Risk-Adapted Therapy For Patients With Untreated Age-Adjusted International Prognostic Index Low-Intermediate Risk, High-Intermediate Risk, Or High Risk Diffuse Large B Cell Lymphoma

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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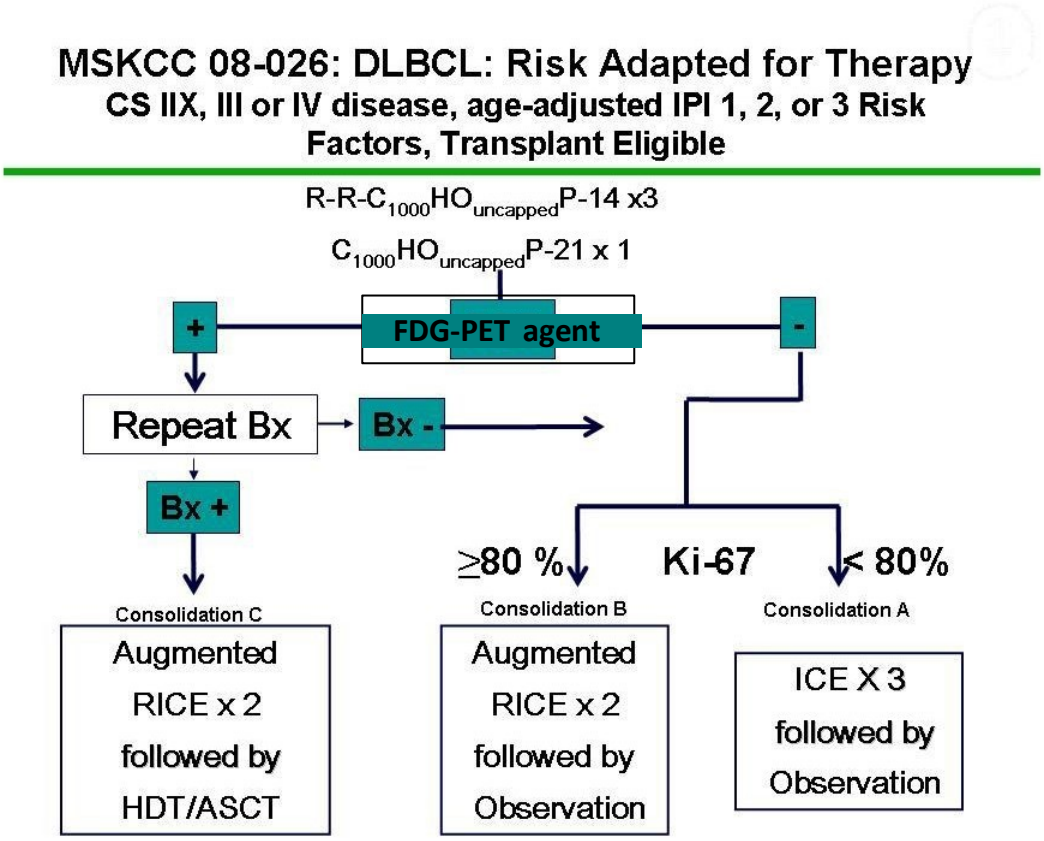
1.0 PROTOCOL SUMMARY AND SCHEMA

The goal of this study is to assess 2 year PFS rates of patients with intermediate and high risk diffuse large B cell lymphoma who are treated according to an accelerated treatment program that incorporates chemotherapy and rituximab and uses risk stratification to one of three consolidation programs based upon results of interim restaging FDG-PET evaluation; positive FDG-PET is confirmed by biopsy.

Schema is depicted below:



2.1 OBJECTIVES AND SCIENTIFIC AIMS

2.2 Primary objective

To determine the 2-year PFS and overall survival from the start of induction therapy conditional on attaining either a negative FDG-PET or a negative biopsy at the interim evaluation. The probability of this outcome will be evaluated separately in the Ki-67 <80 (Consolidation A) and the Ki-67 ≥80 (Consolidation B) cohorts.

2.3 Secondary Objectives

a. To obtain preliminary data on biodistribution, dosimetry and potential clinical usefulness of the proliferation marker [18F] fluorothymidine (FLT) in patients with diffuse large cell lymphoma, using combined positron emission tomography/computed tomography (FLT-PET/CT). These scans will be obtained at baseline, and prior to the start of cycle 3; the earliest the second scan can be obtained is the day after prednisone completion. FLT-PET scans will be done for the first 60 patients.

b. To determine the role of CT volumetric analysis compared to standard unidimensional CT in this patient population. These scans will be obtained at baseline (when possible), after cycle 4 of therapy and at the conclusion of treatment.

3.1 BACKGROUND AND RATIONALE

3.2 Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common lymphoid malignancy in the United States and Europe accounting for one third of cases. In the past 5 years, several phase III random assignment trials have demonstrated an improvement in PFS with the addition of the chimeric anti-CD20 monoclonal antibody rituximab to CHOP or CHOP-like chemotherapy regimens.(Coiffier, Lepage et al. 2002; Feugier, Van Hoof et al. 2005; Habermann, Weller et al. 2006; Pfreundschuh, Trumper et al. 2006) However, patients < 60 years of age with unfavorable prognostic features have not been included in these randomized trials; in this cohort of patients the PFS is < 50%. The standard of care remains controversial for these patients. These patients are the subject of the current study.

3.3 Pre-Treatment Prognostic Factors

The most widely used clinical models for prognosis are the International Prognostic Index (IPI) and the more commonly used, age-adjusted IPI (aaIPI). The aaIPI consists of three factors (adverse factors include: Eastern Cooperative Oncology Group Performance Status [ECOG PS] ≥ 2; LDH > normal; Ann Arbor clinical stage III or IV) and is applied independently to groups of patients either uniformly ≤ 60 years of age or > 60 years of age; the four risk groups are determined by the number of adverse factors: Low (L), 0; Low-Intermediate (LI), 1; High-Intermediate (HI) 2; and High (H) 3. For example, the aaIPI has been particularly useful in the analysis of the results of trials in a restricted age group such as those involving high dose therapy (HDT) and ASCT (Hamlin, Zelenetz et al. 2003) or uniform treatment of the older patient. (Feugier, Van Hoof et al. 2005) As useful as

clinical models have been in identifying risk groups, they do not identify specific abnormalities that could lead to therapy tailored to molecular lesions.

The work of the Lymphoma, Leukemia, Myeloma Profiling Project (LLMPP) has identified two subtypes of DLBCL: germinal center (GC); and activated B cell (ABC). (Alizadeh, Eisen et al. 1999; Rosenwald, Wright et al. 2002) Subsequent work has associated the ABC tumors with constitutive activation of the NFκB signaling pathway. (Rosenwald, Wright et al. 2002; Feuerhake, Kutok et al. 2005) In patients treated with doxorubicin-based chemotherapy programs without rituximab the ABC subtype of DLBCL has an inferior outcome compared to the GC subtype (Rosenwald, Wright et al. 2002); however, this difference may be overcome by the addition of rituximab. (Farinha, Sehn et al. 2006) Furthermore, molecular studies have validated the clinical findings (Hamlin, Portlock et al. 2004) that primary mediastinal large B cell lymphoma (PMLBCL) is a distinct subtype of DLBCL; the molecular features are more closely related to Hodgkin Lymphoma (HL) than either the GC or ABC subtypes of DLBCL.(Rosenwald, Wright et al. 2003; Savage, Monti et al. 2003) In addition outcome of some of the more unusual subtypes of aggressive lymphoma are yet to be defined in the era of rituximab-based chemotherapy. Though gene signatures predictive of outcome have been developed, they remain impractical as they depend on gene expression array analysis which is still some years away from routine clinical use. However, the predictive models have been adapted to quantitative polymerase chain reaction (PCR) using only 6 genes (Lossos, Czerwinski et al. 2004) and immunohistochemistry using only 3 antibodies (Hans, Weisenburger et al. 2004); both of these models have been able to predict outcome in patients treated with conventional chemotherapy, but remain to be validated in patients treated with immuno-chemotherapy.

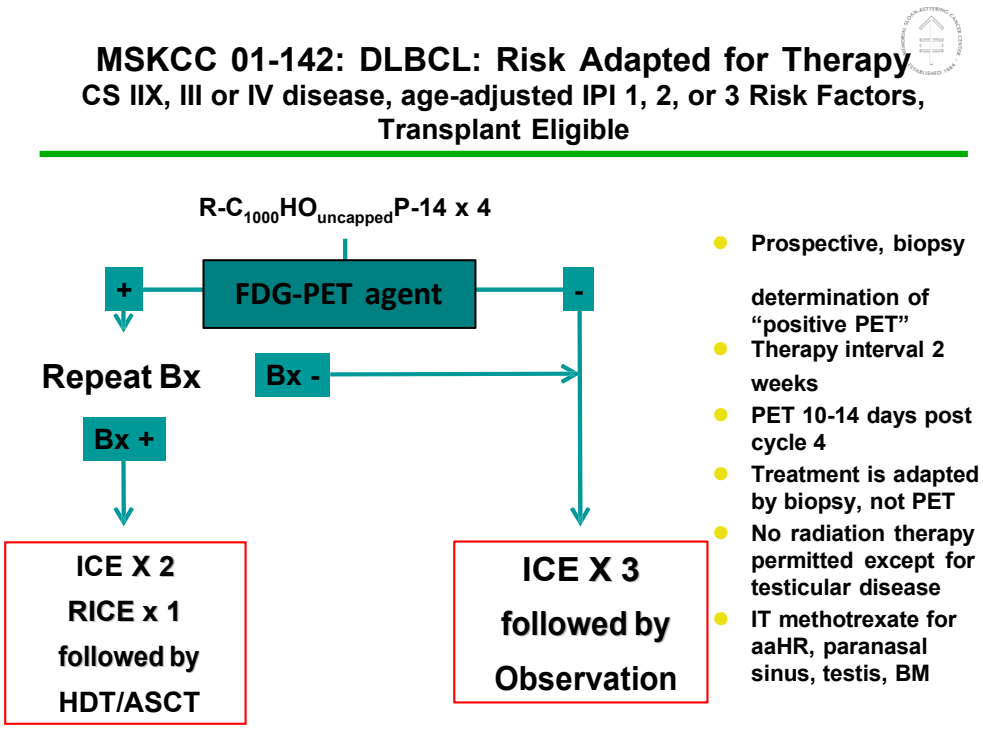
3.4 Interim Evaluation

Though pre-treatment factors influence outcomes of patients with DLBCL, none provides a definitive prediction of outcome. Thus, early identification of patients who may or may not respond to standard therapy may provide the opportunity to adapt therapy. This is an important area of ongoing investigation by the Lymphoma Service at MSKCC. Ideally, patients with a negative interim result would be destined to do well and those with a positive results fair poorly. We and others have used early restaging FDG-PET in this setting. The published literature suggests that those patients with a negative interim restaging FDG-PET scan have $\geq 80\%$ chance of being progression-free at 3 years; however patients with a positive test have PFS that ranges from 10-50%. Hence, the positive predictive value of an interim restaging FDG-PET scan is suspect. Despite these data, many major centers change therapy to a more aggressive approach, an autologous stem cell transplant, if the interim FDG-PET scan is positive, nearly always without biopsy confirmation of active disease.

3.5 MSKCC Protocol 01-142

As stated above in patients < 60 yrs. old, therapy for poor risk (aaIPI HIR or HR) DLBCL remains controversial. The standard of care in the United States is treatment with R-CHOP-21 (every 3 weeks). However, in many centers in the United States and

internationally, patients with aaIPI HIR or HR disease receive consolidation therapy with high dose therapy (HDT) and ASCT despite the lack of a clear overall survival improvement compared to the use of HDT and ASCT in the relapsed setting. We recently completed a risk-adapted, phase II study for patients with stage IIX, III, and IV DLBCL with 1-3 risk factors defined by the age-adjusted IPI (MSKCC protocol 01-142). Induction therapy consisted of 4 cycles of R-CHOP-14 (doses of cyclophosphamide-1000 mg/m^2, doxorubicin-50 mg/m^2 and un-capped vincristine at 1.4 mg/m^2). After interim restaging with FDG-PET, patients with a negative FDG-PET scan received non-cross resistant chemotherapy with 3 cycles of ICE. If the PET scan was positive, a repeat biopsy was performed, and if negative, ICE was administered; if positive, therapy consisted of ICE x 3, followed by HDT and ASCT.



Eighty-seven patients have received therapy on study. Baseline characteristics include: At a median follow-up of 30 months the event-free survival (EFS) is 88%. Only one patient had progressive disease on R-CHOP-14. At interim restaging, 31/86 pts had FDG-PET avid disease of which only 4 had a positive biopsy. There was no difference in PFS for pts with an interim restaging negative FDG-PET scan (50/55) vs. positive FDG-PET positive (27/31), p=0.36; hence the false positive rate of the interim restaging FDG-PET scan was 87%. Pts with PMLBL had the same outcome as patients with standard DLBCL, p=0.41. In univariate analysis, the only factor that had a negative prognostic impact was Ki-67 $\geq$ 80, p=0.0006. Our-dose dense approach overcame the poor prognostic features of the standard prognostic models used for DLBCL, and obviates the need for an upfront ASCT in nearly all patients. (Moskowitz CH 2006)

We were unable to risk-adapt therapy based upon imaging modalities and surprisingly Ki-67 expression has prognostic import in this patient population. This followup study focuses on these 2 issues.

3.6 Nuclear Medicine Imaging

The International Working Group response criteria did not provide striking discrimination in outcomes of patients between those categorized as a partial response (PR) and those categorized as a complete response (CR). Recently, it has been shown that inclusion of FDG-PET at the conclusion of therapy can dramatically enhance the discrimination between CR and PR in patients with DLBCL; thus, FDG-PET has been incorporated in to a modified version of the International Working Group response criteria.

In MSKCC 01-142, the role of interim re-staging evaluation with FDG-PET was limited by the very poor positive predictive value; based upon biopsy evaluation of the abnormal site of activity. However, we confirmed others findings that the negative predictive value was high. The false positive FDG-PET appears to be influenced by a number of variables including: intralesional inflammation; time between therapy and scan; and influence of the immunotherapy. The study design of MSKCC 01-142 clearly did not permit optimal use of FDG-PET. In the current study we have modified several treatment parameters we hope will improve the positive predictive value of FDG-PET.

^{18}F Fluorothymidine PET

3'-deoxy-3'-[(18)F] fluorothymidine ([(18)F]FLT) is a new PET radiotracer that can be used to assess tumor cell proliferation (Mier, Haberkorn et al. 2002). Imaging with FLT takes advantage of the fact that pyrimidine nucleosides and several of their analogues are phosphorylated to the respective monophosphate (MP) by thymidine kinase 1 (TK-1) and are incorporated into DNA. FLT is also substrate for thymidine kinase-1 (TK-1), which has been demonstrated both *in vitro* (Rasey, Grierson et al. 2002) and *in vivo* (Buck, Halter et al. 2003; Vesselle, Grierson et al. 2003; Wagner, Seitz et al. 2003). TK-1 activity is up-regulated in cells entering the S-phase, whereas the protein is nearly undetectable in growth arrested cells. TK-1 catalyzes the phosphorylation of FLT to FLT-monophosphate. Because it lacks a 3'-hydroxyl group, very little FLT is incorporated into DNA. Thus, FLT measures an early event in DNA synthesis, rather than DNA incorporation. Nevertheless, many reports have shown a positive correlation between FLT uptake and S-phase fraction of cells *in* vitro (Seitz, Wagner et al. 2001; Rasey, Grierson et al. 2002; Schwartz, Tamura et al. 2003) and the fraction of proliferating cells in vivo (MIB-1; Ki-67) (Vesselle, Grierson et al. 2002). Accordingly, FLT might be a useful imaging agent to monitor the early response to therapy in cancer patients. While there are no convincing clinical data at this time, some studies (Dittmann, Dohmen et al. 2002; Apisarnthanarax, Alauddin et al. 2006) showed a close correlation between FLT uptake in tumor cell cultures or xenografts and growth arrest. Since there is limited clinical experience with this new radiotracer in patients undergoing chemotherapy, we will obtain data to a) assess biodistribution, b) verify published dosimetry data, and c) address the potential clinical usefulness of this new imaging agent in patients with lymphoma treated on this new study and correlate the results with other clinical and biologic prognostic factors. The data derived from this study will tell us if and how (time point of imaging, details of image acquisition) PET with FLT will be meaningful in lymphoma patients. It is expected that FLT will be the next PET tracer to be approved for broad clinical use by the FDA. However, it is essential to establish the utility of this tracer in the evaluation of lymphoma. In this study, we will examine the

biodistribution of FLT in patients with DLBCL and determine what impact therapy has on that distribution. It is hoped that FLT imaging may provide an early read out on treatment response. Therefore, we will obtain scans at baseline and after the first or second cycle of chemotherapy.

3.7 Volumetric Segmentation and Response Assessment in Lymphoma

Traditionally, tumors have been measured with a single diameter (uni-dimension) on computed tomography (CT) before, during, and after therapy, and the changes of the measurement are used to assess tumor response to therapy. However, these conventional measurement techniques may not accurately reflect true tumor size change since most tumors and lymph nodes, in particular, are not perfectly spherical and they do not change symmetrically. Continuous advances in CT imaging technology have afforded the capability of acquiring "isotropic" images, allowing tumor volumes to be measured with higher degrees of accuracy. A question facing us is whether change in tumor volume can serve as a better marker for response assessment than the single or two diameters used by conventional methods. Our hypotheses are that volume change of a lymphomatous mass measured on longitudinal CT images may serve as a more accurate surrogate for therapy response compared to unidimensional size changes. Residual masses after therapy, especially in lymphoma patients, often contain fibrosis or necrosis that cannot be differentiated from viable tumor with anatomic CT imaging. However even functional FDG-PET imaging has a modest false negative rate and as indicated above potential for false positives. Therefore, the two may play a complementary role. Accurate anatomic localization and size measurement using CT will continue playing an important role in the detection, diagnosis, staging, and response assessment in lymphoma.

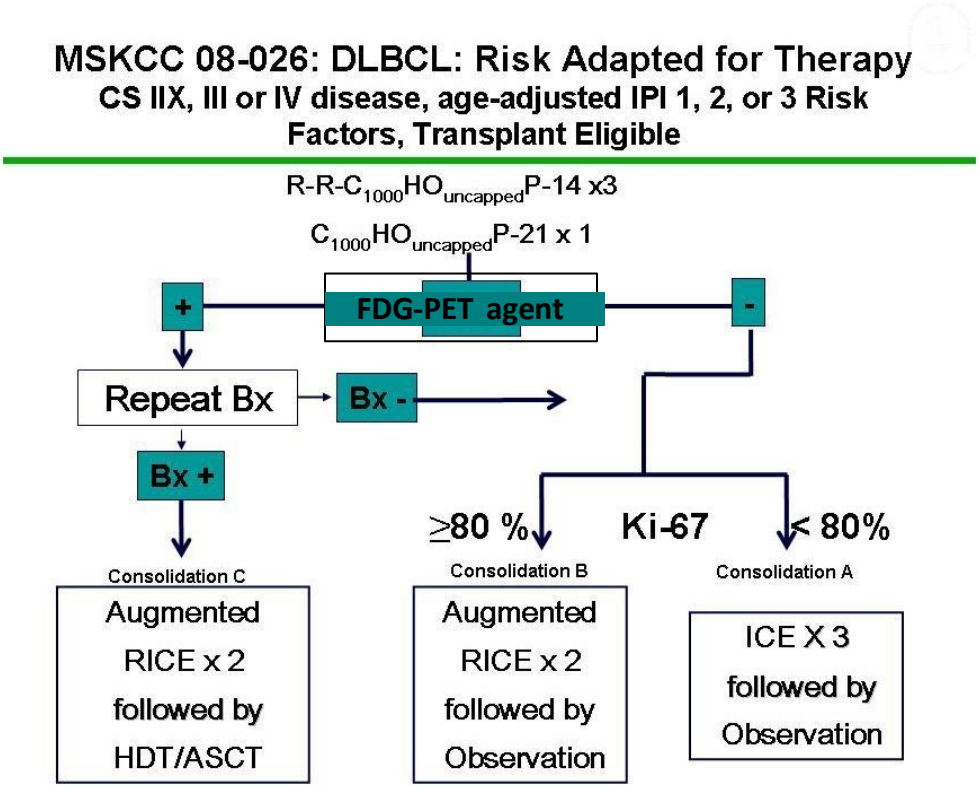
An automated lymph node segmentation algorithm has been developed which will greatly improve the efficiency of routine radiological/oncological image interpretation, as well as provide a methodology of objective and reproducible tumor size determination. This is essential to the evaluation of volumetric techniques to be used in response assessment and to the acceptance of such techniques in clinical practice, and may ultimately play the same important role in the detection of other solid tumors that metastasize to the lymph nodes.

3.8 Proposed Treatment and Rationale

Our dose-dense R-CHOP-14/ICE program used in MSKCC 01-142 was highly efficacious. However, we identified two major limitations. First, as designed, the interim FDG-PET (without a confirmatory biopsy) was not able to identify patients destined to relapse. Second, patients with high tumor growth fractions indicated by Ki-67 staining of $\geq$ 80% had a significant poorer outcome. The current phase II study attempts to address these limitations by selecting alternative therapy for patients with high growth fractions and by incorporating new multiple imaging modalities to predict which patient may benefit from a consolidative upfront ASCT. Risk stratification will continue to be based upon biopsy confirmation of abnormal interim restaging.

4.1 OVERVIEW OF STUDY DESIGN / INTERVENTION

4.2 Design



Patient accrual

Transplant eligible patients between the ages of 18 and 65 with CD20+ diffuse large B cell lymphoma. Patients must meet eligibility criteria outlined in section 6.0.

End of Study (for each patient)

End of study will be defined as either death, loss to follow-up, early withdrawal, or removal from study, failure to achieve a CR, 2-year relapse-free survival and 5-year overall survival. Patients will be followed until the end of study.

Number of centers: Single institution
Number of patients: 90
Estimated study duration: 44-48 months

4.3 Intervention

All induction and consolidation treatment visits have a +/- 3 day window (excluding the interim restaging scans).

Antimicrobial Prophylaxis: Throughout induction and all consolidation chemotherapy (excluding transplant), the following antimicrobial prophylaxis will be given: Trimethoprim/Sulfamethoxazole 160/800 (DS) oral twice daily TIW (patients with known allergy to Trimethoprim/Sulfamethoxazole can receive alternative pneumocystis carinii prophylaxis), Acyclovir 400 mg oral bid, and Fluconazole 100 mg oral qd. For prophylaxis during Consolidation C transplant, see below.

INDUCTION: RR-CHOP-14 Chemotherapy for Three Cycles

Each cycle lasts approximately 14 days.
A total of 3 cycles of RR-CHOP-14 will be given. One cycle of CHOP will follow.

There are no dose reductions of the Rituximab, cyclophosphamide, or doxorubicin. If patients develop grade III/IV neurotoxicity from vincristine, the dose can be reduced at the discretion of the primary attending. Treatment is delayed until the absolute neutrophil count is > 1000/ul and the platelet count is > 50,000/ul.

<u>Cycles 1-3: RR-CHOP-14</u>

Day -2 or Day 2:
Rituximab 375 mg/m^2 IVPB

Day 0:
Rituximab 375mg/m^2 IVPB
Cyclophosphamide 1000 mg/m^2 IVPB
Doxorubicin 50mg/m^2 IVP
Vincristine 1.4 mg/m^2 (no cap) IVP
Prednisone 100mg PO daily for five days
Alternatively, Prednisone may be started on Day 1 and continue through Day 5.

Growth factor support:
G-CSF SQ Days 6-10 at either 300ug or 480 ug /day OR Pegfilgrastim 6mg once 24-48 hrs post completion of intravenous chemotherapy.

Day 0 of next cycle is day 14 as long as ANC ≥ 1000 and platelets ≥50 k (this requirement is not applicable for patients with bone marrow involvement); RCHOP in cycle 3 and CHOP in cycle 4 should be two weeks apart also.

<u>Cycle 4: CHOP, no rituximab will be administered</u>

This cycle will last 21 days

Day 0:
Cyclophosphamide 1000 mg/m^2 IVPB
Doxorubicin 50mg/m^2 IVP
Vincristine 1.4 mg/m^2 (no cap) IVP
Prednisone 100mg PO daily for five days.
Alternatively, Prednisone may be started on Day 1 and continue through Day 5.

Growth factor support:
G-CSF SQ Days 6-10 at either 300ug or 480 ug/day OR Pegfilgrastim 6mg once 24-48 hrs post completion of intravenous chemotherapy.

Interim restaging CT (with volumetric analysis) and FDG-PET scanning will be done on days 17-20 of cycle 4 of induction chemotherapy.

CONSOLIDATION

Risk-Adapted based on Biopsy and Pre-treatment Ki-67. If the interim FDG-PET scan is positive in a site of measurable disease and correlates to disease shown on the CT scan, the patient will undergo a repeat biopsy.

If the biopsy is negative, the patient will receive consolidation A or B depending upon pre-treatment Ki-67 expression; if positive the patient will receive consolidation C. Patients whose bone marrow was initially positive and remains positive post-induction will receive consolidation C.

Consolidation A: Patients whose disease is FDG-PET negative or patients whose FDG-PET scan is positive but repeat biopsy is negative and whose initial Ki-67 expression is < 80% will receive 3 cycles of standard dose ICE Chemotherapy.

Each cycle of ICE lasts 14 days. Patients must have a platelet count of 50,000/ul and an ANC of at least 1000/ul to proceed to subsequent cycles of ICE. For delays of greater than 2 weeks, the PI must be notified and it the delay must be reported the IRB/PB. Creatinine clearance is estimated from 12 hour urine collections obtained on admission.

Days 1-3:
Etoposide 100 mg/ m^2 IVPB Days 1, 2, 3
Carboplatin AUC 5 (maximum dose 800 mg [equivalent to CrCl of 135 ml/min) IVPB
AUC dosing is calculated by the Calvert Formula:
AUC 5 = 5 x (CrCl+25)

Day 2:
Ifosfamide 5 g/m^2 admixed with MESNA 5 g/m^2 IVCI over 24 hours beginning on Day 2.

Growth factor support:
Pegfilgrastim 6mg 24-48 hrs post completion of chemotherapy or G-CSF SQ Days 5-12 at either 300ug or 480 ug/day

<u>Consolidation B:</u> Patients whose disease is FDG-PET negative or patients whose FDG-PET scan is positive but repeat biopsy is negative and whose initial Ki-67 expression is ≥80% will receive 2 cycles of augmented RICE Chemotherapy (as per MSKCC protocol 03-075).

Days 1 and 3:
Rituximab 375 mg/m^2 IVPB

Admit for RICEaug chemotherapy. Each cycle of RICEaug lasts 21 days. Patients must have a platelet count of 50,000/ul and an ANC of at least 1000/ul to proceed to subsequent cycles of RICEaug (this requirement is not applicable for patients with bone marrow involvement). For delays of greater than 2 weeks, the PI must be notified and it the delay must be reported the IRB/PB. Creatinine clearance is estimated from 12 hour urine collections obtained on admission.

Days 4-6:
Etoposide 200 mg/m^2 IVPB q12 hrs x 3
Ifosfamide 5 g/m^2/day administered with MESNA 5 g/m^2/day mixed IVCI over 24 hours x 2 starting on Day 4 (Total dose of both Ifosfamide and MESNA is 10 gm/m^2)
Carboplatin AUC 5 (maximum dose 800 mg equivalent to CrCl of 135 ml/min) IVPB on Day 6

AUC dosing is calculated by the Calvert Formula:
AUC 5 = 5 x (CrCl+25)

Growth factor support:
Pegfilgrastim 6mg 24-48 hrs post completion of chemotherapy or G-CSF SQ Days 5-12 at either 300ug or 480 ug/day.

<u>Consolidation C:</u> Patients with biopsy proven disease after induction therapy
Patients whose bone marrow remain positive at interim restaging will have the option of getting an allogeneic stem cell transplant, in lieu of an ASCT, if they have an acceptable HLA match donor. The allogeneic stem cell transplant regimen will be decided by the MSK Bone Marrow Transplant Service.

Part 1: RICEaug Chemotherapy for 2 cycles (as above)
However, after Cycle 2 patients will receive G-CSF at 10 ug/kg instead of pegfilgrastim, continuing until the completion of leukapheresis.

Part 2: Stem Cell Collection
The target yield for leukapheresis will be $5x10^6$ CD34+ cells/kg. Leukapheresis will continue for up to 5 days until the target yield is reached.

Part 3: High dose chemoradiotherapy and ASCT
Patients will be eligible to receive IFRT if clinically indicated beginning 2 weeks prior to initiation of high dose chemotherapy.

High dose cytoreduction will be with CBV-N chemotherapy.

Day 0 is the day of stem cell reinfusion; CBV-N will be administered as follows:

- Mitoxantrone (45 mg/m2) IVPB x 1 on day – 8
- Carmustine (300 mg/m2) IVPB x 1 on day – 4
- Cyclophosphamide (1500 mg/m2) IVPB daily x 4 days on day – 7, - 6, - 5, - 4
- Etoposide (250 mg/m2) IVPB daily x 4 days on day – 7, - 6, - 5, - 4

PBPC will be infused approximately 24-48 hours after completion of chemotherapy (day 0).

Post Stem Cell Rescue Rituximab Maintenance
No later than Day +35 post ASCT patients will receive rituximab bimonthly for 6 doses.

Radiation Therapy

Radiation therapy is not permitted for patient treated on this study other than as stipulated above in Consolidation C and for scrotal radiation in patients with testicular lymphoma.

Intrathecal Prophylaxis
Patients will receive 6 doses of intrathecal methotrexate or cytarabine during the course of induction and consolidation therapy in the following circumstances:

Testicular involvement
Paranasal sinus or nasopharynx involvement
Bone marrow involvement by large cell lymphoma
Patients with aaIPI HR disease
Patients with more than 2 extra-nodal sites of disease

Antimicrobial Prophylaxis
Antimicrobial prophylaxis for Augmented RICEx2 is the same as specified in Consolidation B. Antimicrobial prophylaxis for transplant phase: On admission: Ciprofloxacin 500 mg PO b.i.d. (continue until the patient requires broad spectrum antibiotics for neutropenic fever) Fluconazole 100 mg PO or IV b.i.d. (continue until the ANC is > 1000/mm3 X 3 days or until amphotericin B therapy is initiated). Nystatin powder applied to the groin and the axilla BID Vitamin K 10 mg PO or sc. one to three times per week unless added to TPN. Day +5 : G-CSF 480 ug sc. QD (continue until ANC > 1000/mm3 x 3 days.)

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Doxorubicin
Mechanism of action: is an anthracycline antibiotic derived as a fermentation product of Streptomyces peucetius (caesius). The drug is tightly bound to DNA, preventing DNA-directed DNA and RNA synthesis. The drug may also act via a free radical mechanism. It appears to be active in all phases of the cell cycle.
Formulation: The drug is supplied reconstituted in 10, 50 and 200 mg vials.
Storage: Reconstituted solutions are stable at room temperature for 24 hours and under refrigeration for 48 hours.
Administration: The drug is administered via a freely-flowing intravenous line over 15 minutes. Care must be taken to avoid extravasation.
Toxicity: include nausea, vomiting, itching, hives or red rash at the injection site. Urine can be pink or red in color for as long as 48 hours after the treatment. Alopecia, stomatitis, and reversible myelosuppression can occur.
Extravasation may occur if leakage around the intravenous site occurs.
Cardiomyopathy has been reported with this compound, usually in patients who have received total doses in excess of 500 mg/m2.

Cyclophosphamide
Mechanism of action: a nitrogen mustard derivative, is converted to polyfunctional alkylating metabolites by hepatic microsomal enzymes. It interferes with DNA replication and RNA transcription, and possesses potent immunosuppressive activity.
Formulation: The drug is supplied as a lyophilized powder in 100 mg, 200 mg, 500 mg, 1 g, and 2 g vials.
Preparation/Storage: It is reconstituted to result in a concentration of 20 mg/mL. It is stable for 24 hours at room temperature or for 6 days refrigerated (2°-8° C).
Toxicity: include nausea, vomiting, anorexia, edema, cardiomyopathy, skin rash, alopecia, reversible myelosuppression, hemolytic anemia, possible sterility, hemorrhagic cystitis, and syndrome of inappropriate antidiuretic hormone production.

Vincristine
Mechanism of action: is a member of the vinca alkaloid class of natural product anti-tumor agents. It exerts its antineoplastic effects by binding to tubulin, resulting in inhibition of microtubule assembly. This, in turn, blocks formation of the mitotic spindle resulting in the accumulation of cells in mitosis.
Formulation: The drug is supplied reconstituted to a concentration of 1 mg/ Ml
Preparation/Storage: The drug is administered via a freely-flowing intravenous line over 1-2 minutes, with care taken to avoid extravasation.
Toxicity: include peripheral neuropathy, constipation, alopecia, metallic taste in the mouth, mild nausea, paraesthesia and paresis. Extravasation may result in soft tissue necrosis.

Rituximab (Rituxan®, C2B8)

Mechanism of action: Rituximab binds to the CD20 antigen expressed on B-cells and causes cell death by complement mediated lysis and ADCC.
Formulation: 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. Rituximab is supplied as 100 mg and 500 mg sterile, preservative-free, single-use vials.
Preparation: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. Do not infuse rituximab concomitantly with another IV solution or other IV medications. The appropriate dose is withdrawn and diluted to a final concentration of 1-4 mg/ml in either 0.9% sodium chloride or 5% dextrose solution. The solution is then stable at 2° to 8°C for 24 hours and at room temperature for an additional 12 hours.
Storage: Vials can be stored at 2° to 8°C. They should be protected from sunlight.
Administration: The first infusion should be administered at an initial rate of 50 mg/hr. If hypersensitivity or infusion-related events do not occur, the rate may be increased by 50 mg/hr every 30 minutes up to a maximum of 400 mg/hr. Subsequent infusions may be started at 100 mg/hr and the rate increased by 100 mg/hr at every 30 minutes to a maximum of 400 mg/hr, as tolerated. Patients will be premedicated with acetaminophen 650-mg po, diphenhydramine 50 mg IV, and lorazepam 0.5 mg IV 30 minutes prior to beginning the rituximab infusion. For severe reactions, the infusion will be stopped and can be resumed at 50% of the prior rate once the reactions are treated and symptoms resolved.
Toxicity: common: Fever, chills, fatigue, headache; less common: nausea, vomiting, rhinitis, pruritus, hypotension; rare: neutropenia, thrombocytopenia, asthenia, arthritis, vasculitis, lupus-like syndrome, pleuritis, bronchiolitis obliterans, uveitis, optic neuritis, and skin reactions such as toxic epidermal necrolysis and pemphigus.

Fatal Infusion Reactions: Severe and fatal cardiopulmonary events, including angioedema, hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, and cardiogenic shock, have been reported. These severe reactions typically occurred during the first infusion with time to onset of 30-120 minutes.

Cardiac Events: Patients with preexisting cardiac conditions, including arrhythmia and angina, have had recurrences of these cardiac events during rituximab infusions.

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

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 and in patients administered concomitant cisplatin.

Mucocutaneous Reactions: Severe bullous skin reactions, including fatal cases of toxic epidermal necrolysis and paraneoplastic pemphigus, have been reported in patients treated with rituximab. The onset of reaction has varied from 1 to 13 weeks following rituximab exposure.

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 post-marketing 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 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]).

Infectious Events: 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, 1-588 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. Serious infectious events (Grade 3 or 4), including sepsis, occurred in 2% of patients.

Other Serious Viral Infections: The following additional serious viral infections, either new, reactivated or exacerbated, have been identified in clinical studies or postmarketing reports. The majority of patients received Rituxan in combination with chemotherapy or as part of a hematopoietic stem cell transplant. These viral infections included JC virus (progressive multifocal leukoencephalopathy [PML]), cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C. In some cases, the viral infections occurred up to one year following discontinuation of Rituxan and have resulted in death.

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 4 months after the initiation of rituximab and approximately one month after the last dose.

PML is a rare demyelinating disease of the brain caused by infection with the JC virus that usually leads to death or severe disability. JC virus infection resulting in PML and death has been reported rarely in patients with hematologic malignancies receiving rituximab. The majority of these patients had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Cases of PML resulting in death have also been reported in patients with systemic lupus erythematosus (SLE) treated with rituximab. These patients with SLE had longstanding disease, history of prior immunosuppressant therapy, and were diagnosed with PML within 12 months of their last infusion of rituximab.

Physicians should consider PML in any patient presenting with new onset neurologic manifestations. Consultation with a neurologist, brain MRI, and lumbar puncture should be considered as clinically indicated. In patients who develop PML, rituximab should be discontinued and reductions or discontinuation of any concomitant chemotherapy or immunosuppressive therapy should be considered.

Bowel Obstruction and Perforation: Abdominal pain, bowel obstruction and perforation, in some cases leading to death, were observed in patients receiving Rituxan in combination with chemotherapy for DLBCL. In post-marketing reports, which include both patients with low-grade or follicular NHL and DLBCL, the mean time to onset of symptoms was 6 days (range 1−77) in patients with documented gastro-intestinal perforation. Complaints of abdominal pain, especially early in the course of treatment, should prompt a thorough diagnostic evaluation and appropriate treatment.

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

Supplier: Genentech, Inc., IDEC Pharmaceuticals Corp.

Ifosfamide (Ifex®)
Mechanism of action: Ifosfamide is activated in the liver by microsomal enzymes and the subsequent ifosfamide mustard causes direct alkylation of DNA.
Formulation: Ifosfamide is supplied in single dose vials for constitution and administration by IV infusion. Each contains 1 gram or 3 grams of sterile ifosfamide.
Preparation: Injections are prepared by adding sterile water to the vial. The 1-gram dose is mixed with 20 mL and the 3-gram dose with 60 mL for a final concentration of 50 mg/mL.
Storage: The dry powder may be stored at room temperature.

Toxicity: Alopecia, nausea and vomiting, hematuria, gross hematuria, CNS toxicity, infection, renal dysfunction, allergic reactions and at high doses, cardiotoxicity.
Supplier: Bristol-Myers Squibb

Carboplatin (Paraplatin®)
Mechanism of action: Carboplatin binds to DNA and causes cross-linking with a non-cell cycle dependent tumor cell lysis. It inhibits DNA synthesis by altering the template via the formation of intrastrand cross-links.
Formulation: Paraplatin® is supplied as a sterile lyophilized powder available in single-dose vial containing 50 mg, 150 mg, and 450 mg of carboplatin for administration by IV infusion. Each vial contains equal parts of carboplatin and mannitol.
Preparation: Immediately before use the content of each vial must be reconstituted with sterile solution: 50 mg strength with 5 mL, 150 mg with 15 mL and 450 mg with 45 mL. These solutions produce a concentration of 10 mg/mL. The solution is stable for 8 hours at room temperature.
Storage: Unopened vials are stable for the life indicated on the insert if protected from light.
Toxicity: Myelosuppression, nausea, vomiting, peripheral neuropathy, ototoxicity, hepatic toxicity, electrolyte abnormalities, hypomagnesemia, hypocalcemia, and allergic reactions.
Supplier: Bristol-Myers Squibb

VP-16 (etoposide, Vepesid®)
Mechanism of action: Induction of an irreversible blockade of cells in the premitotic phases of the cell cycle leading to accumulation of cells in late S or G2 phases. This mechanism is secondary to interference of the scissors-reunion reaction of the enzyme topoisomerase II.
Formulation: VP-16 injection is available in 100-mg (5-mL) sterile multiple-dose vials. The pH is 3-4. Each mL contains 20-mg etoposide, 2-mg citric acid, 30-mg benzyl alcohol, 80-mg polysorbate 80, 650-mg polyethylene glycol 300 and 30.5% alcohol.
Preparation: The computed dose is diluted in 500 mL of normal saline and given by intravenous infusion over 1 hour.

Storage: Unopened vials of VP-16 are stable for 24 months at room temperature. Vials are diluted as recommended to a concentration of 0.2 or 0.4 mg/mL and are stable for 96 and 48 hours respectively, at room temperature under normal light in both plastic and glass containers.
Toxicity: Leukopenia, thrombocytopenia, alopecia, nausea, vomiting, headache, fever, hypotension, anorexia, and allergic reactions.
Supplier: Bristol-Myers Squibb

Mesna (Mesnex®)
Mechanism of action: Mesna was developed as a prophylactic agent to inhibit hemorrhagic cystitis induced by ifosfamide and is analogous to the cysteine-cystine system; mesna is rapidly metabolized to mesna disulfide and acts as a free radical scavenger.

Formulation: Mesna is a sterile preservative free aqueous solution of clear, colorless appearance in clear glass vials for IV administration. Mesna injection contains 100 mg/ml Mesna, 0.25 mg/ml acetate disodium, and sodium hydroxide to maintain pH 6.5-8.5.
Preparation: For IV administration the drug is diluted in sterile solution to make a final concentration of 20 mg/ml.
Storage: Diluted solutions are chemically and physically stable for 24 hours at room temperature. It is recommended that solutions be refrigerated and used within 6 hours.
Toxicity: Nausea, vomiting, diarrhea
Supplier: Bristol-Myers Squibb

Neupogen® (Filgrastim, G-CSF)
Mechanism of action: NEUPOGEN® is a human protein, which is involved in the promotion of the growth and maturation of granulocytic progenitors and the stimulation of functional activity.
Formulation: Available as a recombinant DNA product supplied as 1 or 2 ml vials containing clear colorless sterile protein solution.
Storage: It can be stored at 2-6°C and is stable for at least 30 months.
Toxicity: Bone pain, exacerbation of preexisting autoimmune disorders, transient and reversible changes in alkaline phosphatase, uric acid and LDH.
Supplier: Amgen, Inc.

Neulasta® (Pegfilgrastim, G-CSF)
Mechanism of action: NEULASTA® is a human protein, which is involved in the promotion of the growth and maturation of granulocytic progenitors and the stimulation of functional activity. It is a covalent conjugate of recombinant methionyl human G-CSF (Filgrastim) and monomethoxypolyethylene glycol
Formulation: Available as a pegalated recombinant DNA product supplied as .6mL prefilled syringe containing clear colorless sterile protein solution.
Storage: It can be stored at 2-8°C and is stable for at least 30 months.
Toxicity: Bone pain, exacerbation of preexisting autoimmune disorders, transient and reversible changes in alkaline phosphatase, uric acid and LDH, nausea, fatigue, alopecia, diarrhea, vomiting, constipation, fever, anorexia, skeletal pain, headache, taste perversion, dyspepsia, myalgia, insomnia, abdominal pain, arthralgia, generalized weakness, peripheral edema, dizziness, granulocytopenia, stomatitis, mucositis, and neutropenic fever
Supplier: Amgen, Inc.

^{18}F Fluorothymidine
Please see section 3.5 Background and Rationale.
FLT will be synthesized by the MSKCC cyclotron facility. FLT has been synthesized by the MSKCC cyclotron facility for about 2 years and has been used in patients with gastric cancer at MSKCC, and in patients with a variety of diseases (e.g., lung, esophageal and colorectal cancer) in several institutions in this country and Europe. No side effects have been reported from any of the institutions. The primary source of the FLT will be the MSKCC cyclotron facility; however, alternative commercial sources are available to ensure consistent supply of FLT. If a commercial supplier of FLT is used for a particular study, the

supplier will be required to meet all of the acceptance criteria outlined in the FDA-approved MSKCC FLT IND (#104742) prior to administration. Here at MSKCC, we have extensively tested the FLT for toxicity and pyrogenicity, and the product has met all requirements. The radiochemical purity is > 95%. For each scan, we will inject 8mCi of FLT. By doing so, the effective dose equivalent from these 2 scans will be 3.87 rem. Although FLT will be administered as part of an FDA-approved IND application, based on published dosimetry data, the dose from FLT is indeed within the (more conservative) dose restrictions set forth for radiopharmaceutical studies done under the aegis of the radioactive drug research committee (see Appendix table 1).

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

- Histologic diagnosis of diffuse large B cell lymphoma, PMLBL, or follicular lymphoma grade 3B confirmed by the department of hematopathology at MSKCC. Patients with discordant bone marrow involvement (i.e. involvement by small cleaved cells or small lymphocytic lymphoma) are eligible
- Tumors express CD20 as determined by immunohistochemistry.
    - Ki-67 evaluation of tumor tissue
- Patients must have stage III, or IV disease. Patients with IIX disease must have at least one other age-adjusted IPI risk factor.
    - KPS ≤ 70
    - LDH > upper limit of normal
- All patients must have FDG-PET avid (minimum SUV 2.5) measurable disease.
- Patients must have normal baseline cardiac function based upon echocardiogram or gated blood pool scan (MUGA) with an ejection fraction ≥ 50%
- Patients must have a serum creatinine of ≤ 1.5 mg/dl; if creatinine >1.5 mg/dl creatinine clearance must be >60 ml/minute.
- Patients must have ANC>1000/mcl and Platelets>50,000/mcl. If patient has cytopenias due to bone marrow involvement, these requirements are not applicable.
- Patients must have a bilirubin level of < 2.0 mg/dl in the absence of a history of Gilbert's disease (or pattern consistent with Gilbert's).
- Patients must be Hepatitis B surface antigen negative, Hepatitis B core antibody negative, and Hepatitis C negative.
- All patients of childbearing and child-creating age must be using an acceptable form of birth control from the initiation of treatment on study until 1 year after completion of chemotherapy and/or transplant.
- Women who are pre-menopausal must have a negative pregnancy test
- Age between 18 and 65
- Patients must be HIV negative. This test may be pending in a patient without risk factors, as determined by the patient's physician.
- If patients have a history of malignancy other than cutaneous basal cell or squamous cell carcinoma, they must be disease-free for ≥ 5 years at the time of enrollment.
- Patients or their guardians must be capable of providing informed consent.

- Patients must be suitable to undergo stem cell transplant

6.3 Subject Exclusion Criteria

- Any lymphoma subtype other than DLBCL, PMLBL, follicular lymphoma grade 3B.
- Patients with either parenchymal brain or lepto-meningeal involvement.
- No more than 14 days of prednisone therapy between the diagnostic biopsy of either DLBCL, PMLBL, or follicular lymphoma grade 3B and the initiation of treatment on study.
- Known pregnancy or breast-feeding.
- Medical illness unrelated to NHL which in the opinion of the attending physician and principal investigator will preclude administration of chemotherapy safely. This includes patients with uncontrolled infection, chronic renal insufficiency, myocardial infarction within the past 6 months, unstable angina, cardiac arrhythmias other than chronic atrial fibrillation and chronic active or persistent hepatitis, or New York Heart Association Classification III or IV heart disease.
- History of any malignancy for which the disease-free interval is <5 years, excluding curatively treated cutaneous basal cell or squamous cell carcinoma and carcinoma in-situ of the cervix.

7.0 RECRUITMENT PLAN

Patients seen in the inpatient or outpatient setting who meet eligibility criteria will be recruited to this study. A Lymphoma disease management team physician will evaluate all patients. Participation is voluntary. The patient will be made aware of their diagnosis, current nature of this treatment program. All patients will be required to sign a statement of informed consent that conforms to FDA and IRB/PB guidelines.

8.1 PRETREATMENT EVALUATION

All patients will have the following baseline studies:

Within 2 weeks prior to treatment initiation

- Complete history and physical
- CBC with differential
- Electrolytes (Na, K, Cl, CO2), BUN, Cr, bilirubin, total protein, albumin, alkaline phosphatase, uric acid, phosphorus, AST, ALT, LDH, urinalysis, and pregnancy test in pre-menopausal women
- EKG

Within 4 weeks prior to treatment initiation:

- Documentation of ejection fraction by echocardiogram or MUGA scan
- Documentation of HIV seronegativity at MSKCC
- Hepatitis B surface antigen & core antibody, Hepatitis C antibody
- CT scans of the chest, abdomen, and pelvis (with volumetric analysis when possible)

- FDG-PET/CT scan
- Bilateral Bone marrow biopsy
    - Note: Bilateral bone marrow biopsy not required if unilateral bone marrow biopsy within 4 weeks prior to treatment initiation shows involvement by lymphoma
- Creatinine clearance if serum Cr>1.5 mg/dl
- FLT PET/CT (only the first 60 patients will receive the FLT-PET scan):
    - **FLT PET/CT can be waived for the following patients:**
        - Patients who have aggressive disease that requires immediate treatment; these patients may enroll on the protocol without an FLT PET scan.
        - Patients with other extenuating circumstances, as determined by the principle investigators of the study.
        - Patients who enroll on study after 60 patients have already been imaged with an FLT-PET scan

    - Patients should be fasted for 6 hours, but liberal intake of water is allowed
    - Two Intravenous lines will be established: one line for FLT administration (Mediport or forearm) and the other line for obtaining one blood sample (forearm).
    - An area of interest will be determined based on prior CT scan and/or FDG PET, for instance, the largest nodal mass identified on CT and/or lesion with them most intense FDG uptake
    - Patient will be placed in the FDG-PET/CT scanner. A low dose scout view and CT of the selected body region (1 field of view = 15 cm) will be obtained.
    - Approximately 8mCi (296 MBq) FLT will be injected intravenously and dynamic images will be acquired for up to 40 min over this lesion. During that time the patient will rest comfortably in the PET scanner.
    - Following dynamic image acquisition, the patient will be removed from the scanner and will have an opportunity to stretch, use the rest room etc.
    - Then a PET/CT scan of the body, extending from skull base to approximately the upper thighs, will be obtained. Again, during this scan the patient will rest comfortably on the scanner bed, but this time the table will move consecutively through the scanner. One three (3) ml blood sample will be obtained for metabolite analysis at the end of the scan.
    - The IV lines will be removed at the end of the study
    - The radiopharmacy will keep a log of all activities administered under this protocol.

FLT PET is considered investigational, and thus these scans will be performed under an FDA-approved Investigational New Drug (IND) application. The results of the FLT scans will have no impact on patient management.

<u>Prior to ICE administration:</u>

- Tissue blocks or 10 unstained slides, if original biopsy done at outside institutions, to further characterize the underlying lymphoma
- Ki-67 staining of tumor

9.0 TREATMENT INTERVENTION/PLAN

All induction and consolidation treatment visits have a +/- 3 day window (excluding the interim restaging scans).

Antimicrobial Prophylaxis: Throughout induction and all consolidation chemotherapy (excluding transplant), the following antimicrobial prophylaxis will be given: Trimethoprim/Sulfamethoxazole 160/800 (DS) oral twice daily TIW (patients with known allergy to Trimethoprim/Sulfamethoxazole can receive alternative pneumocystis carinii prophylaxis), Acyclovir 400 mg oral bid, and Fluconazole 100 mg oral qd. For prophylaxis during Consolidation C transplant, see below.

INDUCTION: RR-CHOP-14 Chemotherapy for Three Cycles
Each cycle lasts approximately 14 days.
A total of 3 cycles of RR-CHOP-14 will be given. One cycle of CHOP will follow.

There are no dose reductions of the Rituximab, cyclophosphamide, or doxorubicin. If patients develop grade III/IV neurotoxicity from vincristine, the dose can be reduced at the discretion of the primary attending. Treatment is delayed until the absolute neutrophil count is > 1000/ul and the platelet count is > 50,000/ul.

Cycles 1-3: RR-CHOP-14
Day -2 or Day 2:
Rituximab 375 mg/m^2 IVPB

Day 0:
Rituximab 375mg/m^2 IVPB
Cyclophosphamide 1000 mg/m^2 IVPB
Doxorubicin 50mg/m^2 IVP
Vincristine 1.4 mg/m^2 (no cap) IVP
Prednisone 100mg PO daily for five days
Alternatively, Prednisone may be started on Day 1 and continue through Day 5.

Growth factor support:
G-CSF SQ Days 6-10 at either 300ug or 480 ug /day OR Pegfilgrastim 6mg once 24-48 hrs post completion of intravenous chemotherapy.

Day 0 of next cycle is day 14 as long as ANC ≥ 1000 and platelets ≥50 k (this requirement is not applicable for patients with bone marrow involvement); RCHOP in cycle 3 and CHOP in cycle 4 should be two weeks apart also.

Cycle 4: CHOP, no rituximab will be administered
This cycle will last 21 days

Day 0:
Cyclophosphamide 1000 mg/m^2 IVPB
Doxorubicin 50mg/m^2 IVP
Vincristine 1.4 mg/m^2 (no cap) IVP
Prednisone 100mg PO daily for five days.
Alternatively, Prednisone may be started on Day 1 and continue through Day 5.

Growth factor support:
G-CSF SQ Days 6-10 at either 300ug or 480 ug/day OR Pegfilgrastim 6mg once 24-48 hrs post completion of intravenous chemotherapy.

Interim restaging CT (with volumetric analysis) and FDG-PET scanning will be done on days 17-20 of cycle 4 of induction chemotherapy.

CONSOLIDATION
Risk-Adapted based on Biopsy and Pre-treatment Ki-67. If the interim FDG-PET scan is positive in a site of measurable disease and correlates to disease shown on the CT scan, the patient will undergo a repeat biopsy. If the biopsy is negative, the patient will receive consolidation A or B depending upon pre-treatment Ki-67 expression; if positive the patient will receive consolidation C. Patients whose bone marrow was initially positive and remains positive post-induction will receive consolidation C.

Consolidation A: Patients whose disease is FDG-PET negative (any residual lesion seen on companion CT with FDG uptake < blood pool activity in large vessels in the same field of view) or patients whose FDG-PET scan is positive but repeat biopsy is negative and whose initial Ki-67 expression is < 80% will receive 3 cycles of standard dose ICE Chemotherapy.

Each cycle of ICE lasts 14 days. Patients must have a platelet count of 50,000/ul and an ANC of at least 1000/ul to proceed to subsequent cycles of ICE. For delays of greater than 2 weeks, the PI must be notified and it the delay must be reported the IRB/PB. Creatinine clearance is estimated from 12 hour urine collections obtained on admission.

Days 1-3:
Etoposide 100 mg/ m^2 IVPB Days 1, 2, 3
Carboplatin AUC 5 (maximum dose 800 mg [equivalent to CrCl of 135 ml/min) IVPB
AUC dosing is calculated by the Calvert Formula:
AUC 5 = 5 x (CrCl+25)

Day 2:
Ifosfamide 5 g/m^2 admixed with MESNA 5 g/m^2 IVCI over 24 hours beginning on Day 2.

Growth factor support:
Pegfilgrastim 6mg 24-48 hours post completion of chemotherapy or G-CSF SQ Days 5-12 at either 300ug or 480 ug/day.

Consolidation B: Patients whose disease is FDG-PET negative or patients whose FDG-PET scan is positive but repeat biopsy is negative and whose initial Ki-67 expression is ≥80% will receive 2 cycles of augmented RICE Chemotherapy (as per MSKCC protocol 03-075).

Days 1 and 3:
Rituximab 375 mg/m^2 IVPB

Admit for RICEaug chemotherapy. Each cycle of RICEaug lasts 21 days. Patients must have a platelet count of 50,000/ul and an ANC of at least 1000/ul to proceed to subsequent cycles of RICEaug. For delays of greater than 2 weeks, the PI must be notified and it the delay must be reported the IRB/PB. Creatinine clearance is estimated from 12 hour urine collections obtained on admission.

Days 4-6:
Etoposide 200 mg/m^2 IVPB q12 hours x 3
Ifosfamide 5 g/m^2/day administered with MESNA 5 g/m^2/day mixed IVCI over 24 hours x 2 starting on Day 4 (Total dose of both Ifosfamide and MESNA is 10 gm/m^2)
Carboplatin AUC 5 (maximum dose 800 mg equivalent to CrCl of 135 ml/min) IVPB on Day 6

AUC dosing is calculated by the Calvert Formula:
AUC 5 = 5 x (CrCl+25)

Growth factor support:
Pegfilgrastim 6mg 24-48 hours post completion of chemotherapy or G-CSF SQ Days 5-12 at either 300ug or 480 ug/day.

Consolidation C: Patients with biopsy proven disease after induction therapy
Patients whose bone marrow remain positive at interim restaging will have the option of getting an allogeneic stem cell transplant, in lieu of an ASCT, if they have an acceptable HLA match donor. The allogeneic stem cell transplant regimen will be decided by the MSK Bone Marrow Transplant Service.

Part 1: RICEaug Chemotherapy for 2 cycles (as above)
However, after Cycle 2 patients will receive G-CSF at 10 ug/kg instead of pegfilgrastim, continuing until the completion of leukapheresis.

Part 2: Stem Cell Collection
The target yield for leukapheresis will be 5x10^6 CD34+ cells/kg. Leukaphereses will continue for up to 5 days until the target yield is reached.

Part 3: High dose chemoradiotherapy and ASCT
Patients will be eligible to receive IFRT if clinically indicated beginning 2 weeks prior to initiation of high dose chemotherapy.

High dose cytoreduction will be with CBV-N chemotherapy.

Day 0 is the day of stem cell reinfusion; CBV-N will be administered as follows:

- Mitoxantrone (45 mg/m2) IVPB x 1 on day – 8
- Carmustine (300 mg/m2) IVPB x 1 on day – 4
- Cyclophosphamide (1500 mg/m2) IVPB daily x 4 days on day – 7, - 6, - 5, - 4
- Etoposide (250 mg/m2) IVPB daily x 4 days on day – 7, - 6, - 5, - 4

PBPC will be infused approximately 24-48 hours after completion of chemotherapy (day 0).

Post Stem Cell Rescue Rituximab Maintenance
No later than Day +35 post ASCT patients will receive rituximab bimonthly for 6 doses.

Radiation Therapy

Radiation therapy is not permitted for patient treated on this study other than as stipulated above in Consolidation C and for scrotal radiation in patients with testicular lymphoma.

Intrathecal Prophylaxis
Patients will receive 6 doses of intrathecal methotrexate or cytarabine during the course of induction and consolidation therapy in the following circumstances:

Testicular involvement
Paranasal sinus or nasopharynx involvement
Bone marrow involvement by large cell lymphoma
Patients with aaIPI HR disease
Patients with more than 2 extra-nodal sites of disease

Antimicrobial Prophylaxis
Antimicrobial prophylaxis for Augmented RICEx2 is the same as specified in Consolidation B. Antimicrobial prophylaxis for transplant phase: On admission: Ciprofloxacin 500 mg PO b.i.d. (continue until the patient requires broad spectrum antibiotics for neutropenic fever) Fluconazole 100 mg PO or IV b.i.d. (continue until the ANC is > 1000/mm3 X 3 days or until amphotericin B therapy is initiated). Nystatin powder applied to the groin and the axilla BID Vitamin K 10 mg PO or sc. one to three times per week unless added to TPN. Day +5 : G-CSF 480 ug sc. QD (continue until ANC > 1000/mm3 x 3 days.)

10.1 EVALUATION DURING TREATMENT/INTERVENTION

10.2 Pre-Treatment Evaluation

Prior to treatment as per institutional guidelines, patients will have a repeat Echocardiogram or MUGA scan and PFT's (PFTs for Consolidation C only).

10.3 Evaluation During Treatment

- Physical exam, CBC prior to each cycle of therapy, and assessment of toxicity prior to each chemotherapy.

- Interim restaging (including all previously positive imaging studies and bone marrow examinations) 2-3 weeks after fourth cycle of induction; patients with FDG-PET negative disease will receive consolidation A/B and those with FDG PET avid disease will undergo repeat biopsy. A positive FDG PET scan is defined as follows: any uptake equal to or greater than surrounding background activity. This is dependent upon the location of the lesion; therefore the SUV value itself cannot be used as a criteria for a positive or negative scan.

- **FLT PET**
  One FLT PET/CT scan will be obtained prior to the start of cycle 2 (first 30 patients on study) or prior to the start of cycle 3 (the next thirty patients to receive FLT PET scans); the earliest the scan can be obtained is the day after prednisone completion in that cycle. If the FLT PET scan was waived at baseline, a follow-up FLT PET scan after cycle 1 or 2 is not required.
  The first 30 consecutive patients who enroll to the study will undergo FLT PET scanning at baseline and prior to the start of cycle 2; an additional 30 patients (not necessarily consecutive) will receive FLT PET scans at baseline and prior to cycle 3. Scans will be obtained as described above under 8.0. FLT imaging is exploratory, therefore no therapeutic decisions will be based on FLT scan findings in this trial. Interim analyses of our first set of patient's shows that dynamic images may have to be acquired for up to 60 minutes in order to capture significant data points for kinetic analysis. Therefore, we will obtain dynamic images over a selected body region/lesion for up to 60 min, followed by a scan of the torso from skull base to upper thigh. One three (3) ml blood sample will be taken at the end of the scan for metabolite analysis.

  Funding for FLT studies was initially intended for 60 patients. Now that 60 patients have undergone the FLT-PET scan at baseline and either after cycle 1 (Cohort 1) or cycle 2 (Cohort 2), the FLT-PET scan will now be replaced by an FDG-PET scan that will be done after cycle 2 for the remaining 30 patients to enroll on study (Cohort 3). The results of this FDG-PET scan after cycle 2 will be for research purposes only and will have no impact on patient management.

10.4 Post-Treatment Evaluation

Consolidation A/B:
4-6 weeks post completion of ICE-based chemotherapy, CT scans (with volumetric analysis) and FDG PET scans will be repeated. Patients will be seen on a three to four month basis for the first two years post-therapy. Imaging studies, either a CT or a FDG PET scan will be done at 5-7 month intervals post-therapy for the first two years and then at the discretion of the attending physician thereafter.

Consolidation C:
Patients will be seen every one to three weeks post transplant until the restaging evaluation, a CT scan (with volumetric analysis) and a FDG PET scan, at 90-120 days post-treatment. Thereafter, patients will be seen on a one to three month basis for the first two years post-transplant. Imaging studies, either a CT or a FDG PET scan will be done at 5-7 months after the initial imaging studies for the first two years and then at the discretion of the attending physician thereafter.

11.1 TOXICITIES/SIDE EFFECTS

Toxicity will be graded according to NCI toxicity criteria version 3.0. The side effects and expected toxicities associated with the various agents are listed in section 5.0 and in the Investigator's Brochure; any toxicity that is not listed is considered unexpected. In addition, placement of a leukapheresis catheter can be associated with pneumothorax, deep venous thrombosis, infection and bleeding.

11.2 Collecting and Reporting

Non-hematologic toxicities:
CHOP chemotherapy has been standard of care for lymphoma management since 1975, and ICE chemotherapy is standard management for relapsed aggressive lymphoma based upon randomized data and has been administered to >1500 pts at MSKCC since 1993, when we were the first institution to do a phase 2 clinical trial with combination therapy. Therefore, **we will not be reporting the data of expected grade I-II non-hematologic toxicities to the IRB/PB**. The following are the most common non-hematologic toxicities that have occurred and are expected in most patients:

- Febrile Neutropenia
- Diarrhea
- Peripheral Neuropathy
- Constipation
- Fever
- Nausea
- Fatigue
- Headache
- Mucositis
- Vomiting

We will be recording and reporting unexpected grade I-II and all grade III-V non-hematologic toxicities to the IRB/PB as Serious Adverse Events. Neutropenic fever is expected and will not be reported to the IRB/PB. Any patient who has neutropenic sepsis and positive blood cultures will be reported to the IRB/PB**.**

Hematologic toxicities (Complete Blood Count Abnormalities):
All patients on study will have laboratory data collected, both in their medical records and in MSK's database, CRDB. This includes all grades I-V hematologic toxicities. **All**

grade I-III hematologic toxicities are expected and will not be reported to the IRB/PB. The following are the most common expected hematologic toxicities in most patients who enroll on study:

- Low hemoglobin
- Low lymphocytes
- Low platelets
- Low leukocytes
- Low neutrophil/granulocyte count

Grade IV/V hematologic toxicities will be captured in the patient's medical record, as well as MSK's database, CRDB. **The only grade IV hematologic toxicity that will be reported to the IRB/PB is thrombocytopenia with evidence of bleeding. Grade IV thrombocytopenia without evidence of bleeding and requiring a blood transfusion will not be reported to the IRB/PB. All grade V hematologic toxicities will be reported to the IRB/PB.**

Electrolyte and Liver Function Test Abnormalities (Comprehensive Metabolic Panel Abnormalities)

All electrolyte and liver function test abnormalities will be captured in CRDB.
Grade I-III abnormalities in glucose, albumin, alkaline phosphatase, potassium, sodium, magnesium, phosphorus, bilirubin, and calcium are expected with this course of treatment and will not be reported to the IRB/PB; grade IV/V abnormalities will be reported to the IRB/PB. Grade II-V liver function test abnormalities in AST and ALT and grade III-V abnormalities in creatinine, amylase, and lipase will be reported to the IRB/PB.

ALL grade V events will be reported to the IRB/PB if a participant is enrolled and actively participating in the trial OR when event occurs within 30 days of the last protocol treatment intervention.

For detailed information regarding SAE reporting, see section 17.2.

11.3 Expected Toxicities:

The expected side effects and toxicities associated with the various agents are listed below, in section 5.0 and in the Investigator's Brochure; any toxicity that is not listed is considered unexpected.

Etoposide: Myelosuppression, alopecia, nausea, vomiting, headache, fever, hypotension, anorexia, and allergic reactions.

Doxorubicin: Nausea, vomiting, itching, hives or red rash, alopecia, stomatitis, reversible myelosuppression, extravasation, and cardiomyopathy.

Cyclophosphamide: Nausea, vomiting, anorexia, edema, cardiomyopathy, skin rash, alopecia, reversible myelosuppression, hemolytic anemia, possible sterility, hemorrhagic cystitis, and syndrome of inappropriate antidiuretic hormone production.

Vincristine: peripheral neuropathy, constipation, alopecia, metallic taste in the mouth, mild nausea, paraesthesia and paresis. Extravasation may result in soft tissue necrosis.

Ifosfamide: Alopecia, nausea and vomiting, hematuria, gross hematuria, CNS toxicity, infection, renal dysfunction, allergic reactions and at high doses, cardiotoxicity.

Carboplatin: Myelosuppression, nausea, vomiting, peripheral neuropathy, ototoxicity, hepatic toxicity, electrolyte abnormalities, hypomagnesemia, hypocalcemia, and allergic reactions.

Neupogen: Bone pain, exacerbation of preexisting autoimmune disorders, transient and reversible changes in alkaline phosphatase, uric acid and LDH.

Mesna: Nausea, vomiting, diarrhea.

Rituximab: Fever, chills, nausea, asthenia, hypotension, angioedema, respiratory distress, tumor lysis syndrome, neutropenia. A very rare side effect is progressive multifocal leukoencephalopathy (PML); it is almost always fatal.

[18F]FLT:

Placement of a catheter for infusion of [18F] FLT and blood samples may cause pain, bruising, infection and venous scarring. Standard medical care will be used to minimize these risks.

When FLT was given to HIV patients in higher concentrations liver failure was seen, but in this study less than 1000 fold of FLT will be used. (Flexner et. al. 1994) In many patients where FLT has been studied in the U.S. and Europe, none of this was documented.

12.0 Criteria for Therapeutic Response/Outcome Assessment

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 FDG-PET negative (b)	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology,

		Variably FDG-avid or PET negative; regression to normal size on CT		immunohistochemistry should be negative
PR	Regression of measurable 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; FDG-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 identified node > 1 cm in short axis Lesions FDG-PET positive if FDG-avid lymphoma or FDG-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.

Determining Overall Best Response: Since this is a combination therapy protocol, remission status and best response is determined one-month post completion of treatment. The interim scan is not used to determine a patient's remission status or overall best response; rather, the interim scan is used only to determine whether a patient needs to have a biopsy and the outcome of this biopsy determines the type of consolidation treatment a patient receives on protocol.

13.0 CRITERIA FOR REMOVAL FROM STUDY

The following patients will be removed from study:

- Patients who have progression of disease while on treatment. These patients may be offered alternate treatments.
- Patients who develop unacceptable toxicity.
- Patients who develop active HBV infection or hepatitis.
- Patients who request that they be removed from study. This will not compromise the care they receive at this institution.
- Patients who are non-compliant with treatment or follow-up.

14.0 BIOSTATISTICS

This protocol implements a risk adaptive therapeutic approach for patients with untreated diffuse large B cell lymphoma. All patients will receive RR-CHOP-14 induction chemotherapy. If their Ki-67 pretreatment evaluation is <80, then the patient will be assigned to ICE consolidation therapy (Consolidation A), otherwise they will receive augmented RICE consolidation therapy (Consolidation B). An additional component of this study is that patients will receive a FDG-PET scan and biopsy interim evaluation. Patients that are biopsy positive will not receive Consolidation A or B. Instead they will receive consolidation C, which is augmented RICE followed by a HDT/ASCT consolidation therapy, or allogeneic stem cell transplant if a patient's bone marrow remains positive after induction therapy and they have an acceptable HLA match donor.

The primary outcome of this study is remaining alive and progression free for two years from the start of induction therapy conditional on attaining either a negative FDG-PET or a negative biopsy at the interim evaluation. The probability of this outcome will be evaluated separately in the Ki-67 <80 cohort (Consolidation A) and the Ki-67 ≥80 cohort (Consolidation B). All patients that do not experience the progression free survival endpoint and have a negative biopsy at the interim evaluation will attempt to be followed for a minimum of 2 years from initiation of therapy on protocol. Patients who have a negative biopsy and are lost to follow up prior to 2 years who are alive will be counted as failures for the primary endpoint.

For Ki-67 <80 and either a negative FDG-PET or a negative biopsy at the interim evaluation, the therapy will not be considered sufficiently active if the two year progression free survival probability is less than 0.80. Fifty patients will be accrued to this cohort. If at the end of the trial, 45 patients are alive and progression free at 24 months (+/-2 months), then this combination therapy will be considered promising in this patient population. This design has a type 1 error equal to 0.05 and has power greater than 0.95 when the two-year progression free survival probability is 0.95.

For Ki-67 ≥80 and either a negative FDG-PET or a negative biopsy at the interim evaluation, the therapy will not be considered sufficiently active if the two-year progression free survival probability is less than 0.50. Twenty six patients will be

accrued to this cohort. If at the end of the trial, 17 patients are alive and progression free at 24 months (+/-2 months), then this combination therapy will be considered promising in this patient population. This design has a type 1 error equal to 0.10 and has power greater than 0.90 when the two-year progression free survival probability is 0.75.

At the conclusion of the study, within each study cohort, the probability of progression over time will be computed using the cumulative incidence function (competing risks methodology) to account for patients removed from the follow-up due to a positive biopsy at the interim evaluation. In addition, a competing risks regression model will be employed to explore the factors that are associated with the time to progression.

Based on our experience in MSKCC 01-142, we expect an accrual of approximately 2 patients per month; thus, the study will take approximately 44-48 months to complete. Enrollment will continue until 26 patients with high Ki-67 are enrolled, not necessarily stopping when 90 patients are accrued overall.

Secondary endpoints:
The reference radiologists will evaluate all sites of disease on sequential imaging studies (pre-treatment, after cycle 4, and at conclusion of therapy) in this research study. The secondary endpoints will be evaluated in as many patients as possible (all consolidations, A, B and C, will be included).

Functional imaging:
Patients will undergo FDG PET/CT at baseline, after cycle 4 of chemotherapy and after the end of treatment. Diagnostic CT will also be obtained at these time points. In contrast, FLT PET/CT will be done at baseline and after cycle 1 or cycle 2 of chemotherapy, for the first 60 patients who undergo the FLT-PET scan. The remaining 30 patients to enroll on study will receive an additional FDG PET scan after cycle 2.
In this protocol, we will obtain preliminary data on biodistribution, and potential clinical usefulness of the proliferation marker [18F] fluorothymidine (FLT) in patients with diffuse large cell lymphoma, using combined positron emission tomography/computed tomography (FLT-PET/CT). For the first 30 consecutive patients, the FLT PET scans will be obtained at baseline (prior to therapy) and after cycle 1. After the first 30 patients are accrued to the study, an additional 30 patients (not necessarily consecutive) will receive FLT PET scans at baseline and after cycle 2 of chemotherapy. We will study the biodistribution of FLT in large cell lymphoma and changes in FLT distribution in response to chemotherapy. The latter may provide first insights into the potential clinical usefulness of FLT in monitoring the response to chemotherapy in lymphoma. Note, however, that FLT PET is exploratory only; that is, FLT findings will not affect treatment decisions.
FLT PET will be obtained as a dynamic study, with image acquisition for up to 40 min over one 15 cm field of view (for one ion more than one lesion(s) identified on previous CT scan and/or FDG PET). This will be followed by a whole body scan from the skull base to at least the upper thigh (further extending if disease more distally was found clinically or on the prior FDG PET study).

In the analysis, we will correlate FLT findings with CT and FDG PET findings (e.g., does uptake occur in all lesions seen on CT and/or FDG PET, and what is the intensity of such uptake in a given organ (e.g., liver versus lung) and in comparison to FDG uptake). A two sample non-parametric test will be used to assess whether there is a difference in FLT SUV after the first or second cycle of chemotherapy, or in the degree of decline in FLT uptake (baseline → post cycle 1 or post cycle 2), between groups of patients with response on CT and/or FDG PET after cycle 4 of chemotherapy. The correlation between FLT and FDG SUV uptake will be assessed via Spearman rank correlation coefficient. We will correlate the degree of Ki-67 staining at baseline with FLT uptake in the baseline scan and the improvement on FLT scan done between baseline and cycle 1 or between the baseline scan and cycle 2 . We will also investigate if changes in FLT uptake (baseline → post cycle 1 or 2) correlate with ultimate patient outcome (DFS; binary outcome).

The data analysis equipment and software for nuclear medicine imaging is continuously changing and evolving. As new imaging analysis methods are developed, we will apply those that are optimal to the imaging purpose, including automated and semi-automated determination of quantitative measures such as standardized uptake values (SUV), location and extent of lesion, site within the body, gating lesion motion to respiration/pulse, and all other kinetic approaches to determine uptake.

CT Volumetric Analysis:
To determine the role of CT volumetric analysis compared to standard CT in this patient population. We will explore the relative tumor burden determined following means: unidimensional measurements of the largest cross-sectional dimension; sum of the products of the maximal perpendicular cross-sectional measurements; volumetric sum of lymph node masses. These measurements will be determined at baseline whenever possible, after 4 cycles of therapy and at the end of therapy. The three CT volumetric measurements will be compared via the ranked based Friedman's test for paired data.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

Patients wishing to enroll will be registered after signing an informed consent.

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the written consent/verbal script and a completed Eligibility Checklist must be faxed to PPR.

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization and to coordinate the activities of the protocol study team.
The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.
Data to be collected will include: FDG-PET scan results, CR, PR and failure rates, CD34+ cell yields, toxicities of treatment, and duration of treatment.

16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates, extent, and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

Retention of Records: All documentation of adverse events, records of study drug receipt and dispensation, and all IRB/PB correspondence will be retained for at least 2 years after the investigation is completed.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, and there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.1 PROTECTION OF HUMAN SUBJECTS

Potential Risks

Potential risks and adverse events associated with this trial include: fever, chills, asthenia, hypotension, anaphylaxis, tumor lysis syndrome, death, CNS toxicity, microscopic and gross hematuria, nausea, vomiting, alopecia, cardiotoxicity, neutropenia, febrile neutropenia, thrombocytopenia, anemia, peripheral neuropathy, ototoxicity, hepatic toxicity, renal insufficiency, electrolyte abnormalities, allergic reactions, teratogenicity, pneumothorax, deep venous thrombosis, and catheter-related sepsis.

Mild to moderate medullary bone pain is the most common side effect associated with G-CSF therapy and occurs in approximately 20-25% of patients. It is effectively treated with non-narcotic analgesics. Other side effects include transient and reversible changes in alkaline phosphatase, uric acid, and LDH. Exacerbation of pre-existing autoimmune disorders, subclinical splenomegaly, alopecia, and cutaneous vasculitis are rarely reported.

Potential Benefits

Patients who achieve a CR with CHOP chemotherapy do significantly better than those patients who fail upfront therapy. Patients on this trial may have a higher probability of achieving a CR than they would with standard CHOP and therefore may have a longer relapse-free and overall survival.

Provisions for preventing and treating adverse events

Treatment of febrile neutropenia, cytopenias, ifosfamide-related gross and microscopic hematuria, and catheter related sepsis, thrombosis, and pneumothorax will be in

accordance with standard medical practices employed at MSKCC. Rituximab administration will be premedicated with acetaminophen, Diphenhydramine, and Ativan in order to prevent infusion-related adverse effects. Infusion will be titrated as tolerated as described in section 5.0. In the event of an adverse reaction, the infusion will be stopped, the patient will be assessed and treatment will be administered in accordance with standard medical practice.
Patients will receive standard anti-emetics as prophylaxis against nausea and vomiting.

Alternatives/Options for treatment

For patients eligible, alternative therapy would consist of CHOP in standard dosing, in an accelerated fashion, or R-CHOP

Costs

The patient will be responsible for all costs related to treatment and complications of treatment, including G-CSF, pegfilgrastim, and all hospitalizations. FLT is investigational and the patients will not pay for the FLT scans.

Privacy and confidentiality

Confidentiality will be maintained within the limits of the law. Only qualified individuals from MSKCC; the National Cancer Institute; the FDA; Genentech; will be able to review patients' medical records. Neither the patients' names nor other identifying information will be used in reports or publications arising from this study.

17.2 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

17.3 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org containing the following information:

Fields populated from the CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following information:
    - An explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
    - If an amendment will need to be made to the protocol and/or consent form

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB AE report should be completed as above and the FDA assigned IND/IDE number written at the top of the report. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office

In the event of an adverse event, the first concern will be for the safety of the subject. Investigators are required to report all **serious adverse events**, regardless of causality to rituximab, whether **expected** or **unexpected**, to Genentech Drug Safety and the IRB/PB.

All serious adverse 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 (i.e., 30 days since last treatment on protocol). Serious criteria, definitions, and guidance for reporting follow.

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

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

- Results in **death** (i.e. the AE caused or lead to death)

- Is **life-threatening** (i.e. the AE placed the subject at immediate risk of death; it does not apply to an AE which hypothetically might have caused the death if it were more severe)

- Requires or prolongs inpatient **hospitalization** (i.e. the AE required at least a 24-hour inpatient hospitalization or prolonged a hospitalization beyond the expected length of

stay; hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not SAEs by this criterion). Hospitalizations for uncomplicated febrile neutropenia do not need to be reported as SAEs.

- 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** in section 5.0, section 11.1 or characterized in the current Investigator Brochure.

Unexpected adverse events are those **not listed** in section 5.0, section 11.0, 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.

Attribution: All serious adverse events will be graded according to CTCAE version 3.0 and will be recorded in MSKCC's CRDB database and reported to the IRB/PB. The following categories and definitions of causal relationship to treatment intervention as determined by the physician will be used:

- Definite: The SAE is *clearly related* to treatment intervention
- Probable: The SAE is *likely related* to treatment intervention
- Possible: The SAE *may be related* to treatment intervention
- Unlikely: The SAE is *doubtfully related* to treatment intervention
- Unrelated: The SAE is *clearly NOT related* to treatment intervention

Reportable events are those which occur within 30 days from the last day of treatment on protocol.

Reporting of Serious Adverse Events Associated with Rituximab

All serious adverse events (SAEs) outlined above that we will be reporting, regardless of causality to rituximab should be recorded on the institution's own Serious Adverse Event report form (with patient identifying information removed with the exception of D.O.B., initials, subject number) and faxed to:

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

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

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

Study Drug Relationship:

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

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

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDIX 1

	Absorbed Doses (1)				
	F18-FLT1	1 * 8 mCi FLT	1 FLT PET-CT 0.9 rad (2) + 8 mCi FLT	2 FLT PET-CT 2 * 0.9 rad + 2 * 8 mCi FLT	3 FLT PET-CT 3 * 0.90 rad + 3 * 8 mCi FLT
Target Organ	**rad/m Ci**	**rad**	**rad**	**rad**	rad
Adrenals	0.08	0.61	1.51	3.03	4.54
Bone Surfaces	0.06	0.47	1.37	2.74	4.10
Brain	0.01	0.10	1.00	2.00	3.00
Breasts	0.03	0.25	1.15	2.30	3.45
Gall Bladder Wall	0.06	0.50	1.40	2.80	4.20
Heart Wall	0.06	0.49	1.39	2.79	4.18
Kidneys	0.13	1.05	1.95	3.91	5.86
Large Intestine - Lower Wall	0.02	0.13	1.03	2.07	3.10
Large Intestine - Upper Wall	0.05	0.37	1.27	2.53	3.80
Lens of Eye	0.04	0.31	1.21	2.42	3.63
Liver	0.17	1.34	2.24	4.49	6.73
Lungs	0.04	0.30	1.20	2.40	3.60
Muscle / Other tissue	0.06	0.50	1.40	2.79	4.19
Pancreas	0.09	0.68	1.58	3.16	4.74
Red Marrow	0.09	0.71	1.61	3.22	4.83
Skin	0.02	0.13	1.03	2.06	3.09
Small Intestine	0.05	0.42	1.32	2.64	3.96
Stomach Wall	0.05	0.42	1.32	2.63	3.95
Testes	0.05	0.39	1.29	2.58	3.87
Thyroid	0.04	0.31	1.21	2.42	3.62
Total Body	0.05	0.37	1.27	2.55	3.82
Urinary Bladder Wall		0.00			
45-min Voiding Interval	0.03	0.24	1.14	2.27	3.41
1-hr Voiding Interval	0.04	0.32	1.22	2.43	3.65

1.5-hr Voiding Interval	0.06	0.47	1.37	2.75	4.12
2-hr Voiding Interval	0.08	0.63	1.53	3.07	4.60
Effective Dose Equivalent ("rem")	**0.10**	**1.04**	**1.94**	**3.87**	5.81

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21.1 APPENDIX 2

21.2 Treatment Timeline: Screening Period

a. FLT-PET/CT scans will be performed under an IND
b. Creatinine clearance only if serum Cr> 1.5 mg/dl
c. Documentation of HIV seronegativity must be performed at MSKCC.
d. A tissue biopsy confirming the Diffuse Large B Cell Lymphoma diagnosis. Results must be confirmed by MSKCC
e. Pregnancy test in pre-menopausal women only
f. The CT scan should be done with volumetric analysis when possible
g. Unless not required per protocol
h. Bilateral bone marrow biopsy not required if unilateral bone marrow biopsy done within 4 weeks prior to treatment initiation shows involvement by lymphoma

Treatment	**Screening**		
Visit	Prior to ICE administration	Within one month of treatment initiation	Within 2 weeks treatment of initiation
Hepatitis B surface antigen & core antibody		X	
Hepatitis C antibody		X	
Echocardiogram or MUGA		X	
Ki-67 Staining of tumor	X		
Tissue blocks or 10 unstained slides	X		
HIV test[c]		X	
CT Scan of Chest/Abdomen/Pelvis[f]		X	
FDG-PET/CT scan		X	
FLT-PET/CT scan[g]		X[a]	
Bilateral Bone Marrow Biopsy[h]		X	
Creatinine Clearance		X[b]	
Complete history			X
Physical Exam			X
CBC w/ differential			X
Comprehensive Metabolic Panel			X
Urinalysis			X
Pregnancy Test[e]			X
EKG			X

21.3 Treatment Timeline for Induction and Interim Restaging

Treatment	Induction								Interim Restaging
Visit	Cycles 1-3, Day -2[d]	Cycles 1-3, Day 0	Cycles 1-3, Day 2	Cycles 1-3, Days 6-10	**POST cycle 1 or Cycle 2**	Cycle 4[f] Day 0	Cycle 4 Days 0-4	Cycle 4 Days 6-10	Cycle 4 Days 17-20
CT Scan of Chest/Abdomen/ Pelvis[i]									X
FDG-PET/CT scan									X
FLT-PET/CT					X[a, b, c]				
Bilateral Bone Marrow Biopsy									X[g]
Physical Exam	X					X			
CBC w/ differential	X					X			
Rituximab 375 mg/m^2 IVPB	X[j]	X	X[j]						
Cyclophosphamide 1000 mg/m^2 IVPB		X				X			
Doxorubicin 50 mg/m^2 IVPB		X				X			
Vincristine 1.4 mg/m^2 IVP (no cap)		X				X			
Prednisone 100 mg PO daily for 5 days		X					X		
Growth Factor Support[e]				X				X	
Antimicrobial Prophylaxis[h]	X	X	X	X	X	X	X	X	X

a. FLT-PET/CT scans will be performed under an FDA IND.
b. The FLT-PET scan should be performed after completion of prednisone in cycle 1 or cycle 2 and before the first dose of Rituximab in cycle 2 of induction therapy. The first 30 consecutive patients on study had the FLT PET scan after cycle 1; the next 30 who have an FLT PET scan will have their FLT PET scan after cycle 2.
c. Only 60 patients will receive FLT-PET scan. For the subsequent 30 patients who enroll on study, FLT-PET scan at baseline and after cycle 2 will not be done and will be replaced with an FDG-PET scan after cycle 2.
d. Day 0 of next cycle is Day 14 as long as ANC $\geq$ 1000 and platelets $\geq$ 50,000.
e. SQ at either 300ug/day or 480 ug/day OR Pegfilgrastim 6 mg once 24-48 hrs post completion of intravenous chemotherapy.
f. Cycle 4 will last 21 days.
g. Bilateral Bone Biopsy for patients with a positive scan only, can be done at any point post-therapy in cycle 4. Only unilateral biopsy required at interim if unilateral biopsy at baseline showed involvement by lymphoma.
h. Trimethoprim/Sulfamethoxazole 160/800 (DS) oral twice daily TIW (patients with known allergy to Trimethoprim/Sulfamethoxazole can receive alternative pneumocystis carinii prophylaxis), Acyclovir 400 mg oral bid, and Fluconazole 100 mg oral qd

i. The CT scan must be done with volumetric analysis
j. Rituximab is to be given EITHER on Day -2 or Day 2, not on both days.

21.4 Treatment Timeline for Consolidation A

Treatment	Consolidation A[1, 2]					
Visit	Cycles 1-3, Day 1	Cycles 1-3, Day 2	Cycles 1-3, Day 3	Cycles 1-3, Day 4	Cycles 1-3, 24-48 hours post completion of chemotherapy	4-6 weeks post completion of cycle 3
Physical Exam	X					
CBC	X					
Etoposide 100 mg/m^2 IVPB	X	X	X			
Carboplatin AUC 5 IVPB[3]		X				
Ifosfamide 5 g/m^2 with MESNA 5 g/m^2 IVCI[4]		X ⇒				
Pegfilgrastim 6 mg					X	
CT scan[6]						X
FDG PET scan						X
Antimicrobial Prophylaxis[5]	X	X	X	X	X	X

1. Consolidation A: Patients whose disease is FDG-PET negative or patients whose FDG-PET scan is positive but repeat biopsy is negative and whose initial Ki-67 expression is ≥80% will receive 3 cycles of standard dose ICE Chemotherapy.
2. Patients must have a platelet count of 50,000/ul and an ANC of at least 1000/ul to proceed to subsequent cycles of ICE.
3. Maximum dose 800 mg (equivalent to CrCl of 135 ml/min). AUC dosing is calculated by the Calvert Formula: AUC 5 = 5 x (CrCl+25)
4. Ifosfamide 5 g/m^2 admixed with MESNA 5 g/m^2 IVCI over 24 hours beginning on Day 2.
5. Trimethoprim/Sulfamethoxazole 160/800 (DS) oral twice daily TIW (patients with known allergy to Trimethoprim/Sulfamethoxazole can receive alternative pneumocystis carinii prophylaxis), Acyclovir 400 mg oral bid, and Fluconazole 100 mg oral qd
6. The CT scan must be done with volumetric analysis

21.5 Treatment Timeline for Consolidation B

Treatment	Consolidation B[1, 2]					
Visit	Cycles 1-2, Day 1	Cycles 1-2, Day 3	Cycles 1-2, Day 4	Cycles 1-2, Day 6	Cycles 1-2, 24-48 hours post completion of cycle	4-6 weeks post completion of cycle 2
Physical Exam	X					
CBC	X					
Etoposide 100 mg/m^2 IVPB			X ⇨			
Carboplatin AUC 5 IVPB[4]				X		
Ifosfamide 5 g/m^2 with MESNA 5 g/m^2 IVCI[5]			X ⇨			
Pegfilgrastim 6 mg					X	
Rituximab 375 mg/m^2 IVPB	X	X				
CT scan[7]						X
FDG-PET scan						X
Antimicrobial Prophylaxis[6]	X	X	X	X	X	X

1. Consolidation B: Patients whose disease is FDG-PET negative or patients whose FDG-PET scan is positive but repeat biopsy is negative and whose initial Ki-67 expression is ≥80 will receive 2 cycles of augmented RICE Chemotherapy (as per MSKCC protocol 03-075)
2. Patients must have a platelet count of 50,000/ul and an ANC of at least 1000/ul to proceed to subsequent cycles of ICE.
3. Etoposide is administered every 12 hours starting on day 4.
4. Maximum dose 800 mg (equivalent to CrCl of 135 ml/min). AUC dosing is calculated by the Calvert Formula: AUC 5 = 5 x (CrCl+25)
5. Ifosfamide 5 g/m^2 admixed with MESNA 5 g/m^2 IVCI over 24 hours beginning on Day 4.
6. Trimethoprim/Sulfamethoxazole 160/800 (DS) oral twice daily TIW (patients with known allergy to Trimethoprim/Sulfamethoxazole can receive alternative pneumocystis carinii prophylaxis), Acyclovir 400 mg oral bid, and Fluconazole 100 mg oral qd
7. The CT scan must be done with volumetric analysis

21.6 Treatment Timeline for Consolidation C

Treatment	Consolidation C[1,2] Part I					Part II	Part III
Visit	Cycles 1-2, Day 1	Cycles 1-2, Day 3	Cycles 1-2, Day 4	Cycles 1-2, Day 6	Cycles 1-2, 24-48 hours post completion of cycle	Stem cell collection, post cycle 2[13]	Stem Cell Transplant & Post transplant
Physical Exam	X						
CBC	X						
Etoposide 100 mg/m^2 IVPB[3]			X	⇒			
Carboplatin AUC 5 IVPB[4]				X			
Ifosfamide 5 g/m^2 with MESNA 5 g/m^2 IVCI[5]			X	⇒			
Pegfilgrastim 6 mg					X		
Rituximab 375 mg/m^2 IVPB	X	X					X[10]
FDG-PET Scan							X[8]
CT scan[11]							X[8]
Leukapheresis						X[6]	
High dose chemoradiotherapy and ASCT[7]							X
Bone Marrow Biopsy							X[9]
Antimicrobial Prophylaxis[12]	X	X	X	X	X	X	X

1. Consolidation B: Patients whose disease is FDG-PET negative or patients whose FDG-PET scan is positive but repeat biopsy is negative and whose initial Ki-67 expression is ≥80 will receive 2 cycles of augmented RICE Chemotherapy (as per MSKCC protocol 03-075)
2. Patients must have a platelet count of 50,000/ul and an ANC of at least 1000/ul to proceed to subsequent cycles of ICE.
3. Etoposide is administered every 12 hours starting on day 4.
4. Maximum dose 800 mg (equivalent to CrCl of 135 ml/min). AUC dosing is calculated by the Calvert Formula: AUC 5 = 5 x (CrCl+25)
5. Ifosfamide 5 g/m^2 admixed with MESNA 5 g/m^2 IVCI over 24 hours beginning on Day 4.
6. The target yield for leukapheresis will be 5x10^6 CD34+ cells/kg. Leukaphereses will continue for up to 5 days until the target yield is reached.
7. Patients will be eligible to receive IFRT if clinically indicated beginning 2 weeks prior to initiation of high dose chemotherapy. (CBV-N) it will be administered as follows:
   Mitoxantrone (45 mg/m2) IVPB x 1 on day – 8
   Carmustine (300 mg/m2) IVPB x 1 on day – 4
   Cyclophosphamide (1500 mg/m2) IVPB daily x 4 days on day – 7, - 6, - 5, - 4
   Etoposide (250 mg/m2) IVPB daily x 4 days on day – 7, - 6, - 5, - 4
   PBPC will be infused approximately 24-48 hours after completion of chemotherapy (day 0).
8. 90-120 Days after high dose therapy.
9. Only necessary if patient had a positive bone marrow biopsy at restaging.

10. No later than Day +35 post ASCT patients will receive rituximab bimonthly for 6 doses.
11. The CT scan must be done with volumetric analysis
12. Antimicrobial prophylaxis for Augmented RICEx2 is the same as specified in Consolidation B. Antimicrobial prophylaxis for transplant phase: On admission: Ciprofloxacin 500 mg PO b.i.d. (continue until the patient requires broad spectrum antibiotics for neutropenic fever) Fluconazole 100 mg PO or IV b.i.d. (continue until the ANC is > 1000/mm3 X 3 days or until amphotericin B therapy is initiated). Nystatin powder applied to the groin and the axilla BID Vitamin K 10 mg PO or sc. one to three times per week unless added to TPN. Day +5 : G-CSF 480 ug sc. QD (continue until ANC > 1000/mm3 x 3 days.)
13. Patients whose bone marrow remain positive at interim restaging will also have the option of getting an allogeneic stem cell transplant, in lieu of an ASCT, if they have an acceptable HLA match donor. The allogeneic stem cell transplant regimen will be decided by the MSK Bone Marrow Transplant Service