCHEDULE AND DOSES

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>ROUTE</th>
<th>DAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>750 mg/M²</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>50 mg/M²</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.4 mg/M²/day (max. 2.0 mg)</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>Prednisone</td>
<td>100 mg (total dose)</td>
<td>PO</td>
<td>1 – 5</td>
</tr>
</tbody>
</table>

Repeat sequence at 21 days unless counts are not acceptable, then repeat at 28 day intervals.

CENTRAL NERVOUS SYSTEM THERAPY FOR PATIENTS WITH POSITIVE CSF CYTOLOGY
Patients with positive CSF cytology at diagnosis will receive intrathecal Methotrexate at a dose of 12 mg plus Ara-C at a dose of 50 mg two times a week until the CSF is clear and then once a week for 2 doses, and continue with one dose at the start of each remaining CHOP cycle. The CHOP therapy will be followed with 2400 cGy of cranial/spinal radiotherapy to be initiated after recovery of counts from the last cycle of CHOP.

PROPHYLACTIC THERAPY FOR PATIENTS WITH LYMPHOMA INVOLVING THE SINUSES, ORBIT, TESTES, OR PARASPINOUS AREAS
Patients with aggressive NHL with sites of involvement mentioned above will receive prophylactic CSF treatment starting with cycle 1 of CHOP. They should receive intrathecal Methotrexate at a dose of 12 mg with each cycle of CHOP.

GROWTH FACTORS
Hematopoietic growth factors may be used at physician’s discretion.

PROPHYLACTIC ANTIBIOTICS
Sulfamethoxazole/trimethoprin (Bactrim DS or Septra DS) at a dose of one tablet twice a day on two days every week.
B. TOXICITY
1. **Hematologic Toxicity**: If absolute granulocyte count is <1500/cmm or platelet count is <100,000/cmm on day 22 then delay one week; if still low one week later, proceed with the doses outlined below (no other drug doses are reduced regardless of blood counts):

   **DOSE ATTENUATION SCHEDULE FOR COUNTS**

<table>
<thead>
<tr>
<th>Absolute granulocyte count</th>
<th>Platelet Count</th>
<th>Percent dose of Cyclophosphamide and Doxorubicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000 – 1499</td>
<td>75,000 – 100,000</td>
<td>50%</td>
</tr>
<tr>
<td>&lt;1000</td>
<td>&lt;75,000</td>
<td>0%</td>
</tr>
</tbody>
</table>

   Vincristine and Prednisone are not reduced regardless of blood counts.

   **DOSE ATTENUATION SCHEDULE FOR AGE**

   NO adjustment will be made for age.

2. **Neurotoxicity**: If muscle weakness sufficient to interfere with normal self care or debilitating ileus occurs, reduce or eliminate vincristine doses as needed to prevent worsening. The vincristine dose should not be reduced solely because of dysesthesia and parasthesias.

3. **Hyperglycemia**: Prednisone induced hyperglycemia should be managed with oral hypoglycemics, or dietary alteration, and if necessary daily subcutaneous insulin as needed to keep patients from having polyruia or sustained blood glucose above 300 mg/dl.
I. ELIGIBILITY
Any biopsy proven non-Hodgkin’s lymphoma with the following WHO classification subtypes:
Peripheral T-cell, Angioimmunoblastic T-cell, and Anaplastic T-cell. (See T-cell - Standard Therapy Schema.)

II. STANDARD STAGING EVALUATION
Modify as needed to document all initial disease sites adequately for follow-up evaluation.
A. History and physical examination.
B. Chest x-ray.
C. Laboratory:
   CBC, differential, platelet count, Serum LDH, AST (SGOT), alkaline phosphatase, bilirubin,
   creatinine, uric acid, calcium, beta-2-microglobulin (if available).
D. Bone marrow aspiration and biopsy.
E. Evaluation of intra-abdominal and retroperitoneal disease. This usually includes abdominal and pelvic CT and/or possible abdominal ultrasound.
F. Thoracic CT, if necessary, to document the extent of chest or mediastinal disease.
G. Whenever possible, PET scan should be done as part of the initial evaluation.
H. Additional scans and biopsy as needed to unequivocally document the extent of disease especially sites of extra-nodal involvement.
III. TREATMENT AND DOSE ALTERATIONS
It is very important that treatment be given on time finishing in the planned number of cycles. All drugs should be given in FULL doses on time unless SPECIFIC toxicity requires dose reduction.

A. SCHEDULE AND DOSES

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>ROUTE</th>
<th>DAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>750 mg/M(^2)</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>12 mg/M(^2)</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.4 mg/M(^2)/day</td>
<td>IV (max. 2.0 mg)</td>
<td>1</td>
</tr>
<tr>
<td>Prednisone</td>
<td>100 mg (total dose)</td>
<td>PO</td>
<td>1 – 5</td>
</tr>
</tbody>
</table>

Repeat sequence at 21 days unless counts are not acceptable, then repeat at 28 day intervals.

CENTRAL NERVOUS SYSTEM THERAPY FOR PATIENTS WITH POSITIVE CSF CYTOLOGY
Patients with positive CSF cytology at diagnosis will receive intrathecal Methotrexate at a dose of 12 mg plus Ara-C at a dose of 50 mg two times a week until the CSF is clear and then once a week for 2 doses, and continue with one dose at the start of each remaining CNOP cycle. The CNOP therapy will be followed with 2400 cGy of cranial/spinal radiotherapy to be initiated after recovery of counts from the last cycle of CNOP.

PROPHYLACTIC THERAPY FOR PATIENTS WITH LYMPHOMA INVOLVING THE SINUSES, ORBIT, TESTES, OR PARASPINOUS AREAS
Patients with aggressive NHL with sites of involvement mentioned above will receive prophylactic CSF treatment starting with cycle 1 of CNOP. They should receive intrathecal Methotrexate at a dose of 12 mg with each cycle of CNOP.

GROWTH FACTORS
Hematopoietic growth factors may be used at physician’s discretion.

PROPHYLACTIC ANTIBIOTICS
Sulfamethoxazole/trimethoprin (Bactrim DS or Septra DS) at a dose of one tablet twice a day on two days every week.
B. **TOXICITY**

1. **Hematologic Toxicity:** If absolute granulocyte count is <1500/cmm or platelet count is <100,000/cmm on day 22 then delay one week; if still low one week later, proceed with the doses outlined below (no other drug doses are reduced regardless of blood counts):

   **DOSE ATTENUATION SCHEDULE FOR COUNTS**

<table>
<thead>
<tr>
<th>Absolute granulocyte count</th>
<th>Platelet Count</th>
<th>Percent dose of Cyclophosphamide and Mitoxantrone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000 – 1499</td>
<td>75,000 – 100,000</td>
<td>50%</td>
</tr>
<tr>
<td>&lt;1000</td>
<td>&lt;75,000</td>
<td>0%</td>
</tr>
</tbody>
</table>

   Vincristine and Prednisone are not reduced regardless of blood counts.

   **DOSE ATTENUATION SCHEDULE FOR AGE**

   NO adjustment will be made for age.

2. **Neurotoxicity:** If muscle weakness sufficient to interfere with normal self care or debilitating ileus occurs, reduce or eliminate vincristine doses as needed to prevent worsening. The vincristine dose should not be reduced solely because of dysesthesia and parasthesias.

3. **Hyperglycemia:** Prednisone induced hyperglycemia should be managed with oral hypoglycemics, or dietary alteration, and if necessary daily subcutaneous insulin as needed to keep patients from having polyruia or sustained blood glucose above 300 mg/dl.
Involved field radiation therapy will be recommended following completion of chemotherapy to those groups so indicated in the T-cell Lymphoma - Standard Therapy Schema.

**Radiation Fields**

Radiotherapy will include the prechemotherapy target volume plus a 2 cm margin around the planning volume. No attempt will be made to cover contiguous nodal sites prophylactically. In the case of pre-chemotherapy, bulky sites (ex-mediastinal adenopathy), the target volume may be modified to include the post chemotherapy target volume, in order to decrease the risk of toxicity (ex: interstitial pneumonitis).

CT – based treatment planning dosimetry is recommended. Dose uniformity of +/- 5% is the goal. Tissue compensators, wedged field within a field boost, 3-D conformal (including IMRT) techniques are encouraged to achieve the uniformity goal.

**Radiation Doses**

A dose of 40 Gy (39.6 Gy – 40.5 Gy) delivered over 20 – 27 fractions. The dose fraction size will be adjusted to patient tolerance.

Weekly CBC with differential is recommended during radiation therapy.
Hodgkin’s Lymphoma

- Clinical Trials

Previously Untreated

IRB NO: 287-01  A Randomed Phase III Trial of ABVD versus Stanford V ± Radiation Therapy in Locally Extensive and Advanced Stage Hodgkin’s Disease with 0-2 Risk Factors (CALGB 59905)

IRB NO: 359-04  Phase II Trial of Doxorubicin, Vinblastine and Gemcitabine (AVG) Chemotherapy for Non-Bulky Stage I and II Hodgkin’s Lymphoma (CALGB 50203)

Previously Treated – Non-Transplant

IRB NO: 437-03  A Phase II Multi-Dose Study of SGN-30 (anti-CD30 Mab) in Patients with Refractory or Recurrent Hodgkin’s Disease or Anaplastic Large Cell Lymphoma

IRB NO: 338-04  A Phase II Study of PS-341 (Bortezomib) in Patients with Relapsed or Refractory Hodgkin’s Lymphoma (CALGB 50206)

Previously Treated – Transplant

IRB NO: 389-00  Allogeneic Peripheral Blood Stem Cell Transplantation with a Minimally Myelosuppressive Regimen of Pentostatin and Low-Dose Total-Body Irradiation

- Standard Therapy

Treatment Schema for Hodgkin’s Lymphoma

Stanford V (for patients <60)
CHLVPP/ABV (for patients ≥60)
ABVD

- Radiotherapy
Hodgkin’s Lymphoma

Referral Pager: (402) 888-5615

<table>
<thead>
<tr>
<th>Previously Untreated</th>
<th>Salvage Therapy</th>
<th>Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRB NO: 359-04 Phase II Trial of Doxorubicin, Vinblastine and Gemcitabine (AVG) Chemotherapy for Non-Bulky Stage I and II Hodgkin Lymphoma (CALGB 50203)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Phase III Trial ABVD vs. Stanford V ± Radiotherapy

Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

IRB NO: 287-01

Title: A Randomized Phase III Trial of ABVD Versus Stanford V ± Radiation Therapy in Locally Extensive and Advanced Stage Hodgkin's Disease (CALGB 59905)

Principal Investigator: Philip Bierman, M.D.

Clinical Coordinator/Data Manager: Susan Allen, R.N.

Telephone: (402) 559-8155

Pager: (402) 888-2537

Purpose:
To compare the failure-free survival in patients with locally extensive and advanced stage Hodgkin's disease (HD) treated with standard ABVD chemotherapy versus patients given Stanford V chemotherapy ± radiotherapy.

Patient Eligibility:
1. Histologically proven Hodgkin's disease (HD). The diagnosis should be made by excisional biopsy whenever possible. If a major surgery is required (thoracotomy or laparotomy) a fine needle aspirate or biopsy may suffice if 1) the morphology is unequivocal and 2) immunohistochemical studies are consistent with the diagnosis of HD.
2. Previously untreated Hodgkin's disease with no more than two adverse risk factors and locally extensive or advanced stage disease.
3. Locally extensive clinical stage I-IIA/B and massive mediastinal adenopathy (mass ≤a maximum intrathoracic diameter on standing posterior-anterior chest x-ray) or advanced clinical stage III-IV.
4. All eligible subjects age 19 or older may participate.
5. ECOG performance status 0-2.
6. Required Laboratory Data: WBC ≥4000/mm³; Platelet count ≥100,000/mm³; Creatinine ≤2.0 mg/dl, Bilirubin ≤5.0 mg/dl.
7. Patients with documented marrow involvement at the time of registration are not required to meet the hematologic parameters above.

Exclusion Criteria:
1. Women must not be pregnant or breast-feeding.
2. Women of child bearing potential and sexually active males are strongly advised to use an accepted and effective method of birth control.
3. Not known to be HIV positive.
4. Patients must be disease free of prior prior invasive malignancies for ≥5 years with the exception of curatively-treated basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix.
5. No prior chemotherapy. No prior radiotherapy. Prior treatment with corticosteroids is acceptable.
6. Determination of ejection fraction would be desirable in patients over age 50 and those who have a history of cardiac disease.
Phase III Trial ABVD vs. Stanford V ± Radiotherapy

**Treatment Plan:** Registered patients will be randomized to one of two arms: ABVD vs. Stanford V.

**Arm A:** Patients randomized to Arm A will receive ABVD-doxorubicin, bleomycin, vinblastine, and dacarbazine on the first day of treatment and again on the 15th day of treatment. The patient will then have 2 weeks off with each cycle repeated every 4 weeks. Radiation therapy will be given 2 weeks after the end of ABVD to patients with very large masses in the chest if the disease was limited to sites above the diaphragm. The duration of radiation therapy is about 4 weeks for a total dose of 36 cGy.

**Arm B:** Patients randomized to Arm B will receive Stanford V - doxorubicin, vinblastine, nitrogen mustard, etoposide, vincristine, bleomycin and prednisone once or twice a week for a total of 12 weeks. The schedule is as follows:

1) Doxorubicin = by vein once weekly on weeks 1, 3, 5, 7, 9, 11
2) Vinblastine = by vein once weekly on weeks 1, 3, 5, 7, 9, 11
3) Nitrogen Mustard = by vein once weekly on weeks 1, 5, 9
4) Etoposide = by vein twice weekly on weeks 3, 7, 11
5) Vincristine = by vein once weekly on weeks 2, 4, 6, 8, 10, 12
6) Bleomycin = by vein once weekly on weeks 2, 4, 6, 8, 10, 12
7) Prednisone = by mouth every other day for 12 weeks

Radiation therapy will be given two weeks after the completion of chemotherapy to all areas of the body with lymph nodes initially $\geq 5$ cm, that being the largest one. Radiation therapy will also be delivered to the spleen if it is abnormal by CT scan of the abdomen. Radiation therapy will be given Monday through Friday for about four weeks for a total dose of 36 cGy to be delivered.

The patient will continue to take the chemotherapy until it is decided the treatment is no longer working or until the patient decides he/she no longer wants to participate. Follow-up studies and disease assessment should be continued every 2 months for the first year, every 3 months for the second year, every 4 months for the third year, every 6 months for years four and five, and yearly thereafter. The follow up will include history and physical exam, tumor measurements, tobacco use evaluation, reproductive health assessment, pulmonary function tests, CBC with differential and platelet count, CT scans and x-rays.

**NOTE:** This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

IRB NO: 359-04

Title: Phase II Trial of Doxorubicin, Vinblastine and Gemcitabine (AVG) Chemotherapy for Non-Bulky Stage I and II Hodgkin’s Lymphoma (CALGB 50203)

Principal Investigator: Philip Bierman, M.D.

Clinical Coordinator/Data Manager: Maribeth Hohenstein, R.N.
Telephone: (402) 559-9053
Pager: (402) 888-2717

Purpose:
1. To evaluate the complete response rate (CR or Cru) of doxorubicin, Vinblastine, and gemcitabine (AVG) in the treatment of non-bulky stage I and II Hodgkin’s lymphoma (HL).
   • To evaluate the event-free survival in this patient group.
   • To evaluate the toxicity of AVG in this patient group.
   • To describe the role of PET scanning in determining the presence of residual disease, and predicting clinical relapse following AVG chemotherapy in the patient group.

Patient Eligibility:
1. Histologically documented HL sub-classified according to the WHO modification of the Rye Classification and staged according to the modified Ann Arbor Staging Classification system. Patients must have clinical stage IA, IB, IIA, or IIB. Patients with E extensions will be eligible if all other criteria have been met. Nodular lymphocyte predominant HL is excluded.
2. Core biopsies are acceptable if they contain adequate tissue for primary diagnosis and immunophenotyping. Fine needle aspirate cytologies and bone marrow biopsies as the sole means of diagnosis are not acceptable.
3. Patients may not have a mediastinal mass > 0.33 maximum intrathoracic diameter on standing postero-anterior chest x-ray or peripheral or retroperitoneal adenopathy > 10 cm in its largest diameter.
4. Bone marrow biopsy is required for pretreatment evaluation. Bilateral biopsies are preferred but not required.
5. No prior treatment (chemotherapy or radiation therapy) for Hodgkin’s lymphoma.
6. Measurable disease must be present either on physical examination or imaging studies. All tumor mass measurable in two dimensions and >2cm is acceptable. Lesions that are considered intrinsically non-measurable include the following:
   • bone lesions;
   • leptomeningeal disease;
   • ascites;
   • pleural/pericardial effusion;
   • inflammatory breast disease;
   • lymphangitis cutis/pulmonis;
   • abdominal masses that are not confirmed and followed by imaging techniques;
   • cystic lesions;
   • lesions that are situated in a previously irradiated area.
Patient Eligibility (continued):
7. Age ≥ 19 years.
9. LVEF by CHEO or MUGA within institutional normal limits.
10. DLCO ≥ 60% with no symptomatic pulmonary disease.
11. No known HIV infection.
12. Non-pregnant and nonlactating.
13. Patients must give written informed consent.
14. Required baseline laboratory data:
   - ANC ≥ 1000
   - Platelet count ≥ 100,000
   - Serum bilirubin ≤ 2.0
   - Serum creatinine ≤ 2.0
   - AST ≤ 2 x ULN

Treatment Plan:
Patients with newly diagnosed stage IA, IB, IIA, IIB Hodgkin’s lymphoma, previously untreated, will be eligible to participate in this trial. Patients will receive 2 cycles of Doxorubicin, Vinblastine and Gemcitabine (AVG) chemotherapy. PET scans will be used in addition to conventional tumor assessments prior to treatment, after two cycles and at the completion of chemotherapy. Patients with persistent positive PET results following 6 cycles of AVG will be followed, and repeat PET and CT scans will be performed 3 months later. Patients with a positive PET at 3 months post treatment will have a biopsy performed.

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

IRB NO: 437-03

Title: A Phase II Multi-Dose Study of SGN-30 (anti-CD30 Mab) in Patients with Refractory or Recurrent Hodgkin’s Disease or Anaplastic Large Cell Lymphoma

Principal Investigator: R. Gregory Bociek, M.D.

Clinical Coordinator/Data Manager: Maribeth Hohenstein, R.N.  
Telephone: (402) 559-9053  
Pager: (402) 888-2717

Purpose:
1. To determine the objective response rate of SGN-30 in two study groups, patients with HD and patients with ALCL.
2. To determine the duration of response in patients with Hodgkin’s disease and in patients with ALCL.
3. To investigate the toxicity profile of SGN-30 at a dose of 6 mg/kg.

Patient Eligibility:
All patients will be screened prior to entry into this study. Only those patients who meet all patient selection criteria will be entered into this study.

1. Patients must have refractory or recurrent HD or refractory or recurrent ALCL.
2. Patients must have histologically confirmed CD30+ HD or ALCL. Immunohistochemistry or flow cytometry may be performed on either original diagnostic biopsy material or biopsy tissue of relapsed disease.
3. Patients must have bi-dimensional measurable disease on physical examination or radiologic evaluation.
4. Patients must have failed systemic chemotherapy either as initial therapy for advanced disease or as salvage therapy after initial radiotherapy for early stage disease.
5. Patients may have received no more than four treatments (radiation, chemotherapy, and/or biologics) prior to enrollment.
6. Patients may have received no more than one stem cell transplantation.
7. Patients who have undergone stem cell transplantation must have received at least one therapy post-transplantation. Patients who have not had stem cell transplantation must be considered ineligible or refuse treatment by stem cell transplantation. Treatments associated with bone marrow transplant, such as mobilization and conditioning, will be considered as one regimen.
8. Minimum of 4 weeks from last therapy (including radiotherapy or chemotherapy); a minimum of 6 weeks from last treatment with nitrogen mustard agents, melphalan or BCNU.
9. ECOG performance status #2 (Appendix B) with a life expectancy ≥3 months.
10. Age must be at least 19 years.

11. Required baseline laboratory data:
   • Absolute neutrophil count ≥1,250/µL
   • Platelet count ≥75,000/µL
   • Serum bilirubin level #1.5 x ULN
   • Serum creatinine #1.5 x ULN and BUN #1.5 x ULN
   • BUN #1.5 times ULN
Patient Eligibility (continued):
12. Patients must be available for periodic blood sampling, study related assessments and management of toxicity at the treating institution.
13. For females of child bearing age a negative a HCG within 3 days prior of enrollment. All patients must agree to use an effective contraceptive method during the course of study.
14. Patients must provide informed consent.

Exclusion Criteria:
Any of the following criteria will disqualify the patient from participation in this study:
1. A diagnosis of primary cutaneous ALCL.
2. Patients who have been treated previously with any anti-CD30 antibody.
3. Receipt of any therapeutic mAbs, unless a recent serum testing reveals no antibody titer and no evidence of anti-chimeric or anti-murine antibody in the peripheral circulation.
4. Patients receiving any investigational biological agent within eight weeks of enrollment or any other investigational agent within four weeks of enrollment.
5. Patients with known hypersensitivity to recombinant proteins or any excipient contained in the drug formulation.
6. Patients with a history of other malignancies during the past five years with the exception of adequately treated basal or squamous cell skin cancer or cervical carcinoma in situ.
7. Active viral, bacterial, or systemic fungal infection; patients who are know to be HIV, Hepatitis B, or Hepatitis C positive.
8. Symptomatic cardiac disease including ventricular dysfunction, coronary artery disease or arrhythmias.
10. Female patients who are pregnant or breastfeeding.
11. Any serious underlying medical condition which would impair the ability of the patient to receive or tolerate the planned treatment.
12. Dementia or altered mental status that would prohibit the understanding and rendering of informed consent.

Treatment Plan:
SGN-30 6mg/kg will be given by weekly two-hour IV infusion on Days 1, 8, 15, 22, 29, and 36. A missed dose may be administered on Day 43. All supportive measures consistent with optimal patient care will be provided throughout the study according to institution standards. Routine follow-up every 12 weeks will continue for patients in response until disease progression.

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
A Phase II Study of PS-341 (Bortezomib) in Patients with Relapsed or Refractory Hodgkin’s Lymphoma (CALGB 50206)

Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

IRB NO: 338-04

Title: A Phase II Study of PS-341 (Bortezomib) in Patients with Relapsed or Refractory Hodgkin’s Lymphoma (CALGB 50206)

Principal Investigator: Philip Bierman, M.D.

Clinical Coordinator/Data Manager: Susan Allen, R.N.  
Telephone: (402) 559-8155  
Pager: (402) 888-2537

Patient Eligibility:
1. Histologically documented classical Hodgkin’s lymphoma that is recurrent or refractory to standard chemo.
2. Patients must have relapsed or progressed after at least one prior therapy.
3. Patients must have recovered from previous treatments or returned to their baseline in the judgment of the enrolling physician.
4. Patients with relapsed or refractory disease following stem cell transplantation are permitted.
   - Age ≥ 19 years.
   - Performance status 0-2.
   - Measurable disease greater than 1 cm.

Laboratory Values:
- ANC ≥ 750/μL
- Platelet count ≥ 75,000 μL
- Serum Creatinine #2.5mg/dL
- Bilirubin #1.5 x upper limits of normal
- AST #2.5 x upper limits of normal

Exclusion Criteria:
1. Patients with nodular lymphocyte-predominant Hodgkin’s lymphoma.
2. Patients who have a curative option with high-dose therapy and stem cell transplantation.
3. Patients with sensory or motor peripheral neuropathy ≥ grade 2.
4. Prior treatment with PS-341 or other proteasome inhibitors.
5. Patients who are pregnant or nursing.

Treatment Plan:
For all cycles, bortezomib will be administered as an IV bolus injection of 1.3 mg/m² over 3 – 5 seconds on Days 1, 4, 8, and 11 of a 21 day cycle. Patients will receive a minimum of 2 cycles of therapy.

Response will be assessed Q 2 cycles. Patients who have stable disease or continued response may continue treatment with bortezomib for a maximum of eight cycles or until evidence of progression or unacceptable toxicity.

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

**IRB NO: 389-00**

**Title:** Allogeneic Peripheral Blood Stem Cell Transplantation with a Minimally Myelosuppressive Regimen of Pentostatin and Low-Dose Total-Body Irradiation

**Principal Investigator:** R. Gregory Bociek, M.D.

**Planned Accrual Total:** Anticipated accrual will be 40 patients

**Clinical Coordinator/Data Manager:** Beth Schreiner, R.N., M.S.N.  
**Telephone:** (402) 559-6729  
**Pager:** (402) 888-3610

**Purpose:**

To assess the safety and efficacy of a minimally myelosuppressive regimen with pentostatin and low-dose total body irradiation (TBI) followed by allogeneic peripheral blood stem cell transplantation (allo PSCT). Secondary objective is to assess GM-CSF (cytokine therapy) toxicity and potential therapeutic efficacy. Patients with persistent or progressive disease who fail or do not qualify for the cytokine therapy portion of the study will become candidates for donor leukocyte infusions.

**Patient Eligibility:**

1. Age 19-75 years.
2. Patients who relapse after autologous stem cell transplant.
3. Patients who are candidates for autologous or conventional allogeneic stem cell transplant, but who do not qualify functionally (from the point of view of organ function or performance status) for a myeloablative protocol.
4. Any patient, where in the opinion of the primary treating oncologist, non-myeloablative therapy would be the treatment option in the best patients interest providing the patient fits all other eligibility.
5. Available related or unrelated allogeneic stem cell donor matched at HLA-A, B and DR loci (6 antigen match). One antigen mismatch related or unrelated donor will also be acceptable, molecular typing needs to be used at each HLA-A, B, or DR loci in case of mismatched unrelated donor.
6. Diseases:
   A. Acute myelogenous leukemia or acute lymphocytic leukemia
      first complete remission at high risk of relapse
      >=second complete remission
      minimal residual disease (<10% blasts*)
   B. Chronic myelogenous leukemia
      first chronic phase
      accelerated phase (<10% blasts*)
      blast phase with minimal residual disease (<10% blasts*)
      second chronic phase
Patient Eligibility (continued):
C. Chronic lymphocytic leukemia
   recurrence after the front line regimen (related donor transplant)
   chemorefractory disease (unrelated donor transplant)
   T-CLL in partial remission or any minimal residual disease
D. Myelodysplastic syndromes refractory anemia with or without ringed sideroblasts RAEB, RAEB-T, and CMML (<10% blasts [*both in PB and BM])
E. Multiple myeloma - after receiving at least one regimen of prior chemotherapy
F. Non-Hodgkin’s Lymphomas:
   1. Small Lymphoplasmacytic Lymphoma (B-SLL, B-LPL): recurrence after a front line regimen (related donor transplant), chemorefractory disease (related or unrelated donor transplant)
   2. Follicular Low-Grade Lymphoma, Marginal Zone Lymphomas (splenic, nodal, or extranodal/MALT type): chemorefractory disease or >2 prior regimens
   3. Mantle Cell Lymphoma: first complete or partial remission, refractory disease, failed prior ASCT
   4. Diffuse Large B-cell Lymphoma, Follicular Large cell Lymphoma, Peripheral T-cell Lymphoma, Anaplastic Large Cell Lymphoma: refractory disease, failed prior ASCT
   5. Burkitt or Acute Lymphoblastic Lymphomas: high-risk disease in remission, chemosensitive persistent or recurrent disease
   6. Cutaneous T-cell lymphomas: (Mycosis Fungoides, Sezary Syndrome): chemorefractory disease or >2 prior regimens
G. Hodgkin’s Disease: refractory or persistent disease and not candidate for ASCT, failed prior ASCT
H. Agnogenic myeloid metaplasia with myelofibrosis: hemoglobin 4,000 or >30,000 circulating blood or marrow blasts or clonal abnormality

Exclusion Criteria:
1. Progressive disease within 8 weeks of prior therapy or within 12 weeks after prior autologous stem cell transplantation.
2. Active CNS malignancy or Patients who are HIV seropositive.
3. Active, uncontrolled infection or immediate life-threatening condition at the time of enrollment or significant organ dysfunction.

Study period:
Pentostatin 4 mg/m2/d IV QD x 3 days will be administered with 1000 cc NS hydration before and after pentostatin three weeks prior to stem cell infusion (days -21, -20, and -19). Total Body Irradiation will be given on Day -1. This will be followed by infusion of donor stem cells on Day 0. Patients will receive standard GVHD prophylaxis.

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age</th>
<th>Stage</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Subtype</td>
<td></td>
<td>I – IIA</td>
<td>Stanford V x 8 weeks and Radiotherapy (30 Gy to involved field if &lt;5 cm; 35 Gy to involved field if ≥5 cm) or ABVD (x 16 wks/4 cycles), followed by Radiotherapy, if maintenance of fertility is an overriding factor</td>
</tr>
<tr>
<td>&lt;60</td>
<td></td>
<td>IIB, III, IV</td>
<td>Stanford V x 12 weeks and Radiotherapy (35 Gy to any residual site, if initial site was ≥5 cm) if PET positive → biopsy; if positive → ABMT or ABVD (x 6 months) if maintenance of fertility is an overriding factor</td>
</tr>
<tr>
<td>≥60</td>
<td></td>
<td>I – IIA</td>
<td>ABVD x 4 and Radiotherapy (30 Gy to involved field if &lt;5 cm; 35 Gy to involved field if ≥5 cm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IIB, III, IV</td>
<td>ABVD or ChlVPP/ABV x 6</td>
</tr>
</tbody>
</table>
I. ELIGIBILITY
A. Required:
   1. Biopsy proven Hodgkin’s Lymphoma (any subtype)
   2. Age <60 years old.

II. STANDARD STAGING EVALUATION
Modify as needed to document all initial disease sites adequately for follow-up evaluation:
A. History and physical examination.
B. Chest x-ray.
C. Laboratory:
   CBC, differential, platelet count, Serum LDH, AST (SGOT), alkaline phosphatase, bilirubin,
   creatinine, uric acid calcium.
D. Bone marrow aspiration and biopsy.
E. Evaluation of intra-abdominal and retroperitoneal disease. This usually includes abdominal and
   pelvic CT and/or possibly abdominal ultrasound.
F. Thoracic CT, if necessary, to document the extent of chest or mediastinal disease.
G. Whenever possible, PET should be done as part of the initial evaluation.
H. Additional scans and biopsy as needed to unequivocally document the extent of the disease
   especially sites of extra-nodal involvement.
III. TREATMENT AND DOSE ALTERATIONS

It is very important that treatment be given on time finishing in the planned number of cycles. All drugs should be given in FULL doses on time unless SPECIFIC toxicity requires dose reduction.

A. SCHEDULE AND DOSES

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>ROUTE</th>
<th>SCHEDULE *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>25 mg/m²</td>
<td>IV</td>
<td>Days 1 and 15</td>
</tr>
<tr>
<td>Vinblastine†</td>
<td>6 mg/m²</td>
<td>IV</td>
<td>Days 1 and 15</td>
</tr>
<tr>
<td>Mechlorethamine</td>
<td>6 mg/m²</td>
<td>IV</td>
<td>Day 1</td>
</tr>
<tr>
<td>Vincristine†</td>
<td>1.4 mg/m²</td>
<td>IV §</td>
<td>Days 8 and 22</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>5 U/m²</td>
<td>IV</td>
<td>Days 8 and 22</td>
</tr>
<tr>
<td>Etoposide</td>
<td>60 mg/m²</td>
<td>IV</td>
<td>Days 15 and 16</td>
</tr>
<tr>
<td>Prednisone ‡</td>
<td>40 mg/m²</td>
<td>PO</td>
<td>QOD</td>
</tr>
</tbody>
</table>

Abbreviations: IV, intravenous; PO, oral; QOD, every other day.

* Treatment cycle repeated every 28 days, for total of 3 cycles.
† Vinblastine dose decreased to 4 mg/m² and vincristine dose to 1 mg/m² during cycle 3 for patients ≥ 50 years of age.
‡ Tapered by 10 mg QOD starting at week 10.
§ Maximum dose, 2.0 mg.

Follow with radiotherapy to bulk disease.

Prophylactic antimicrobial, antifungal and antibiotic dose and schedule:

- Acyclovir (#252) 200 mg, 1 tab, PO TID
- Fluconazole (#84) 200 mg, 1 tab, PO qd until gone
- Bactrim, DS (#48) 1 tab, PO BID (Saturday and Sunday)
B. **TOXICITY**

1. **Hematologic:** Doses of doxorubicin, vinblastine, mechlorethamine, and etoposide are decreased by 35% for an absolute neutrophil count less than 1,000/μL when at Day 1 of a cycle. Delay therapy for 1 week for an absolute neutrophil count less than 500/μL.

   **DOSE ATTENUATION SCHEDULE FOR COUNTS**

<table>
<thead>
<tr>
<th>Absolute granulocyte count</th>
<th>Percent dose of Myelosuppressive Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1,000/μL</td>
<td>35%</td>
</tr>
<tr>
<td>&lt;500/μL</td>
<td>0%</td>
</tr>
</tbody>
</table>

   No dose modifications of Bleomycin, vincristine, or prednisone are made on the basis of blood cell counts.

   All patients who require a dose reduction or dose delay for hematologic toxicity receive granulocyte colony-stimulating factor (G-CSF) 5/μL/kg as required to maintain dose intensity.

2. **Pulmonary:** Before the initiation of therapy and before every dose of Bleomycin, pulmonary tests, including diffusing capacity of the lungs for carbon monoxide (DLCO), vital capacity, and forced inspiratory volume in one second (FEV1) should be obtained. Should the patient have rales on physical examination or decreasing pulmonary function, as defined by a 25% decline in the DLCO with a stable hemoglobin, the Bleomycin should be **DISCONTINUED**.

3. **Neurologic:** If muscle weakness sufficient to interfere with normal self care or debilitating ileus occurs, reduce or eliminate vincristine/vinblastine doses as needed to prevent worsening. The vincristine/vinblastine dose should not be reduced solely because of dysesthesia and parasthesias.

4. **Metabolic:** Prednisone induced hyperglycemia should be managed with reduced caloric intake, and if necessary daily subcutaneous insulin as needed to keep patients from having pylori or sustained blood glucose above 300 mg/dl.
I. ELIGIBILITY
A. Biopsy proven Hodgkin’s Lymphoma (any subtype)
   1. Age ≥ 60 years old.
   2. Stage II B, III A, III B, IV A, or IV B.

II. STANDARD STAGING EVALUATION
Modify as needed to document all initial disease sites adequately for follow-up evaluation.
A. History and physical examination.
B. Chest x-ray.
C. Laboratory:
   CBC, differential, platelet count, Serum LDH, AST (SGOT), alkaline phosphatase, bilirubin,
   creatinine, uric acid, calcium.
D. Bone marrow aspiration and biopsy.
E. Evaluation of intra-abdominal and retroperitoneal disease. This usually includes abdominal and
   pelvic CT and/or possibly abdominal ultrasound.
F. Thoracic CT, if necessary, to document the extent of chest or mediastinal disease.
G. Whenever possible, PET should be done as part of the initial evaluation.
H. Additional scans and biopsy as needed to unequivocally document the extent of the disease
   especially sites of extra-nodal involvement.
III. TREATMENT AND DOSE ALTERATIONS
It is very important that treatment be given on time finishing in the planned number of cycles. All drugs should be given in FULL doses on time unless SPECIFIC toxicity requires dose reduction.

A. SCHEDULE AND DOSES

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>ROUTE</th>
<th>DAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorambucil</td>
<td>6 mg/m²/day</td>
<td>PO</td>
<td>1 – 7</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>6 mg/m²</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>100 mg/m²/day</td>
<td>PO</td>
<td>1 – 7</td>
</tr>
<tr>
<td>Prednisone</td>
<td>40 mg/day</td>
<td>PO</td>
<td>1 – 14</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>25 mg/m²</td>
<td>IV</td>
<td>8</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>10 U/m² (max. 15 U)</td>
<td>IV</td>
<td>8</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.4 mg/m² (max. 2 mg)</td>
<td>IV</td>
<td>8</td>
</tr>
</tbody>
</table>

Repeat cycle every 28 days for 6 cycles.

Follow with radiotherapy to bulk disease.

B. TOXICITY
1. Hematologic: If absolute granulocyte count is <1500/cmm or platelet count is <125,000/cmm when at Day 1 of a cycle delay one week. If still low one week later, proceed with the doses outlined below (no other drug doses are reduced regardless of blood counts):

DOSE ATTENUATION SCHEDULE FOR COUNTS

<table>
<thead>
<tr>
<th>Absolute granulocyte count</th>
<th>Platelet Count</th>
<th>Percent dose of Myelosuppressive Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1,500</td>
<td>75,000 – 125,000</td>
<td>50%</td>
</tr>
<tr>
<td>&lt;500</td>
<td>&lt;75,000</td>
<td>0%</td>
</tr>
</tbody>
</table>
B. **TOXICITY (continued):**

2. **Pulmonary:** Before the initiation of therapy and before every dose of Bleomycin, pulmonary tests, including diffusing capacity of the lungs for carbon monoxide (DLCO), vital capacity, and forced inspiratory volume in one second (FEV1) should be obtained. Should the patient have rales on physical examination or decreasing pulmonary function, as defined by a 25% decline in the DLCO with a stable hemoglobin, the Bleomycin should be **DISCONTINUED**.

3. **Neurologic:** If muscle weakness sufficient to interfere with normal self care or debilitating ileus occurs, reduce or eliminate vincristine doses as needed to prevent worsening.

4. **Metabolic:** Prednisone induced hyperglycemia should be managed with reduced caloric intake, and if necessary daily subcutaneous insulin as needed to keep patients from having polyuria or sustained blood glucose above 300 mg/dl.
Systemic Therapy for Hodgkin’s Lymphoma Using Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine

**ABVD**

Effective: January 1, 2000

I. **ELIGIBILITY**
A. Biopsy proven Hodgkin’s Lymphoma (any subtype)

II. **STANDARD STAGING EVALUATION**
Modify as needed to document all initial disease sites adequately for follow-up evaluation.
A. History and physical examination.
B. Chest x-ray.
C. Laboratory:
   - CBC, differential, platelet count, Serum LDH, AST (SGOT), alkaline phosphatase, bilirubin, creatinine, uric acid, calcium.
D. Bone marrow aspiration and biopsy.
E. Evaluation of intra-abdominal and retroperitoneal disease. This usually includes abdominal and pelvic CT and/or possibly abdominal ultrasound.
F. Thoracic CT, if necessary, to document the extent of chest or mediastinal disease.
G. Whenever possible, PET should be done as part of the initial evaluation.
H. Additional scans and biopsy as needed to unequivocally document the extent of the disease, especially sites of extra-nodal involvement.
III. TREATMENT AND DOSE ALTERATIONS
It is very important that treatment be given on time finishing in the planned number of cycles. All drugs should be given in FULL doses on time unless SPECIFIC toxicity requires dose reduction.

A. SCHEDULE AND DOSES

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>ROUTE</th>
<th>DAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adriamycin</td>
<td>25 mg/m²</td>
<td>IV</td>
<td>1, 15</td>
</tr>
<tr>
<td>Bleomycin*</td>
<td>10 U/m²</td>
<td>IV</td>
<td>1, 15</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>6 mg/m²</td>
<td>IV</td>
<td>1, 15</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>375 mg/m²</td>
<td>IV</td>
<td>1, 15</td>
</tr>
</tbody>
</table>

* Bleomycin (give 1 unit test before first dose)
Premeds for Bleomycin (after test dose):
Acetaminophen (650 mg)
Diphenhydramine
Repeat cycle every 28 days.

B. TOXICITY

1. Hematologic: If absolute granulocyte count is <1500/cmm or platelet count is <125,000/cmm when at Day 1 of a cycle delay one week. If still low one week later, proceed with the doses outlined below (no other drug doses are reduced regardless of blood counts):

   **DOSE ATTENUATION SCHEDULE FOR COUNTS**

<table>
<thead>
<tr>
<th>Absolute granulocyte count</th>
<th>Platelet Count</th>
<th>Percent dose of Myelosuppressive Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1,500</td>
<td>75,000 - 125,000</td>
<td>50%</td>
</tr>
<tr>
<td>&lt;500</td>
<td>&lt;75,000</td>
<td>0%</td>
</tr>
</tbody>
</table>

2. Pulmonary: Before the initiation of therapy and before every dose of Bleomycin, pulmonary tests, including diffusing capacity of the lungs for carbon monoxide (DLCO), vital capacity, and forced inspiratory volume in one second (FEV1) should be obtained. Should the patient have rales on physical examination or decreasing pulmonary function, as defined by a 25% decline in the DLCO with a stable hemoglobin, the Bleomycin should be DISCONTINUED.

3. Neurologic: If muscle weakness sufficient to interfere with normal self care or debilitating ileus occurs, reduce or eliminate vinblastine doses as needed to prevent worsening. The vinblastine dose should not be reduced solely because of dysesthesia and parasthesias.
HODGKIN’S LYMPHOMA - Standard Therapy
Radiation Therapy Guidelines

Radiation Fields

The sites to be treated will include those clinically or radiographically visible sites as identified at the initial staging evaluation. No attempt will be made to treat non-involved contiguous nodal/extranodal sites. A 2 cm margin will be used around the pre-treatment target planning volume mediastinal-hilar.

The mediastinal target volume width will be adjusted to reflect the post-chemotherapy volume in order to decrease the risk of pulmonary toxicity.

CT – based on treatment planning dosimetry is recommended. Dose uniformity of +/- 5% is the goal. Tissue compensators, wedged field within a field boost, 3-D conformal (including IMRT) techniques are encouraged to achieve the uniformity goal.

A dose of 30 Gy in 17-20 fractions will be delivered for pre-chemotherapy tumor volumes less than 5 cm. A dose of 35-36 Gy in 20-23 fractions will be delivered for pre-chemotherapy volumes greater than or equal to 5 cm.

CBC with differential is recommended during radiation therapy.
HODGKIN’S LYMPHOMA - High Dose Therapy (ASCT)
Involved Field Radiation Therapy

Consider I.F. Radiotherapy For:

A. Bulky disease ≥ 5 cm.
B. Disease which could be encompassed within the field, respecting history of prior radiation therapy and normal tissue tolerance.
C. Disease refractory to pre-transplant cytoreductive therapy.
D. Persistent disease (by CT, gallium scan, or biopsy) post high dose therapy.

Sequencing of I.F. Radiotherapy:

A. I.F. radiotherapy should be given following recovery of counts following high dose therapy.
B. I.F. radiotherapy may be given prior to high dose therapy for special circumstances, e.g.:
   • Obstructive pneumonitis secondary to hilar adenopathy.
   • Spinal cord compression or other CNS event.
   • Etc.

Radiation Fields:

I.F. radiotherapy will include the pre-transplant target volume plus a 2 cm margin around the planning volume. No attempt will be made to cover contiguous nodal sites prophylactically. In the case of pre-high dose therapy bulky sites (ex: mediastinal adenopathy), the target volume may be modified to include the post-high-dose therapy target volume, in order to decrease the risk of toxicity (ex: interstitial pneumonitis)

Radiation Doses:

For patients with CR following high dose therapy, the radiation doses should be limited to 30.6 Gy in 17 fractions. For patients with persistent disease following high dose therapy or patients with pretreatment bulky disease (≥ 5 cm) boosting to 36 Gy in 20 fractions would be considered. A decrease in dose fraction size may be used in certain locations (ex: abdominal sites) if required for patient tolerance.
Non-Therapeutic Research

- IRB NO: 084-01 Quality of Life Post-Hematopoietic Stem Cell Transplant
- IRB NO: 412-99 Immunological and Molecular Studies of B-Chronic Lymphocytic Leukemia
- IRB NO: 041-03 Microarray Analysis of Patients with Diffuse Large B-cell Lymphoma treated with CHOP/Rituximab
- IRB NO: 270-03 Prospective Collection of Data of Possible Prognostic Relevance in Patients with Follicular Lymphoma
- IRB NO: 189-04 The National Lymphocare Study: An Observational Study of Treatment, Outcomes, and Prognosis in Patients with Follicular Non-Hodgkin’s Lymphoma
Quality of Life Post-Hematopoietic Stem Cell Transplant

Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

IRB NO: 084-01-FB

Title: Quality of Life Post-Hematopoietic Stem Cell Transplant

Principal Investigator: James C. Lynch, Ph.D.

Clinical Coordinator/Data Manager: Mary Morris, B.S.N., M.S.  Telephone: (402) 559-6233  Email: memorris@unmc.edu

Purpose:
1. Implement prospective assessment of the quality of life of patients undergoing hematopoietic stem cell transplantation (HSCT) at baseline (pre-transplant), at day 100, and at yearly post-transplant intervals for the duration of the study.
2. Estimate the participation and retention rates of HSCT recipients in order to demonstrate the feasibility of longitudinal assessment of quality of life in this patient population.

Inclusion Criteria:
1. Transplant for hematologic malignancy.
2. Able to read and write English.
3. Resident of U.S. or Canada.
4. Transplant physician approval and informed consent.
5. Age >19 at transplant.

Exclusion Criteria:
1. Age <19 at transplant.

Quality of Life Questionnaires utilized:
1. MOS SF-36.
2. City of Hope, Quality of Life-Bone Marrow Transplant (modified).
3. Functional Assessment of Cancer Therapy – Bone Marrow Transplantation.

Note: This is an abbreviated description. Please contact the coordinator listed for complete information.
Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

**IRB No:** 412-99

**Title:** Immunological and Molecular Studies of B-Chronic Lymphocytic Leukemia.

**Principal Investigator:** R. Gregory Bociek, M.D.

**Clinical Coordinator/Data Manager:** Marge Moragues R.N., B.S.N., O.C.N.
**Telephone:** (402) 559-2471  
**Fax:** (402) 559-8101

**Purpose:** To investigate defective cellular cytotoxic functions in CLL patients and to develop suitable approaches to overcome the problem so as to provide better long term survival of CLL patients. The studies proposed will use leukemic cells and blood mononuclear cells from CLL patients.

**Eligibility Criteria:**
Patients with a new diagnosis of B-Chronic Lymphocytic Leukemia or B-Small Lymphocytic Lymphoma (B-CLL).

**Exclusion Criteria:**
There are no restrictions to participation in the study based on gender, race, or ethnic origin.

**Study Plan:**
The goal is to collect blood and bone marrow samples of patients with B-Chronic lymphocytic leukemia (B-CLL) at various stages of disease and therapy.

**Note:** This is an abbreviated description. Please contact the coordinator listed for complete information.
Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

**IRB NO: 041-03**

**Title:** Microarray Analysis of Patients with Diffuse Large B-cell Lymphoma Treated with CHOP/Rituximab

**Principal Investigator:** Julie Vose, M.D.

**Clinical Coordinator/Data Manager:** Paul Johnson, B.S.  
**Telephone:** (402) 559-6745

**Purpose:**  
The primary purpose of this study is to evaluate the gene expression analysis of previously untreated patients with diffuse large B-cell lymphoma who are treated with CHOP/Rituximab.

**Patient Eligibility:**
1. Patients with a diagnosis of localized or advanced stage diffuse large B-cell non-Hodgkin’s lymphoma expressing the CD20 surface antigen (as measured by immunohistochemistry or flow cytometry on peripheral blood, marrow, or tumor tissue). Patients with composite histology that is >50% diffuse large B-cell NHL are also eligible.  
   OR  
   Patients with a suspected lymphoma in which an initial diagnostic biopsy is planned.

2. Patients with stage I or non-bulky stage II will be treated as localized disease. Patients with bulky stage II (at least one tumor mass ≥5 cm), or stage III or stage IV disease will be treated as advanced disease.

3. Adequate lymph node tissue for gene expression analysis.

**Exclusion Criteria:**
1. Patients with known HIV infection.
2. Patients who are on another protocol involving non-FDA approved biologics or drugs.
3. Vulnerable subjects.
4. Subjects unable to give informed consent.

**Study Period:**
Prior to initiation of chemotherapy, a lymph node biopsy will be collected and sent to UNMC for analysis. Patients will then be treated with standard CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy in combination with Rituximab (Rituxan). Patients will receive three to four cycles of therapy if they have localized lymphoma or six to eight consecutive cycles of Rituximab in combination with CHOP chemotherapy if they have advanced stage lymphoma. Each cycle is 21 days apart.
Microarray Analysis of Patients with Diffuse Large B-cell Lymphoma Treated with CHOP/ Rituximab

Study Period (continued):
After completion of therapy and documentation of response to therapy, patients would be followed every 3 months for the first year, every 4 months for the second year, every 6 months for the third and fourth years, and once yearly after that time by the oncologist with physical exam and standard bloodwork.

Note: This is an abbreviated description. Please contact the coordinator listed for complete information.
Prospective Collection of Data of Possible Prognostic Relevance in Patients with Follicular Lymphoma

Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

IRB No: 270-03

Title: Prospective Collection of Data of Possible Prognostic Relevance in Patients with Follicular Lymphoma

Principal Investigator: Julie M. Vose, MD

Planned Accrual Total: Approximately 6-10 eligible patients per year will be enrolled at UNMC over 3 years.

Clinical Coordinator/Data Manager: Heather Brady, BA, MPH

Telephone: (402) 559-8570

Purpose:
The purpose of the study is to validate the Follicular Lymphoma International Prognostic Index (FLIPI) and to verify whether a prospective collection of data would allow the development of a more accurate prognostic index.

Patient Eligibility:
Adult patients ages ≥19 years of age may enroll.
1. Patients with newly diagnosed follicular lymphoma
2. Patients with histologically confirmed diagnosis of follicular lymphoma according to REAL/WHO classification (any grade)
3. Written informed consent

Exclusion Criteria: None

Study Period:
There are no experimental procedures involved in this study. For patients that choose to participate, tissue from a clinically indicated lymph node biopsy to be or already performed on them will be sent to the laboratory at the University of Nebraska Medical Center (UNMC) so that a confirmation of follicular lymphoma diagnosis may be performed. The patient may choose to donate a small amount of blood and/or tissue from a lymph node biopsy for future research tests that have not yet been determined. Routine care may include regular physical examinations, biopsy, blood draws, CT scans or other evaluations as medically indicated. Patients will receive whatever form of treatment determined appropriate by their physician. Patients will be followed for five years for progression and survival.

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
The National Lymphocare Study: An Observational Study of Treatment, Outcomes, and Prognosis in Patients with Follicular Non-Hodgkin’s Lymphoma

Due to Institutional Review Board and Scientific Review Committee guidelines, patients must be evaluated and enrolled at UNMC before participating in this trial.

IRB No: 189-04

Title: The National Lymphocare Study: An Observational Study of Treatment, Outcomes, and Prognosis in Patients with Follicular Non-Hodgkin’s Lymphoma

Principal Investigator: Julie M. Vose, MD

Planned Accrual Total: Approximately 6 eligible patients per year will be enrolled at UNMC over 5 years.

Clinical Coordinator/Data Manager: Telephone:
Heather Brady, BA, MPH (402) 559-8570

Purpose:
The purpose of the study is to define differences in outcome for patients with follicular non-Hodgkin’s lymphoma (NHL) by comparing the outcomes and safety of common front-line and subsequent therapeutic strategies.

Patient Eligibility:
1. Adult patients ≥19 years of age may enroll.
2. Patients with newly diagnosed follicular lymphoma (within 6 months prior to enrollment)
3. Patients with histologically confirmed diagnosis of follicular lymphoma according to REAL classification, as assessed by the local pathologist and treating physician (composite follicular lymphomas are eligible, even minority percent follicular lymphoma)
4. Written informed consent

Exclusion Criteria: None

Study Period:
There are no experimental procedures involved in this study. Routine care may include regular physical examinations, biopsy, blood draws, CT scans or other evaluations as medically indicated. Patients will receive whatever form of treatment determined appropriate by their physician. Patients will be followed until death, withdrawal of consent, loss to follow-up or study termination for progression, subsequent treatments and survival.

NOTE: This is an abbreviated inclusion/exclusion list. Please contact the coordinator listed for the complete checklist.
Appendices

Appendix A ............................................................................................................. Staging – Ann Arbor Classification
Appendix B ............................................................................................................. Karnofsky Scale
Appendix C ............................................................................................................. International Prognostic Indexes
Appendix D ............................................................................................................. Response Criteria (revised 1/2000)
Appendix E ............................................................................................................. Lymphoma Classification (modified WHO)

Data Management Forms

Appendix F ............................................................................................................. Registration
Appendix G ............................................................................................................. Initial Staging (Set A)
Appendix H ............................................................................................................. Treatment (Set B)
Appendix I ............................................................................................................. Follow-up (Set C)
Appendix J ............................................................................................................. Compensation
STAGING – ANN ARBOR CLASSIFICATION

Stage I - involvement of a single lymph node region* (I) or a single extralymphatic organ or site (IE). (*lymphoid tissue includes spleen, lingual and palatine tonsils, adenoids (pharyngeal tonsils), thymus and Waldeyer’s ring.)

Stage II - involvement of two or more lymph node regions on the same side of the diaphragm (II) or single node region plus localized extra lymphatics or organ/site (IIE).

Stage III - involvement of lymph node regions on both sides of the diaphragm (III), which may be accompanied by localized involvement of extralymphatic organ or site (IIIE), by involvement of the spleen (IIIS), or both (IIIES).

For patients with Hodgkin’s Lymphoma, Stage III is further subclassified as:

*III1: Disease limited to upper abdomen, e.g., spleen, or splenic hilar; celiac or porta hepatic nodes.
*III2: Involvement of paraaortic, iliac, inguinal, or mesenteric nodes with or without disease in the upper abdomen.

Stage IV - diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement.
## EVALUATION OF PERFORMANCE STATUS (Karnofsky Scale)

<table>
<thead>
<tr>
<th>Description</th>
<th>Scale (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal; no complaints</td>
<td>100</td>
</tr>
<tr>
<td>Able to carry on normal activities; minor signs or symptoms of disease</td>
<td>90</td>
</tr>
<tr>
<td>Normal activity with effort</td>
<td>80</td>
</tr>
<tr>
<td>Cares for self; unable to carry on normal activity or to do active work</td>
<td>70</td>
</tr>
<tr>
<td>Requires occasional assistance, but able to care for most of his/her needs</td>
<td>60</td>
</tr>
<tr>
<td>Requires considerable assistance and frequent medical care</td>
<td>50</td>
</tr>
<tr>
<td>Disabled; requires special care and assistance</td>
<td>40</td>
</tr>
<tr>
<td>Severely disabled; hospitalization indicated though death not imminent</td>
<td>30</td>
</tr>
<tr>
<td>Very sick; hospitalization necessary; active supportive treatment necessary</td>
<td>20</td>
</tr>
<tr>
<td>Moribund</td>
<td>10</td>
</tr>
<tr>
<td>Dead</td>
<td>0</td>
</tr>
</tbody>
</table>

### INTERNATIONAL PROGNOSTIC INDICATORS FOR **DIFFUSE LYMPHOMA (IPI)**

Stage III or IV  
Karnofsky score ≤70  
Age >60  
LDH > upper limits of normal  
Extranodal sites >1

<table>
<thead>
<tr>
<th>NUMBER OF RISK FACTORS</th>
<th>RISK GROUP</th>
<th>5-YEAR SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 1</td>
<td>Low</td>
<td>73%</td>
</tr>
<tr>
<td>2</td>
<td>Low-Intermediate</td>
<td>51%</td>
</tr>
<tr>
<td>3</td>
<td>High-Intermediate</td>
<td>43%</td>
</tr>
<tr>
<td>4 - 5</td>
<td>High</td>
<td>26%</td>
</tr>
</tbody>
</table>

### INTERNATIONAL PROGNOSTIC INDICATORS FOR **FOLLICULAR LYMPHOMA (FLIPI)**

Stage III or IV  
Hemoglobin level < 120 g/L  
Age > 60  
LDH > upper limits of normal  
Nodal areas > 4

<table>
<thead>
<tr>
<th>NUMBER OF RISK FACTORS</th>
<th>RISK GROUP</th>
<th>5-YEAR SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 1</td>
<td>Low</td>
<td>88%</td>
</tr>
<tr>
<td>2</td>
<td>Low-Intermediate</td>
<td>71%</td>
</tr>
<tr>
<td>3</td>
<td>High-Intermediate</td>
<td>57%</td>
</tr>
<tr>
<td>4 - 5</td>
<td>High</td>
<td>43%</td>
</tr>
</tbody>
</table>
The following response criteria has now become the standard for response assessment by the Nebraska Lymphoma Study Group (NLSG).

**Response Criteria for Non-Hodgkin’s Lymphoma***

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Physical Examination</th>
<th>Lymph Nodes</th>
<th>Lymph Node Masses</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>CRu</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Indeterminate</td>
</tr>
<tr>
<td></td>
<td>Normal, Normal</td>
<td>Normal, Normal</td>
<td>&gt;75% decrease</td>
<td>Normal or indeterminate</td>
</tr>
<tr>
<td>PR</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Normal, ≥50% decrease</td>
<td>≥50% decrease</td>
<td>≥50% decrease</td>
<td>Irrelevant</td>
</tr>
<tr>
<td></td>
<td>Decrease in liver/spleen</td>
<td>≥50% decrease</td>
<td>≥50% decrease</td>
<td>Irrelevant</td>
</tr>
<tr>
<td>Relapse/Progression</td>
<td>Enlarging liver/spleen; new sites</td>
<td>New or increased</td>
<td>New or increased</td>
<td>Reappearance</td>
</tr>
</tbody>
</table>


Note: See text for definitions of “normal” and “indeterminate.”
Appendix D (page 2 of 3)

Response Criteria – International Working Group Recommendations

The following criteria are considered anatomic definitions (see prior table). In the future, as additional radiographic, laboratory, and functional studies become more widely available and clearly demonstrate predictive value, they may be recommended as well.

**CR requires** the following:
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., lactate dehydrogenase [LDH]) definitely assignable to NHL.
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). 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).
3. The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable on physical examination. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic size. For instance, spleens thought to be of normal size may contain lymphoma, whereas an enlarged spleen may not necessarily reflect the presence of lymphoma, but variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes. The determination of splenic volume or splenic index by CT scan are cumbersome and not widely used. Any macroscopic nodules in any organs detectable on imaging techniques should no longer be present. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.
4. 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. The sample on which this determination is made must be adequate (≥20 mm biopsy core). Flow cytometric, molecular, or cytogenetic studies are not considered part of routine assessment to document persistent disease at the present time. These studies should only be incorporated into trials examining important research questions.

**CR/Unconfirmed (CRu)** includes patients who fulfill criteria 1 and 3 above, but with one or more of the following features:
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.
2. Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia).
Appendix D (page 3 of 3)

PR requires the following:
1. ≥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.
2. No increase in the size of the other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by at least 50% in the SPD.
4. With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease.
5. Bone marrow assessment is irrelevant for determination of a PR because it is assessable and not measurable disease; however, if possible, 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).
6. No new sites of disease.

Stable disease is defined as less than a PR (see above) but is not progressive disease (see below).

Relapsed disease (CR, CRu) requires the following:
1. Appearance of any new lesion or increase by ≥50% in the size of previously involved sites.
2. ≥50% increase in greatest diameter of any previously identified node greater than 1 cm in its short axis or in the SPD of more than one node.

Progressive disease (PR, nonresponders) requires the following:
1. ≥50% increase from nadir in the SPD of any previously identified abnormal node for PRs or nonresponders.
2. Appearance of any new lesion during or at the end of therapy.

Response Assessment
Response is currently assessed on the basis of clinical, radiologic, and pathologic (i.e., bone marrow) criteria.
1. CT scans remain the standard for evaluation of nodal disease. Thoracic, abdominal, and pelvic CT scans are recommended even if those areas were not initially involved because of the unpredictable pattern of recurrence in NHL. Studies should be performed no later than 2 months after treatment has been completed to assess response. This interval may vary with the type of treatment, e.g., a longer period may be more appropriate for biologic agents where the anticipated time to response may be greater.
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.
# RESEARCH CLASSIFICATION FOR NEBRASKA LYMPHOMA STUDY GROUP

## B-CELL NEOPLASMS

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP-ALL</td>
<td>Precursor B-cell lymphoblastic leukemia</td>
<td>TP-ALL</td>
<td>Precursor T-cell acute lymphoblastic leukemia</td>
</tr>
<tr>
<td>BP-LBL</td>
<td>Precursor B-lymphoblastic lymphoma</td>
<td>TP-LBL</td>
<td>Precursor T-lymphoblastic lymphoma</td>
</tr>
<tr>
<td>B-CLL</td>
<td>B-cell chronic lymphocytic leukemia</td>
<td>T-PLL</td>
<td>T-cell prolymphocytic leukemia</td>
</tr>
<tr>
<td>B-SLL</td>
<td>Small lymphocytic lymphoma</td>
<td>T-GLP</td>
<td>T-cell granular lymphocytic proliferation</td>
</tr>
<tr>
<td>B-PDLL</td>
<td>B-prolymphocytic leukemia</td>
<td>NK-GLP</td>
<td>NK-cell granular lymphocytic proliferation</td>
</tr>
<tr>
<td>B-HCL</td>
<td>Hairy cell leukemia</td>
<td>NK-AL</td>
<td>Aggressive NK-cell leukemia</td>
</tr>
<tr>
<td>B-LPL</td>
<td>Lymphoplasmacytic lymphoma</td>
<td>T-ATLL</td>
<td>Adult T-cell lymphoma/leukemia</td>
</tr>
<tr>
<td>B-PCM</td>
<td>Plasma cell myeloma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-PC</td>
<td>Plasmacytoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-SMZL</td>
<td>Splenic marginal zone B-cell lymphoma</td>
<td>T-PTCL-MC</td>
<td>Peripheral T-cell lymphoma, mixed cell</td>
</tr>
<tr>
<td>B-EMZL</td>
<td>Extramedullary marginal zone B-cell lymphoma, MALT type</td>
<td>T-PTCL-LE</td>
<td>Peripheral T-cell lymphoma, lymphoepithelioid</td>
</tr>
<tr>
<td>B-NMZL</td>
<td>Nodal marginal zone B-cell lymphoma</td>
<td>T-PTCL-AI</td>
<td>Peripheral T-cell lymphoma, angioimmunoblastic</td>
</tr>
<tr>
<td>B-NMCL</td>
<td>Nodular mantle cell lymphoma</td>
<td>T-SS</td>
<td>Sezary syndrome</td>
</tr>
<tr>
<td>B-DMCL</td>
<td>Diffuse mantle cell lymphoma</td>
<td>NK/T-NL</td>
<td>Nasal NK/T-cell lymphoma</td>
</tr>
<tr>
<td>B-BMCL</td>
<td>Blastic mantle cell lymphoma</td>
<td>NK/T-PL</td>
<td>Peripheral NK/T-cell lymphoma</td>
</tr>
<tr>
<td>B-BL</td>
<td>Burkitt’s lymphoma</td>
<td>NK-BL</td>
<td>Blastic NK-cell lymphoma</td>
</tr>
<tr>
<td>B-FL-1</td>
<td>Follicular lymphoma, grade 1 (small cleaved)</td>
<td>T-HSGDL</td>
<td>Hepatosplenic gamma-delta T-cell lymphoma</td>
</tr>
<tr>
<td>B-FL-2</td>
<td>Follicular lymphoma, grade 2 (mixed cell)</td>
<td>T-PGDL</td>
<td>Peripheral gamma-delta T-cell lymphoma</td>
</tr>
<tr>
<td>B-FL-3</td>
<td>Follicular lymphoma, grade 3, (large noncleaved)</td>
<td>T-EATL</td>
<td>Enteropathy-type T-cell lymphoma</td>
</tr>
<tr>
<td>B-FL-3.1</td>
<td>Follicular lymphoma, grade 3 (large cleaved cell)</td>
<td>T-SPTL</td>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
</tr>
<tr>
<td>B-FL-3.2</td>
<td>Follicular lymphoma, grade 3 (small noncleaved cell)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-DLCL-1</td>
<td>Diffuse follicle center lymphoma, grade 1 (small cleaved cell)</td>
<td>PTCL-UC</td>
<td>Peripheral T-cell lymphoma, unclassifiable</td>
</tr>
<tr>
<td>B-DLCL-2</td>
<td>Diffuse follicle center lymphoma, grade 2 (mixed cell)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-DLCL-NC</td>
<td>Diffuse large B-cell lymphoma, noncleaved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-DLCL-C</td>
<td>Diffuse large B-cell lymphoma, cleaved</td>
<td>CL</td>
<td>Composite lymphoma, specify types and percents</td>
</tr>
<tr>
<td>B-DLCL-AP</td>
<td>Diffuse large B-cell lymphoma, immunoblastic plasmacytoid</td>
<td>N-HL-NOS</td>
<td>Non-Hodgkin’s lymphoma, not otherwise specified</td>
</tr>
<tr>
<td>B-DLCL-INOS</td>
<td>Diffuse large B-cell lymphoma, immunoblastic, not otherwise specified</td>
<td>N-HL-UC</td>
<td>Unclassified non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>B-DLCL-THR</td>
<td>Diffuse large B-cell lymphoma, T-cell/histiocyte-rich</td>
<td>PTLD</td>
<td>Post-transplantation lymphoproliferative disorder</td>
</tr>
<tr>
<td>B-DLCL-LG</td>
<td>Diffuse large B-cell lymphoma, lymphomatoid granulomatosis</td>
<td>EBVLD</td>
<td>EBV-driven lymphoproliferative disorder</td>
</tr>
<tr>
<td>B-DLCL-AP</td>
<td>Diffuse large B-cell lymphoma, anaplastic</td>
<td>MCD</td>
<td>Mast cell disease</td>
</tr>
<tr>
<td>B-DLCL-PB</td>
<td>Diffuse large B-cell lymphoma, plasmablastic</td>
<td>LCH</td>
<td>Langerhans cell histiocytosis</td>
</tr>
<tr>
<td>B-DLCL-IV</td>
<td>Diffuse large B-cell lymphoma, intravascular</td>
<td>DHN</td>
<td>Dendritic/histiocytic neoplasm</td>
</tr>
<tr>
<td>B-DLCL-PE</td>
<td>Diffuse large B-cell lymphoma, primary effusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-DLCL-NOS</td>
<td>Diffuse large B-cell lymphoma, not otherwise specified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-BL</td>
<td>Burkitt’s lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-BLL</td>
<td>Burkitt’s-like lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-UCL-LG</td>
<td>Unclassifiable low-grade B-cell lymphoma</td>
<td>ALP</td>
<td>Atypical lymphoid proliferation</td>
</tr>
<tr>
<td>B-UCL-HG</td>
<td>Unclassifiable high-grade B-cell lymphoma</td>
<td>SUS</td>
<td>Suspicious for lymphoid malignancy</td>
</tr>
<tr>
<td>B-UCL</td>
<td>Unclassifiable B-cell lymphoma</td>
<td>NEG</td>
<td>Negative for lymphoid malignancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ND</td>
<td>Non-diagnostic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>INAD</td>
<td>Inadequate for diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GS</td>
<td>Granulocytic sarcoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA</td>
<td>Carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>THY</td>
<td>Thymoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OM</td>
<td>Other malignancy, specify type</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FH</td>
<td>Follicular hyperplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RH</td>
<td>Reactive hyperplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IM</td>
<td>Infectious mononucleosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AFH</td>
<td>Angiofollicular hyperplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NL</td>
<td>Necrotizing lymphadenitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GL</td>
<td>Granulomatous lymphadenitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SHML</td>
<td>Sinus histiocytosis with massive lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ONM</td>
<td>Other non-malignant disorder, specify type</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix E (page 2 of 2)

RESEARCH CLASSIFICATION FOR NEBRASKA LYMPHOMA STUDY GROUP

MYELOPROLIFERATIVE DISEASES

CML Chronic myelogenous leukemia
CNL Chronic neutrophilic leukemia
HES Chronic eosinophilic leukemia/hypereosinophilic syndrome
CIM Chronic idiopathic myelofibrosis
PV Polycythemia vera
ET Essential thrombocytopenia
MPD-UC Myeloproliferative disorder, unclassifiable
MPD-NOS Myeloproliferative disorder, not otherwise specified

MYELODYSPLASTIC/MYELOPROLIFERATIVE SYNDROMES

CMML Chronic myelomonocytic leukemia
ATCML Atypical chronic myelomonocytic leukemia
JMML Juvenile myelomonocytic leukemia
MDPS-UC Myelodysplastic/myeloproliferative syndrome, unclassifiable

MYELODYSPLASTIC SYNDROMES

RA Refractory anemia
RARS Refractory anemia with ringed sideroblasts
RCMLD Refractory cytopenia with multilineage dysplasia
RAEB Refractory anemia with excess blasts
MDS-5q Myelodysplastic syndrome with isolated chromosome -5q
MDS-UC Myelodysplastic syndrome, unclassifiable
MDS-NOS Myelodysplastic syndrome, not otherwise specified

ACUTE MYELOID LEUKEMIA

AML-MO Acute myeloid leukemia, minimally differentiated
AML-M1 Acute myleoid leukemia, without maturation
AML-M2 Acute myeloid leukemia, with maturation
AML-M3 Acute promyelocytic leukemia
AML-M4 Acute myelomonocytic leukemia
AML-M4E Acute myelomonocytic leukemia, with abnormal bone marrow eosinophils
AML-M5 Acute monocytic leukemia
AML-M6 Acute erythroid leukemia
AML-M7 Acute megakaryocytic leukemia
AML-M8 Acute basophilic leukemia
AML-NOS Acute myeloid leukemia, not otherwise specified
AML subtype-MLD Acute myeloid leukemia, with multilineage dysplasia

AL-BP ACUTE BIPHENOTYPIC LEUKEMIA

AL-AL ACUTE LEUKEMIA OF AMBIGUOUS LINEAGE

AL-NOS ACUTE LEUKEMIA, NOT OTHERWISE SPECIFIED

TR THERAPY-RELATED MYELOID NEOPLASMS

Type of disorder – TR (e.g., AML-M2-TR)

APMMF ACUTE PANMYELOSIS WITH MYELOFIBROSIS

<table>
<thead>
<tr>
<th>PHENOTYPE METHOD</th>
<th>PHENOTYPE</th>
<th>PHENOTYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>B</td>
<td>B-cell</td>
</tr>
<tr>
<td>F</td>
<td>T</td>
<td>T-cell</td>
</tr>
<tr>
<td>FC</td>
<td>N</td>
<td>Null</td>
</tr>
<tr>
<td>G</td>
<td>HD</td>
<td>Hodgkin’s</td>
</tr>
<tr>
<td>O</td>
<td>M</td>
<td>Myeloid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OP</td>
</tr>
</tbody>
</table>
Appendix F

LYMPHOMA STUDY GROUP

PATIENT REGISTRATION ★
Please FAX, Mail or Call-In the following information. Our office will issue a registration number and return it to you.

1. Today’s Date: / / 

2. Patient’s Name: ____________________________________________

3. Date of Birth: / / 

4. Sex: 1-Male
   2-Female
   
   5. Ethnicity: 1. White, non Hispanic
   2. White, Hispanic
   3. Black, non Hispanic
   4. Black, Hispanic
   5. Native American
   6. Asian
   7. Pacific Islander
   8. Native Alaskan
   9. Other (please specify) ______________________

6. Date of Original Diagnosis: / / 

   Diagnosis: ____________________________________________

7. Planned Treatment Protocol: ______________________________________

   Date to Start Protocol: / / 

8. Previous Therapy Given: ______________________________________

9. Your Institution: ____________________________________________

   City: ____________________________ State: _______________________

10. Primary Oncologist: ________________________________________

11. Nurse/Data Manager: ____________________________

   Phone Number: ____________________________ Fax Number: ____________

Patient Registration Number (OHNO):

★ Submit patient consent form at this time

Attention: Nebraska Lymphoma Study Group
FAX Number: (402) 559-7902
Phone Number: (402) 559-6203

Address: University of Nebraska Medical Center
987680 Nebraska Medical Center
Omaha, NE 68198-7680
Appendix G (Page 1 of 3)

Lymphoma Standard Therapy
On Study - Set A Form

Patient Name: ___________________________ UNMC Hospital No.: ___________________________

Registration Number (OHNO): ___________________________ City/Physician Code: ___________________________

1. Date of Birth: / / 

2. Patient’s Gender: 1-Male / 2-Female 

3. Date of Diagnosis: / / 

4. Patient’s Ethnic Origin:

1-White, non-Hispanic
2-White, Hispanic
3-Black, non-Hispanic
4-Black, Hispanic
5-Native American
6-Asian
7-Pacific Islander
8-Native Alaskan
9-Other, specify: ___________________________

5. Family Cancer History:
Have any of the subjects’ blood relatives ever been diagnosed as having any type of lymphoma or leukemia, Hodgkin’s disease or multiple myeloma? (1-no, 2-yes)

If YES, please provide the following information on these blood relatives: grandparents, parents, aunts and uncles, brother and sisters, sons and daughters, and grandsons and granddaughters. If more than one relative, specify “sister #2”, “daughter #1”, etc. Please mark the disease category for each relative (X) and give the age of the relative at the time of diagnosis (see example).

<table>
<thead>
<tr>
<th>Relationship to Subject</th>
<th>Lymphoma, Any Type</th>
<th>Leukemia, Any Type</th>
<th>Hodgkin’s Disease</th>
<th>Multiple Myeloma</th>
<th>Age (years) At Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0. Example - #1 Sister</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>49</td>
</tr>
</tbody>
</table>

1. 

2. 

3. 

4. 

5.
Appendix G (Page 2 of 3)

OH Number:

Instructions: This form is to be completed on data prior to the initiation of standard therapy. Use ND if test was not done. Please send copies of all lab and staging documentation.

INITIAL PRESENTATION DATA:

6. HIV: (1-negative, 2-positive)

7. Serum LDH: IU/L High Normal: IU/L

8. Beta-2 Microglobulin: mg/L High Normal: mg/L

9. Monoclonal Serum Protein Spike: (1-no, 2-yes)

10. WBC: K/cmm

11. Granulocytes: % (Segs + Bands)

12. Lymphocytes: %

13. Hemoglobin: g/dL

14. Platelet Count: K/cmm

15. Splenomegaly: (1-no, 2-yes)

16. Performance status: 1 - Ambulatory (Karnofsky ≥80, ECOG ≤1)

2 - Non-Ambulatory (Karnofsky ≤70, ECOG ≥2)

17. Maximum dimension of largest mass: cm

18. Lymphatic sites of involvement: (1-no, 2-yes) If YES, mark all nodes >1.5 cm that apply below.

<table>
<thead>
<tr>
<th>Lymphatic Sites of Involvement</th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waldeyer’s Ring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supraclavicular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axillary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mediastinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Intra-thoracic Nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paraaortic/Retroperitoneal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iliac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesenteric</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celiac/Hepatic/Splenic Nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spleen (focal lesions only)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inguinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other, specify:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
19. **Extra** nodal site(s) of involvement (mark all that apply): 

<table>
<thead>
<tr>
<th>Extra nodal Sites of Involvement</th>
<th>Involved</th>
<th>Proven by:</th>
<th>Biopsy</th>
<th>Imaging Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Marrow</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver (focal lesions, only)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meninges</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidural</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone (osseous), specify:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin/Subcutaneous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small Intestine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large Intestine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pericardium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctiva</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orbit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nose or Nasal Cavity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paranasal Sinuses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salivary Glands</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other, specify:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

20. Disease confined to one site (i.e., Localized)? (1-no, 2-yes) 

21. Ann Arbor stage: I  IE  II  IIE  III  IIIE  IV 

22. Systemic B-symptom(s) present: (1-no, 2-yes) fevers $>100^\circ F$; night sweats; weight loss of $\geq 10\%$
Appendix H (Page 1 of 2)

Lymphoma Standard Therapy
Treatment – Set B Form

Patient Name: ___________________________ UNMC Hospital No.: ______________

OH Number: ______________ City/Physician Code: __________________

**Instructions:** This form is to be completed after the end of initial planned treatment. Please send restaging documentation.

1. **Height:** cm  
2. **BSA:** \( M^2 \)  
3. **Weight:** Kg

List drugs administered. Complete cycle number, date of day one each cycle, and doses given.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>/ /</td>
<td>/ /</td>
<td>/ /</td>
<td>/ /</td>
<td>/ /</td>
<td>/ /</td>
<td>/ /</td>
<td>/ /</td>
</tr>
</tbody>
</table>

**Day 1 Doses (mg/day) Unless Otherwise Specified**

**Chemo/Immuno therapy**

1. 

2. 

3. 

4. 

5. 

6. 

7. 

8. 

**Prophylactic Antibiotics**  
(1-No, 2-Yes)

**Growth Factor**  
(1-No, 2-Yes)

**TYPE of Growth Factor**

<table>
<thead>
<tr>
<th>1-G-CSF</th>
<th>2-GM-CSF</th>
<th>3-IL3</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-EPO</td>
<td>5-PIXY</td>
<td>6-Other, specify</td>
</tr>
</tbody>
</table>
Appendix H (Page 2 of 2)

Lymphoma Standard Therapy
Treatment – Set B Form

RESPONSE TO INITIAL CHEMOTHERAPY (evaluate at the end of all planned cycles)

4. Overall objective response:

   4-NR/SD (no response/stable disease)
   2-CRU      5-PD (progressive disease)
   3-PR

   Date Response Reached

5. If initial therapy was chemotherapy, was adjuvant radiotherapy given? (1-no, 2-yes)

Radiotherapy (as initial therapy or adjuvant):

<table>
<thead>
<tr>
<th>Site</th>
<th>Inclusive Dates (mm/dd/yy)</th>
<th>Total Dose</th>
<th>Port</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Begin</td>
<td>End</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>/</td>
<td>/</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>/</td>
<td>/</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>/</td>
<td>/</td>
<td></td>
</tr>
</tbody>
</table>

1 Total Dose in rads

RESPONSE POST RADIOThERAPY

6. Overall objective response:

   Date Response Reached

7. If treatment has ended, reason for treatment termination:

   5-patient withdrawal of consent
   6-other complicating disease, specify: _____________________________
   7-other, specify: _____________________________

COMMENTS:__________________________

________________________________________________________________________
Appendix I

Lymphoma Standard Therapy
Follow-up – Set C Form

Patient Name: ______________________________ UNMC Hospital No.: ______________________________

OH Number: ______________________________ City/Physician Code: ______________________________

INSTRUCTIONS: This form is to be completed every six months after initial treatment while alive, or in the event of a patient’s death. Submit documentation of progression and/or death.

Time period covered by this form: / / TO / / /

1. Date last seen by physician: / / 

2. Any new malignancies? (1-no, 2-yes) If yes, specify: ______________________________

3. Date last known alive: / / 

4. Is this patient on yearly follow-up? (1-no, 2-yes)

5. Did the patient have progressive disease/relapse during this time period? (1-no, 2-yes)

6. Date of progression: / / 

7. List salvage therapy administered: ______________________________

8. Did the patient die? (1-no, 2-yes) 9. Date of death: / / 

10. Cause of death:
   1-Progressive Disease
   2-Excessive Toxicity (specify: ______________________________)
   3-Unrelated Reason (specify: ______________________________)
   4-Secondary Malignancy (specify: ______________________________)

11. Immediate cause of death: ______________________________
    Secondary to: ______________________________

12. Death information obtained from:
   1-Autopsy 2-Medical Records/Death Certificate
   3-Physician 4-Relative or Friend
   5-Other – specify: ______________________________

Comments: ______________________________
LSG COMPENSATION REQUEST FORM

Submit with completed data forms and supporting documentation to:

LYMPHOMA STUDY GROUP (LSG)
University of Nebraska Medical Center
987680 Nebraska Medical Center
Omaha, NE 68198-7680

Nurse/Data Manager: ____________________________  Date: __________________________

Please make check payable to:

Name: ______________________________________
Address: ____________________________________
_____________________________________________
_____________________________________________

TIN/SS#: ____________________________________

SETS SUBMITTED:

<table>
<thead>
<tr>
<th>Patient Name</th>
<th>OH #</th>
<th>Registration *</th>
<th>Sets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
</tbody>
</table>

* stipend awarded only for registration forms received by LSG within 2 weeks of day 1, cycle 1.

COMPENSATION REQUESTED:

<table>
<thead>
<tr>
<th>Number</th>
<th>Per Set</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registration</td>
<td>$10.00</td>
<td></td>
</tr>
<tr>
<td>Set A</td>
<td>$50.00</td>
<td></td>
</tr>
<tr>
<td>Set B</td>
<td>$15.00</td>
<td></td>
</tr>
<tr>
<td>Set C</td>
<td>$10.00</td>
<td></td>
</tr>
</tbody>
</table>

Total $
HEMATOLOGIC MALIGNANCY NETWORK

Mailing Address:
University of Nebraska Medical Center
987680 Nebraska Medical Center
Omaha, NE  68198-7680

Shipping Address:
University of Nebraska Medical Center
Lied Transplant Center (LTC) 8th Floor
Omaha, NE  68198-7680

Leukemia & Myeloma Physicians:
Marcel Devetten, M.D.  (402) 559-5166
Lori Maness, M.D.  (402) 559-3742

GVHD/Long-term Follow-up Case Manager
Susan Kruse, R.N., O.C.N.  (402) 559-7793

Transplant Case Managers
Susan Kruse, R.N., O.C.N.  (402) 559-7793
Katie Sgourakis, R.N., B.S.N.  (402) 559-8011

Research Coordinators
Mardelle Ludwig, R.N., M.P.A.  (402) 559-7507
Jill Nienaber, R.N.  (402) 559-4135
Beth Schreiner, R.N., M.S.N.  (402) 559-6729

Data Management
Lu Caniglia, C.C.R.P.  (402) 559-8012
Michele Gaul, B.S.  (402) 559-8571
ALL

Transplant Protocols

**Autologous**

089-98  
High-Dose Carmustine, Etoposide, Cytarabine and Melphalan, (BEAM) Followed by Autologous Bone Marrow Transplantation or Peripheral Blood Stem Cell Transplantation  
Hematologic Malignancies  
<70 years with MM, AML or ALL.

**Allogeneic – Unrelated**

186-93  
Treatment of Hematologic Malignancies by Allogeneic BMT Using Unrelated HLA-Matched Donors  
Age <50, ALL, AML, CML, CLL, MM, MDS, malignant lymphoma. Means to pay for transplant. LEF >50%, DLCO >50%, Karnofsky >80%. Adequate liver and kidney function, no other serious disease, life expectancy >100 days.

**Allogeneic – Related**

205-95  
Phase II, Busulfan and Cyclophosphamide Followed by Allo Stem Cell Transplant for Treatment of Hematologic Malignancies  
Age 19-65, diagnosis of ALL, AML, MDS, CML, CLL, NHL, HD, or MM. Matched related donor.

281-98  
Treatment of Hematologic Malignancies with Cy-TBI Followed by Allogeneic Stem Cell Transplantation  
Age 19-55 hematologic cancer that has not responded to treatment, relapsed or is likely to relapse. LEF >50%, DLCO >50%, Karnofsky >70%. Adequate liver and kidney function, no other serious disease, life expectancy >100 days.

**Allogeneic – Mini**

389-00  
Allogeneic Peripheral Blood Stem Cell Transplantation with a Minimally Myelosuppressive Regimen of Pentostatin and Low-Dose Total-Body Irradiation  
Age 19-75 years. Any leukemia, lymphoma, or MDS. Patients who relapse after autologous stem cell transplant are not eligible for conventional autologous or allogeneic protocols. HLA-matched related or unrelated donor.

**CLINICAL TRIALS**

416-03  
A Phase III Randomized, Multicenter Trial Comparing G-CSF Mobilized Peripheral Blood Stem Cell with Marrow Transplantation from HLA Compatible Unrelated Donors  
Age 0-66, Diagnosis of AML, ALL, CML, Myelodysplastic syndromes, or other myeloproliferative diseases, 6/6 or 5/6 matched unrelated donor.
AML

Transplant Protocols

**Autologous**

089-98  
High-Dose Carmustine, Etoposide, Cytarabine and Melphalan, (BEAM) Followed by Autologous Bone Marrow Transplantation or Peripheral Blood Stem Cell Transplantation  
Hematologic Malignancies  
<70 years with MM, AML or ALL.

**Allogeneic – Unrelated**

186-93  
Treatment of Hematologic Malignancies by Allogeneic BMT Using Unrelated HLA-Matched Donors  
Age <50, ALL, AML, CML, CLL, MM, MDS, malignant lymphoma. Means to pay for transplant. LEF >50%, DLCO >50%, Karnofský >80%. Adequate liver and kidney function, no other serious disease, life expectancy >100 days.

**Allogeneic – Related**

205-96  
Phase II, Busulfan and Cyclophosphamide Followed by Allo Stem Cell Transplant for Treatment of Hematologic Malignancies  
Age 19-65, diagnosis of ALL, AML, MDS, CML, CLL, NHL, HD, or MM. Matched related donor.

281-98  
Treatment of Hematologic Malignancies with Cy-TBI Followed by Allogeneic Stem Cell Transplantation  
Age 19-55 hematologic cancer that has not responded to treatment, relapsed or is likely to relapse. LEF >50%, DLCO >50%, Karnofský >70%. Adequate liver and kidney function, no other serious disease, life expectancy >100 days.

**Allogeneic – Mini**

389-00  
Allogeneic Peripheral Blood Stem Cell Transplantation with a Minimally Myelosuppressive Regimen of Pentostatin and Low-Dose Total-Body Irradiation  
Age 19-75 years. Any leukemia, lymphoma, or MDS. Patients who relapse after autologous stem cell transplant are not eligible for conventional autologous or allogeneic protocols. HLA-matched related or unrelated donor.

**CLINICAL TRIALS**

376-03  
A Randomized, Open-Label Study of Oral CEP-701 Administered in Sequence With Standard Chemotherapy to Patients With Relapsed Acute Myeloid Leukemia (AML) Expressing FLT-3 Activating Mutations  
Age 18 years of age, AML, relapsed disease following first CR of duration 1 month (30 days) to 24 months (730 days), FLT-3 activating mutation positive status after point of initial relapse, adequate liver and kidney function, ECOG = 0, 1, or 2, life expectancy >3 months.
AML

CLINICAL TRIALS (continued)

416-03 A Phase III Randomized, Multicenter Trial Comparing G-CSF Mobilized Peripheral Blood Stem Cell with Marrow Transplantation from HLA Compatible Unrelated Donors
   Age 0-66, Diagnosis of AML, ALL, CML, Myelodysplastic syndromes, or other myeloproliferative diseases, 6/6 or 5/6 matched unrelated donor.

111-04 Phase III Randomized Study of Induction Chemotherapy Followed by Cytogenetic Risk-Adapted Intensification Therapy Followed by Immunotherapy with rIL-2 (NCS #373364, IND #1969) vs. Observation in Previously Untreated Patients with AML < 60 Years (CALGB 19808-10)
   Age 19-60, diagnosis of AML, no prior treatment.

265-04 An Open-Label Extended-Use of Oral CEP-701 in Patients with Hematologic and Non-Hematologic Malignancies Who Have Completed a Clinical Study of CEP-701
   Age 19 and older. The patient must have completed a previous clinical study of oral CEP-701 and would benefit by continuing treatment with CEP-701. The patient must enter this study within 30 days after completing the previous clinical study with CEP-701; or, if the patient received chemotherapy after the previous study with CEP-701, within a window of 3 to 14 days after receiving the final dose of chemotherapy.

297-04 A Phase I/II Study of Clofarabine and Cytosine Arabinoside Remission Induction Therapy for Older Adults (≥60 years) with Newly Diagnosed Acute Myeloid Leukemia
   Age > 60 years with newly diagnosed Acute Myeloid Leukemia.

STANDARD THERAPY STATEMENT

We follow the NCCN clinical guidelines for AML (available at www.nccn.org).
Transplant Protocols

**Autologous** - None at this time.

**Allogeneic – Unrelated**

186-93  Treatment of Hematologic Malignancies by Allogeneic BMT Using Unrelated HLA-Matched Donors

*Age <50, ALL, AML, CML, CLL, MM, MDS, malignant lymphoma.  Means to pay for transplant.  LEF >50%, DLCO >50%, Karnofsky >80%.  Adequate liver and kidney function, no other serious disease, life expectancy >100 days.*

**Allogeneic – Related**

205-95  Phase II, Busulfan and Cyclophosphamide Followed by Allogeneic Stem Cell Transplant for Treatment of Hematologic Malignancies

*Age 19-65, diagnosis of ALL, AML, MDS, CML, CLL, NHL, HD, or MM.  Matched related donor.*

281-98  Treatment of Hematologic Malignancies with Cy-TBI Followed by Allogeneic Stem Cell Transplantation

*Age 19-55 hematologic cancer that has not responded to treatment, relapsed or is likely to relapse.  LEF >50%, DLCO >50%, Karnofsky >70%.  Adequate liver and kidney function, no other serious disease, life expectancy >100 days.*

**Allogeneic – Mini**

389-00  Allogeneic Peripheral Blood Stem Cell Transplantation with a Minimally Myelosuppressive Regimen of Pentostatin and Low-Dose Total-Body Irradiation

*Age 19-75 years.  Any leukemia, lymphoma, or MDS.  Patients who relapse after autologous stem cell transplant are not eligible for conventional autologous or allogeneic protocols.  HLA-matched related or unrelated donor.*

**CLINICAL TRIALS**

535-00  A Phase 2 Study of VELCADE in Subjects with Relapsed or Refractory Mantle Cell Lymphoma

039-03  A Phase II Study of PS-341 in Low–Grade Lymphoproliferative Disorders

075-04  A Multi-Center, Open-Label, Dose-Escalation Study to Evaluate the Safety, Efficacy, and Exposure to TRM-1 (Fully Human Monoclonal Antibody to TRAIL-R1) in Subjects with Relapsed or Refractory Non-Hodgkin’s Lymphoma

155-04  Phase III Randomized Trial to Evaluate the Efficacy and Safety of Second-line Therapy with Fludara plus Alemtuzumab (CAMPATH, MabCampath) versus Fludara Alone in Patients with B-Cell Chronic Lymphocytic Leukemia (Protocol # CAM 314)

**STANDARD THERAPY STATEMENT**

We follow the NCCN clinical guidelines for CLL (available at [www.nccn.org](http://www.nccn.org)).
CML

Research Protocols

A Non-randomized Open-Label Study of Molecular Response to High Dose Gleevec (Imatinib Mesylate, Formerly Known as ST1571) in Patients with Newly Diagnosed Chronic Phase Chronic Myelogenous Leukemia

Transplant Protocols

**Allogeneic – Unrelated**

186-93 Treatment of Hematologic Malignancies by Allogeneic BMT Using Unrelated HLA-Matched Donors
Age <50, ALL, AML, CML, CLL, MM, MDS, malignant lymphoma. Means to pay for transplant. LEF >50%, DLCO >50%, Karnofsky >80%. Adequate liver and kidney function, no other serious disease, life expectancy >100 days.

**Allogeneic – Related**

205-95 Phase II, Busulfan and Cyclophosphamide Followed by Allogeneic Stem Cell Transplant for Treatment of Hematologic Malignancies
Age 19-65, diagnosis of ALL, AML, MDS, CML, CLL, NHL, HD, or MM. Matched related donor.

281-98 Treatment of Hematologic Malignancies with Cy-TBI Followed by Allogeneic Stem Cell Transplantation
Age 19-55 hematologic cancer that has not responded to treatment, relapsed or is likely to relapse. LEF >50%, DLCO >50%, Karnofsky >70%. Adequate liver and kidney function, no other serious disease, life expectancy >100 days.

**Allogeneic - Mini**

389-00 Allogeneic Peripheral Blood Stem Cell Transplantation with a Minimally Myelosuppressive Regimen of Pentostatin and Low-Dose Total-Body Irradiation
Age 19-75 years. Any leukemia, lymphoma, or MDS. Patients who relapse after autologous stem cell transplant are not eligible for conventional autologous or allogeneic protocols. HLA-matched related or unrelated donor.

**CLINICAL TRIALS**

416-03 A Phase III Randomized, Multicenter Trial Comparing G-CSF Mobilized Peripheral Blood Stem Cell with Marrow Transplantation from HLA Compatible Unrelated Donors
Age 0-66, Diagnosis of AML, ALL, CML, Myelodysplastic syndromes, or other myeloproliferative diseases, 6/6 or 5/6 matched unrelated donor.

**STANDARD THERAPY STATEMENT**

We follow the NCCN clinical guidelines for CML (available at [www.nccn.org](http://www.nccn.org)).
GVHD

Research Protocols

Newly Diagnosed

355-03  Multi-Center Phase III Double Blind Trial to Evaluate the Efficacy of Mycophenolate Mofetil Added to Prednisone plus Cyclosporine or Tacrolimus for Treatment of Newly Diagnosed Chronic Graft Versus Host Disease

Inclusion Criteria:
1. Refractory, *Chronic GVHD
2. Active, ** or Progressive, *** Chronic GVHD
3. Confirmation of Chronic GVHD is required by GVHD team
4. Patients with a performance status of ECOG 0-2
MDS

Research Protocols

Special Exception Protocol for 5-Azactidine (NSC 102816) in Patients with Myelodysplastic Syndrome (NCI GroupC)
Must have diagnosis of MDS, age >19, no uncontrolled infections and Karnofsky >50%.

Transplant Protocols

**Allogeneic – Unrelated**

186-93 Treatment of Hematologic Malignancies by Allo BMT using Unrelated HLA-Matched Donors
Age <50, ALL, AML, CML, CLL, MM, MDS, malignant lymphoma. Means to pay for transplant. LEF >50%, DLCO >50%, Karnofsky >80%. Adequate liver and kidney function, no other serious disease, life expectancy >100 days.

**Allogeneic – Related**

205-95 Phase II, Busulfan and Cyclophosphamide Followed by Allogeneic Stem Cell Transplant for Treatment of Hematologic Malignancies
Age 19-65, diagnosis of ALL, AML, MDS, CML, CLL, NHL, HD, or MM. Matched related donor.

281-98 Tx of Hematologic Malignancies w/Cyclophosphamide & TBI Followed by AlloSCT
Age 19-55, diagnosis of AML, MDS, ALL, CLL, or CML. LEF >50%, DLCO >50%, Karnofsky >70%. Adequate liver and kidney function, no other serious disease, life expectancy >100 days.

**Allogeneic - Mini**

389-00 Allogeneic Peripheral Blood Stem Cell Transplantation with a Minimally Myelosuppressive Regimen of Pentostatin and Low-Dose Total-Body Irradiation
Age 19-75 years. Any leukemia, lymphoma, or MDS. Patients who relapse after autologous stem cell transplant are not eligible for conventional autologous or allogeneic protocols. HLA-matched related or unrelated donor.

**CLINICAL TRAILS**

416-03 Phase III Randomized, Multicenter Trial Comparing G-CSF Mobilized Peri. Blood Stem Cell with Marrow Transplantation from HLA Compatible Unrelated Donors
Age 0-66, Diagnosis of AML, ALL, CML, myelodysplastic syndromes, or other myeloproliferative diseases, 6/6 or 5/6 matched unrelated donor.

330-04 Phase II Study of an Oral VEGF Receptor Tyrosine Kinase Inhibitor (PTK787 / ZK 222584) (IND #66370, NSC #719335) in Myelodysplastic Syndrome (MDS)
19 and over, diagnosis of primary or therapy related MDS, no prior history of leukemia, no autologous stem cell or allogeneic transplantation within 12 months.

**STANDARD THERAPY STATEMENT**
We follow the NCCN clinical guidelines for MDS (available at www.nccn.org).
Mini Allogeneic Transplant

**Allogeneic - Mini**

389-00 Allogeneic Peripheral Blood Stem Cell Transplantation with a Minimally Myelosuppressive Regimen of Pentostatin and Low-Dose Total-Body Irradiation Age 19-75 years. Any leukemia, lymphoma, or MDS. Patients who relapse after autologous stem cell transplant are not eligible for conventional autologous or allogeneic protocols. HLA-matched related or unrelated donor.
Multiple Myeloma

Transplant Protocols

**Allogeneic – Unrelated**

186-93 Treatment of Hematologic Malignancies by Allogeneic BMT Using Unrelated HLA-Matched Donors

*Age <50, ALL, AML, CML, CLL, MM, MDS, malignant lymphoma. Means to pay for transplant. LEF >50%, DLCO >50%, Karnofsky >80%. Adequate liver and kidney function, no other serious disease, life expectancy >100 days.*

**Allogeneic – Related**

205-95 Phase II, Busulfan and Cyclophosphamide Followed by Allogeneic Stem Cell Transplant for Treatment of Hematologic Malignancies

*Age 19-65, diagnosis of ALL, AML, MDS, CML, CLL, NHL, HD, or MM. Matched related donor.*

281-98 Treatment of Hematologic Malignancies with Cy-TBI Followed by Allo SCT

*Age 19-55 hematologic cancer that has not responded to treatment, relapsed or is likely to relapse. LEF >50%, DLCO >50%, Karnofsky >70%. Adequate liver and kidney function, no other serious disease, life expectancy >100 days.*

**Allogeneic - Mini**

389-00 Allogeneic Peripheral Blood Stem Cell Transplantation with a Minimally Myelosuppressive Regimen of Pentostatin and Low-Dose Total-Body Irradiation

*Age 19-75 years. Any leukemia, lymphoma, or MDS. Patients who relapse after autologous stem cell transplant are not eligible for conventional autologous or allogeneic protocols. HLA-matched related or unrelated donor.*

**CLINICAL TRIALS**

309-03 A Trial of Tandem Autologous Stem Cell Transplants +/- Post Second Autologous Transplant Maintenance Therapy Versus Single Autologous Stem Cell Transplant Followed by Matched Sibling Non-myeloablative Allogeneic Stem Cell Transplant for Patients with Multiple Myeloma

*Age 19-70, Stage II or III multiple myeloma, \( \geq 4.0 \times 10^6 \) CD34+ cells/kg divided autograft, 3 months of initial therapy, within 2-10 months of initial therapy.*

156-04 A Randomized Multicenter Study to Compare the Safety and Efficacy of \(^{166}\)Ho-DOTMP plus Melphalan to Melphalan Alone as Conditioning for Autologous Peripheral Blood Stem Cell Transplant in Subjects with Primary Refractory MM

*Age 19-75 years, Meet institutional guidelines for autologous pbsct; un-manipulated autologous graft containing \( \geq 2.0 \times 10^6 \) CD34+ cells/kg.*

**STANDARD THERAPY STATEMENT**

We follow the NCCN clinical guidelines for MM (available at [www.nccn.org](http://www.nccn.org)).