THE UNIVERSITY OF TEXAS
M.D.ANDERSON CANCER CENTER

DIVISION OF MEDICINE

A RANDOMIZED PHASE II STUDY OF RITUXIMAB WITH ABVD VERSUS STANDARD ABVD FOR PATIENTS WITH ADVANCED-STAGE CLASSICAL HODGKIN LYMPHOMA WITH POOR RISK FEATURES (IPS SCORE > 2)

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1.0 OBJECTIVES:

1.1 Primary:

To evaluate the event free survival (EFS) following therapy with rituximab plus ABVD or standard ABVD in patients with newly diagnosed classical Hodgkin lymphoma who have poor prognosis defined as International prognostic score (IPS) of > 2.

1.2 Secondary:

1.2.1 To compare the effect of the two treatment arms on PET scan results after 2 cycles of therapy

1.2.2 To compare the effect of the two treatment arms on the level of circulating malignant Hodgkin stem cells

2.0 BACKGROUND:

2.1 **Hodgkin lymphoma:** The world health organization (WHO) classification of Hodgkin lymphoma (HL) distinguished between two major subtypes, classical HL and nodular lymphocyte predominant HL.[1] Approximately 95% of patients with HL will have the classical HL histology, which is characterized by the presence of rare malignant Hodgkin and Reed Sternberg (HRS) cells among an overwhelming number of benign reactive cells. In recent years, new studies shed more light on the biologic and molecular features of HRS cells providing hopes that new targeted therapy may be developed to enhance the cure rate and to reduce treatment-related toxicity.

2.2 **Current standard therapy of classical HL:** Based on several randomized studies comparing ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) with other multi-drug regimens, ABVD became the most widely used combination regimen for the treatment of patients with advanced HL.[2-4] Chemotherapy alone (6-8 cycles) is usually considered to be sufficient for the treatment of patients with advanced stage classical HL. However, involved field radiation therapy is frequently added at the end of chemotherapy to areas of bulky disease. This combined modality approach has been recently compared to chemotherapy (MOPP/ABV) alone in a randomized trial in patients with advanced stage classical HL, and showed no survival advantage, especially in those who achieved complete remission after the completion of chemotherapy.[5] Furthermore, meta-analysis review of fourteen clinical trials comparing chemotherapy with combined modality also showed no survival advantage for those receiving the combined modality approach.[6] Newer treatment programs such as Stanford-V and BEACOPP have shown successful results, but remain less widely used compared with ABVD.[7-9] Although BEACOPP has been shown to be superior to ABVD-like regimens in large scale randomized trials, the superiority of Stanford-V over standard ABVD has not yet been established.[10] Because ABVD may cure only 50-65% of patients with poor risk advanced stage HL, more intensive programs such as BEACOPP may add benefit, despite the increased toxicity. Patients with good risk features have a high cure rate with ABVD, so the use of more intensive and more toxic regimens in this patient population should be used with caution, and preferably within a clinical trial.

2.3 **The International Prognostic Index (IPS):** HL is staged according to the Cotswold modification of the Ann Arbor staging system.[12] Only imaging studies and bone marrow biopsies (clinical staging) are used for stage assignment and treatment planning. The international prognostic score (IPS) was developed to further guide therapy of patients with advanced stage HL.[11] In this model, seven factors are used [Table 1]. Using this model, 42% of patients with advanced stage HL are expected to have an IPS score of >2 (3-7), and those patients are expected to have a 55% 5-year freedom from progression with ABVD-like therapy. In contrast, patients with IPS score 0-2 are expected to have 74% 5-year freedom from progression. Thus, patients with IPS score of > 2 have a poor outcome with current standard therapy, and will be included in this proposed study.

Table 1
International Prognostic Score (IPS) for Advanced HL[11]
1. Sex : male
2. Age: ≥ 45
3. Stage: IV
4. Hemoglobin <10.5 g/dl
5. WBC: ≥ 15,000/
6. Lymphocyte count < 600/ or < 8% of WBC
7. Serum albumin < 4 g/dl

2.4 **Rational for using rituximab for the treatment of classical HL:**

2.4.1 ***Role of reactive B-cells in the microenvironment:*** HRS cells are surrounded by an overwhelming number of reactive cellular infiltrate. These reactive cells are not bystander cells, as once thought of. In contrast, they frequently provide survival signals to HRS cells.[13] The role of the microenvironment in supporting the survival and growth of HRS cells is best illustrated by the difficulty of establishing HRS-derived cell lines. Once HRS cells are taken out of the microenvironment, it is extremely difficult to grow them in culture. It is, therefore, ironic that the host own immune cells are providing survival factors to the malignant cells, creating an "immune-betrayal" phenomenon. Therefore, we hypothesized that eliminating these reactive cells from the microenvironment may deprive HRS cells from critical survival factors and may lead to their growth arrest and death.[13]

2.4.2 ***The putative Hodgkin stem cells are CD20+ cells:*** The rationale for using rituximab in classical HL was recently strengthened by the identification of putative HL stem cells that express CD20.[14] In a landmark study, a group from Johns Hopkins University studied HL cell lines (L428, KM-H2) and found that each line contained a small (<5%) subpopulation of cells that did not express the typical HRS markers CD15 and CD30. Instead, this small subpopulation resembled memory B cells (CD19+CD20+CD27+) and possessed most of the clonogenic capacity of the HL cell lines. Using Aldefluor, a fluorescent aldehyde that is a substrate for aldehyde dehydrogenase (ALDH) that is highly expressed in both normal and malignant stem cells, the clonogenic subpopulation within the HL cell lines also expressed high ALDH activity, while the predominant HRS cells exhibited low ALDH activity. Subsequently, the same investigators examined CD19+ cells that were isolated from the marrow or blood of 5 HL patients. The ALDH-high CD19+ cells were a highly enriched population of immunoglobulin (Ig) light chain-restricted CD27+ memory B cells that represented 0.7 to 3% of the circulating CD19+ cells. These ALDHhigh CD19+ cells also displayed clonal Ig gene rearrangement by polymerase chain reaction (PCR) amplification. In two of these patients, CD15+CD30+ HRS cells were isolated from a fresh diagnostic lymph node and contained the same clonal Ig gene rearrangement as the circulating ALDHhigh CD19+ B cells. Thus, clonotypic memory B cells can be found in both HL cell lines and

patients. These data suggest that these clonotypic memory B cells circulate in relatively high numbers even in early stage patients, and may represent the HL stem cells.[14]

2.5 **Results with rituximab plus ABVD:** The clinical activity of rituximab in patients with relapsed classical HL (irrespective of CD20 expression by HRS cells) was recently examined by our group at M. D. Anderson Cancer Center, in which rituximab was used to deplete CD20+ reactive B lymphocytes from HL microenvironment.[15] Twenty-two heavily pretreated patients with classical HL were treated with six weekly doses of rituximab. Five (22%) patients achieved partial or complete remissions, and eight additional patients had stable disease. Clinical remissions were observed in patients irrespective of CD20 expression by HRS cells, but were observed in patients whose disease was confined to the lymph nodes. In a follow-up study, we combined rituximab with ABVD (R-ABVD) chemotherapy to treat patients with newly diagnosed classical HL.[16, 17] In this phase II study, 65 patients with classical HL were treated with R-ABVD. With a median follow up of 32 months, the estimated event-free survival (EFS) is 82% and overall survival 100%. Importantly, the EFS was improved for all risk categories: for patients with a prognostic score of 0-1 the EFS was 92%, for score 0-2 was 86%, and for score 3-5 was 73% (Fig 1, Table 2).

Table -2 : Event free survival (EFS) observed in patients treated with R-ABVD compared to historical data with ABVD alone. EFS is shown in different groups according to IPS.

IPS Group	ABVD 3-year EFS	R-ABVD 3-year EFS
0-1	79%	95%
0-2	74%	87%
2	67%	76%
>1	60%	76.5%
>2	55%	77%
>3	47%	71%

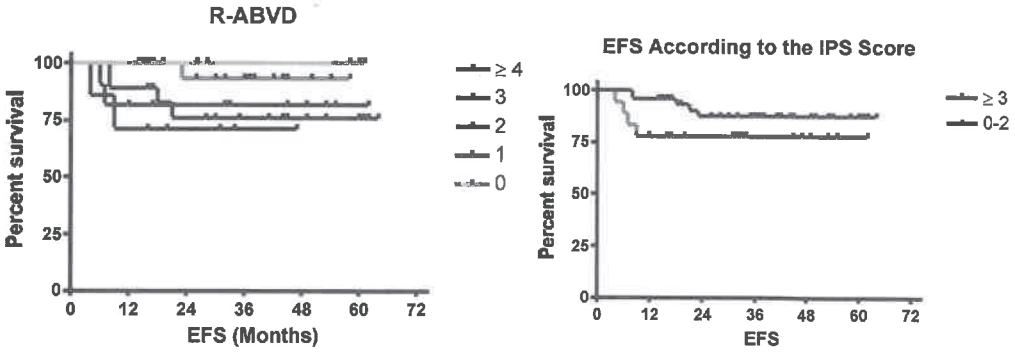


Figure 1: Event free survival (EFS) in 65 patients treated with rituximab plus ABVD (R-ABVD); (Left) results are shown in 5 risk groups according to the international prognostic score (IPS). (Right) results are shown in patients with IPS score of 0-2 and > 2. The same data is shown in Table 2.

2.6: **Role of early PET imaging in predicting treatment outcome:** While the IPS may predict treatment outcome in patients with advanced HL, others have recently examined

the prognostic role of PET imaging after starting therapy. Using this approach, Hutchings and colleagues prospectively assessed the value of positron emission tomography with 2-[18F]fluoro-2-deoxy-D-glucose (FDG-PET) after two cycles of chemotherapy for prediction of progression-free survival (PFS) and overall survival (OS) in Hodgkin lymphoma (HL).[18] Seventy-seven consecutive, newly diagnosed patients underwent FDG-PET at staging, after two and four cycles of chemotherapy, and after completion of chemotherapy. After two cycles of chemotherapy, 61 patients had negative FDG-PET scans and 16 patients had positive scans. Eleven of 16 FDG-PET-positive patients progressed and 2 died. Three of 61 FDG-PET-negative patients progressed; all were alive at latest follow-up. Survival analyses showed strong associations between early FDG-PET after two cycles and PFS ($P < .001$) and OS ($P < .01$). Thus, a positive early interim FDG-PET is highly predictive of progression in patients with advanced-stage HL.

2.7 **Proposal:** based on the encouraging phase-II data from MDACC, we propose to confirm these results in a randomized study focusing on patients with poor risk features (IPS score > 2). Furthermore, we will compare the effect of these two treatment arms on PET imaging after 2 cycles of therapy, and on the level of circulating HL stem cells, and correlate these results with EFS.

3.0 DRUG INFORMATION:

Rituximab

Rituximab is a genetically engineered, chimeric, murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant pre-B and mature B cells. The antibody is an IgG_1 κ immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids (based on cDNA analysis) and has an approximate molecular mass of 145 kD. Rituximab has a binding affinity for the CD20 antigen of ~8.0 nM.

3.1 Safety Profile

No dose-limiting effects were observed in the Phase I/II studies. Reported adverse events including fever, chills, headache, nausea, vomiting, rhinitis, and mild hypotension, occurred primarily during rituximab infusions and typically responded to an interruption of the infusion and resumption at a slower rate. Hypersensitivity reactions such as hypotension, bronchospasm, and angioedema have occurred in association with Rituxan infusion. Deaths within 24 hours of infusion have been reported. These follow an infusion reaction complex, which include cardiopulmonary events (see below). Other adverse events included tumor lysis syndrome, mucocutaneous events, hepatitis B reactivation, neutropenia, thrombocytopenia, asthenia, other hematologic events, cardiac and cardiopulmonary events.

Hematologic Events: In clinical trials, Grade 3 and 4 cytopenias were reported in 48% of patients treated with rituximab; these include: lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of

lymphopenia was 14 days (range, 1 to 588 days) and of neutropenia was 13 days (range, 2 to 116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following Rituximab therapy were reported. In addition, there have been a limited number of postmarketing reports of prolonged pancytopenia, marrow hypoplasia, and late onset neutropenia (defined as occurring 40 days after the last dose of rituximab) in patients with hematologic malignancies. In reported cases of late onset neutropenia (NCI-CTC Grade 3 and 4), the median duration of neutropenia was 10 days (range 3 to 148 days). Documented resolution of the neutropenia was described in approximately one-half of the reported cases; of those with documented recovery, approximately half received growth factor support. In the remaining cases, information on resolution was not provided. More than half of the reported cases of delayed onset neutropenia occurred in patients who had undergone a prior autologous bone marrow transplantation. In an adequately designed, controlled, clinical trial, the reported incidence of NCI-CTC Grade 3 and 4 neutropenia was higher in patients receiving rituximab in combination with fludarabine as compared to those receiving fludarabine alone (76% [39/51] vs. 39% [21/53]).

Cardiac Events: Patients with preexisting cardiac conditions, including arrhythmia and angina, have had recurrences of these cardiac events during rituximab infusions. In rare cases, severe and fatal cardiopulmonary events, including hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, and cardiogenic shock, have occurred, mostly in association with infusion-related reactions. Nearly all fatal infusion-related events occurred in association with the first infusion. Fatal cardiac failure has been observed.

Cardiopulmonary Events: In rare cases, severe and fatal cardiopulmonary events, including hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, and cardiogenic shock, have occurred (4-7/10,000 patients or 0.04-0.07%.) Nearly all fatal infusion-related events occurred in association with the first infusion.

Tumor Lysis Syndrome: Although rare, tumor lysis syndrome has been reported in postmarketing studies and is characterized in patients with a high number of circulating malignant cells (>25,000 µl) by rapid reduction in tumor volume, renal insufficiency, hyperkalemia, hypocalcemia, hyperuricemia, and hyperphosphatemia.

Hepatitis B Reactivation: Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with rituximab. The majority of patients received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately four months after the initiation of rituximab and approximately one month after the last dose.

Renal Events: Rituximab has been associated with severe renal toxicity including acute renal failure requiring dialysis, and in some cases has lead to death. Renal toxicity has occurred in patients with high numbers of circulating malignant cells (>25,000/mm^2) or high tumor burden who experience tumor lysis syndrome.

Infections: RITUXAN induced B-cell depletion in 70% to 80% of patients with NHL and was associated with decreased serum immunoglobulins in a minority of patients; the lymphopenia lasted a median of 14 days (range, 1 to 588 days). Infectious events occurred in 31% of patients: 19% of patients had bacterial infections, 10% had viral

infections, 1% had fungal infections, and 6% were unknown infections. Incidence is not additive because a single patient may have had more than one type of infection. Serious infectious events (Grade 3 or 4), including sepsis, occurred in 2% of patients.

Mucocutaneous Reactions: Severe bullous skin reactions, including fatal cases of toxic epidermal necrolysis, have been reported rarely in patients treated with rituximab. Paraneoplastic pemphigus has been reported very rarely in NHL and CLL patients undergoing chemotherapy plus rituximab treatment. The onset of reaction has varied from 1 to 13 weeks following rituximab exposure.

Additional Safety Signals: The following immune serious adverse events have been reported to occur in patients following completion of rituximab infusions: arthritis, rash, polyarthritis, disorders of blood vessels (vasculitis, serum sickness and lupus-like syndrome),eye disorders (uveitis and optic neuritis), and pleuritis, lung disorders including interstitial pneumonitis, and scarring of the lung (bronchiolitis obliterans) that may result in fatal outcomes.

3.2 Usual Dose:
The recommended dosage of rituximab is 375 mg/m^2 given as an IV infusion once weekly for four or eight doses. Actual body weight measured within 4 weeks prior to initial treatment with rituximab will be used for calculations of body surface area. Rituximab may be administered in an outpatient setting.

DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. Do not infuse rituximab concomitantly with another IV solution or other IV medications.

3.3 Preparation for Administration: Use appropriate aseptic technique. Withdraw the necessary amount of rituximab and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride USP or 5% Dextrose in Water USP. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

3.4 Administration: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. Infusion and hypersensitivity reactions may occur. Premedication, consisting of acetaminophen and diphenhydramine, should be considered before each infusion of rituximab. Premedication may attenuate infusion-related events. Since transient hypotension may occur during rituximab infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to rituximab infusion.

Administration Guidelines for Adult Patient Population

First Infusion: The rituximab solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. Rituximab should not be mixed or diluted with other drugs. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in

50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. Rituximab infusion should be interrupted for severe reactions. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100mg/hr to 50mg/hr) when symptoms have completely resolved. Most patients who have experienced non-life-threatening infusion-related reactions have been able to complete the full course of rituximab therapy

Subsequent Infusions: If the subject tolerated the first infusion well, subsequent rituximab infusions can be administered at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr as tolerated. If the first infusion was not well tolerated, the guidelines for the first infusion should be followed for the subsequent infusions.

Subsequent Infusions: If hypersensitivity or infusion-related events occurred during the first infusion, subsequent infusions should be administered in the same manner as the first infusion.

If the subject tolerated the first infusion well, subsequent rituximab infusions should be administered intravenously through a dedicated line at an initial rate of 1.0 mg/kg/hr (to maximum of 100 mg/hr) for the first hour. If hypersensitivity or infusion-related events do not occur, the infusion rate will be escalated by 1.0 mg/kg/hr (maximum 100 mg increase per hour) every 30 minutes, to a maximum rate of 400 mg/hr. If a hypersensitivity or infusion related event develops, the infusion should be temporarily slowed or interrupted. The infusion can continue at one half the previous rate upon improvement of patient symptoms.

3.5 Rituximab Storage

Rituximab vials are stable at 2° to 8°C (36° to 46°F). Do not use beyond expiration date stamped on carton. Rituximab vials should be protected from direct sunlight. Rituximab solutions for infusion are stable at 2° to 8°C (36° to 46°F) for 24 hours and at room temperature for an additional 24 hours. However, since rituximab solutions do not contain a preservative, diluted solutions should be stored refrigerated (2° to 8°C). No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

3.6 Rituximab Overdosage

There has been no experience with overdosage of rituximab in human clinical trials. Single doses higher than 500 mg/m^2 have not been tested in controlled studies.

BLEOMYCIN

Available Dosage Forms: 15 units per vial of parenteral injection
Ingredient: Bleomycin Sulfate 15 units per vial
Packaging Information: Store between 2 to 8°C (36 and 46°F)
Supplier: Bristol-Myers Oncology Division

Solution Preparation
(Direction for reconstitution)
For IV use: reconstitute the contents in 5 mL or more of 0.9% sodium chloride injection or 5% dextrose injection
For IM or SQ use: Reconstitute the contents in 1 to 5 mL of sterile water for injection, 0.9% sodium chloride, 5% dextrose injection or bacteriostatic water for injection
Stability
(Original Product)
Intact vials are stable under refrigeration and bear an expiration date.
They are stable for 28 days at room temperature.
(Reconstituted Solution)
Manufacturer states that the reconstituted bleomycin in sodium chloride 0.9% and D5W is stable for 24 hours at room temperature. When stored under refrigeration with sodium chloride 0.9%, it is stable for 4 weeks; however, because of the risk of microbial contamination in products without preservatives, it is recommended that the solutions be used within 24 hours on constitution.
Route of Administration
Bleomycin can be administered by intramuscular, intravenous, intra-arterial, subcutaneous and intra-pleural route.
Toxicity Profile:
Pulmonary Effects: Interstitial pneumonitis occurs in approximately 10% of patients receiving the drug. Bleomycin pneumonitis occasionally progresses to pulmonary fibrosis and has resulted in death in approximately 1% of patients receiving the drug. Pulmonary toxicities occur most commonly in elderly patients above 70 and those receiving a total dosage of more than 400 Units, however, pulmonary toxicities are unpredictable and reportedly have developed after a total dosage of < 200 units in younger patients.
Mucocutaneous Effects: 50% of patients receiving bleomycin will have mucocutaneous side effects such as urticaria or erythematous swelling, lesions may then become tender and pruritic. Hyperpigmentation, patchy hyperkeratosis, ichtosis, rash, striae, vesiculation, peeling and bleeding can also occur.
Cardiovascular Effects: Heterogeneous events such as myocardial infarction, cerebrovascular accidents, thrombotic microangiopathy or cerebral arteritis can occur.
Hematologic Effects: Leukopenia, anemia and thrombocytopenia
Others: Febrile episodes, nausea, vomiting, pain at tumor site, hypotension may occur.

DOXORUBICIN

Available Dosage Forms: 10, 20, 50, 100, 150 mg lyophilized powder for injection. Aqueous solution for injection 2 mg/mL
Ingredients: For lyophilized powder for injection: for each 10 mg of doxorubicin, 50 mg of lactose will be added. For aqueous solution for injection: also contains sodium chloride 0.9%
Packaging Information: Store between 2 and 8°C (36 and 46°F)
Protect from light.
Supplier: Various
Solution Preparation
(Direction for reconstitution)
Reconstitute by adding 5 mL (10 mg vial), 10 mL (20 mg vial), 25 mL (50 mg vial), 50 mL (100 mg vial) or 75 mL (150 mg vial) of 0.9% sodium chloride injection to the vial and shaking to dissolve, producing a solution containing 2 mg/mL of doxorubicin. Use of bacteriostatic water for injection is not recommended. An appropriate volume of air should be withdrawn from the vial during reconstitution to avoid excessive pressure buildup.
Stability
(Original Product):
Dry powder is stable for 2 years when stored in the unopened vials in a dry place protected from light.
(Reconstituted Solution)
Reconstituted solution is stable at room temperature for 24 hours, and for 48 hours under refrigeration. Freezing solutions is not recommended. Reconstituted solutions should be protected from light.
Route of Administration
Intravenous injection to be given no less than 3-5 minutes, depending on the size of the vein and the dose; intravenous slow infusion and continuous intravenous infusion.
Toxicity Profile:
Hematologic: Leukopenia, anemia, thrombocytopenia
Cardiac Effects: Acute transient abnormalities with abnormal EKG findings, which can include ST-T wave changes, T-wave flattening and ST-segment depression, and arrhythmia's; chronic cumulative cardiotoxicity includes congestive heart failure and cardiorespiratory decompensation, including dilation of the heart, pleural effusion and venous congestion which may be irreversible and unresponsive to cardiac supportive therapy.
Gastrointestinal Effects: Stomatitis and esophagitis, nausea and vomiting
Dermatologic Effects: Complete alopecia, symptoms of radiation recall in patients with previous radiation treatment, resulting in erythema with vesiculation, nonpitting edema, severe pain and moist desquamation in sites which were previously subjected to radiation therapy.
Others: Extravasation, facial flushing, rare incidences of fever and chills

VELBAN

Description: Velban (Sterile Vinblastine Sulfate, USP) is vincaleukoblastine sulfate (1:1). It is the salt of an alkaloid extracted from *Vinca rosea* Linn, a common flowering herb known as the periwinkle (more properly known as *Catharanthus roseus* G. Don). Previously, the generic name was vincaleukoblastine, abbreviated VLB. It is a stathmokinetic oncolytic agent. When treated in vitro with this preparation, growing cells are arrested in metaphase. Vinblastine sulfate is a white to off-white powder. It is freely soluble in water, soluble in methanol, and slightly soluble in ethanol. It is insoluble in benzene, ether, and naphtha. The clinical formulation is supplied in a sterile form for intravenous use only. Vials of Velban contain 10 mg (0.011 mmol) of vinblastine sulfate, in the form of a white, amorphous, solid lyophilized plug, without excipients. After reconstitution with sodium chloride solution, the pH of the resulting solution lies in the range of 3.5 to 5.
Clinical Pharmacology: Tissue-culture studies suggest an interference with metabolic pathways of amino acids leading from glutamic acid to the citric acid cycle and to urea. Pharmacokinetic studies in patients with cancer have shown a triphasic serum decay pattern following rapid intravenous injection. The initial, middle, and terminal half-lives are 3.7 minutes, 1.6 hours, and 24.8 hours respectively. Since the major route of excretion may be through the biliary system, toxicity from this drug may be increased when there is hepatic excretory insufficiency. Following injection of tritiated vinblastine in the human cancer patient, 10% of the radioactivity was found in the feces and 14% in the urine; the remaining activity was not accounted for.
Hematologic Effects: Clinically, leukopenia is an expected effect of Velban (Vinblastine Sulfate, USP), and the level of the leukocyte count is an important guide to therapy with this drug. Following therapy with nadir in white-blood-cell count may be expected to occur 5 to 10 days after the last day of drug administration. Recovery of the white blood count is fairly rapid thereafter and is usually complete within another 7 to 14 days. With the smaller doses employed for maintenance therapy, leukopenia may not be a problem.

DTIC-Dome

Description: DTIC-Dome Sterile (dacarbazine) is a colorless to an ivory colored solid which is light sensitive. Each vial contains 100 mg of dacarbazine, or 200 mg of dacarbazine (the active ingredient), anhydrous citric acid and mannitol. DTIC-Dome is reconstituted and administered intravenously (pH 3-4). DTIC-Dome is an anticancer agent.

Clinical Pharmacology: In a patient with renal and hepatic dysfunction, the half-lives were lengthened to 55 minutes and 7.2 hours. Although the exact mechanism of action of DTIC-Dome is not known, three hypotheses have been offered:
1. inhibition of DNA synthesis by acting as a purine analog
2. action as an alkylating agent
3. Interaction with SH groups

Indications and Usage: DTIC-Dome is indicated in the treatment of metastatic malignant melanoma. In addition, DTIC-Dome is also indicated for Hodgkin's disease as a secondary-line therapy when used in combination with other effective agents.

Contraindications: DTIC-Dome is contraindicated in patients who have demonstrated a hypersensitivity to it in the past.

Warnings: Hemopoietic depression is the most common toxicity with DTIC-Dome and involves primarily the leukocytes and platelets, although, anemia may sometimes occur.

Leukopenia and thrombocytopenia may be severe enough to cause death. The possible bone marrow depression requires careful monitoring of white blood cells, red blood cells, and platelet levels. Hemopoietic toxicity may warrant temporary suspension or cessation of therapy with DTIC-Dome. Hepatic toxicity accompanied by hepatic vein thrombosis and hepatocellular necrosis resulting in death, has been reported. The incidence of such reactions has been low; approximately 0.01% of patients treated.

4.0 PATIENT ELIGIBILITY:

Inclusion Criteria:

a. Previously untreated patient with classical Hodgkin's lymphoma patients with stage III and IV.

b. International Prognostic Score of > 2 (patient must have > 2 of the following risk features: Male, ≥45 years of age, Stage IV, Albumin <4, WBC ≥15, Lymphocytes <8% or <600, Hgb <10.5)

c. Must sign a consent form

d. Must be older than 16 years

e. Must have adequate bone marrow reserve (ANC ≥ 1,500/uL, Platelet > 100,000/uL)

f. LVEF ≥ 50% by MUGA scan or echocardiogram

g. Serum creatinine < 2 mg/dl, serum bilirubin < 2 mg/dl, AST or ALT <2x ULN

h. Bi-dimensionally measurable disease

Exclusion Criteria:

a. Lymphocyte Predominant Hodgkin's Lymphoma

b. Known HIV infection.

c. Pregnant women and women of child bearing age who are not practicing adequate contraception

d. Prior chemotherapy or radiation therapy.

e. Severe pulmonary disease as judged by the PI including COPD and asthma

f. Active infection requiring treatment with intravenous therapy

g. Presence of CNS lymphoma

h. Concomitant malignancies or previous malignancies within the last 5 years (exception made for adequately treated basal or squamous cell carcinoma of the skin or carcinoma in situ of cervix)

i. Active hepatitis B or C infection

5.0 TREATMENT PLAN

5.1 To register a patient from centers outside MDACC, fax the following forms provided in the CRFs: 1) Onstudy 2)Disease Description 3)eligibility criteria with supporting documentation showing patient's eligibility to:

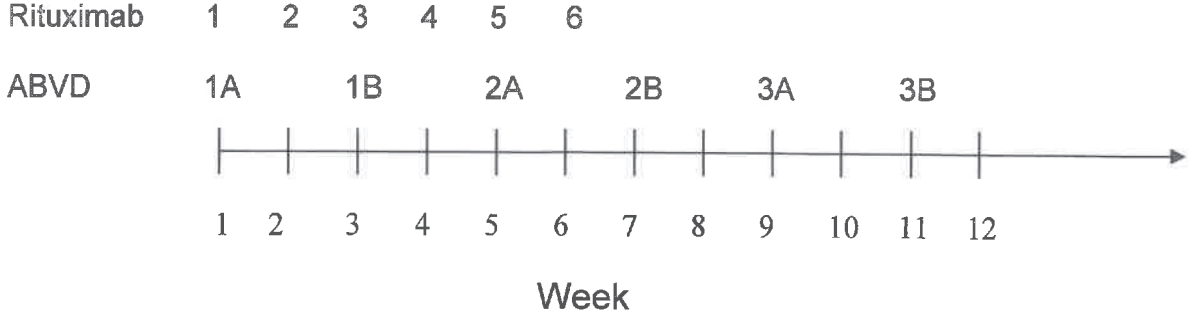
[redacted]
Amanda Copeland
Ph: 713-792-3455
Pgr: 713-606-2298
Fax: 713-794-5656

Page Amanda Copeland (713 606-2298) or call (713-792-3455) to inform of pending registration.

Patients will then be randomized by MDACC to either Arm A or B, and the registering center will be notified of the randomization result.

5.2 Arm A will consist of patients receiving RITUXIMAB I.V. weekly x 6 weeks at a dose of 375 mg/m2. ABVD will be given at standard dose and schedule as shown below. The treatment schema is as follows:

	Arm A		ARM B
Week	Rituximab	ABVD	ABVD
1 (day 1)	X	X 1A	X 1A
2 (day 8)	X		
3 (day 15)	X	X 1B	X 1B
4 (day 22)	X		
5 (day 29)	X	X 2A	X 2A
6 (day 36)	X		
7		X 2B	X 2B
9		X 3A	X 3A
11		X 3B	X 3B
13		X 4A	X 4A
15		X 4B	X 4B
17		X 5A	X 5A
19		X 5B	X 5B
21		X 6A	X 6A
23		X 6B	X 6B



5.3 Total doses of rituximab will be 6 and of ABVD will be 12 doses (6 cycles). Rituximab may be given on the same day of ABVD therapy. For cycle 1 only, Rituximab may be given on day 2, if time constraints do not allow both ABVD and Rituximab to be given on day 1.This research study protocol allows the subject to receive up to 6 infusions of rituximab. Even if the treatment is shown to be of benefit, additional infusions of rituximab beyond that allowed in the protocol cannot be given to the subject while she/he is participating in this study.

Patients of MDACC and randomized to the ABVD arm, will be allowed to receive treatment with their local MD. Patients of MDACC and randomized to the RABVD arm, will be required to receive all Rituximab containing regimens at MDACC but can receive standard ABVD with local MD. (see appendix A).

5.4 A summary of the two treatment arms is shown in the table below.

Drug	Dose		Route
	Arm-A	Arm-B	
Rituximab	375 mg/m^2	---	Iv
Adriamycin	25 mg/m^2	25 mg/m^2	Iv
Bleomycin	10 U/m^2	10 U/m^2	Iv
Velban	6 mg/m^2	6 mg/m^2	Iv
DTIC	375 mg/m^2	375 mg/m^2	iv

5.5 Radiation therapy

Radiation therapy is not allowed

5.6 **Supportive care**: Patients may receive primary prophylaxis with filgrastim or peg-filgrastim at the treating physician's discretion after each dose of ABVD or R-ABVD. The use of erythropoietin is allowed as per ASCO/ASH guidelines

5.7 **Dose modification/Toxicity Management:**

A number of measures will be taken to ensure the safety of patients participating in this study. These measures will be addressed through exclusion criteria (see Section 4.0) and routine monitoring as follows. Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, blood pressure, and laboratory measurements. Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study.

5.7.1 Rituximab

No dose reduction of rituximab is allowed. Treatment of infusion-related symptoms with diphenhydramine and acetaminophen is recommended. Additional treatment with bronchodilators or IV saline may be indicated. Epinephrine, antihistamines, and corticosteroids should be available for

immediate use in the event of a hypersensitivity reaction to rituximab (e.g., anaphylaxis). In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100mg/hr to 50mg/hr) when symptoms and laboratory abnormalities have completely resolved.

5.7.2 ABVD dose modification for hematologic toxicity :

Day of Treatment ANC	ABVD dose level
> 1,000 / μL	0
≤ 1,000 / μL	Delay treatment until ANC > 1000/ μL then give filgrastim or peg-filgrastim with subsequent cycles. At the discretion of the treating physician, chemotherapy may be given without delays
< 1,000/ μL despite growth factor support	At the discretion of the treating physician reduce DTIC by 25%

5.7.3 ABVD dose modification for non-hematologic toxicity (except nausea, vomiting, alopecia, and fatigue):

Grade	ABVD dose level
0-2	0
3	-1 (reduce DTIC by 25%)
4	Remove from study

5.7.4 For suspected or symptomatic bleomycin lung toxicity: Stop bleomycin and treat with steroids as clinically indicated. For patients older than 60 years, patient with smoking history, or those with bulky mediastinal mass, bleomycin may be omitted for the last 2 cycles at the attending physician's discretion.

5.8 Immunization during B-Cell Depletion

Efficacy and/or safety of immunization during periods of B-cell depletion have not been adequately studied. It is recommended that a patient's vaccination record and possible requirements be reviewed. Per the investigator's discretion, the patient may have any required vaccination/booster administered at least 4 weeks prior to the initiation of study treatment. Review of the patient's immunization status for the following vaccinations is recommended: tetanus; diphtheria; influenza; pneumoccocal polysaccharide; *Varicella*; measles, mumps and rubella (MMR); and hepatitis B. Patients who are considered to be at high risk for hepatitis B virus (HBV) infection and for whom the investigator has determined that immunization is indicated should complete the entire HBV vaccine series at least 4 weeks prior to participation in the study.

5.9 Data Collection and multi-center procedure

Data will be collected on uniform CRFs provided by MDACC. These are to be completed for baseline information and throughout the study as required by the protocol and faxed within 4 weeks after completion of each cycle to:

Tian Tian
Ph:713-792-2860 Fax: 713-794-5656

After patients have completed therapy, completed CRFs will be faxed within 1 month of patient's follow-up visit.

5.10

MDACC's data monitoring committee will review the study. Quarterly conference calls among Principal Investigators and support staff will take place to review enrollment and any safety issues concerning protocol, and to discuss the need for any protocol amendments.

6.0 PRETREATMENT EVALUATION (within 4 weeks of starting treatment):

6.1 History and physical examination

6.2 Determine IPS score. (Only patients with IPS score of 2 or higher are eligible)

6.3 CBC, with differential count and platelet count.

6.4 Serum Chemistries: glucose, BUN, creatinine, uric acid, total bilirubin, alkaline phosphatase, LDH, total protein, albumin, SGOT(AST), SGPT (ALT), and calcium.

6.5 Immunology: Hepatitis B and C will be tested in all patients.

6.6 Appropriate imaging studies which should include at least a chest x-ray (CXR), CT scans of the neck, chest, abdomen and pelvis,

6.7 PET scan

6.8 Measurement of LVEF by MUGA or echocardiogram

6.9 Bone marrow biopsy/aspirate

6.10 Serum pregnancy tests for women of child bearing age

7.0 EVALUATION DURING THE CHEMOTHERAPY ADMINISTRATION

7.1 CBC with differential at the beginning of each ABVD dose (within 2 days)

7.2 Monthly serum electrolytes

7.3 Repeat imaging studies every 2 cycles of ABVD.

7.4 PET scan after 2 cycles of therapy (approximately 2 months), and every 2 cycles until it becomes negative (if clinically indicated) .

7.5 Repeat bone marrow biopsy/aspirate if was positive prior to starting therapy at the end of ABVD therapy.

8.0 FOLLOW UP EVALUATION

After completion of therapy, patients will have follow up evaluation to determine the disease status every 3 months during the first year of follow up, every 4 months during the second year, every 6 months during years 3-5, and once a year thereafter. Follow up evaluation will include physical examination and appropriate blood tests and imaging studies, as clinically indicated.

9.0 CRITERIA FOR RESPONSE:

The Revised Response Criteria for Malignant Lymphoma[19] will be used as shown in Table-3 :

Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

10.0 CRITERIA FOR DISCONTINUING THERAPY:

- Active HBV infection or hepatitis (Subjects who are carriers of hepatitis B at the time of discontinuation from study treatment will continue to be followed for clinical and laboratory signs of active HBV infection and for signs of hepatitis)
- Severe or life-threatening anaphylaxis or hypersensitivity reaction
- Inability of subject to comply with study requirements
- Determination by the investigator that it is no longer safe for the subject to continue therapy
- Increasing disease, at any time during treatment or of less than PR after a minimum of 6 courses of therapy. Sometimes, a patient's disease will

progress so rapidly that it is appropriate to change therapy after a single course. Patients who are not responding will be considered failures on this regimen and if medically stable will be offered an alternative regimen. Patients who develop unacceptable toxicity should be removed from the study.

- Grade 3 or 4 non-hematologic toxicity that are not predicted by ABVD or R-ABVD (alopecia, nausea/vomiting, neuropathy).
- Patient's refusal to continue therapy.

11.0 STATISTICAL CONSIDERATION:

This is a trial to study the chemotherapy ABVD (Adriamycin, Bleomycin, Vinblastine, and Dacarbazine) with or without rituximab in treating patients with Hodgkin Lymphoma. Patients will be enrolled into the study at the accrual rate of 3 patients per month with an additional thirty-nine months follow-up period.

Objective

The primary objective of the study is to evaluate the efficacy of the combination regimen of rituximab and ABVD chemotherapy (R-ABVD) and ABVD alone measured as event-free survival (EFS).

Sample Size and Power

According to the historical data, the three-year EFS rate is 55% for the patients treated with ABVD and 77% for the patients treated with R-ABVD. A 22% improvement in three-year EFS rate is considered a clinically significant outcome for the groups. The corresponding hazard ratio between the R-ABVD group and the ABVD group is 0.437 based on the assumption that the time to event follows an exponential distribution. Assuming two-sided type I error rate of 0.05, accrual rate of 3 patients per month, and additional 39 months of follow-up, a trial with 54 patients each arm will have 80% of power to detect a 22% improvement in three-year EFS rate. Two interim analyses will be performed to allow for the early termination of the trial in light of evidence that one treatment arm is superior to the other treatment arm or there is no difference between the two treatment arms. In order to provide an overall significance level of 0.05 for the study, the interim analyses will use a Lan-DeMets monitoring boundary with an O'Brien-Fleming stopping rule (Cytel 2004). The interim analyses will be performed when 17 and 35 out of the expected 52 events have been observed. Using O'Brien-Fleming outer test boundaries, the two-sided Z-score test cut-offs at the two interims and final analyses for rejecting the null hypothesis will be ± 3.71, 2.51, and 1.96, respectively. The inner (futility) Z-score boundaries for stopping and accepting the null are 0.04, 0.95, and 1.96. By factoring in the 10% of patient drop-out rate, the total number of patients will be enrolled to the study is120.

Analysis Plans

Patients' demographic information at baseline will be analyzed, with data summarized in tables listing the number of subjects per treatment group in order to assess comparability. The student t-test or the Wilcoxon test will be used to compare continuous variables between two different patient groups. The chi-square test or the Fisher's exact test will be applied to assess the association between two categorical variables. Logistic regression will be utilized to assess the effect of patient prognostic factors on the response rate.

Expression of CD19 and CD20 will be measured overtime. The distribution of biomarkers will be examined first by the exploratory data analysis using scatter plot matrix, box plots, BLiP plot (Lee, 1997) and trellis plot, etc. Correlation among continuous biomarkers will be examined by Pearson or Spearman rank correlation coefficients. The association on discrete biomarkers will be tested by chi-square or Fisher's exact test. McNemar's test will be applied to test the change of a single discrete biomarker over time. Repeated measures analysis including mixed effects model will be performed to analyze biomarkers change over time.

Time-to-event outcomes, including event-free survival and overall survival, will be estimated using Kaplan-Meier method. The log-rank test will be performed to test the difference in time-to-event distributions between patient groups. Cox proportional hazards model will be utilized to include multiple covariates in the time-to-event analysis.

Toxicity data will be summarized by frequency tables. The association between the types and severity of toxicity and the treatment groups will be evaluated. No formal statistical testing will be performed on these summary data.

For the efficacy endpoint, intend-to-treat analysis will be applied to the randomized and eligible patients. For the toxicity endpoint, per-treated analysis will be used to include any patient who received the treatment – regardless of the eligibility nor the duration or dose of the treatment received.

12.0 REPORTING OF ADVERSE EVENTS

12.1 Adverse Event and Reporting Definitions

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

An **adverse event (AE)** is any untoward medical occurrence in a subject participating in an investigational trial or protocol regardless of causality assessment. An adverse event can be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, syndrome or disease associated with or occurring during the use of an investigational product whether or not considered related to the investigational product. AEs will be recorded on the paper CRF forms and faxed to Amanda Copeland at 713-

794-5656 for each cycle completed. These should be sent within 4 weeks of completion of that cycle.

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

- Results in **death** (i.e. the AE caused or lead to death)
- Is **life-threatening** (i.e. the AE placed the subject at immediate risk of death; it does not apply to an AE which hypothetically might have caused the death if it were more severe)
- Requires or prolongs inpatient **hospitalization** (i.e. the AE required at least a 24-hour inpatient hospitalization or prolonged a hospitalization beyond the expected length of stay; hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not SAEs by this criterion)
- Is **disabling** (i.e. the AE resulted in a substantial disruption of the subject's ability to carry out normal life functions)
- Is a **congenital anomaly/birth defect** (i.e., an adverse outcome in a child or fetus of a subject exposed to the trial drug prior to conception or during pregnancy)
- It does not meet any of the above serious criteria but **may jeopardize the subject** and **may require medical or surgical intervention** to prevent one of the outcomes listed above

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

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

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

12.2 Reporting of Serious Adverse Events Associated with Rituximab

All serious adverse events (SAEs) regardless of causality to rituximab (this applies to both expected and unexpected events) should be recorded on the Serious Adverse Event form and faxed within 24 hours of notification of SAE occurrence to:

[redacted]
Amanda Copeland
Ph 713-792-9455
Pgr 713-606-2298
Fax 713-794-5656

SAE Reporting Guidelines:

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the SAE form:

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

Follow-up information:

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

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

Occasionally Genentech and/or MDACC may contact the reporter for additional information, clarification, or current status of the subject for whom and adverse event was reported. For questions regarding SAE reporting, you may contact Amanda Copeland at MDACC, noted above.

Study Drug Relationship:

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

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

13.0 REFERENCES:

1. Harris, N.L., et al., *The World Health Organization classification of neoplasms of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting--Airlie House, Virginia, November, 1997.* Hematol J, 2000. **1**(1): p. 53-66.
2. Connors, J.M., *State-of-the-art therapeutics: Hodgkin's lymphoma.* J Clin Oncol, 2005. **23**(26): p. 6400-8.
3. Johnson, P.W., et al., *Comparison of ABVD and alternating or hybrid multidrug regimens for the treatment of advanced Hodgkin's lymphoma: results of the United Kingdom Lymphoma Group LY09 Trial (ISRCTN97144519).* J Clin Oncol, 2005. **23**(36): p. 9208-18.
4. Canellos, G.P., *Is ABVD the standard regimen for Hodgkin's disease based on randomized CALGB comparison of MOPP, ABVD and MOPP alternating with ABVD?* Leukemia, 1996. **10 Suppl 2**: p. s68.
5. Aleman, B.M., et al., *Involved-field radiotherapy for advanced Hodgkin's lymphoma.* N Engl J Med, 2003. **348**(24): p. 2396-406.
6. Loeffler, M., et al., *Meta-analysis of chemotherapy versus combined modality treatment trials in Hodgkin's disease. International Database on Hodgkin's Disease Overview Study Group.* J Clin Oncol, 1998. **16**(3): p. 818-29.
7. Connors, J.M., *ABVD, the Stanford V regimen, and BEACOPP for Hodgkin's lymphoma: what should an oncologist do?* Clin Lymphoma, 2005. **6**(1): p. 50-1.
8. Bartlett, N.L., et al., *Brief chemotherapy, Stanford V, and adjuvant radiotherapy for bulky or advanced-stage Hodgkin's disease: a preliminary report.* J Clin Oncol, 1995. **13**(5): p. 1080-8.
9. Diehl, V., et al., *Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease.* N Engl J Med, 2003. **348**(24): p. 2386-95.
10. Gobbi, P.G., et al., *ABVD versus modified stanford V versus MOPPEBVCAD with optional and limited radiotherapy in intermediate- and advanced-stage Hodgkin's lymphoma: final results of a multicenter randomized trial by the Intergruppo Italiano Linfomi.* J Clin Oncol, 2005. **23**(36): p. 9198-207.

11. Hasenclever, D. and V. Diehl, *A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease.* N Engl J Med, 1998. **339**(21): p. 1506-14.
12. Lister, T.A., et al., *Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting.* J Clin Oncol, 1989. **7**(11): p. 1630-6.
13. Younes, A. and A. Carbone, *Clinicopathologic and molecular features of Hodgkin's lymphoma.* Cancer Biol Ther, 2003. **2**(5): p. 500-7.
14. Jones, R.J., et al., *Clonotypic B Cells Circulate in Hodgkin's Lymphoma (HL).* ASH Annual Meeting Abstracts, 2006. **108**(11): p. 470-.
15. Younes, A., et al., *A pilot study of rituximab in patients with recurrent, classic Hodgkin disease.* Cancer, 2003. **98**(2): p. 310-4.
16. Younes, A., et al., *Gemcitabine Plus Rituximab Therapy of Patients with Relapsed and Refractory Classical Hodgkin Lymphoma.* Blood (ASH Annual Meeting Abstracts), 2005. **106**(11): p. 1498-.
17. Younes, A., et al., *Six Weekly Doses of Rituximab Plus ABVD for Newly Diagnosed Patients with Advanced Stage Classical Hodgkin Lymphoma: Depletion of Reactive B-Cells from the Microenvironment by Rituximab.* Blood (ASH Annual Meeting Abstracts), 2005. **106**(11): p. 1499-.
18. Hutchings, M., et al., *FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma.* Blood, 2006. **107**(1): p. 52-59.
19. Cheson, B.D., et al., *Revised response criteria for malignant lymphoma.* J Clin Oncol, 2007. **25**(5): p. 579-86.

Appendix A
Outside Physician Participation During Treatment

1 MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician.

This will be documented in the patient record

2 A letter to the local physician will outline the patient's participation in the clinical trial and will request local physician agreement to supervise the patient's care

3 Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.

4 Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.

5 A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.

6 Documentation to be provided by the local physician will include drug administration records, progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.

7 The home physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.

8 Patients will return to MDACC every 2 months for evaluation.

9 Patients randomized to the ABVD alone treatment group will be allowed to receive ABVD with their local MD. For those randomized to the Rituximab group, they will be allowed to receive ABVD at home with their local MD once they have completed the Rituximab component (ie. first 6 weeks). Rituximab must be given at MDACC.