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PHASE II STUDY OF RITUXIMAB IN COMBINATION WITH METHOTREXATE, DOXORUBICIN, CYCLOPHOSPHAMIDE, LEUCOVORIN, VINCRISTNE, IFOSFAMIDE, ETOPOSIDE, CYTARABINE AND MESNA (R-MACLO/IVAM) IN PATIENTS WITH PREVIOUSLY UNTREATED MANTLE CELL LYMPHOMA

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SCHEMA

Patients older than 18 years and less than 72 years of age, with previously untreated mantle cell lymphoma and ECOG Performance Status 0-2.

TREATMENT

Treatment is given on an inpatient basis and patients should receive cycles 1 and 2 during the same hospitalization, followed by a 2 week resting period and then cycles 3 followed by a 1 week resting period, and then cycle 4. Patients in complete remission will receive maintenance therapy with Rituximab every 6 months for a total of 3 years.

Cycles 1 and 3

DAY	DRUG
1	Rituximab 375 mg/m^2 IV according to institutional standard protocol.
1	Doxorubicin 45 mg/m^2 IV bolus according to institutional standard protocol.
1	Vincristine 1.5 mg/m^2 IV push (maximum of 2 mg) according to institutional standard protocol.
1	Cyclophosphamide 800 mg/m^2 IV given in 100 ml NS IV over 30 (+/-15) minutes according to institutional standard protocol.
2-5	Cyclophosphamide 200 mg/m^2 IV given in 100 ml NS IV over 30 (+/-15) minutes according to institutional standard protocol.
8	Vincristine 1.5 mg/m^2 IV push (maximum of 2 mg) according to institutional standard protocol.
10	Methotrexate 1,200 mg/m^2 in 250 ml D5W IV over 1 hour (+/-30 min) followed byMethotrexate3,000mg/m^2 in 1,000 ml D5W by continuous infusion over 23 (+/-2) hours (130 mg/m^2 every hour for 23 hours).
11+	Leucovorin 100 mg/m^2 IV beginning 36 (+/-4) hours after start of Methotrexate infusion followed by Leucovorin 10 mg/m^2 IV every 6 (+/-30 min) hours until Methotrexate level is$\leq$ 0.1µmol/L.
13+	G-CSF 480 mcg SQ daily. Stop G-CSF after 2 consecutive ANC $\geq$1,000 cells/mm^3.

Cycle 2 will be scheduled to begin after 2 consecutive ANC $\geq$ 1,500 cells/mm^3 and chemotherapy orders are finalized.

SPECIAL INSTRUCTIONS

Pre-medications:
Patients will be pre-medicated for nausea/vomiting or hypersensitivity according to institutional standards. Pre-medications may vary based on subject's medical history.

CBC:
Will be drawn every other day during Chemotherapy administration.
Starting on Day 14,CBC will be drawn every day until the end of the cycle.

Methotrexate level:
First Methotrexate level to be obtained 24 hours (+/- 2 hrs) after completion of Methotrexate and daily until level is ≤ 0.1 µmol/L.

Methotrexate Precautions:
If Creatinine is ≥ grade 3 on cycle 1 reduce Methotrexate to 75%.
Patients with Pleural Effusion, if not drained do not administer Methotrexate.

Leucovorin:
Leucovorin dose may be adjusted per PI discretion to ensure subject safety.

G-CSF:
Obtain CBC every other day, starting day 9. GCFS will be given daily until ANC is 1,000 cell/mm^3, at which point, GCSF will be stopped and CBC drawn daily. After stopping G-CSF, if WBC becomes less than 1000µL, restart G-CSF 480 µg SQ daily for 3 days and repeat CBC. If subject is of large body habitus, G-CSF can be increased to 600 µg SQ daily at discretion of treating physician, after the initial dose of 480 µg. When ANC is 1,500, start cycle 2

Cycles 2 and 4

To start immediately after Cycle 1 and one to two weeks after cycle 3 once ANC is ≥ 1500 cells/mm^3

DAY	DRUG
-1	NS 200 mL/hr x 12 hours (+/- 1 hr) prior to Ifosfamide
1	Rituximab 375 mg/m^2 IV according to standard protocol.
1 and 2	Cytarabine 2 grams/m^2 IV every 12 hours (+/-60 mins) x 4 doses according to institutional standard protocol
1-5	Ifosfamide 1.5 grams/m^2 IV QD x 5 days according to institutional standard protocol
1-5	Mesna 360 mg/m^2 IV every 3 hours (+/-30 mins) x 5 days according to institutional standard protocol
1-5	Etoposide 60 mg/m^2 IV daily x 5 days according to institutional standard protocol
7	G-CSF 480 µg SQ daily (start Day 7) according to institutional standard protocol

SPECIAL INSTRUCTIONS

Pre-medications:
Patients will be pre-medicated for nausea/vomiting or hypersensitivity according to institutional standards. Pre-medications may vary based on subject's medical history.

Cytarabine:
Will be given over 3 hours (+/- 1 hr)

Ifosfamide:
Will be given over 1 hour (+/- 30 min) daily on days 1-5.

Ifosfamide Level:
Obtain U/A daily, hold ifosfamide if >5 RBC/HPF, resume per physician's orders

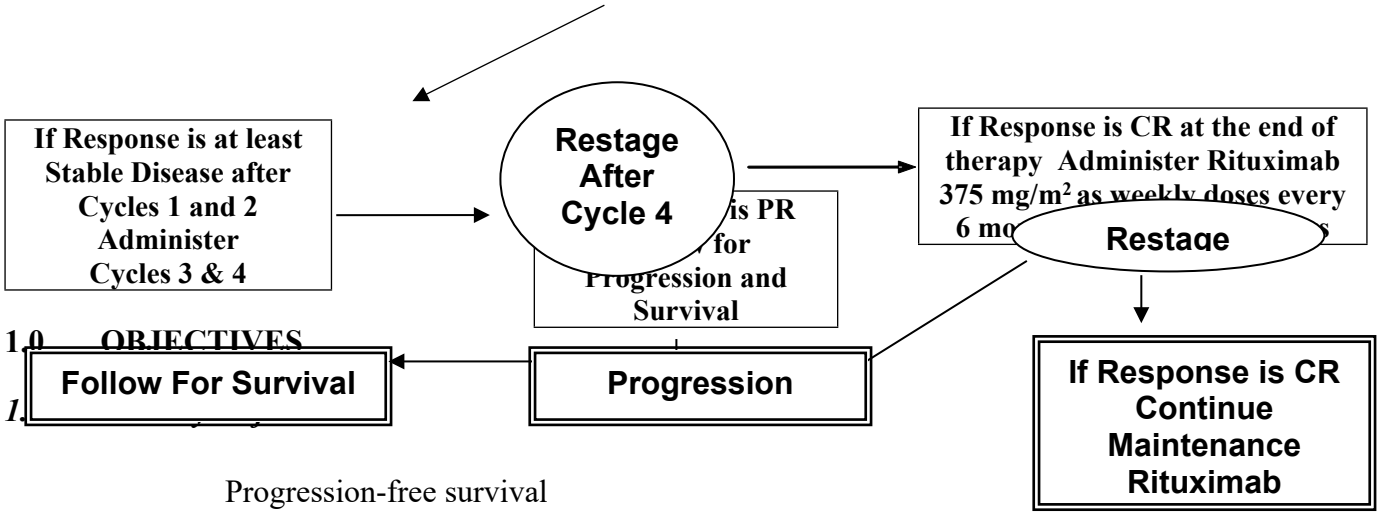
Mesna:
Give Mesna in 50 mL D5W over 20 minutes (+/- 10 mins)

Etoposide:
Give Etoposide in 250 mL D5W over 1 hour (+/- 30 mins)

G-CSF:
After stopping G-CSF, if WBC becomes less than 1000/µL, restart G-CSF 480 µg SQ daily for 3 days and repeat CBC. Obtain CBC every other day starting Day 9.

Scheduled Labs (cycles 2 through 4):

- Days 1, 3 and 5: CBC with differential.
- Starting Day 7: CBC with differential every day, until ANC reaches 1500cells/mm^3 for two consecutive days or per physician's orders.
- Days 1 through 5: Urinalysis.



1.0 OBJECTIVES

1.1 Primary Objective

Progression-free survival

1.2 Secondary Objectives

1.2.1 Overall survival

1.2.2 Response Rate

1.2.3 Toxicity

2.0 BACKGROUND

Mantle cell lymphoma (MCL), a subtype of non-Hodgkin's lymphoma (NHL), was recently recognized as a distinct disease entity. The term MCL was proposed in 1992 to unify previously defined subtypes of NHL, such as diffuse poorly differentiated lymphocytic lymphoma, intermediate differentiated lymphocytic lymphoma, centrocytic lymphoma, and diffuse small cleaved cell lymphoma, into a single disease entity [1]. According to the International Lymphoma Study Group (ILSG), MCL represents 6% of all NHLs [2]. MCL is derived from a subset of naive pre-germinal center cells, andmay present with two cytological variants: typical (lymphocytic) or blastic[3-4]. In addition, there are three possible patterns of involvement: mantle-zone, nodular or diffuse [4]. It has been suggested that the treatment response and survival of the diffuse and nodular patterns are worse than those involving the mantle cell zone. Majlis et al reported 3-year survival rates for mantle-zone, nodular, and diffuse type of 100%, 50%, and 55% respectively [5]. The monoclonal B-cells express CD19, CD20, CD22, HLA-DR, CD5, surface IgM and, in most cases, surface IgD. They are negative for CD23 and CD10 (CALLA) antigens [6].

The characteristic cytogenetic abnormality in MCL is the t(11;14) (q13;q32) translocation. Band 11q23 includes the BCL-1 locus, which is the site of the PRAD1 (CCND1) gene encoding for cyclin D1. This rearrangement results in translocation of the BCL-1 locus to the immunoglobulin heavy chain gene enhancer region located at 14q32, causing cyclin D1 over-expression. Cyclin D1 interacts with cyclin dependent kinases 4 and 6 to facilitate the progression of cell through G1 into S phase of proliferation [7].

MCL is one of the worst types of NHL since it incorporates some of the undesirable features of both low-grade and high-grade lymphomas, namely incurability and rapid course respectively [7]. Most of the patients present with advanced stage, high international prognostic index (IPI), and extranodal involvement. The incidence of Stage III and IV varies between 75 to 90% of the patients [2, 4, 6-8]. In addition, there is a high incidence of extranodal involvement, the most common sites being bone marrow (61-79%), spleen (31-60%), liver (13-30%), peripheral blood (12-30%), and gastrointestinal tract (18-20%) [6-9]. Central nervous system (CNS) involvement occurs in about 4% of the patients and is associated with poor prognosis [10].

The long-term survival for patients with MCL is generally poor, with only about 27% of the patients surviving 5 years after diagnosis and 11% of the patients being disease-free after 5 years. In addition, the ILSG found no 5-year survivors with IPI index 4/5, placing MCL among the lymphomas with worse overall prognosis [2]. Despite response rates of 50% to 70% to different regimens, all patients eventually develop disease progression after chemotherapy, with the mean survival around 3 years [11].

Several studies using combination chemotherapy with or without anthracyclines (CHOP or COP) showed responses between 56% and 90%, with CR rates ranging from 9% to 58%. However, relapse-free survival was relatively short with average of 15 to 20 months. Median survival in most studies ranged from 28 to 52 months [12]. Therapy with fludarabine alone or in combination with other chemotherapeutic agents has been tested in small trials. In a recent study, Cohen et al obtained response rates of 66% (30% CR) in a study involving 30 patients treated with fludarabine and cyclophosphamide. The overall survival for patients receiving this combination as first line therapy has not been reached at 43 months, although failure- free survival was 28 months [13]. In another study involving 29 patients, Zinzani et al achieved a 63% overall response (28% CR) using fludarabine alone or in combination with idarubicin[14]. Rituximab has also been tested in MCL. Igarashi et al treated 21 patients with refractory or relapsed MCL, achieving a 31% response rate (no CR observed) [15]. Howard et al obtained a 96% response rate (48%n CR) in 25 patients with MCL, using a combination of CHOP and rituximab. 25 patients were evaluated for molecular remission, which was seen in 9 of them. However, the achievement of CR or molecular remission did not translate into a prolonged progression-free survival, which was 16.6 months [16]. Khouri et al, treated patients with Hyper-CVAD, an aggressive regimen alternating cycles of cyclophosphamide, doxorubicin, vincristine, and dexamethasone and high-dose methotrexate and cytarabine. This regimen induced a 93% response rate with 38% CR. This therapy was followed by stem cell transplantation and 93% of previously untreated patients were alive at 3 years post-transplant, 73% of them disease-free [19].

Although encouraging results have been reported for stem cell transplant (SCT), its role in the treatment of patients with MCL remains unknown. Overall 3-year survival for MCL patients previously treated ranges between 24% to 59%, with one study, performed by Milpied et al, reporting 80% overall survival at 4 years [20- 22]. Event-free survival (EFS) or progression-free survival (PFS) at three years however, ranges between 17% to 48%[19, 22]. Stewart et al, reported a 23% overall survival for SCT in MCL patients in first remission. EFS/PFS however, was only 8% [23]. There have been few small studies on the use of allogeneic SCT in MCL. The reported overall survival is 55% to 62% at 2 years [24-25].

Due to unsatisfactory results obtained with both conventional chemotherapy and SCT, it has become clear that new high-dose intense chemotherapeutic regimens are needed to improve the survival rates for patients with MCL. Similar intensity protocols have been used for treatment of Burkitt's lymphoma. Magrath treated patients with Burkitt's lymphoma using the CODOX-M protocol, which consisted of cyclophosphamide, doxorubicin, prednisone, vincristine, high-dose methotrexate and intrathecal methotrexate, alternating with IVAC (ifosfamide, etoposide, high-dose cytarabine and intrathecal methotrexate). This regimen resulted in excellent disease control and was relatively well tolerated in both children and adults [17]. Mead et al used this same regimen in 52 patients with Burkitt's lymphoma. All patients developed grade 3 and 4 neutropenia and 64% of the patients developed grade 3 and 4 thrombocytopenia. The only other significant side effect was mucositis, observed in about 40% of the cases [18].

We have therefore developed a similar intense protocol combining most of the agents that demonstrated activity in MCL in an attempt to provide a better disease control with improved response rates and overall survival.

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.

Patients achieving a complete remission to induction therapy will receive maintenance therapy with Rituximab for 3 years that was recently shown to prolong progression free survival in other subtypes of lymphoma.

In an initial phase II study of R-MACLO-IVAM 22 patients were enrolled. 21 completed therapy and all achieved complete remission and one patient died of sepsis on day 14. Seventeen patients remain alive and relapse-free with a median follow up of 33 months. Although the results are very promising, we did observe some toxicity, including grade 2 elevation of creatinine post methotrexate and intolerability of thalidomide in many patients. The proposed study comes to address these toxicities while trying to preserve regimen efficacy.

3.0 PATIENT SELECTION

3.1. Inclusion Criteria

3.1.1 Previously untreated, histologically confirmed mantle cell lymphoma,

3.1.2 Measurable or evaluable disease (at least one site with >1.5 cm in diameter

3.1.3 All stages are eligible

3.1.4 Age > 18 years

3.1.5 ECOG performance status 0, 1, or 2

3.1.6 Adequate hepatic function:

- Bilirubin < 3 mg/dL
- Transaminases (SGOT and/or SGPT) < than 2.5 times the upper limit of normal for the institution, unless due to lymphomatous involvement

3.1.7 Serum creatinine< 1.5 mg/dl

3.1.8 Ability to give informed consent

3.1.9 Women of childbearing potential must have a negative pregnancy test within 72 hours of entering into the study. Males and females must agree to use adequate birth control if conception is possible during the study. Women must avoid pregnancy and men avoid fathering children while in the study

3.1.10 Life expectancy greater than 6 months

3.2 Exclusion Criteria

3.2.1 Previous chemotherapy, immunotherapy or radiotherapy for this mantle cell lymphoma

3.2.2 Concurrent active malignancies, with the exception of in situ carcinoma of the cervix and basal cell carcinoma of the skin

3.2.3 Grade 3 or 4 cardiac failure and/or ejection fraction < 50.

3.2.4 Psychological, familial, sociological or geographical conditions that do not permit treatment and/or medical follow-up required to comply with the study protocol.

3.2.5 Patients with a known history of HIV or AIDS

3.2.6 Presence of hepatitis or HBV infection

3.2.7 Pregnant or breast-feeding women.

3.2.8 CNS involvement

4.0 TREATMENT PLAN

Treatment will be administered in the hospital, with the first and second cycles occurring during the

same admission.

4.1 Cycle 1

DAY	DRUG
1	Rituximab 375 mg/m^2 IV according to standard protocol.
1	Doxorubicin 45 mg/m^2 IV bolus according to institutional standard protocol.
1	Vincristine 1.5 mg/m^2 IV push (maximum of 2 mg) according to institutional standard protocol.
1	Cyclophosphamide 800 mg/m^2 IVgiven in 100 ml NS IV over 30 (+/- 15) minutes according to institutional standard protocol.
2-5	Cyclophosphamide 200 mg/m^2 IVgiven in 100 ml NS IV over 30 (+/- 15) minutes according to institutional standard protocol.
8	Vincristine 1.5 mg/m^2 IV push (maximum of 2 mg) according to institutional standard protocol.
10	Methotrexate 1,200 mg/m^2 in 250 ml D5W IV over 1 hour (+/-30 min) followed by Methotrexate 3,000 mg/m^2 in 1,000 ml D5W by continuous infusion over 23 (+/-2) hours (130 mg/m^2 every hour for 23 hours).
11+	Leucovorin 100 mg/m^2 IV beginning 36 (+/-4)hours after start of Methotrexateinfusion followed by Leucovorin 10 mg/m^2 IV every 6 (+/- 30 min) hours until Methotrexate level is$\leq$ 0.1µmol/L.
13+	G-CSF 480 mcg SQ daily. Stop G-CSF after 2 consecutive ANC $\geq$1,000 cells/mm^3.

Cycle 2 will be scheduled to begin after 2 consecutive ANC $\geq$ 1,500 cells/mm^3 and chemotherapy orders are finalized.
SPECIAL INSTRUCTIONS **Pre-medications**: Patients will be pre-medicated for nausea/vomiting or hypersensitivity according to institutional standards.Pre-medications may vary based on subject's medical history. **CBC**: Will be drawn every other day during Chemotherapy administration. Starting on Day 14,CBC will be drawn every day until the end of the cycle. **Methotrexate level**: First Methotrexate level to be obtained 24 hours (+/- 2 hrs) after completion of Methotrexate and daily until level is $\leq$ 0.1 µmol/L.

Methotrexate Precautions:
If Creatinine is ≥ grade 3 on cycle 1 reduce Methotrexate to 75%.
Patients with Pleural Effusion, if not drained do not administer Methotrexate.

Leucovorin:
Leucovorin dose may be adjusted per PI discretion to ensure subjects safety.

G-CSF:
After stopping G-CSF, if WBC becomes less than 1000µL, restart G-CSF 480 µg SQ daily for 3 days and repeat CBC. If subject is of large body habitus, G-CSF can be increased to 600 µg SQ daily at discretion of treating physician, after the initial dose of 480 µg.

*G-CSF dosage may be changed based on clinical consideration of treating physician.

4.2 Cycle 2

To start immediately after Cycle 1 once ANC is ≥ 1500 cells/mm3 (see above)

DAY	DRUG
-1	NS 200 mL/hr x 12 hours (+/- 1 hr) prior to Ifosfamide
1	Rituximab 375 mg/m^2 IV according to institutional standard protocol.
1 and 2	Cytarabine 2 grams/m^2 IV every 12 hours (+/-60 mins) x 4 doses according to institutional standard protocol
1-5	Ifosfamide 1.5 grams/m^2 IV QD x 5 days according to institutional standard protocol
1-5	Mesna 360 mg/m^2 IV every 3 hours (+/-30 mins) x 5 days according to institutional standard protocol
1-5	Etoposide 60 mg/m^2 IV daily x 5 days according to institutional standard protocol
7	G-CSF 480 µg SQ daily (start Day 7) according to institutional standard protocol

SPECIAL INSTRUCTIONS

Pre-medications:
Patients will be pre-medicated for nausea/vomiting or hypersensitivity according to institutional standards. Pre-medications may vary based on subject's medical history.

Cytarabine:
Will be given over 3 hours (+/- 1 hr)

Ifosfamide:
Will be given over 1 hour (+/- 30 min) daily on days 1-5.

Ifosfamide Level:
Obtain U/A daily, hold ifosfamide if >5 RBC/HPF.

Mesna:
Give Mesna in 50 mL D5W over 20 minutes (+/- 10 mins)

Etoposide:
Give Etoposide in 250 mL D5W over 1 hour (+/- 30 mins)

G-CSF:
After stopping G-CSF, if WBC becomes less than 1000/µL, restart G-CSF 480 µg SQ daily for 3 days and repeat CBC.Obtain CBC every other day starting Day 9.

*G-CSF dosage may be changed based on clinical consideration of treating physician.

4.3 Cycle 3

To start 7-14 days after discharge from hospital

DAY	DRUG
1	Rituximab 375 mg/m^2 IV according to institutional standard protocol.
1	Doxorubicin 45 mg/m^2 IV bolus according to institutional standard protocol.
1	Vincristine 1.5 mg/m^2 IV push (maximum of 2 mg) according to institutional standard protocol.
1	Cyclophosphamide 800 mg/m^2 IVgiven in 100 ml NS IV over 30 (+/- 15) minutes according to institutional standard protocol.
2-5	Cyclophosphamide 200 mg/m^2 IVgiven in 100 ml NS IV over 30 (+/- 15) minutes according to institutional standard protocol.
8	Vincristine 1.5 mg/m^2 IV push (maximum of 2 mg) according to institutional standard protocol.

10	Methotrexate 1,200 mg/m^2 in 250 ml D5W IV over 1 hour (+/-30 min) followed by Methotrexate 3,000mg/m^2 in 1,000 ml D5W by continuous infusion over 23 (+/-2) hours (130 mg/m^2 every hour for 23 hours).
11+	Leucovorin 100 mg/m^2 IV beginning 36 (+/-4)hours after start of Methotrexateinfusion followed by Leucovorin 10 mg/m^2 IV every 6 (+/- 30 min) hours until Methotrexate level is≤ 0.1µmol/L.
13+	G-CSF 480 mcg SQ daily. Stop G-CSF after 2 consecutive ANC ≥1,000 cells/mm^3.

Cycle 2 will be scheduled to begin after 2 consecutive ANC ≥ 1,500 cells/mm³ and chemotherapy orders are finalized.

SPECIAL INSTRUCTIONS

Pre-medications:
Patients will be pre-medicated for nausea/vomiting or hypersensitivity according to institutional standards.Pre-medications may vary based on subject's medical history.

CBC:
Will be drawn every other day during Chemotherapy administration.
Starting on Day 14,CBC will be drawn every day until the end of the cycle.

Methotrexate level:
First Methotrexate level to be obtained 24 hours (+/- 2 hrs) after completion of Methotrexate and daily until level is ≤ 0.1 µmol/L.

Methotrexate Precautions:
If Creatinine is ≥ grade 3 on cycle 1 reduce Methotrexate to 75%.
Patients with Pleural Effusion, if not drained do not administer Methotrexate.

Leucovorin:
Leucovorin dose may be adjusted per PI discretion to ensure subjects safety.

G-CSF:
After stopping G-CSF, if WBC becomes less than 1000µL, restart G-CSF 480 µg SQ daily for 3 days and repeat CBC. If subject is of large body habitus, G-CSF can be increased to 600 µg SQ daily at discretion of treating physician, after the initial dose of 480 µg.

G-CSF dosage may be changed based on clinical consideration of treating physician.

4.4 Cycle 4

To start immediately within one to two weeks after Cycle 3 once ANC is ≥ 1500 cells/mm^3 (see above)

DAY	DRUG
-1	NS 200 mL/hr x 12 hours (+/- 1 hr) prior to Ifosfamide
1	Rituximab 375 mg/m^2 IV according to institutional standard protocol.
1 and 2	Cytarabine 2 grams/m^2 IV every 12 hours (+/-60 mins) x 4 doses according to institutional standard protocol
1-5	Ifosfamide 1.5 grams/m^2 IV QD x 5 days according to institutional standard protocol
1-5	Mesna 360 mg/m^2 IV every 3 hours (+/-30 mins) x 5 days according to institutional standard protocol
1-5	Etoposide 60 mg/m^2 IV daily x 5 days according to institutional standard protocol
7	G-CSF 480 µg SQ daily (start Day 7) according to institutional standard protocol

SPECIAL INSTRUCTIONS

Pre-medications:
Patients will be pre-medicated for nausea/vomiting or hypersensitivity according to institutional standards. Pre-medications may vary based on subject's medical history.

Cytarabine:
Will be given over 3 hours (+/- 1 hr)

Ifosfamide:
Will be given over 1 hour (+/- 30 min) daily on days 1-5.

Ifosfamide Level:
Obtain U/A daily, hold ifosfamide if >5 RBC/HPF.

Mesna:
Give Mesna in 50 mL D5W over 20 minutes (+/- 10 mins)

Etoposide:
Give Etoposide in 250 mL D5W over 1 hour (+/- 30 mins)

G-CSF:
After stopping G-CSF, if WBC becomes less than 1000/µL, restart G-CSF 480 µg SQ daily for 3 days and repeat CBC.Obtain CBC every other day starting Day 9.

*G-CSF dosage may be changed based on clinical consideration of treating physician.

4.5 Supportive Care Guidelines

All antibiotics may be administered as clinically indicated.

4.6 Duration of Therapy

Treatment will consist of up to 4 cycles of therapy. Response assessment by CT and PET scans will be performed post Cycle 2. Once the final cycle of therapy is completed, response evaluation will be performed based on pre-study CT scans, PET/ Scan/endoscopy or any staging scans that were positive at baseline. (PI approval required if treating with less than 4 cycles).

Subjects in complete remission will be given Rituximab 375 mg/m^2 IV, per institution guidelines, as 4 weekly doses every 6 months for a total of 3 years or until progression of disease or if the subject is unable to tolerate further treatment. Rituximab should begin 6 months from date of discharge +/- 21 days. Maintenance therapy, premedications can be changed based on clinical consideration from treating physician. Timelines for giving premedications are given per institutional guidelines. Subject may be discharged after

administration of Rituximab, once stable.

5.0 Clinical and Laboratory Evaluations

5.1 Baseline/Pretreatment Evaluations

The following will be obtained no more than 28 days prior to the initiation of therapy (See Appendix 5):

5.1.1 Complete medical history to include:

5.1.1.1 Date of initial diagnosis of lymphoma. A copy of the pathology report must be available in the medical record.

5.1.1.2 Presence or absence of "B"-symptoms (unexplained fevers, night sweats, involuntary weight loss greater than 10% normal body weight)

5.1.1.3 History of other symptoms related to mantle cell lymphoma.

5.1.1.4 History of drug allergies

5.1.1.5 Medication list to include all medications taken within 30 days of study entry.

5.1.2 Complete physical examination: includes ECOG performance score, vital signs, weight, height, neurologic examination, careful measurement of all palpable peripheral lymph nodes, and measurement of other sites of disease present on physical examination.

5.1.3 Laboratory tests:

5.1.3.1 Hematology: CBC, platelet count, and differential

5.1.3.2 Blood chemistries: to include sodium, potassium, chloride, CO_2, creatinine, calcium, uric acid, total bilirubin, AST, ALT, alkaline phosphatase, total protein, albumin, LDH, Hepatitis B and C, Beta-2 microglobulin.

5.1.3.3 Urine pregnancy test for women of child bearing age within 72 hours of study entry

5.1.4 Other tests

5.1.4.1 EKG

5.1.4.2 MUGA or Echocardiogram

5.1.5 Staging Evaluation (-28 to D1): The following will be done for baseline.

5.1.5.1 CT scan of the chest with contrast.

5.1.5.2 Bone scan/bone films if clinically indicated.

5.1.5.3 CT of the abdomen and pelvis with contrast.

5.1.5.4 Brain CT or MRI scan if clinically indicated

5.1.5.5 Pet scan.

5.1.5.6 Colonoscopy with or without upper endoscopy, if clinically indicated.

5.1.5.7 Bone Marrow Biopsy and Aspirate.

5.2 Evaluations during treatment:

See Appendix 5 for a study calendar

5.2.1 Physical examination including ECOG performance score, weight and vital signs will be repeated on day 1 (+/- 3 days) of each chemotherapy cycle. Disease measurable on physical examination should be measured in two dimensions.

5.2.2 CBC and differential will be repeated at the start of each chemotherapy cycle.

5.2.3 CMP, Bicarbonate, creatinine, BUN, liver function tests (including total bilirubin, alkaline phosphatase, AST, ALT, and LDH will be obtained at the start of each chemotherapy cycle.

5.2.4 **For cycles 2 and 4 only** – daily U/A during Ifosfamide therapy.

5.2.5 Restaging evaluation:
After second cycle – CT scan of chest, abdomen, pelvis and Neck and PET scans will be obtained. At the end of the treatment (after final cycle) – all staging exams that were positive at baseline will be repeated. CT, PET scan in all the patients and bone marrow biopsy and aspiration and colonoscopy/endoscopy, if clinical involvement was present at initial staging.

5.3 Maintenance Treatment Evaluations

The studies listed below (5.3.1-5.3.5) are required at the indicated intervals until disease progression or death (whichever occurs first). Patients who have disease progression and

are alive are followed for survival only – no additional studies are required after disease progression.

For all patients who achieve CR after their final cycle of in-patient therapy, the following studies should be obtained monthly for the first 3 months, then every 3 months for 2 years, then every 6 months for years 3 through 5 and yearly thereafter:

5.3.1 Medical History

5.3.2 Complete physical examination: includes ECOG performance score, vital signs, weight, body surface area (during Rituximab treatment), neurologic examination, careful measurement of all palpable peripheral lymph nodes, and measurement of other sites of disease present on physical examination.

5.3.3 CBC, CMP, LDH and Beta-2.

The following studies should be obtained every 3 months for years 1 and 2, every 6 months for 3-5 years, then annually after year 5 or more frequently if clinically indicated:

5.3.4 Restaging evaluation (CT as indicated) will be performed

5.3.5 Bone Marrow biopsy and aspiration, if clinically indicated.

Windows for maintenance therapy, as well as follow-up visits are (+/- 21 days)

5.4 Early discontinuation of therapy

Patients going off study prior to completion of therapy will have a complete physical examination, and blood drawn for the following studies: CBC with differential and platelets, Electrolytes, creatinine, BUN, liver function tests (including total bilirubin, alkaline phosphatase, AST, ALT, LDH, Uric Acid and Beta-2 microglobulin.

6.0 Dosing Delays/Dose Modifications

6.1 Hematologic Toxicity

No dose modifications will be made for hematologic toxicity. We do expect severe pancytopenia and thrombocytopenia.

6.1.1 Day One Counts for each cycle of chemotherapy

6.1.1.1 If ANC < 1000 cells/mm^3 delay chemotherapy for up to 2-3 weeks. If by 4 weeks ANC has not increased to 1500 cells/mm^3 the patient will be withdrawn from treatment at the discretion of the PI.

6.2 Non-Hematologic Toxicity

6.2.1 **Doxorubicin** – If severe cardiotoxicity develops (ejection fraction less than 40% or symptomatic heart failure), this agent will be discontinued.

6.2.2 **Vincristine** – will be discontinued in the case of grade 3 or 4 neurotoxicity.

6.2.3 **Methotrexate** – dose will be decreased by 25% in the case of grade 3 or 4 renal toxicity. Dose will be omitted per PI discretion in case of undrained pleural effusion.

6.2.4 **Cytarabine** – will be discontinued in the case of grade 3 or 4 neurotoxicity attributed to Cytarabine.

6.2.5 **Cyclophosphamide and Ifosfamide** – will be discontinued if hemorrhagic cystitis occurs.

7.0 Agent Formulation and Procurement

7.1 Rituximab (Rituxan)

Rituximab is a chimeric anti-CD20 antibody that targets the CD20 antigen present during most phases of B cell development.

7.1.1 Drug preparation: Rituximab is present in 100 and 500 mg single-use vials formulated in 25 nM sodium citrate. It should be diluted in 0.9% sodium chloride or 5% dextrose to a final concentration of 1 to 4 mg/mL.

7.1.2 Administration: This agent is given only by IV route.

Infusion should be started at an initial rate of 50 mg/hour and, if no toxicity is observed during one hour, it should be escalated by increments of 50 mg/hour every 30 minutes to a maximum infusion rate of 300 mg/hour. Patient should be monitored for infusion-related events, which usually occur 30 to 120 minutes after the start of the first infusion. Infusion should be stopped immediately in the presence of signs or symptoms of an allergic reaction. Patients should then be treated with corticosteroids, diphenhydramine, acetaminophen, and IV fluids. In most cases, infusion can be restarted at 50% of the dose once symptoms have completely resolved.

7.1.3 Side effects

Common (> 30%)	Uncommon (< 30%)	Rare (< 5%)
Chills	Angioedema	Angina
Fever	Bronchospasm	Cardiac arrhythmias
Fatigue	Dyspnea	
Facial flushing	Abdominal pain	
Pruritus	Abdominal swelling	
Urticaria	Agitation	
Vomiting	Anemia	
Hypotension	Anxiety	
Headache	Loss of appetite	
	Arthralgia	
	Back pain	
	Conjunctivitis	
	Cough	
	Diarrhea	
	Dry eyes	
	Hypertension	
	Insomnia	
	Myalgia	
	Pain at the injection site	
	Peripheral edema	
	Sore throat	
	thrombocytopenia	

There is also a risk of serious virus infections occurring after discontinuation of rituximab. The following serious viral infections new, reactivated or exacerbated have been identified: JC virus (progressive multi-focal 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 rituximab and have resulted in death.

Abdominal pain, bowel obstruction and perforation, in some cases leading to death, were observed in patients receiving rituximab in combination with chemotherapy for diffuse large B-cell lymphoma.

Patients with Rheumatoid Arthritis (RA) are at an increased risk for cardiovascular events compared to the general population. 3 cardiovascular deaths occurred in studies where patients with RA were treated with rituximab.

7.2 Doxorubicin (Adriamycin)

Doxorubicin is an antibiotic that works by intercalating into DNA, resulting in inhibition of DNA synthesis and function. It also inhibits DNA topoisomerase II and inhibits

transcription through inhibition of DNA-dependent RNA polymerase.

7.2.1 Drug preparation: doxorubicin is available in 10, 20, 50, 100, and 150 mg vials for intravenous use. It should be diluted with 0.9% sodium chloride to yield a final concentration of 2 mg/mL.

7.2.2 Administration: IV Infusion.

Since it is vesicant, administration should be slowly over 3 to 5 minutes with a rapid flowing IV. Careful monitoring is necessary to avoid extravasation. In case of extravasation, infusion should be immediately stopped, the extremity should be elevated, and ice should be applied to the involved site.

7.2.3 Side effects

Common (> 30%)	**Uncommon (< 30%)**	**Rare (< 5%)**
Esophagitis Hair loss Infection Leukopenia Nausea Red colored urine Stomatitis Vomiting	Congestive heart failure Darkening of the soles and palms Diarrhea Hyperpigmentation of the fingernails Uric acid nephropathy	Allergic dermatitis Allergic reaction Anaphylaxis Bronchospasm Drug fever Hives Shortness of breath Skin rash Wheezing

7.3 Vincristine (Oncovin)

Vincristine is a vinca alkaloid that works by inhibiting tubulin polymerization. It causes a disruption in the formation of microtubule assembly during mitosis, resulting in an arrest in cell division and ultimately, cell death.

7.3.1 Drug preparation: vincristine is available in 1, 2, and 5 mg vials at a concentration of 1 mg/mL for intravenous use. It should be diluted in 0.9% sodium chloride or 5% dextrose.

7.3.2 Administration: IV Infusion.

7.3.3 Side Effects

Common (> 30%)	**Uncommon (< 30%)**	**Rare (< 5%)**
Autonomic toxicity Hair loss Hyperuricemia Neurotoxicity	Bloating Cellulitis Diarrhea Hyponatremia	Leukopenia Stomatitis Thrombocytopenia

	Nausea SIADH syndrome Skin rash Vomiting Weight loss	

7.4 Cyclophosphamide (Cytoxan)

Cyclophosphamide is an alkylating agent that cross-links with DNA resulting in inhibition of its synthesis and function.

7.4.1 Drug preparation: cyclophosphamide for intravenous use is available in 100, 200, 500, 10000, and 2000 mg vials. It should be diluted with sterile water.

7.4.2 Administration: IV Infusion

7.4.3 Side Effects

Common (> 30%)	**Uncommon (< 30%)**	**Rare (< 5%)**
Loss of appetite Darkening skin Hyperpigmentation of the fingernails Hair loss Infection Irregular menstrual periods Leukopenia Nausea Stomach pain Vomiting	Acute myocarditis Anemia Hemorrhagic cystitis Diarrhea Facial flushing Headache Hyperuricemia Increased sweating SIADH syndrome Thrombocytopenia	Allergic dermatitis Allergic reaction Anaphylaxis Angioedema Bronchospasm Dyspnea Hepatitis Hives Hyperglycemia Itching Pain at the injection site Skin rash Stomatitis

7.5 Methotrexate

Methotrexate is an antimetabolite agent that works by inhibition of dihydrofolate reductase.

7.5.1 Drug preparation: Methotrexate is available in 50, 100, 200, and 1000 mg single-use vials for intravenous use. It may be further diluted in 0.9% sodium chloride.

7.5.2 Administration: IV Infusion.

With high-dose therapy (> 1 g/m^2), it is important to vigorously hydrate the

patient and add sodium bicarbonate in the intravenous fluid to ensure that the urine pH is greater than 7.0 at the time of the drug infusion. Drug levels should also be monitored every 24 hours, starting 24 hours after infusion.

7.2.3 Side effects

Common (> 30%)	**Uncommon (< 30%)**
Loss of appetite	Renal failure
Azotemia	Acne
Bacterial infection	Oils
Cutaneous vasculitis	Cirrhosis
Gastroenteritis	Demyelination
Gastric ulcers	Hair loss
Stomatitis	Itching
Hyperuricemia	Pneumonitis
Leukopenia	Pulmonary fibrosis
Nausea, Vomiting	Skin rash
Nephropathy	
Thrombocytopenia	

7.6 Leucovorin (folinic acid)

Leucovorin is a reduced folate which replaces intracellular stores of reduced folates following inhibition of dihydrofolate reductase by methotrexate or other antifolate analogs.

7.6.1 Drug preparation: Leucovorin is available in 50, 100, and 350 mg vials for intravenous or intramuscular use. Vials can be reconstituted with sterile water and then further diluted with 0.9% sodium chloride or 5% dextrose water.

7.6.2 Administration: IV Infusion.

7.6.2 Side effects are rare and include allergic reaction and seizures.

7.7 Etoposide (VP16)

Etoposide is a topoisomerase II inhibitor.

7.7.1 Drug preparation: Etoposide is available as single-dose vials containing Etoposide phosphate equivalent to 100 mg of Etoposide for intravenous use. It should be diluted in 5 ml or 10 ml of sterile water, 0.9% sodium chloride or 5% dextrose water to a final concentration of 20 or 10 mg/mL.

7.7.2 Administration: IV Infusion.

7.7.3 Side effects

Common (> 30%)	**Uncommon (< 30%)**	**Rare (< 5%)**
Anemia Loss of appetite Hair loss Leukopenia Nausea Thrombocytopenia Vomiting	Diarrhea Stomatitis weakness	Allergic dermatitis Anaphylaxis Angioedema Neurotoxicity Phlebitis Skin rash

7.8 Ifosfamide (Ifex)

Ifosfamide is an alkylating agent.

7.8.1 Drug preparation: Ifosfamide is available in 1 g single-dose vials for intravenous use, prepackaged with mesna. It should be reconstituted with sterile water and may be further diluted in 0.9% sodium chloride or 5% dextrose water to a final concentration of 0.6 to 20 mg/mL.

7.8.2 Administration: IV Infusion

7.8.3 Side effects

Common (> 30%)	**Uncommon (< 30%)**	**Rare (< 5%)**
Dysuria Hair loss Encephalopathy Hepatotoxicity Leukopenia Nausea Thrombocytopenia Urinary frequency	Hemorrhagic cystitis Infection Nephrotoxicity phlebitis	Cardiotoxicity Dyspnea Polyneuropathy Stomatitis

Vomiting		

7.9 Mesna (Mesnex)

Mesna is a synthetic sulfhydryl compound used to prevent ifosfamide and cyclophosphamide-induced hemorrhagic cystitis.

7.9.1 Drug preparation: mesna is available in 200 mg glass ampoules or as a 1000 mg multi-dose vial for intravenous use. It should be diluted with 0.9% sodium chloride or 5% dextrose.

7.9.2 Administration: IV Infusion.

7.9.3 Side effects

Uncommon (< 30%)	**Rare (< 5%)**
Diarrhea Nausea Unpleasant taste Vomiting	Allergic dermatitis Allergic reaction Skin rash

7.10 Cytarabine (AraC)

Cytarabine is an antimetabolite that, after phosphorylation, incorporates into DNA resulting in inhibition of its synthesis and function.

7.10.1 Drug preparation: cytarabine is available in 100, 500, 1000, and 2000 mg multi-dose vials for intravenous use. It should be diluted in sterile water with benzyl alcohol and then further diluted with 50 to 100 ml of 0.9% sodium chloride or 5% dextrose.

7.10.2 Administration: IV Infusion

7.10.3 Side effects

Common (> 30%)	**Uncommon (< 30%)**	**Rare (< 5%)**
Loss of appetite Infection Leukopenia Nausea Stomatitis Thrombocytopenia vomiting	Neurologic toxicity Hyperuricemia Sensation disturbances	Bone pain Cellulites in the site of injection Chest pain Diarrhea Diffuse interstitial pneumonitis Dizziness Esophagitis

7.11 Filgrastim (Neupogen)			Fever Hair loss Headache Hepatotoxicity Jaundice Malaise Megaloblastic anemia Muscle pain Pruritus Pulmonary edema Skin rash Thrombophlebitis Urinary retention

Filgrastim is a colony-stimulating factor that activates the proliferation, differentiation, and activation of granulocyte progenitor cells.

7.11.1 Drug preparation: Filgrastim is available in single-dose, preservative-free vials containing 300 mcg (1 mL volume) or 480 mcg (1.6 mL volume) of G-CSF for intravenous or subcutaneous injection.

7.11.2 Administration: Subcutaneous.

7.11.3 Side effects

Common (> 30%)	**Uncommon (< 30%)**	**Rare (< 5%)**
Arthralgia Headache Itching Medullary bone pain Myalgia Skin rash	Leukocytosis Pain at the site of injection	Allergic reaction Anaphylactic reaction Splenic rupture Splenomegaly Arrhythmias Vasculitis Sweet's syndrome

8.0 MEASUREMENT OF EFFECT

For the purposes of this study, patients should be evaluated for response at the completion of 2nd and final cycle of therapy; for years 1 and 2; response should be evaluated every 3 months (+/- 21 days), years 2 through 5 every 6 months (+/- 21 days) and yearly, thereafter. Additional diagnostic tests will be required if clinically indicated.

8.1 Definitions

Response category	Physical exam	Lymph nodes	Lymph node masses	Bone marrow
CR	Normal	Normal	Normal	Normal
CR (u)	Normal	Normal	Normal or > 75% decrease	Normal indeterminate
PR	Normal	Normal or ≥ 50% decrease	Normal or ≥ 50% decrease	Positive or irrelevant
Relapse/progressive disease	Enlarging liver, spleen or other sites	New or increased	New or increased	Reappearance

CR – complete response; **CR (u)** – complete response/unconfirmed; **PR** - partial response

8.2 Response Criteria

8.2.1 **CR** requires the following:

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

2. All lymph nodes and nodal masses must have regressed to normal size. Previously involved nodes that were between 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to ≤ 1 cm in their greatest transverse diameter after treatment, or by >75% in the sum of the products of the greatest diameters (SPD) may be used to confirm CR.

3. The spleen, if considered to be enlarged before therapy on the basis if a CT scan, must have regressed in size and must not be palpable on physical exam. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic sizes.

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

8.2.2 **CR/unconfirmed (CR (u))** requires the following:

1. Residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the SPD. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD compared with the size of the original mass.

2. Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia).

8.2.3 **PR** requires the following:

1. > 50% decrease in SPD of the six largest dominant nodes or nodal masses.

2. No increase in the size of other nodes, liver, or spleen.

3. Splenic or hepatic nodules must regress by at least 50% in the SPD.

4. With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease.

5. Bone marrow assessment is irrelevant for the determination of a PR because it is assessable and not measurable disease.

6. No new sites of disease.

8.2.4 **Stable disease (SD)** is defined as less than a PR but not a progressive disease

8.2.5 **Relapsed disease (CR or CR (u))** requires the following:

1. Appearance of any new lesion or increase by ≥ 50% in the size of previously involved sites.

2. ≥ 50% increase in greatest diameter of any previously identified node greater than 1 cm in its short axis or in the SPD of more than one node.

8.2.6 **Progressive disease (PR or non-responders)** requires the following:

1. ≥ 50% increase from nadir in the SPD of any previously identified abnormal node for PRs or non-responders.

2. Appearance of any new lesion during the end of therapy.

8.3 Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

8.4 Duration of stable disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

8.5 Progression-Free Survival

Upon finishing therapy, patients will be followed at 6 month (+/- 30 days) intervals to document the progression-free interval.

9.0 ADVERSE EVENT REPORTING

9.1 Adverse Event (AE) Definitions

Adverse events (AE's) will use the descriptions and grading scales found in the NCI Common Toxicity Criteria Version 3.0 in Appendix II.

9.1.1 A ***serious adverse event*** (experience) or reaction is any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

The definition of serious adverse event (experience) also includes ***important medical events***. Medical and scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or **may require intervention** to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

9.1.2 **Expected events** are those that have been previously identified as resulting from administration of the agent.

9.1.3 An adverse event is considered ***unexpected*** when either the type of event or the severity of the event is *not* listed in: the current NCI Agent-Specific Adverse Event List; the investigator's brochure, drug package insert or the drug information section of this protocol.

9.1.4 The definition of ***related*** is that there is a reasonable possibility that the drug caused the adverse experience

9.1.5 ATTRIBUTION – The determination of whether an adverse event is related to a medical treatment or procedure. Attribution categories:

- Definite – The adverse event is *clearly related* to the investigational agent(s).
- Probable – The adverse event is *likely related* to the investigational agent(s).
- Possible – The adverse event *may be related* to the investigational agent(s).
- Unlikely – The adverse event *is doubtfully related* to the investigational agent(s).
- Unrelated – The adverse event *is clearly NOT related* to the investigational agent(s).

9.1.6 **Commercial agents** are those agents not provided under an IND but obtained instead from a commercial source.

9.2 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (please follow directions for routine reporting provided in the Data Reporting Section. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. The following sections provide information about expedited reporting.

9.2.1 Determination of Reporting Requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the grade (severity), the relationship to the study therapy (attribution), and the prior experience (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

9.2.2 Steps to determine if an adverse event is to be reported in an expedited manner:

Step 1: *Identify the type of event using the NCI Common Toxicity Criteria (CTC) Version 3.0.*

The CTC provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTC can be downloaded from the CTEP home page (http://ctep.cancer.gov). Additionally, if assistance is needed, the NCI has an Index to the CTC that provides help for

classifying and locating terms. All appropriate treatment locations should have access to a copy of the CTC.

Step 2: *Grade the event using the NCI CTC.*

Step 3: *Determine whether the adverse event is related to the protocol therapy (investigational or commercial)*.

Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: *Determine the prior experience of the adverse event*.

Step 5: *Review Table 9.3.1 to determine if there are any protocol-specific requirements for reporting of specific adverse events that require special monitoring.*

9.3 Reporting Methods

Table 9.3.1 Reporting for Commercial Agents

Attribution	**Grade 4**		**Grade 5[a]**		**Protocol-specific Requirements/ Exceptions**
	Unexpected	Expected	Unexpected	Expected	See footnote (**b**) for special requirements.
Unrelated or Unlikely					
Possible, Probable, or Definite					

a This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

b The adverse events listed below do not require reporting:Grade 4 myelosuppression

9.3.2 All serious, unusual life-threatening or lethal adverse events which may be study related will be reported within 24 hours by telephone to the Principal Investigator and must be followed by a written report which must be received by the Principal Investigator within 10 business days. The Principal Investigator shall also be responsible for promptly notifying the local Institutional Review Board of all such adverse events. For all fatal events (Grade 5) while on study or within 30 days of treatment, a written report will follow within 10 working days.

9.3.3 All adverse events, regardless of severity, and whether or not ascribed to the study drug administration, will be recorded in the appropriate section of the Case Report

Form. Patients withdrawn from the study due to adverse events will be followed by the investigator until the outcome is determined and, when appropriate, additional written reports and documentation will be provided.

9.3.4 IRB Reporting

9.4.4.1 All unexpected serious adverse events that are possibly, probably or definitely related to the study medications, , events that are more severe than anticipated, events that are more frequent than anticipated, and deaths must be reported to the IRB within ten (10) working days of being made known to the Principal Investigator.

10.0 DATA REPORTING

10.1 Records to be Kept

Case Report Forms (CRFs) will be provided for each subject. Subjects must not be identified by name on any study documents. Subjects will be identified by a Patient Identification Number upon registration.

All data on the CRF must be legibly recorded in black ink or typed. A correction should be made by striking through the incorrect entry with a single line and entering the correct information adjacent to it. The correction must be initialed and dated by the investigator or designated qualified individual. Any requested information that is not obtained as specified in the protocol should have an explanation noted on the CRF as to why the required information was not obtained.

11.0 CRITERIA FOR DISCONTINUATION OF THERAPY

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

11.1 Patients developing a life-threatening infection who are in the chemotherapy portion of the protocol will have chemotherapy interrupted until the infectious process has cleared. The subject will be withdrawn from study treatment only if chemotherapy has been held for more than six weeks.
11.2 Chemotherapy delays for more than six weeks, for any reason.
11.3 Severe toxicities as previously outlined. (Refer to section 9.1)
11.4 Progressive lymphoma at any time while on study.
11.5 Voluntary withdrawal.
11.6 The investigator has the right to remove subjects from study for clinical reasons, which he or she believes to be life-threatening or resulting in significant morbidity to the subject.

12.0 STATISTICAL CONSIDERATION

Since we expect all patients to experience complete or partial response to the therapy, we will use progression-free survival (PFS) as our primary endpoint to measure efficacy. PFS is defined as the time from start of treatment to the earliest one of the following events: relapse (in patients who achieve complete response), disease progression (in patients with partial response or stable disease), or death. (See section 7 for criteria for response, relapse, and disease progression.) All patients who meet eligibility criteria and receive initial treatment will be evaluable for toxicity, progression, and survival; patients who complete at least cycles 1 and 2 of study treatment will be evaluable for response.

Study size and duration. Study size is limited by the availability of eligible patients, which we estimate to be about 4 patients per year. We plan to enroll a total of approximately 28 patients in order to base our main analyses on at least 22 (79%) evaluable patients. Consequently, our study will entail an enrollment period of approximately 6 years and a minimum follow up of two years beyond the last patient is enrolled. The estimated total study duration for this trial will be 8 years.

Study precision. It is expected that study treatment will extend the median time to disease progression to 24 months as compared with the current standard of approximately 18 months in this patient population. Assuming an exponential distribution for time to disease progression, the anticipated effect of study treatment is equivalent to an (absolute) increase of 9% in the proportion of patients alive and progression-free at 18-months from a current rate of 50% to 59% on study.

Assuming no losses to follow-up and 22 evaluable patients, our estimate of the 18-month progression-free survival rate using the Kaplan-Meier method [26] will have a standard error of no more than11% [27].

The following table illustrates the precision of our study for several possible outcomes.

Possible outcomes and corresponding estimates of progression-free survival based on 22 evaluable patients

	~~At 18 months ~~~~~~~~~~~~			
Patients w/o progression	**Proportion**	**Standard error**	**95% CI#**	**Corresponding median***
11	50%	10.7%	29.1% - 70.9%	18 months
13	**60%**	**10.4%**	**39.5% – 80.5%**	**24.4 months**
15	70%	9.8%	50.9% – 89.1%	35 months
18	80%	8.5%	63.3% – 96.7%	55.9 months

#CI: Confidence interval. * Assuming progression free survival follows an exponential distribution.

The middle row in the table above represents the study objective of observing a median PFS of approximately 24 months. This requires that 13 out of 22 patients survive with no evidence of

disease progression for at least 18 months from the start of treatment. If this is the case, then our estimate of the 18-month progression free survival rate will be 60% and we will report a (two-sided) 95% confidence interval estimate of 39.5 to 80.5%.

Statistical analysis: Using the Kaplan-Meier method, we will estimate both progression-free and overall survival rates at 6-, 12-, 18- and 24-months with corresponding two-sided 95% confidence intervals. Medians, if attained, will be reported similarly. The amount of patient follow-up will be characterized descriptively by the range and median for patients who experience the event (progression or death) and those who do not (censored observations).

In addition to the analysis of progression-free and overall survival, patients will be classified by response to treatment according to the criteria in Section 7. We will estimate the complete response (CR) rate with a two-sided 95% confidence interval using the exact binomial method [28]; the relapse rate following CR will be estimated by the method of cumulative incidence. A detailed tabulation will be given of the time to response and the duration of response for each response type. Since our study is small, only a very strong association could be detected between response status (complete versus partial) and either progression-free or overall survival. We will use the log-rank test to explore this association.

Descriptive statistics will be provided for patient demographic variables (age, sex, and race) and for disease characteristics at baseline, including performance status.

Interim monitoring: The Research Team will continuously monitor study accruals, toxicities, and response to treatment. The UM/Sylvester Comprehensive Cancer Center's Data and Safety Monitoring Committee (DSMC) will monitor this protocol according to the Cancer Center's DSM Plan. In its oversight capacity, the DSMC bears responsibility for suspending or terminating this study. DSMC oversight of the conduct of this trial includes ongoing review of accrual and adverse event data, and periodic review of response. The DSMC also reviews reports from internal audits of protocol compliance and data integrity conducted by the University of Miami, Office of Research Compliance Assessment.

The guidelines appearing in this section are offered for DSMC consideration in its review of accumulating study data. These guidelines were developed using Bayesian methods, which can be applied at any stage of enrollment without advance specification of the number of interim analyses to be performed, or the number of evaluable patients at the time such assessments are made [29, 30].Under the Bayesian method, we assign a prior probability (level of belief at the start of the trial) to a range of possible values for the endpoint being monitored. As data on study patients become available, this probability distribution is revised and the resulting posterior probability becomes the basis for recommending either early termination or continuation of the study.

Safety: Early stopping due to toxicity

Since we expect that most patients will experience grade 4 toxicity, trial safety will be monitored on the basis of treatment-related mortality. We suggest that DSMC consider stopping the study early if there is evidence that treatment-related mortality exceeds a rate of 10%. More specifically, DSMC will have evidence in favor of early termination if the posterior probability is 80% or higher that the

true treatment-related mortality rate exceeds 10%. The table below shows specific instances where this guideline is met, thus suggesting early termination due to evidence of an unacceptably high rate of treatment-related mortality.

Numberof treatment-related deaths[#]	Total patients	Observed rate
2	3 to 8	≥ 25% (2 of 8)
3	9 to 16	≥ 19% (3 of 16)
4	17 to 22	≥ 18% (4 of 22)

[#]Deathwithin 30 days of receiving study treatment.

Posterior probabilities used to derive the preceding table are calculated under a prior beta distribution with parameters $\beta_1 = 0.2$ and $\beta_2 = 1.8$, which corresponds to an expected rate of 10% based on prior information roughly equivalent to having studied 2 patients. Furthermore, this prior distribution assigns a small a priori chance (27%) to the possibility that the true rate of treatment-related mortality is 10% or greater.

Lack of efficacy:

We do not propose early stopping guidelines for lack of efficacy, since this is a small study and the primary endpoint, PFS, requires substantial follow up. Thus, interim estimates of PFS prior to completion of study enrollment would be imprecise and would not provide a good basis for considering early termination. We note further that we expect nearly all patients to achieve complete response and this will be monitored closely by the study team for any unexpected findings.

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APPENDIX I

NATIONAL CANCER INSTITUTE (NCI) COMMON TOXICITY CRITERIA (CTC)

The NCI CTC can be viewed on-line at the following NCI web site:

http://ctep.cancer.gov/reporting/ctc.html

APPENDIX II

DATA AND SAFETY MONITORING PLAN

The Sylvester Comprehensive Cancer Center (SCCC) Data and Safety Monitoring Committee (DSMC) will monitor this clinical trial according to the CancerCenter's DSM Plan. In its oversight capacity, the DSMC bears responsibility for suspending or terminating this study.

DSMC oversight of the conduct of this trial includes ongoing review of accrual and adverse event data. The guidelines appearing in Section 12 are offered for DSMC consideration in assessing adverse events. In addition, the DSMC will review reports from all audits, site visits, or study reviews pertaining to this clinical trial and take appropriate action.

APPENDIX III:

DATA SUBMISSION SCHEDULE

FORM	TO BE COMPLETED
BASELINE	
Eligibility Checklist	Prior to registration
SCCC Protocol Enrollment Form	
Consent Forms Signed/dated	
On-study Form	Within 30 days of registration
DURING PROTOCOL THERAPY	
	Due every week for phase I studies, every cycle for phase II-IV studies
AFTER PROTOCOL THERAPY	
Off Treatment Form	Within 14 days of discontinuation/completion of protocol therapy
FOLLOW-UP SCHEDULE (for studies with long term follow-up)	
Follow-up Form	Every 3 months if < 2 years from study entry Every 6 months is 2-5 years from study entry Every 12 months if more than 5 years from study entry
Response Assessment Form	Within 4 weeks of knowledge of progression/relapse
Off Study Form	Within 4 weeks of knowledge of death
Subsequent Malignancy via Adverse Event Log	Within 4 weeks of knowledge of another malignancy

NOTE: FORMS WILL BE CONSIDERED PAST DUE 14 DAYS AFTER THE DUE DATE.

APPENDIX IV

ABBREVIATIONS

ANC	Absolute Neutrophil count
CR	Complete response
PR	Partial Response
G-CSF	granulocyte colony stimulating factor
HBV	Hepatitis B
IHC	Immunohistochemistry
IPI	International Prognostic Index
LDH	Lactate Dehydrogenase
MCL	Mantle Cell Lymphoma
NHL	non-Hodgkin lymphoma
NS	Normal Saline
PCR	polymerase chain reaction
PET	positron emission tomography
PR	Partial response
PD	Partial Response
R-MACLO	Rituximab,Methotrexate,Doxorubicin,Cyclophosphamide,Leucovorin, Vincristine
R-IVAM	Rituximab,Ifosfamide,Etoposide,Cytarabine, Mesna
SAE	severe adverse effect
SCT	Stem Cell Transplant
SD	Stable Disease

Appendix V-Study Calendar

		Screening Baseline Visit	Regis-tration	Cycle 1	Cycle 2	Restage (after cycle 2)	Cycle 3	Cycle 4	Restage (after cycle 4)	EOT 30days post hospital discharge afterlast dose	Maintenance Rituximab	Survival
	Visit Window	-28 to D1		(+/- 3 days)	(+/- 3 day)	(+/-14 days)	(+/- 3 day)	(+/- 3 day)	(+/-14 days)	(+/-14 days)	(+/- 21 days)	-
Baseline	Informed Consent	X		-	-	-	-	-	-	-	-	-
	Medical History	X		-	-	-	-	-	-	-	-	-
	Physical Examination	X		X	X	-	X	X	-	X	X[e]	-
Treatment	R-MACLO	-		X	-	-	X	-	-	-	-	-
	R-IVAM	-		-	X	-	-	X		-	-	-
	RITUXIMAB	-		-	-	-	-	-	-	-	X[d]	-
Safety Assessments	Electrocardiogram (EKG)	X		-	-	-	-	-	-	-	-	-
	MUGA or Echocardiogram	X		-	-	-	-	-	-	-	-	-
	Weight, Height[h]	X		X	X	-	X	X	-	X	X[d]	-
	Vital signs	X		X	X	-	X	X	-	X	X[d,e]	-
	ECOG status	X		X	X	-	X	X	-	X	X[d,e]	-
	Body Surface Area (BSA)	-		X	X	-	X	X	-	-	X[d]	-
	CBC, differential, platelet count	X		X	X	-	X	X	-	X	X[d,e]	-
	CMP and LDH, see protocol	X		X	X	-	X	X	-	X	X[e]	-
	Uric Acid	X		-	-	-	-	-	-	X	X[e]	
	Bicarbonate	X		X	X	-	X	X	-	X	X[e]	-
	Beta-2 microglobulin	X		-	-	-	-	-	-	X	X[e]	-
	Hepatitis B	X		-	-	-	-	-	-	-	-	-
	Urine Pregnancy test(*72 hrs of entering study)*	X		-	-	-	-	-	-	-	-	-
	Urinalysis (U/A)	-		-	X[a]	-	-	X[a]	-	-	-	-
	Concomitant medications[L]	X		-	-	-	-	-	-	-	-	-
	Adverse Events Assessments (CTCAE)			X	X	X	X	X	X	X	X	-
Response Assessments	BrainCT or MRI scan[b]	X		-	-	-	-	-	-	-		
	CT Scan (Chest, Abdomen, Pelvis with contrast)[i]	X		-	-	X[c]	-	-	X[c]	X	X[c,f]	-
	Bone Scan /bone films[b]	X[b]		-		-	-		X[c]	X	X[c,f]	-
	PET Scan[i]	X		-	-	X[c]	-	-	X[c]	X	X[c,f]	-
	Bone Marrow Biopsy & Aspiration	X		-	-	-	-	-	X[c]	X[c]	X[c,f]	-
	Colonoscopy(*with or without endoscopy*)	X		-	-	-	-	-	X[c]	X[c]		-
Survival	Survival [g]			-	-	-	-	-	-	-	-	X[g]

Submit Registration & Eligibility Checklist to CRS prior to Start of Study.

a. Daily U/A during Ifosfamide therapy **b**. If clinically indicated **c.**Repeat those studies which were positive at baseline **d**. For patients in CR after final cycle : Rituximab (375mg/m2, IV as 4 weekly doses every 6 months for a total of 3yrs or until progression of disease (+/-21days). **e**. These studies should be obtained monthly(+/- 21 days) for the first 3 monthsthen every 3 months (+/- 21 days), for 2 years, then 6 months(+/- 21 days) for 3-5years & thereafter. These studies are required at these intervals until disease progression or death (whichever occurs first). **f.** These studies should be obtained every 6 months for 2 years or more frequently if clinically indicated. **g.** Patients who have disease progression (PD) or achieve PR (after final cycle) and are alive are followed for survival only –no additional studies are required after disease progression. h. Height required at screening only. i. -28 to D1 for baseline assessment. j. Only concomitant medications taken while outside of the hospital are recorded. k. Adverse events captured 30 post off treatment or 30 days post end of maintenance portion. L. Conmeds are required only at screening/baseline visit. M. Only if clinically indicated