Ofatumumab with or without Bendamustine for Patients with Mantle Cell Lymphoma Ineligible for Autologous Stem Cell Transplant

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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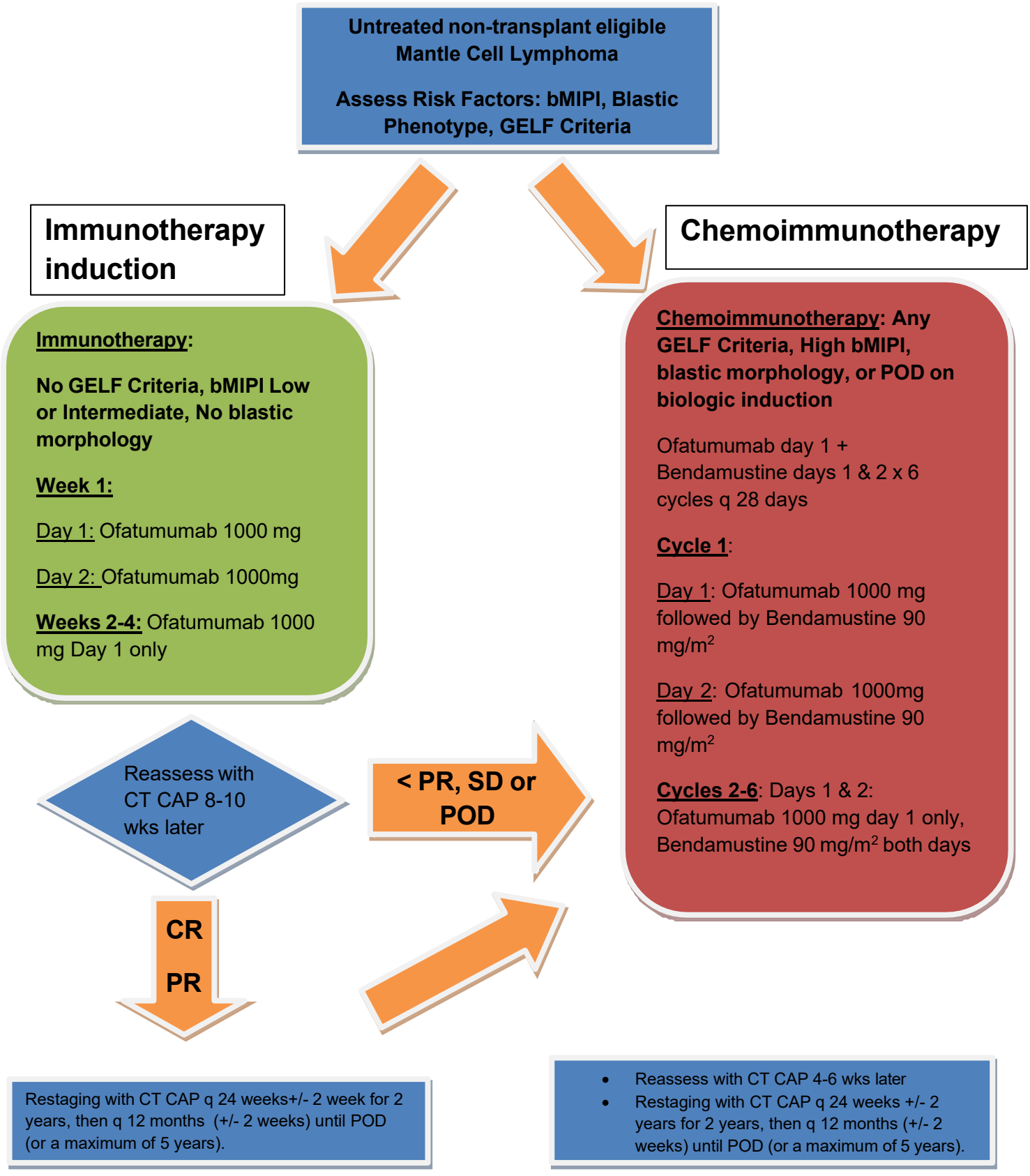
1.0 PROTOCOL SUMMARY AND/OR SCHEMA



In order to improve on existing treatment strategies in the transplant ineligible and elderly patient with mantle cell lymphoma (MCL) a study is being proposed to investigate a novel anti-CD20 monoclonal antibody ofatumumab either alone or in conjunction with Bendamustine. This will be investigated in patients with newly diagnosed MCL who are not eligible for autologous stem cell transplant or 65 years or older.

This regimen was selected because of the safety profile and efficacy of each agent independently. In the non transplant eligible/elderly patient population, goals of therapy are the induction of durable disease control using a program associated with a desirable safety profile while maintaining quality of life. Ofatumumab has the potential, based on better affinity in low CD20 expressing tumors and improved complement dependent cytotoxicity, to improve upon the outcomes of other single agent monoclonal antibodies used in lymphoma. Patients will be stratified based on the use of clinical and biologic risk factors. Patients at lower risk for early disease progression can be identified and stratified to monoclonal only therapy, while those patients with an immediate need for cytoreductive therapy (eg. symptomatic disease or higher risk) would be stratified to the combination regimen.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective:

- To determine the single agent efficacy (as determined by response rate) of the monoclonal antibody ofatumumab alone in low risk patients (as defined in this protocol by: 1) absence of NCCN/GELF (appendix V) criteria for treatment, 2) low or intermediate risk bMIPI (based on calculation obtained from http://www.qxmd.com/calculate-online/hematology/prognosis-mantle-cell-lymphoma-mipi), 3) absence of blastic morphology, 4) Ki-67 <30%.
- To determine the efficacy (as determined by response rate) of the combination ofatumumab + Bendamustine in high risk patients (as defined in this protocol by: 1) the presence of any NCCN/GELF (appendix V) criteria for treatment, 2) high risk bMIPI (based on calculation obtained from http://www.qxmd.com/calculate-online/hematology/prognosis-mantle-cell-lymphoma-mipi), 3) blastic morphology, 4) Ki-67 ≥30%, or 4) patients with <PR, SD or POD following immunotherapy induction.

Secondary Objectives:

- To determine the duration of benefit for this stratified approach for all patients, based on progression free survival (PFS), remission duration (DR), and overall survival (OS).
- In addition we will evaluate toxicity according to Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v4.0). We will investigate the baseline CGA tool as a mechanism to predict toxicity.
- Evaluating microRNA expression in MCL tumor samples derived from this protocol and correlate these with the tumor proliferation index to determine their prognostic utility.
- Through immunohistochemistry, we also intend to explore SOX11 expression as a possible predictor of indolent disease.

Primary Endpoints:

- Immunotherapy induction (low risk patients) the ORR (CR+PR) rate to ofatumumab
- Chemoimmunotherapy induction (High Risk patients) the CR to ofatumumab + Bendamustine

Secondary Endpoints:

- OS, PFS, DFS, DR
- Safety and toxicity profile

3.0 BACKGROUND AND RATIONALE

INTRODUCTION

Mantle cell lymphoma (MCL) is an uncommon, distinct clinical subtype of non-Hodgkin's lymphoma that comprises approximately 8 % of all lymphoma diagnoses (approximately 5000 cases per year) [1]. The prognosis of patients with MCL is the poorest among B- cell lymphoma patients, with a median overall survival (OS) of 3-5 years, and time to treatment failure (TTF) of 18 months [2].There are four histologic subtypes of mantle cell lymphoma (the small cell variant, the marginal zone–like variant, the blastoid variant, and the pleomorphic variant). The blastoid and pleomorphic variants are considered to have the worst prognosis among the subtypes. Since the histologic diagnosis of MCL is often challenging by morphology alone, accurate diagnosis relies on immunohistochemical staining for the purposes of immunophenotyping [3]. It has been found to expresses B cell markers CD5+, CD 20+, CD43 +, cyclin D1 +, CD 10+/-,

and CD 23-[1]. There is variable CD2 and CD3 expression. The genetic hallmark of mantle cell lymphoma is the t(11;14)(q13;q32) chromosomal translocation leading to the upregulation of Cyclin D1, a critical regulator of the G1 phase of the cell cycle [2].

MCL often presents in advanced stage, with involvement of the bone marrow 60% of the time and gastrointestinal tract 30 %-80% of the time. Gastrointestinal involvement often manifests as lymphomatous polyposis of the intestine and has been found to be present in many patients at a microscopic level involving macroscopically normal mucosa. It presents rarely in the CNS. MCL can however manifest itself in the skin, as well as in peripheral blood in a leukemic presentation. The latter can be detected through flow cytometry[4]. The demographic of affected patients is primarily older individuals, mostly men, with a male to female ratio of 2-4:1.

BIOMARKERS

Median survivals have improved over the past several years, but are still estimated to be in the 3-5 yr range [5]. Biologic markers exist to assess increased aggressiveness in MCL. Among these is a clinical risk model called the mantle cell international prognostic index (MIPI), which discriminates patients into different risk categories with disparate survival outcomes. The strongest predictor of survival in patients with MCL was recently identified by gene expression profiling [6]. Twenty proliferation associated genes were identified as being superior to other prognostic molecular markers alone or in combination. However routine gene expression profiling is neither readily available nor practical for clinical use. As such, Ki-67 has emerged as an important and clinically useful surrogate. Our group recently evaluated the use of quantitative image analysis as a method of accurately assessing the proliferative index in patients with MCL, with high reproducibility [7]. Additional biomarkers include blastic morphology, the high cellular proliferative rate as determined by Ki-67 staining and dysregulation of p53.

TREATMENT RATIONALE:

Despite an increasing understanding of the underlying molecular biology of MCL, there remains no standard of care for upfront treatment and with the possible exception of allogeneic bone marrow transplantation there are no known curative options. Based on improved progression free survival (PFS) with intensive chemotherapy induction followed by high dose chemotherapy (HDT) and autologous stem cell transplant (ASCT) consolidation, this treatment strategy is often recommended for younger, eligible patients [8] and is directed at prolonging the

remission duration. However, given a median age at presentation in the sixth decade, more than half of patients are not considered eligible for transplantation secondary to medical co-morbidities. In this patient population the goals of therapy are disease control designed to maximize survival and concurrently maintain quality of life.

For the older patient or in patients where HDT/ASCT is not a viable option, a variety of approaches have been utilized. In elderly patients without an immediate indication for therapy (eg. Low tumor burden as determined by absence of GELF/NCCN criteria), a period of expectant monitoring or single agent monoclonal antibody therapy is frequently employed. The activity of single agent rituximab in MCL, however, is quite modest with overall response rates in the range of 22-34% and median time to progression of less than 12 months. [32, 43, 44] The group at Cornell has reported their experience with deferred initial therapy, demonstrating that expectant monitoring is associated with a median time to therapy of 12 months (range 4-128 months) in selected patients[49]. Additionally, the MIPI and Ki67% have been useful predictors for identifying patients with less biologically aggressive disease and longer survival outcomes. Consequently, an attractive risk stratified approach would incorporate less aggressive therapy initially for biologically less aggressive disease, reserving chemoimmunotherapy for later interventions.

Nationwide, immuno chemotherapy combinations are most frequently utilized. When rituximab is combined with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy, as well as with mitoxantrone, chlorambucil, and prednisolone (MCP), response rates are slightly higher than either chemo or immunotherapy alone; however no improvements in overall survival (OS) or PFS have been found [9-11]. Other more intensive therapies, such as with rituximab combined with cyclophosphamide, doxorubicin, vincristine, and dexamethasone alternating with methotrexate and cytarabine (R-Hyper CVAD/MA), have been associated with increased toxicity in those with MCL greater than 65 years and consequently are not generally feasible or recommended to elderly patients. With a median follow up time of 40 months, in younger patients the 3 year failure free survival (FFS) and OS rates for this regimen were 64% and 82%, respectively. These results are comparable to an ASCT approach, with similar toxicity (8% treatment related deaths)[33]. This same regimen was evaluated in patients 65 years or older by the same authors with lower doses of cytarabine. The median FFS for the entire group was 15 months and there was significant hematologic toxicity [34]. These approaches therefore are not feasible for a large proportion of patients with MCL. Modified intensive chemotherapy regimens

studied in older patients have been less toxic, but also less effective [11].Consequently, new strategies in this particular group of patients are urgently needed, and ideally, developing a treatment program utilizing alternative agents with improved activity and safety profile would be desirable.

Bendamustine:

Bendamustine (Treanda™; Cephalon, Inc, Frazer PA) is a bifunctional alkylating agent consisting of a purine ring and nitrogen mustard moiety. Frequently used in Eastern Germany, it was approved in the United States by the U.S. Food and Drug Administration (FDA) in 2008 for treatment of chronic lymphocytic leukemia (CLL) based on a randomized trial comparing it to chlorambucil as treatment in the first line setting [22]. Overall response rates and OS were higher with Bendamustine. Bendamustine was also approved for patients with indolent B-cell non-Hodgkin's lymphoma progressing during or within 6 months of treatment with rituximab or chemoimmunotherapy.

In vitro studies of Bendamustine have demonstrated rapid production of DNA cross links and strand breaks, inhibition of mitotic checkpoints, and induction of mitotic catastrophe. Bendamustine has demonstrated activity in a broad range of lymphomas (CLL, indolent NHL, MCL), as well as in resistant tumors, including those harboring p53 dysregulation [24]. Phase II single agent data of Bendamustine in rituximab refractory indolent and transformed NHL demonstrated an ORR of 77% (34 % CR/Cru) with a median duration of response of 6.7 months[45].

Bendamustine Combinations:

Three studies had investigated Bendamustine in conjunction with rituximab in MCL [35, 36]. Rummel et al evaluated 63 patients with indolent NHL with previously treated or relapsed disease (16 of who had MCL). Median age of patients was 66, with 68% having stage IV disease. Prior rituximab exposure was not permitted in this study; hence these patients were rituximab naive. The response rates were encouraging, with 75% ORR, CR 50%, and PR 25%. This was replicated in a multicenter trial involving 66 patients [36]; 12 of whom had MCL. Prior rituximab exposure was permitted in this group. Results were similar, with 92% ORR, 42% CR, 17% unconfirmed CR (Cru), and 33% PR. The differences in CR here rate may be related to prior rituximab exposure. Given these promising results, Bendamustine and rituximab were brought to the first line setting in a phase III randomized trial performed by the StiL (Study

Group Indolent Lymphomas, Germany) comparing RCHOP to R-Bendamustine in indolent lymphoma. . Two hundred thirty two patients (45 of whom had MCL) received 6 cycles of BR. The median age of patients was 64 (23% > 70yrs), and most patients had advanced disease (77% stage IV). The overall response rate was 88% and CR was achieved in 42% of patients with mantle cell lymphoma, which was equivalent or better than the RCHOP arm and associated with a more favorable toxicity profile[13]. Consequently, rituximab-bendamustine was established as a viable front line therapy for elderly MCL patients.

Ofatumumab:

Ofatumumab is a novel, fully human anti-CD20 monoclonal antibody with demonstrated activity in CLL and non-Hodgkin's lymphoma. Ofatumumab recognizes a CD20 epitope distinct from rituximab and is associated with similar antibody dependent cell mediated cytotoxicity (ADCC) and increased complement dependent cytotoxicity (CDC) [38]. This activity has been seen even in settings with lower CD20 antigen density and in the presence of complement inhibitors. This improved activity may confer a theoretical advantage over rituximab is select situations (eg. CLL and MCL). In CLL, the safety and efficacy of ofatumumab was evaluated in a phase I/II trial of 33 patients with relapsed or refractory disease [39]. The FDA granted ofatumumab accelerated approval in 2009 for the treatment of CLL refractory to fludarabine and alemtuzumab based on the Hx-CD20-406 multicenter trial. Patients refractory to both fludarabine and alemtuzumab (double refractory, or DR) had an ORR of 51%, and those with bulky disease refractory to fludarabine (BFR) alone had an ORR of 44%[40]. In a recent update of this trial, ORR for BFR patients was 58% and 47% for DR patients [41]. Ofatumumab has efficacy in NHL as well. In a phase I/II study involving patients with follicular lymphoma, the agent was demonstrated to be safe and associated with responses across a range of doses [23]. Objective responses ranged from 20-63%, and these were not dose dependent. Five patients experienced CR.

Ofatumumab was also recently evaluated in combination with CHOP chemotherapy. Fifty nine patients with relapsed or refractory FL were randomized to ofatumumab Day 1,500 mg (Group A) or 1,000 mg (Group B); cyclophosphamide Day 3, 750 mg/m^2; doxorubicin Day 3, 50 mg/m^2; vincristine Day 3, 1.4 mg/m^2; and prednisolone Days 3-7, 100 mg every 3 weeks for 6 cycles. Overall response rates were 90% in Group A and 100% in Group B. Complete response (CR) + unconfirmed CR (CRu) was 69% in Group A and 55% in Group B. Overall, 16 of 21 pts (76%) with FLIPI score 3-5 attained CR/Cru [46].

Rationale for two treatment arms:

As noted above, in recent years there have been a number of advances in identifying risk factors MCL patients regarding prognosis. The best candidates currently include NCCN/GELF criteria, MIPI, proliferative rate (Ki67) and blastic morphology. Furthermore, there is now evidence that subgroups of MCL patients may behave more indolently and that more conservative management, with a initial watch and wait period or less intensive treatment is rational rather than immediate chemoimmunotherapy in the absence of NCCN/GELF indications[49].

We have defined a low risk group as patients without an indication for immediate therapy as determined by no NCCN/GELF criteria for treatment. Additionally, we will utilize the prognostic markers of bMIPI and Ki67 to ensure patients have low to intermediate risk of progression or death. Patients treated with CHOP with Ki67%<10 and Ki67% of 10%-29% have median OS of 112 and 59 months respectively, compared with patients whose Ki67 is 30% or greater where median OS is 35 months. For patients receiving RCHOP chemotherapy, the median OS was not reached for Ki67% <30%, but was 52 months for the high risk group Similarly, the MIPIb can predict overall survival with low risk patients (median OS not reached) and intermediate risk patients (median OS 58 months) having a more protracted disease course compared with high risk disease (median OS 37 months)[50] .

Low risk non-transplant eligible patients, therefore, may not require initial chemoimmunotherapy. Monoclonal antibody therapy alone is an attractive option from a toxicity standpoint, as there is the potential for disease control and prolonging PFS over monitoring alone with a delay in the need for chemotherapy. The currently available agent rituximab has had only modest activity in MCL as a single agent. We propose to investigate Ofatumumab in a population defined as low risk, as this agent has the potential for improved biologic activity over rituximab in MCL and a favorable safety profile.

In high risk non-transplant eligible patients, where there is a clear indication for chemoimmunotherapy, rituximab+Bendamustine has demonstrated improved safety and activity over RCHOP, additionally sparing exposure in the elderly to an anthracycline. Ofatumumab similarly targets CD20, but has improved CDC activity and slower off rates, factors which may improve efficacy in MCL. This group of patients will receive the combination of ofatumumab+Bendamustine. Additionally, for patients initial treated with monoclonal Ab and

either relapsing or having <PR to induction, there is also a clear indication for chemoimmunotherapy. These patients similarly will receive the combination regimen,

MicroRNAs

While advances in understanding MCL pathogenesis have afforded new opportunities in the design of new drugs targeting these mechanisms, improved methods of prognosticating MCL have not emerged. Given the limitations of existing prognostic models, predictive models able to combine the quantification of the proliferation activity with other robust molecular profiles may improve the estimation of patient prognosis in MCL.

MiRNA expression profiling plays an important role in the classification and function of hematologic malignancies. Deletions in miR-15a and miR-16-1 were found in patients with chronic lymphocytic leukemia (CLL) when compared to normal mature CD 5+ lymphocytes from healthy donors. Through BCL-2 targeting, this cluster exhibited tumor suppressor activity. Overexpression caused apoptosis in leukemic cell lines, supporting a future role for miR-15a/16-1 restoration in the treatment of CLL. A putative tumor suppressive role for miR-29b has been reported in acute myelogenous leukemia (AML), by targeting DNA methyltransferases, as well as CDK6 and MCL-1, causing cell death and inhibition of cell proliferation. In MCL, unsupervised hierarchical clustering analysis of highly purified leukemic MCL cells demonstrated dysregulated miRNA profiles compared with normal lymphoid cells. Two distinctive subsets of tumors were revealed, showing significant differences in the IgVH mutational status, proliferation signature, and number of chromosomal alterations.

Studies in AML and CLL have demonstrated the role for miRNAs as novel biomarkers as well. Elevated levels of miR-181 were associated with superior event free survival in patients with high risk AML, whereas in CLL, increased expression of miR-155 and 146 were correlated with progression of disease. In MCL, miR-16 was found to target the 3'untranslated region of cyclin D1, resulting in cyclin D1 overexpression by evading miR-16-1's regulatory effects. Moreover, a miRNA expression signature recently identified five altered miRNAs in over 50% of samples evaluated. Specifically, decreased expression of the miR-29 family was associated with shorter survival in patients with MCL. MiR-29 caused CDK6 inhibition by direct binding to the 3'untranslated region. Down-regulation of the miR-29 family resulted in up-regulation of CDK6 in MCL, suggesting that miR-29 collaborates with cyclin D1 in MCL pathogenesis.

These data support that miRNAs have an important role in the classification, function and prognosis of leukemias and lymphomas. They have potential to improve molecular disease characterization and establish new biomarkers to improve existing methods of prognosticating MCL. Consequently, we hypothesize that a miRNA signature from MCL will enhance existing prognostic methods and identify miRNAs relevant to MCL biology.

While these emerging data suggest that microRNAs may be relevant to MCL pathogenesis, they do not address the question of how to they may influence proliferation or chemoresistance.

SOX11 is a transcription factor specifically expressed in the nucleus of MCL compared with other lymphomas and benign lymphoid tissue. Although the role of SOX11 presently is not known in lymphocyte ontogeny, it is normally expressed in the developing central nervous system in the embryo. SOX11 has recently been shown to be up-regulated in MCL and can distinguish it from other B-cell lymphomas. Additionally SOX11 was found to be equally expressed in D1-positive and D1-negative MCL. Cyclin D1 overexpression is the hallmark of MCL even though approximately 10% of MCLs lack Cyclin D1 expression, and may be misdiagnosed by overreliance on Cyclin D1. Prospectively staining for SOX11 expression immunohistochemically [through a commercially available polyclonal rabbit antibody (Sigma-Aldrich)] may help provide insight into the clinical-pathologic correlates associated with its expression (Ek et al, Blood 2008 (111):2; 800-805, Mozoz et al, Haematologica, 2009 (94):11; 1555-1562).

Please see Appendix III for details regarding experimental design, methods and specimen handling.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

The proposed study is a Simon 2 stage optimal study design investigating the activity of ofatumumab alone or in conjunction with Bendamustine for patients with MCL who are either not candidates for ASCT or aged 65 or older. The study design will allow for an estimation of the single agent response of ofatumumab in patients at low biologic risk for immediate disease progression, as defined in this protocol, based on absent NCCN/GELF criteria for treatment (see appendix V), low risk bMIPI, absent blastic morphology, and Ki-67 <30%. The combined regimen will assess the response rates of the combined chemo-immunotherapy program in

patients with need for cytoreductive therapy, or high risk for disease progression, as defined in this protocol by: 1) Any NCCN/GELF criteria for treatment, 2) high risk bMIPI, 3) blastic morphology, 4) Ki-67 >30%, or 5) POD on biologic induction). Patients will be stratified based on the use of clinical risk factors and the bMIPI. Patients at lower risk for early disease progression can be identified and stratified to monoclonal only therapy, while those patients with an immediate need for cytoreductive therapy (i.e. symptomatic disease or higher risk) would be stratified to the combination regimen.

Immunotherapy:

The immunotherapy strata will plan to enroll a total of 38 untreated patients and assess ORR at 12 weeks post completion of ofatumumab induction. In MCL, single agent rituximab has an ORR ranging between 22-37% in patients with relapsed, refractory disease, and previously untreated disease [32, 43, 44, 47]. Complete responses are between 3 and 14%. In CLL, single agent ofatumumab has an ORR of 47-58% [41], while in follicular lymphoma, ofatumumab has an ORR between 20-63% [23]. **A single agent ORR of ≥60% (20% improvement) to ofatumumab in this setting would be considered promising.**

Chemoimmunotherapy:

The chemoimmunotherapy strata will plan to enroll a total of 38 untreated patients with GELF/NCCN criteria for treatment, high risk bMIPI, or blastic histology. In both first line setting and relapsed settings, the combination of rituximab + Bendamustine as a historic comparator has demonstrated ORR of 75-92%, with a CR rate of 42-50% [13, 35-36]. As this study will stratify for patients with a higher initial risk profile and NCCN/GELF criteria for therapy, responses rates may be lower.

The efficacy will be measured by the sum of complete response and partial response. Since the combination of rituximab-Bendamustine for untreated patients yielded CR rates of approximately 40%, **this study will be considered successful if the complete response rate is at least 60%.**

- **Patients will be stratified by the need for immediate chemoimmunotherapy or immunotherapy induction:**
    - **Parameters for Immunotherapy**:

- No GELF/NCCN criteria for therapy (see appendix V), Biologic MIPI (bMIPI) Low or Intermediate, No Blastic MCL features, Ki67<30%.
  - Blastic features are characterized by a homogeneous population of cells displaying lymphoblastic morphology; and are more likely to have secondary chromosomal aberrations such as p53 mutations or overexpression, del (13q14) or del p16.
  - GELF Criteria: Involvement of => 3 nodal sites, each with diameter => 3 cm, any nodal or extranodal tumor => 7 cm, B symptoms, Massive Splenomegaly, Pleural effusions or peritoneal ascites, Cytopenias (ANC < 1.0, Plt<100K), Leukemic phase
  - bMIPI (age, ECOG, LDH, WBC, MIB-1%) : As per Hoster et al (Hoster E, Dreyling M, Klapper W, et al., A new Prognostic index (MIPI) for patients with advanced stage mantle cell lymphoma. Blood. 2008 Jan 15; 111 (2):558-565). bMIPI calculator available online at http://www.qxmd.com/calculate-online/hematology/prognosis-mantle-cell-lymphoma-mipi

- **Parameters for Chemoimmunotherapy**:
- Patients meeting any GELF/NCCN criteria for therapy, bMIPI high risk, Blastic MCL features or Ki-67≥ 30%.

- Note: Patients with a leukemic phase only presentation of mantle cell lymphoma generally have clinically low-risk disease, regardless of mantle cell IPI calculations. Upon reciew with the principal investigator, these patients may be stratified to the immunotherapy only arm if clinically appropriate.

4.2 Intervention

Patients will receive either ofatumumab alone (immunotherapy schema below) or in conjunction with bendamustine (chemoimmunotherapy schema below) based on their assigned initial risk stratification.

- **Schema for patients receiving Immunotherapy (N= 38)**
  - Ofatumumab Day 1 Week 1: 1000 mg, Day 2 week 1: 1000mg. Patients who exhibit a baseline leukocytosis ≥ 20,000 will receive 300 mg of ofatumumab on day 1, week 1. Thereafter, they can receive the 1000 mg dose
  - Ofatumumab Day 1, Weeks 2-4: 1000 mg
  - Will reassess 8-10 weeks after conclusion of treatment with CT CAP, and following this q 12 wks for 2 yrs, then q 6mo until POD or for a maximum of 5 years
    - Patients with PR or CR at week 8-10: continued monitoring q 12 wks for 2 yrs, then q 6mo until POD or for a maximum of 5 years. At POD

crossover to chemoimmunotherapy regimen (within 4 weeks of date of progression).

- Patients in <PR, i.e. with < 50% reduction in nodal masses, SD or POD: proceed to chemoimmunotherapy regimen directly (within 4 wks of restaging CT CAP). Subsequent follow-up will be as per chemoimmunotherapy arm

- **<u>Schema for patients receiving Chemoimmunotherapy</u> (N=38)**
  - Ofatumumab day 1 + Bendamustine 90 mg/m^2 days 1 & 2 x 6 cycles q 28 days
    - Cycle 1, day 1: Ofatumumab 1000 mg followed by Bendamustine 90 mg/m^2. Patients who exhibit a leukocytosis > or equal to 20,000 will receive 300 mg of ofatumumab on day 1, week 1. Thereafter, they can receive the 1000 mg dose.
    - Cycle 1, day 2: Ofatumumab 1000mg followed by Bendamustine 90 mg/m^2
    - Cycles 2-6: Ofatumumab 1000 mg day 1, Bendamustine 90 mg/m^2 days 1 and 2
  - Will reassess 4-6 weeks after conclusion of treatment with CT CAP, and following this q 12 wks for 2 yrs, then q 6mo until POD or for a maximum of 5 years

We will evaluate data at the conclusion of the first Simon stage.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Bendamustine:

Bendamustine will be prepared and administered as per MSKCC guidelines. Patients will receive bendamustine 90mg/m^2 administered per institutional guidelines for two consecutive days. Cycles will be repeated every four weeks and a total of 6 cycles will be planned.

Identity of Bendamustine medication

Bendamustine HCL (Treanda^{TM}) is commercially supplied Cephalon, Inc. It is supplied as a lyophilized powder for injection with 100mg of drug per vial.

Mechanism of action

Bendamustine HCl acts as an alkylating agent, causing the formation of intra-strand and inter-strand cross-links between DNA bases. This directly inhibits DNA replication, repair, and transcription. In addition, bendamustine HCl has potential purine-analog activity.

Pharmacokinetics and Metabolism

Following intravenous administration, greater than 95% of bendamustine HCl is protein bound. Bendamustine HCl undergoes extensive first-pass metabolism by the liver and is rapidly eliminated from plasma via urine. The elimination half life is biphasic with respective half lives in plasma of 6-10 minutes and 30 minutes.[7]

Packaging, labeling, and storage

Formulation: Bendamustine HCl is supplied as a lyophilized powder for injection in single-use, amber glass vials containing 100mg bendamustine HCl and 170mg mannitol.

Preparation: Reconstitute each vial with 20mL of sterile water for injection to final concentration of 5.0mg/mL. The calculated dose is withdrawn and immediately diluted further in 500mL of 0.9% Sodium Chloride for injection.

Storage: Vials should be refrigerated (2˚-8˚C) and protected from light. The admixture is stable for 3 days when refrigerated (2˚-8˚C) and for 3 hours at room temperature (15˚-30˚C).

Ofatumumab

GlaxoSmithKline will supply commercial ofatumumab to the investigator as content-labelled Ofatumumab vials presented as either 100 mg – acetate formulation, 20 mg/mL, 5 mL fill vials, or 1000 mg – acetate formulation, 20 mg/mL, 50 mL fill vials.

5.1 Mechanisms: Ofatumumab is a monoclonal antibody which binds specifically the extracellular (small) loops of the CD20 molecule (which is expressed on normal B lymphocytes and in B-cell CLL) resulting in potent complement-dependent cell lysis and antibody-dependent cell-mediated toxicity in cells that overexpress CD20.

5.2 Preparation:

Ofatumumab will be prepared as 1000 mL dilution of ofatumumab in sterile, pyrogen-free 0.9% NaCl. Once diluted into saline, the product is stable for up to 48 hours at ambient temperature. However, the product contains no preservative and should be used as soon as possible after dilution.

Preparation of drug solution for intravenous injection by the site pharmacist or designee will be done in accordance with the protocol, and in these dilution instructions.

Ofatumumab intravenous solution will be prepared using standard dilution methods and following general aseptic practice standard to preparation of IV medications. Eyes and hands should be protected when handling ofatumumab.

For intravenous administration, compatibility of the following components for ofatumumab in clinical studies (i.e., not for commercial product) has been established:

Table 1: Dosing Components for Ofatumumab in Clinical Studies

Dosing component	Material of construction	Suggested Vendor
1L Saline Bags	Polyvinyl Chloride (PVC)	Baxter
	Polyolefin [polyethylene* (PE)/polypropylene (PP)]	Baxter, B. Braun
Administration Set	PVC	Baxter
	PVC lined with Polyethylene	B. Braun
Filter Extension Set	Sterilizing-grade (0.22 μm) hydrophilic filter	Durapore brand by Millipore
	Lines made of PVC, filter membrane material polyether sulfone	Baxter
	Lines made of PVC lined with Polyethylene, filter membrane material polyether sulfone	Alaris/Cardinal Health

Preparation of the 1000 mL infusion bags should be done on the day of planned infusion.

* polyethylene (IUPAC name: polyethene)

5.3 Storage: Store intact vials at 2°C to 8°C (36°F to 46°F); do not freeze. Protect from light. Solutions diluted for infusion may be stored for up to 24 hours at 2°C to 8°C (36°F to 46°F); begin infusion within 12 hours of preparation.

5.4 Ofatumumab Preparation and Administration :

Pre-medication before each ofatumumab infusion must be given within 30 minutes to 2 hours prior to the treatment as per the following table:

Table 2: Supplemental Medication

Pre-medication Requirements prior to Ofatumumab Infusions- **Infusion #**	**Acetaminophen (po)** or equivalent (650 mg po x 2)	**Antihistamine (iv or po)** diphenhydramine or equivalent	**Glucocorticoid (iv)** prednisolone or equivalent
1st	1300 mg	50 mg	50 mg
2nd	1300 mg	50 mg	50 mg
3rd -Nth	1300 mg	50 mg	0 – 50 mg[1]

If the 2nd infusion has been completed without the subject experiencing any grade = 3 AEs, pre-medication with glucocorticoid may be reduced or omitted before the 3rd to Nth infusion at the discretion of the investigator.

Materials for Preparation and Administration of Infusion

The following materials are needed when preparing and administering the infusion:

- 1000 mL sterile pyrogen free 0.9% saline (NaCl) infusion bag(s). The solution can be kept at ambient temperature for a maximum of 24 hours after preparation; however, the product does not contain a preservative and dosing should begin as soon as possible after dose preparation.
- Ofatumumab 100 mg and 1000 mg vials (supplied by GSK)
- Needles and syringes (50 mL sterile syringe) not supplied by GSK

Dilution of Ofatumumab

- Ensure the correct container number is used.
- Take a 1000 mL infusion bag (sterile pyrogen free 0.9% saline), remove and dispose of the appropriate amount of saline according to Table 2 or Table 3 below
- Draw the required amount of ofatumumab according to Table 2 (100 mg vials) or Table 3 (1000 mg vials) below
- Inject ofatumumab into the saline bag
- Invert the infusion bag slowly 3 times, avoiding formation of any foam
- Label the infusion bag with the completed label

Table 3 Preparation of Ofatumumab Infusion: 100 mg vials

Dose of Ofatumumab	Infusion bag size	Volume of NaCl to be removed from infusion bag	Volume ofatumumab (number of ofatumumab vials)
300 mg	1000 mL	15 mL	15 mL (3 vials, 5 mL/vial)
1000 mg	1000 mL	50 mL	50 mL (10 vials, 5 mL/vial)

Table 4 Preparation of Ofatumumab Infusion: 1000 mg vials

Dose of Ofatumumab	Infusion bag size	Volume of NaCl to be removed from infusion bag	Volume ofatumumab (number of ofatumumab vials)
1000 mg	1000 mL	50 mL	50 mL (1 vial, 50 mL/vial)

Ofatumumab Infusion Set up

Ofatumumab must be administered by i.v. infusion through an in-line filter and through a well-functioning i.v. catheter (i.v. cannula) into a vein in the arm (or other venous access) by an infusion pump.

Please Note: It is mandatory to use an in-line low protein binding 0.2 micron polyether sulfone filter for all IV dosing of ofatumumab drug product.

DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

Ofatumumab should not be mixed with any other medication. If ofatumumab is to be dosed through an in-dwelling catheter, then, any previous medication should be removed by flushing with normal saline prior to dosing with ofatumumab.

Please note that the infusion site can be used for blood sampling only if there is no risk of contamination of the infusion needle with the saline, infusion solutions, or any other fluid(s). Only a newly inserted needle can be used for the predose blood samples.

- Check subject ID against the label on the infusion bag and ensure the expiry of the solution. The solution must be administered in its entirety to the subject within 48 hours from time of preparation.
- Attach the 1000mL infusion bag to the infusion set (if not done at the pharmacy).
- Attach the in-line filter to the infusion set (closest to the subject). **Note: The in-line filter must be used during the entire infusion.**

- Prime the infusion set and filter with ofatumumab (if not done at the pharmacy).
- In case of a problem with the filter (i.e. clogging/blockage), please change, re-prime the new filter, and continue the infusion.
- In case of problem with infusion set, follow local procedures.
- Collect the pre-dose blood samples, if required.
- Check the backflow from the i.v. cannula according to routine practice at site
- Set the pump at the initial infusion rate 12mL/hr for the first infusion and 25mL/hr for the subsequent infusions (if no grade ≥ 3 infusion-associated AEs were observed in the previous infusion)
- Start the infusion using the following infusion rates (as study applicable).

Immunotherapy:

The first cycle of ofatumumab monotherapy will consist of an infusion of 1000 mg on Day 1 and an infusion of 1000 mg on Day 2 of Cycle 1. For subsequent cycles, a dose of 1000 mg will be infused on Day 1 of weeks 2, 3 and 4; a single cycle will be administered. Patients who exhibit a leukocytosis > or equal to 20,000 will receive 300 mg of ofatumumab on day 1, week 1. Thereafter, they can receive 1000 mg as noted above.

Chemoimmunotherapy:

The first cycle of ofatumumab in combination with chemotherapy will consist of an infusion of 1000 mg on Day 1 and an infusion of 1000 mg on Day 2 of Cycle 1. The cycle length will be four weeks as appropriate based on the concomitant chemotherapy regimen.

For patients who exhibit a leukocytosis > or equal to 20,000: First Infusion of 300mg Ofatumumab

The first dose administered of ofatumumab should be 300 mg to minimize infusion reactions. The initial rate of the first infusion of **300mg** ofatumumab (0.3mg/ml) should be 12ml/h. If no infusion reactions occur the infusion rate should be increased every 30 minutes, to a maximum of 400 ml/h, according to Table 2. If this schedule is followed, the infusion duration will be approximately 4.5 hours.

Table 5 Infusion rate at 1st Ofatumumab infusion

Time	mL/hour
0 – 30 minutes	12
31 – 60 minutes	25
61 – 90 minutes	50
91 – 120 minutes	100
121 - 150 minutes	200
151 - 180 minutes	300
181+ minutes	400

If an infusion reaction develops, the infusion should be temporarily slowed or interrupted. Upon restart, the infusion rate should be half of the infusion rate at the time the infusion was paused. If, however, the infusion rate was 12 mL/hour before the pause, the infusion should be restarted at 12 mL/hour. Hereafter, the infusion rate may be increased according to the judgment of the investigator, in the manner described in this section.

Subsequent infusion of full dose Ofatumumab

If the previous infusion has been completed without grade ≥ 3 infusion-associated AEs, the subsequent infusion of the first full dose of ofatumumab can start at a rate of 25 mL/hour and should be doubled every 30 minutes up to a maximum of 400 ml/h, according to Table 3. Duration of the infusion will be approximately 4 hours if this schedule is followed. If the previous infusion has been completed with grade ≥ 3 infusion associated AEs, the subsequent infusion should start at a rate of 12 mL/hour according to Table 3.

Table 6 Infusion rate at subsequent Ofatumumab infusion

Time	mL/hour
0 – 30 minutes	25
31 – 60 minutes	50
61 – 90 minutes	100
91 – 120 minutes	200
121+ minutes	400

During infusion the patient should be monitored closely and appropriate measurements should be performed whenever judged necessary.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Untreated, non-transplant eligible, newly diagnosed mantle cell lymphoma with measurable disease as determined by CT, and bone marrow biopsy**.**
- Age ≥ 65 years or >18 year and ineligible for HDT/ASCT
- Subjects must not be candidates for intensive high-dose chemotherapy, with or without an autologous stem cell transplant (ASCT), due to one or more of the following factors:
    - Age ≥ 65 years
        - Patients <65 years of age must be ineligible for HDT/ASCT on the basis of comorbidity, organ dysfunction or patient refusal for HDT/ASCT
    - Comorbid disease, such as CAD, CHF, pulmonary dysfunction, liver or kidney dysfunction, precluding high dose therapy secondary to expected increased morbidity and mortality.
        - poor performance status (KPS 70% or less)
        - Ejection fraction <45%
        - Impaired pulmonary function test with DLCO <50% expected
    - Patient refusal
    - Medical conditions which in the opinion of the treating physician and DMT preclude HDT/ASCT.
- Patients must have a serum creatinine clearance ≥ 40 mL/min as per the Jelliffe method or by 12-hour or 24-hour urine creatinine clearance.
- Patients must have ANC>1,000/mcl and Platelets>100,000/mcl (unless secondary to MCL).
- 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).
- Negative serologies for Hepatitis B (HB) defined as a negative test for HBsAg. In addition, if negative for HBsAg but HBcAb positive (regardless of HBsAb status), a HB DNA test will be performed and if negative, patient may be included but must undergo HBV DNA PCR testing at the beginning of treatment and throughout treatment duration, at least every 2 months. In addition patients will require treatment with Entacavir .5mg po qday per MSKCC institutional guidelines (see Appendix III of protocol).
- No active co-morbid cardiac condition such as active CHF or CAD.
- KPS performance ≥ 70%
- Histologically confirmed mantle cell lymphoma classified according to WHO criteria confirmed at MSKCC.
- No prior treatment for mantle cell lymphoma with the exception of corticosteroids for 7 days or less, or 1 course of involved-field radiation.
- No prior malignancies within 5 yrs, unless treated early stage breast cancer, treated carcinoma in situ of the cervix, resected skin malignancies, or treated prostate cancer.
- Women who are pre-menopausal must have a negative serum pregnancy test. Subjects must agree to use appropriate contraception until 4 weeks after the completion of chemotherapy.

- Patients must be HIV negative, and have negative serologies for Hepatitis C.

6.2 Subject Exclusion Criteria

- Subjects who have current active hepatic or biliary disease (with exception of patients with Gilbert's syndrome, asymptomatic gallstones, hepatic involvement by MCL, or stable chronic liver disease per investigator assessment).
- Known pregnancy or breast-feeding.
- Medical illness unrelated to MCL within the prior one month that will preclude administration of chemotherapy safely. This includes patients with uncontrolled infection, chronic renal insufficiency, myocardial infarction within the past 6 months, unstable angina, active congestive heart failure, cardiac arrhythmias other than chronic atrial fibrillation and chronic active or persistent hepatitis.

7.0 RECRUITMENT PLAN

Patients with MCL will be recruited from MSKCC. Patients seen in the inpatient or outpatient setting at MSKCC with histologically confirmed mantle cell lymphoma will be evaluated for this study. An attending physician of the Lymphoma or Hematology service will evaluate all patients to determine their eligibility. If their physician considers them eligible, they will be provided with information regarding the clinical trial and asked to participate. We will enroll 38 patients the single agent Ofatumumab arm, and 38 additional patients for the chemoimmunotherapy arm with Ofatumumab and Bendamustine. We intend to accrue 1-2 patients per month.

8.0 PRETREATMENT EVALUATION

- Consent to utilize tumor sample and/or peripheral blood sample for research (perform clinical correlates).
- Tissue block preferred or at least 10 unstained slides, if available, for confirmation of diagnosis:
    - Immunohistochemistry staining for Ki-67, p53, CD20, CD5, CD23, CD10, cyclin D1. (Cyclin D2, D3 will be obtained as needed, if Cyclin D1 negative)
    - Ki-67 will be determined by optical image assessment whenever technically feasible; standard visual assessment will otherwise be utilized.
- Within 2 weeks prior to initiating treatment:
    - History and physical including height, weight, and vital signs
    - Karnofsky performance status
    - Complete blood count with differential
    - Comprehensive metabolic panel (includes liver function testing, serum LDH)
    - Creatinine clearance evaluation per the Jelliffe method or 12-hour or 24-hour urine creatinine clearance
    - Quantitative serum immunoglobulin levels
    - Serum lactate dehydrogenase

  - Pregnancy test in pre-menopausal women
  - Modified Comprehensive Geriatric Assessment (CGA) & comorbidity *This can be completed either at baseline or cycle 1 day 1 of therapy. It does not need to be completed twice prior to therapy.
    - Non-English speaking patients are not required to participate in the CGA
  - NIA/NCI Co-morbidity Scale (baseline only)
- Within 6 weeks prior to initiating treatment:
  - CT scans of chest, abdomen, and pelvis with contrast for pretreatment staging.
  - CT of neck may be obtained as clinically indicated
    - MRIs may be used instead of CT scans in patients for whom CT scans are contraindicated.
  - Colonoscopy with blind biopsy is advisable when clinically indicated and acceptable from a risk:benefit standpoint as GI tract involvement is common, but this study is not a mandatory per protocol and left to the discretion of the treating physician.
  - Appropriate bone marrow biopsy and aspirate for detection of involvement
  - Electrocardiogram
  - Hepatitis B surface antigen and antibody, core antibody
  - Hepatitis C serology
  - HIV 1/2 antibodies
  - CMV PCR for patients enrolling onto chemoimmunotherapy arm

9.0 TREATMENT/INTERVENTION PLAN

Immunotherapy alone:

- Patients receiving immunotherapy alone will receive ofatumumab every week ± 1 day for 4 weeks.
- During the first week only, there are 2 days of treatment. Thereafter, there is only 1 day of treatment.
- On the first week, ofatumumab will be given on two consecutive days at the same doses: **Week 1**, **day 1**: 1000 mg, **Week 1**, **day 2**: 1000mg. Patients who exhibit a leukocytosis > or equal to 20,000 will receive 300 mg of ofatumumab on day 1, week 1. Thereafter, they can receive 1000 mg as noted above.
- During **weeks 2, 3**, and **4**, patients will only receive ofatumumab on one day: Day 1, 1000 mg.
- 8-10 weeks after completion of ofatumumab, patients will be restaged with CT scans of chest, abdomen and pelvis.
- If a CR or PR is documented, patients will be restaged every 24 weeks for a total of 2 years, and then every 12 months until disease progression, or for a maximum of five years.
  - If restaging documents less than PR, SD, or progression of disease (POD), patients will proceed to the chemoimmunotherapy arm within the next 4 weeks, and receive ofatumumab combined with bendamustine. Patients crossing over to the chemoimmunotherapy induction should complete the pre-treatment investigations in section 8.0 prior to starting chemoimmunotherapy; A repeat bone marrow biopsy can be deferred at this time, but must be repeated to confirm CR post chemoimmunotherapy if appropriate.

Chemoimmunotherapy:

- Patients will receive treatment with both ofatumumab and bendamustine every 4 weeks ± 3 day (every month) for a total of 6 months (cycles). Here, one cycle is one month of treatment.
- As above, on the **first cycle of treatment only**, ofatumumab will be given on two consecutive days at the same doses: **Cycle 1**, day **1**: 1000 mg, **Cycle 1**, day **2**: 1000mg. Patients who exhibit a leukocytosis ≥20,000 will receive 300 mg of ofatumumab on day 1, cycle 1. Thereafter, they can receive 1000 mg as noted above.
- For the first cycle, Bendamustine will be administered together with ofatumumab on day 1 and 2 at 90 mg/m^2.
- For cycles 2 through 6, Ofatumumab will be given with Bendamustine on day 1, and Bendamustine will be given alone on day 2.
- Patients will receive a total of 6 cycles of both ofatumumab and bendamustine (one cycle every 28 days ± 3 days; or approximately 6 months of therapy).
- After 4-6 weeks, patients will undergo restaging with CT of chest, abdomen and pelvis (and neck, as clinically indicated), and subsequently every 24 weeks for a total of 2 years, and then every 12 months until disease progression, or for a maximum of five years.
- CMV PCR will be drawn 4-6 weeks after cycle 6

Dose Adjustments:

Dose Adjustments for Bendamustine: Patients may be delayed up to **17 days** for cytopenias or toxicity prior to removal from study. Treatment will be delayed until the absolute neutrophil count is >1000/mcl and the platelet count is >75,000/mcl. A lower threshold is allowed for patients that have a baseline platelet count ≤100,000/mcl secondary to MCL: their platelet count must be >50,000/mcl prior to treatment. Delays for neutropenia at the time of next cycle, or grade 3-4 neutropenia lasting >7 days during a cycle, will result in Bendamustine dose reduction to 70 mg/m^2 days 1 and 2; Pegylated GCSF or GCSF should be utilized for all subsequent cycles for patients delayed for neutropenia. If cytopenia resolve with G-CSF/Peg-GCSF support, the bendamustine dose may be re-escalated to 90 mg/m^2.

Dose Adjustments for ofatumumab:

Immunotherapy Alone: Ofatumumab weekly dosing may be delayed up to 17 days for cytopenias or toxicity; Treatment will be delayed until the absolute neutrophil count is > 1000/mcl; If cycle 1 day 2 ofatumumab therapy is delayed for toxicity this dose will be omitted, recommencing with weekly dosing; the dose of ofatumumab will not be decreased.

Chemoimmunotherapy: Patients may be delayed up to **17 days** for cytopenias or toxicity prior to removal from study. Treatment will be delayed until the absolute neutrophil count is > 1000/mcl and the platelet count is > 75,000/mcl Delays for neutropenia at the time of next cycle, or grade 3-4 neutropenia lasting >7 days during a cycle, with Bendamustine dose reduction as above; The dose of ofatumumab will not be decreased on study. Pegylated GCSF or GCSF should be utilized for all subsequent cycles for patients delayed for neutropenia. If cytopenia resolve with G-CSF/Peg-GCSF support, the bendamustine dose may be re-escalated to 90 mg/m^2.

The most common adverse event resulting from ofatumumab use is infusion reactions. We will interrupt infusion for infusion reactions of any severity.

- For grade 4 infusion reactions, do not resume the infusion.
- For grade 1, 2, or 3 infusion reaction, if the infusion reaction resolves or remains less than or equal to grade 2, resume infusion with the following modifications according to the initial grade of the infusion reaction:
    - For grade 1 or 2: Infuse at one-half of the previous infusion rate.
    - For grade 3: Infuse at a rate of 12 mL/hour.

After resuming the infusion, the infusion rate may be increased according to the following table or based on patient tolerance.

Ofatumumab doses that cannot be completed secondary to infusion reactions will not be made up:

Table 7

Time	mL/hour
0 – 30 minutes	25
31 – 60 minutes	50
61 – 90 minutes	100
91 – 120 minutes	200
121+ minutes	400

Supportive care: Antiemetics will be provided per institution protocol. Growth factor support with Pegylated GCSF or GCSF will be provided as clinically indicated.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Assessments prior to each cycle of immunotherapy or chemoimmunotherapy:

- Physical exam
- Karnofsky Performance Status
- Assessment for toxicity will be performed prior to each cycle of chemotherapy.
- Modified Comprehensive Geriatric Assessment (CGA) comorbidity will be done prior to cycle 1 and restaging for the immunotherapy arm. For the chemoimmunotherapy arm, the CGA will be performed before each cycle and at restaging. For cycle 1 day 1 only, if the CGA is completed at screening it does not need to be completed on cycle 1 day 1.
    - Non-English speaking patients are not required to complete the CGA.
- CBC (Patients must have ANC>1000/mcl and Platelets>75,000/mcl)
    - Treatment will be delayed until the absolute neutrophil count is > 1000/mcl and the platelet count is > 75,000/mcl.
- Quantitative serum immunoglobulin levels once every other cycle beginning cycle 1 and subsequently at each physician visit after conclusion of treatment for 2 years.
- Comprehensive metabolic panel, including serum LDH:
    - For both immunotherapy and chemoimmunotherapy arms: prior to each cycle and at restaging.

Interim restaging:

- Interim CT scan of chest, abdomen, and pelvis after 3 cycles of chemoimmunotherapy for interim staging per institutional guidelines.
- CT of neck may be obtained as clinically indicated
- MRIs may be used instead of CT scans in patients for whom CT scans are contraindicated.
- CMV PCR post cycle 3 of chemoimmunotherapy

Liver monitoring on Ofatumumab:

- If ALT > 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin), ALT > 8xULN, or ALT ≥ 5xULN for more than 2 weeks, ofatumumab will be stopped and patient will be withdrawn from study.

    - Patients with ALT >3xULN and bilirubin >2xULN, must return to clinic and repeat liver chemistries in 24 hours, and then twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

        - A specialist or hepatology consultation is recommended
        - Liver follow up assessment as per appendix IV

    - Patients with ALT > 8xULN, or ALT ≥ 5xULN for more than 2 weeks, must return to clinic within 24-72 hrs for repeat liver chemistries and then weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.
        - Liver follow up assessment as per appendix IV

    - Patients with ALT ≥5xULN who exhibit a decrease to ALT x≥3xULN, but <5xULN and bilirubin <2xULN without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks can continue ofatumumab.

- Patients must return weekly for repeat liver chemistries until they resolve, stabilize or return to within baseline.
- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor patients twice monthly until liver chemistries normalize or return to within baseline values.
- Liver follow up assessment as per appendix IV

Progressive Multifocal Leukoencephalopathy (PML) monitoring while on Ofatumumab:

- Patient will be monitored for signs and symptoms of PML, such as visual disturbances, ocular movements, ataxia, and changes in mental status such as disorientation or confusion, or any other symptom that may be suggestive of PML in the judgment of the investigator.

Table 8: Testing During and After Immunotherapy (Ofatumumab alone)

Immunotherapy (Ofatumumab alone)						
	Baseline (pretreatment)	**Week 1 (+/-24hr)**	**Week 2 (+/-24hr)**	**Week 3 (+/-24hr)**	**Week 4 (+/-24hr)**	**Restaging**
History, Physical, KPS	X	X	X	X	X	X
Comprehensive Geriatric Assessment	X*	X*				X
NIA/NCI Comorbidity scale	X					
CBC with diff. §	X	X	X	X	X	X
Comp§, LDH§	X	X	X	X	X	X
Creatinine Clearance per the Jelliffe method or by 12 or 24 hour urine creatinine clearance	X					X
HIV 1 and 2 antibodies	X					
Pregnancy test in pre-menopausal women	X					
Serum Immunoglobulins	X	X		X		X
CT CAP (or MRI as clinically	X					X

indicated)						
Colonoscopy with blind biopsy if clinically indicated and at the discretion of the investigator	discretion of investigator					
Bone marrow Biopsy and aspirate with one aspirate sample for research	X					
EKG	X					
Peripheral Blood for research	X					
Hepatitis B surface antigen and antibody, core antibody	X					
Hepatitis C Serology	X					

*****The Comprehensive Geriatric Assessment can either be completed at baseline or week 1 day 1. It does not need to be completed at both time points.

Table 9: Testing During and After Chemoimmunotherapy (Ofatumumab and Bendamustine)

Chemoimmunotherapy (Ofatumumab + Bendamustine)								
	Baseline (pretreatment)	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Restaging**
	Window for Tx	**+/- 72 hr**	**+/- 72 hr**	**+/- 72 hr**	**+/- 72 hr**	**+/- 72 hr**	**+/- 72 hr**	**+/- 72 hr**
History, Physical, KPS	X	X	X	X	X	X	X	X
Comprehensive Geriatric Assessment	X**	X**	X	X	X	X	X	X
NIA/NCI Comorbidity scale	X							
CBC with diff. §	X	X	X	X	X	X	X	X
Comp§, LDH§	X	X	X	X	X	X	X	X
Creatinine Clearance per the Jelliffe method or by 12 or 24 hour urine creatinine clearance	X							

HIV 1 and 2 antibodies	X							
Pregnancy test in pre-menopausal women	X							
Serum Immunoglobulins	X	X		X		X		X
Interim restaging CT CAP (or MRI as clinically indicated)	X				X (prior to cycle 4)			X
Colonoscopy with blind biopsy if clinically indicated and at the discretion of the investigator	discretion of investigator							
Bone marrow Biopsy and aspirate with one aspirate sample for research	X							*X
EKG	X							
Peripheral Blood for research	X							
Hepatitis B surface antigen and antibody, core antibody	X							
Hepatitis C Serology	X							
CMV PCR	X				X			X

*Bone marrow biopsy to confirm CR if appropriate

**The Comprehensive Geriatric Assessment can either be completed at baseline or cycle 1 day 1. It does not need to be completed at both time points.

§ Pretreatment Comp, CBC and LDH may be obtained up to 72 hours prior to treatment to allow for chemotherapy preparation process

- Patients who show a partial or complete response at restaging 8-10 weeks after Ofatumumab alone will continue to be restaged with CT CAP every 24 weeks (+/- 2 weeks) for two years, then every12 months thereafter until disease progresses, or for a maximum of 5 years. Also during follow up, a CBC, comprehensive metabolic panel, serum LDH, quantitative immunoglobulins, and physical exam will be performed at every 12 weeks (+/- 2 weeks), for 2 years, then q 6 months (+/- 2 weeks) thereafter until disease progresses, or for a maximum of 5 years.

- Patients who show less than partial response, stable disease, or progression of disease at restaging 8-10 weeks after Ofatumumab alone will begin the combination of Ofatumumab + Bendamustine within 4 weeks of restaging.

    - Schedule of tests and evaluation follows the same schedule as patients originally stratified to this treatment arm (See table 9), with the exception that HIV and viral Hepatitis serologies, which do not require repeating as repeat baseline testing if crossing over to the chemoimmunotherapy arm within 6 months of last screening

- Patients who show a partial or complete response at restaging 4-6 weeks after Ofatumumab + Bendamustine will continue to be restaged with CT CAP every 24 weeks (+/- 2 weeks) for two years, then every 12 months thereafter until disease progresses, or for a maximum of 5 years. Also during follow up, a CBC, comprehensive metabolic panel, serum LDH, quantitative immunoglobulins, and a physical exam will be performed every 12 weeks (+/- 2 weeks), for 2 years, then q 6 months (+/- 2 weeks) thereafter until disease progresses, or for a maximum of 5 years.

Response Criteria as per Cheson et al, JCO 1999, Response criteria for malignant lymphoma (see section 12.0)**.**

11.0 TOXICITIES/SIDE EFFECTS

Bendamustine

- **Myelosuppression**
  Patients treated with Bendamustine are likely to experience myelosuppression. In the two NHL studies, 98% of patients had Grade 3-4 myelosuppression. Three patients (2%) died from myelosuppression-related adverse reactions; one each from neutropenic sepsis, diffuse alveolar hemorrhage with Grade 3 thrombocytopenia, and pneumonia from an opportunistic infection (CMV). Hematologic nadirs can be observed predominantly in the third week of therapy. Hematologic nadirs may require dose delays if recovery to the recommended values have not occurred by the first day of the next scheduled cycle.
- **Infections**
  Infection, including pneumonia and sepsis, has been reported in patients in clinical trials and in post-marketing reports. Infection has been associated with hospitalization, septic shock and death. Patients with myelosuppression following treatment with Bendamustine are more susceptible to infections.
- **Infusion Reactions and Anaphylaxis**
  Infusion reactions to Bendamustine have occurred commonly in clinical trials. Symptoms include fever, chills, pruritus and rash. In rare instances severe anaphylactic and anaphylactoid reactions have occurred, particularly in the second and subsequent cycles of therapy.
- **Tumor Lysis Syndrome**
  Tumor lysis syndrome associated with Bendamustine treatment has been reported in patients in clinical trials and in post-marketing reports. The onset tends to be within the first treatment cycle of Bendamustine and, without intervention, may lead to acute renal failure and death. Preventive measures

include maintaining adequate volume status, and close monitoring of blood chemistry, particularly potassium and uric acid levels. Allopurinol has also been used during the beginning of Bendamustine therapy. However, there may be an increased risk of severe skin toxicity when Bendamustine and allopurinol are administered concomitantly

- **Skin Reactions**
  A number of skin reactions have been reported in clinical trials and post-marketing safety reports. These events have included rash, toxic skin reactions and bullous exanthema. Some events occurred when Bendamustine was given in combination with other anticancer agents, so the precise relationship to Bendamustine is uncertain. In a study of Bendamustine (90 mg/m^2) in combination with rituximab, one case of toxic epidermal necrolysis (TEN) occurred. TEN has been reported for rituximab Cases of Stevens-Johnson syndrome (SJS) and TEN, some fatal, have been reported when Bendamustine was administered concomitantly with allopurinol and other medications known to cause these syndromes. The relationship to Bendamustine cannot be determined. Where skin reactions occur, they may be progressive and increase in severity with further treatment. Therefore, patients with skin reactions should be monitored closely. If skin reactions are severe or progressive, Bendamustine should be withheld or discontinued.
- **Other Malignancies**
  There are reports of pre-malignant and malignant diseases that have developed in patients who have been treated with Bendamustine, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia and bronchial carcinoma. The association with Bendamustine therapy has not been determined.
- **Extravasation**
  There are postmarketing reports of bendamustine extravasations resulting in hospitalizations from erythema, marked swelling, and pain. Precautions should be taken to avoid extravasation, including monitoring of the intravenous infusion site for redness, swelling, pain, infection, and necrosis during and after administration of Bendamustine.
- **Gastrointestinal Side effects**
  Nausea and vomiting, constipation, diarrhea, stomatitis, decreased appetite. In very rare cases, alopecia.
- **Metabolic Side Effects**
  Hypercalcemia, renal insufficiency, and adrenal hemorrhage, though rare.
- **Fluid Overload**
  Non cardiogenic pulmonary edema may occur, though rare.

Ofatumumab

- **Infusion Reactions**
  Ofatumumab can cause serious infusion reactions manifesting as bronchospasm, dyspnea, laryngeal edema, pulmonary edema, flushing, hypertension, hypotension, syncope, cardiac ischemia/infarction, back pain, abdominal pain, pyrexia, rash, urticaria, and angioedema. Infusion reactions occur more frequently with the first 2 infusions. In a study of patients with moderate to severe chronic obstructive pulmonary disease, an indication for

which Ofatumumab is not approved, 2 of 5 patients developed Grade 3 bronchospasm during infusion.

- **Cytopenias**
  Prolonged (≥1 week) severe neutropenia and thrombocytopenia can occur with Ofatumumab.
- **Progressive Multifocal Leukoencephalopathy**
  Progressive multifocal leukoencephalopathy (PML), including fatal PML, can occur with Ofatumumab. Consider PML in any patient with new onset of or changes in pre-existing neurological signs or symptoms. Discontinue Ofatumumab if PML is suspected, and initiate evaluation for PML including consultation with a neurologist, brain MRI, and lumbar puncture.
- **Hepatitis B Reactivation**
  Hepatitis B reactivation, including fulminant hepatitis and death, occurs with other monoclonal antibodies directed against CD20. Hepatitis B virus (HBV) infection, including fatal infection, can occur in patients taking ofatumumab.
- **Intestinal Obstruction**
  Obstruction of the small intestine can occur in patients receiving Ofatumumab.
- **Immunizations**
  The safety of immunization with live viral vaccines during or following administration of Ofatumumab has not been studied. Live viral vaccines should not be administered to patients who have recently received Ofatumumab since the ability to generate an immune response to any vaccine following administration of Ofatumumab has not been studied.
- **Gastrointestinal Side Effects**
  Diarrhea
- **Other side effects**
  Chills, fever, fatigue.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

From Cheson et al JCO 1999, Response criteria for malignant lymphoma.

Measurable disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm with conventional CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

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 (eg, lactate dehydrogenase [LDH]) definitely assignable to NHL.
2. All lymph nodes and nodal masses must have regressed to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to ≤ 1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).
3. The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable on physical examination. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic size. For instance, spleens thought to be of normal size may contain lymphoma, whereas an enlarged spleen may not necessarily reflect the presence of lymphoma but variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes. The determination of splenic volume or splenic index by CT scan is cumbersome and not widely used.[35,36] Any macroscopic nodules in any organs detectable on imaging techniques should no longer be present. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.
4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat bone marrow aspirate and biopsy of the same site. The sample on which this determination is made must be adequate (≥ 20 mm biopsy core). Flow cytometric, molecular, or cytogenetic studies are not considered part of routine assessment to document persistent disease at the present time. These studies should only be incorporated into trials examining important research questions.

CR/unconfirmed (CRu) includes those patients who fulfill criteria 1 and 3 above, but with one or more of the following features:

1. A residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the SPD. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD compared with the size of the original mass.
2. Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia).

PR requires the following:

1. ≥ 50% decrease in SPD of the six largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following features: (a) they should be clearly measurable in at least two perpendicular dimensions, (b) they should be from as disparate regions of the body as possible, and (c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase in the size of the other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by at least 50% in the SPD.
4. With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease.
5. Bone marrow assessment is irrelevant for determination of a PR because it is assessable and not measurable disease; however, if positive, the cell type should be specified in the report, eg, large-cell lymphoma or low-grade lymphoma (ie, small, lymphocytic small cleaved, or mixed small and large cells).
6. No new sites of disease.

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

Relapsed disease (CR, CRu) requires the following:

1. Appearance of any new lesion or increase by ≥ 50% in the size of previously involved sites.
2. ≥ 50% increase in greatest diameter of any previously identified node greater than 1 cm in its short axis or in the SPD of more than one node.

Progressive disease (PR, nonresponders) requires the following:

1. ≥ 50% increase from nadir in the SPD of any previously identified abnormal node for PRs or nonresponders.
2. Appearance of any new lesion during or at the end of therapy.

Response Assessment

Response is currently assessed on the basis of clinical, radiologic, and pathologic (ie, bone marrow) criteria.

1. CT scans remain the standard for evaluation of nodal disease. Thoracic, abdominal, and pelvic CT scans are recommended even if those areas were not initially involved because of the unpredictable pattern of recurrence in NHL. Studies should be performed no later than 2 months after treatment has been completed to assess response. This interval may vary with the type of treatment, eg, a longer period may be more appropriate for biologic agents where the anticipated time to response may be greater.

2. A bone marrow aspirate and biopsy should only be performed to confirm a CR if they were initially positive or if it is clinically indicated by new abnormalities in the peripheral blood counts or blood smear.

Table 10

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone Marrow
CR	Normal	Normal	Normal	Normal
CRu	Normal	Normal	Normal	Indeterminate
	Normal	Normal	> 75% decrease	Normal or indeterminate
PR	Normal	Normal	Normal	Positive
	Normal	≥50% decrease	≥50% decrease	Irrelevant
	Decrease in liver/spleen	≥50% decrease	≥50% decrease	Irrelevant
Relapse/progression	Enlarging liver/spleen; new sites	New or increased	New or increased	Reappearance

Definition of end points:

Overall Survival

Overall survival is the least ambiguous end point, although it usually is not optimal to use for a lymphoma clinical trial. Overall survival is defined as the time from entry onto the clinical trial (random assignment in a phase III study) until death as a result of any cause. Survival, as well as other time-dependent variables (PFS, event-free survival) should be measured in a randomized trial because data derived from historical controls are unreliable and subject to bias.

Survival should be measured in the intent-to-treat population, including all patients even if they did not fulfill the eligibility criteria. A per-protocol analysis includes all patients who received the treatment to which they were assigned. A treatment-given analysis includes all patients who received a particular treatment. Both of these types of analyses should be interpreted with caution because they are subject to considerable bias.

PFS

PFS is defined as the time from entry onto a study until lymphoma progression or death as a result of any cause. PFS is often considered the preferred end point in lymphoma clinical trials, especially those involving incurable histologic subtypes (eg, follicular, other low-grade lymphoma, or mantle cell lymphoma). PFS reflects tumor growth, and therefore is interpretable earlier than the end point of overall survival. In addition, PFS is not confounded by the administration of subsequent therapy. However, in studies in which failure to respond without progression is considered an indication for another therapy, such patients should be censored at that point for the progression analysis. Whether a prolongation of PFS represents direct clinical benefit or is an acceptable surrogate for clinical benefit depends on the magnitude of the effect and the risk-benefit ratio of the therapy under investigation. Unlike survival, the precise date of progression is generally unknown. It may be defined as the first date of documentation of a new lesion or enlargement of a previous lesion, or the date of the scheduled clinic visit immediately after radiologic assessment has been completed. When there is missing information, censoring of the data may be defined as the last date at which progression status was assessed adequately or the first date of unscheduled new antilymphoma treatment.

Response Duration

Response duration is from the time when criteria for response (i.e., CR or PR) are met, for which the event is the first documentation of relapse or progression.

13.0 CRITERIA FOR REMOVAL FROM STUDY

- Patients found at any time to be ineligible as designated in section 6.0.
- Patients who request to be removed from the study. This will not compromise the care they receive at this institution.
- Patients who are non-compliant with treatment or follow-up.
- Patients who develop unacceptable toxicity
- Patients that develop progression of disease after 4 cycles of the combination of ofatumumab and bendamustine. These patients may be offered alternate treatments or similar treatment off protocol.

14.0 BIOSTATISTICS

This is a Simon 2-stage study investigating the activity of ofatumumab alone or in conjunction with bendamustine for non-transplant eligible untreated mantle cell lymphoma patients. The study design will allow for an estimation of the single agent response in patients at low biologic risk for immediate progression. The combined regimen will assess the efficacy of a chemo-immunotherapy program in patients with need for cytoreductive therapy (high risk).

Immunotherapy alone:

For the low risk arm, it is expected that the new regimen will improve the overall response rate (ORR) from 40% to 60%. To this end, an optimal Simon 2-stage design will be used. In stage 1, 12 patients will enter the study. If 5 or less patients respond, then the study will be terminated early and declared to have a negative result. If 6 or more patients respond, enrollment will be extended to 38 patients. This is, at stage 2, an additional 26 patients will be enrolled. The treatment will be declared effective and worthy of further testing if 19 or more patients respond among the total 38 patients entered. This optimal Simon 2-stage design has a type I error rate of 0.10 and type II error rate at 0.20. The probability of early stopping under the null hypothesis is 67%. The probability of early stopping under the alternative hypothesis is 16%.

Chemoimmunotherapy:

For the high risk arm, it is expected that the new regimen will improve the complete response (CR) rate from 40% to 60%. Therefore the same design as above will be used. The decision to utilize complete remission rate rather than ORR is based on previous research which showed that better quality remissions (eg. Increased CR) are correlated with improved duration of benefit. Furthermore, the ORR with chemoimmunotherapy are generally high (>90%), requiring large numbers of patients to assess for small difference with less clear clinical benefit.

Patients will be followed per every 3 months with imaging (CT CAP) every 3 months for the first 2 years; subsequently, patients will be seen every 3 months with CT CAP every 6 months until progression of disease or a maximum of five years.

We anticipate accrual in 24-36 months.

The secondary objectives contain analysis of the following four survival endpoints: Overall survival (calculated from registration to death); Progression free survival (calculated from registration until progression or death); Remission duration (calculated from confirmation of CR

to progression); Response duration (calculated from confirmation of response (CR/PR) to progression. The first two endpoints will be analyzed using Kaplan-Meier estimation, and log-rank tests or Cox regression models when covariates are involved. The last two endpoints will be analyzed using competing risks tools (with death as a competing risk for progression), and will be done on the subsets of patients who have CR or CR/PR.

As part of an exploratory analysis, patients who initially received immunotherapy induction and crossed over to chemoimmunotherapy at progression will be analyzed from the time of initial enrollment until progression or death. This will allow for assessment of the duration of benefit for sequential immunotherapy -> immunochemotherapy program in elderly patients as a strategy to delay exposure to chemotherapy. Additionally, exploratory analysis of chemoimmunotherapy patients treated previously with immunotherapy induction vs. those directly enrolled onto chemoimmunotherapy will be assessed for toxicity, response rate and efficacy outcomes.

Toxicities (number of occurrences and grades) will be summarized and tabulated. Additionally, the CGA will be assessed as a tool to predict toxicity on study in an exploratory analysis.

The measurement of miRNA expression is dichotomized as either over-expressed or under-expressed, and proliferation is dichotomized as either ≥30% or <30%. Thus a contingency table will be constructed and a Fisher's exact test will be used to examine the correlation.

The standard response criteria for Malignant Lymphoma (Cheson et. Al JCO 25 (5) 2007) currently do not recommend PET imaging for incurable routinely FDG avid lymphomas, including follicular lymphoma and mantle-cell lymphoma. As such, PET imaging is not a protocol defined pre-treatment evaluation. Furthermore, PET imaging post-treatment for confirmation of response is not a standard of care based on these same criteria (Cheson 2007) for Mantle cell lymphoma. Routine surveillance PET imaging is also not supported by current data. Consequently, the clinical trial relies on CT scans to determine baseline pretreatment disease state and response and has no protocol specified PET imaging.

Nevertheless, PET scanning is frequently employed in the clinical management of mantle cell lymphoma patients and may convey important information about disease burden and response to therapy. In instances where a PET scan has been obtained at the discretion of the treating physician, we will prospectively collect this data. This information will not be utilized to determine protocol response, but may be used in a purely exploratory analysis post hoc.

Primary Endpoints:

- Immunotherapy induction (low risk patients) the ORR (CR+PR) rate to ofatumumab
- Chemoimmunotherapy induction (High Risk patients) the CR to ofatumumab + Bendamustine

Secondary Endpoints:

- OS, PFS, DFS, DR
- ORR for chemoimmunotherapy induction
- Safety and toxicity profile according to Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v4.0). The ability for the CGA to predict toxicity will be explored.

These outcome parameters will be assessed for each cohort independently.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 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. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/).The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.2 Randomization

No randomization is to take place.

16.0 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 coordination of 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.

16.1 Quality Assurance

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 and 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.

16.2 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/researchesr/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, plus 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, NIC cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

16.3 Safety Monitoring for Ofatumumab:

Safety Definitions

Adverse Events:

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Events meeting the definition of an AE include:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medial and scientific judgment of the investigator
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication (overdose per se will not be reported as an AE/SAE)

"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Any clinically significant abnormal laboratory finding or other abnormal safety assessments that is associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- B cell depletion and hypogammaglobulinemia due to ofatumumab treatment

Definition of a SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

An overnight hospital stay due to slow infusion rates will not be considered a Serious Adverse Event.

d. Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Medical or 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 subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, 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.

Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator **are** to be recorded as AEs or SAEs.
- All events meeting liver stopping criteria must be recorded as an SAE.
- However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.
- B cell depletion, IgG below LLN, low CD19+ count, and hypogammaglobulinemia due to treatment with ofatumumab are **not** to be reported as AEs or SAEs.
- Infusion related AEs may lead to a prolonged infusion time. Overnight stay at the hospital due to slow infusion rate is **not** to be reported as a SAE.

Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression) does not need to be reported as an SAE. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with investigational product or protocol design/procedures and the disease progression, then this must be reported as an SAE.

Time Period and Frequency of Detecting and SAEs

Once an investigator determines that an event meets the protocol definition of an SAE, the SAE will be reported to GSK within 24 hours of being notified of the event. All SAEs regardless of relationship to investigational product will be collected from the first dose of investigational product to after the last dose of investigational product (minimum of 6 months or until the end of the follow-up period whichever is longer). All SAEs regardless of causality will be collected until the end of the follow-up period.

From the time a subject consents to participate in and completes the study all SAEs assessed **as related to study participation** (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or **related Ofatumumab**, will be reported promptly to GSK.

Any SAE brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to investigational product must be reported to GSK.

Pregnancy

Any pregnancy that occurs during study participation must be reported to GSK. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the investigational product, must be promptly reported to GSK.

In addition, the investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to GSK as described above.

17.0 PROTECTION OF HUMAN SUBJECTS

Potential risks to human subjects include myelosuppression, infections, infusion related reactions to bendamustine and ofatumumab, tumor lysis syndrome, skin reactions, secondary malignancies such as myelodysplastic syndrome, myeloproliferative disorders, extravasation, cytopenias, PML, Hepatitis B reactivation, and intestinal obstruction. All efforts will be made to avoid any complication by completely reviewing patients' symptoms, providing appropriate management, and monitoring blood tests.

Costs to the patient (third party insurer) will include the cost of chemotherapy and hospitalization, blood tests and diagnostic studies, office visits, and those admissions which may be required as a consequence of treatment-related complications.

17.1 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.

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- 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
- The grade of the 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
    - A 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
- If the SAE is an Unanticipated Problem

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

For IND/IDE protocols:
The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office

17.2.1 Reporting Serious Adverse Events to GSK:

All Serious Adverse Events including life-threatening events resulting in required hospitalization, disability, congenital anomaly, death, or progression of the disease being greater than expected. In the event that the investigator identifies an SAE according to protocol definitions, the SAE will be reported to GSK within 24 hours of identification of the SAE after reporting to the IRB.

Send to: GlaxoSmithKline

Attn: Gaetano Bonifacio, MD

Medical Director, Clinical Development, R&D/Medical Affairs, North America

GlaxoSmithKline Oncology, 1250 S. Collegeville Road, Collegeville, PA 19426

Phone number: (610) 917-5239

Fax Number: 1.484.902.3041

Email: Gaetano.a.bonifacio@gsk.com

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.

Participation is voluntary. The consenting physician will inform patients of their diagnosis, current treatment options, including standard treatment, and the risks, benefits and experimental nature of this treatment program. All patients will be required to sign a statement of informed consent

that conforms to FDA and IRB guidelines. Written consent will be obtained by individuals specified in this protocol. Registration of patients is described in section 15.0. All patients will be asked to sign a research authorization form.

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20.0 APPENDICES

III. MSKK Standard for Screening and Treatment of HBV:

http://mskweb5.mskcc.org/inside_mskcc/html/95104.cfm

IV. **GlaxoSmithKline Liver Chemistry Follow-up Assessments for Ofatumumab:**

Viral hepatitis serology including:

- Hepatitis A IgM antibody;
- Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);
- Hepatitis C RNA;
- Cytomegalovirus IgM antibody;

- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
- Hepatitis E IgM antibody (if subject resides outside the US or Canada, or has traveled outside US or Canada in past 3 months);

- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥2xULN
- Obtain complete blood count with differential to assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Record alcohol use on the liver event alcohol intake case report form
- *PK is part of the standard follow-up if a liver event occurs. In the event that there is a liver event a blood sample would need to be drawn for PK. This is only in the event that a liver event occurs, not for all subjects.* Blood sample for pharmacokinetic (PK) analysis, obtained within **5 months** of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of investigational product prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.

The following are required for subjects with ALT ≥3xULN and bilirubin ≥2xULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

V. NCCN/GELF Criteria [48]:

NCCN version 1.2011/GELF Criteria for the initiation of therapy:

- **Involvement of ≥3 nodal sites, each with a diameter of ≥3 cm**
- **Any nodal or extranodal mass with a diameter of ≥7 cm**
- **B symptoms, defined as weight loss >10% body weight, fevers >38.6 degrees, night sweats**
- **Splenomegaly associated with cytopenias or symptoms**
- **Pleural effusions or peritoneal ascites**
- **Cytopenias (leukocytes < 1.0 x 10e9/L and/or platelets <100 x 10e9/L)**
- **Leukemic phase (>5 x 10e9/L malignant cells)**

Note: The presence of any of these factors is an indication for chemoimmunotherapy induction.

Reference:

Doxorubicin-containing regimen with or without interferon alfa-2b for advanced follicular lymphomas: final analysis of survival and toxicity in the Groupe d'Etude des Lymphomes Folliculaires 86 Trial.

Solal-Céligny P, Lepage E, Brousse N, Tendler CL, Brice P, Haïoun C, Gabarre J, Pignon B, Tertian G, Bouabdallah R, Rossi JF, Doyen C, Coiffier B.
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VI. Correlative Science: MicroRNA Determinants of Clinical Outcomes in Mantle Cell Lymphoma:

This protocol, through obtaining tissue specimens, will also be used to evaluate the relevance of miRNAs in MCL. Recent studies of miRNA expression in MCL have revealed several dysregulated miRNAs and suggested potential roles for several miRNAs, including miR-16 and miR-29, in MCL pathogenesis and clinical outcomes[19] [20]. The implication of these studies is that miRNAs may mediate the inherent chemoresistance of MCL cells. In addition, these studies did not consider the proliferation status of the MCL samples tested, suggesting that prognostication of MCL clinical outcomes may be improved by taking both miRNA determinants of MCL chemoresponses and proliferation index/gene signatures into account. We hypothesize that miRNAs may regulate MCL patient outcomes by modulating chemoresponsive pathways, and their expression profiles can be utilized to enhance existing prognostic methods. We aim to identify candidate miRNAs in MCL that mediate chemoresistance, to evaluate the role of miRNAs in MCL chemoresistance and biology, and to identify miRNAs that provide enhanced prognostic information in MCL.

Patients with MCL will be enrolled in this clinical trial and all patients will be asked to consent to provide a sample of bone marrow and/or one tube of peripheral blood in order to characterize miRNAs. If a patient has completed a bone marrow biopsy/aspirate as part of staging outside of MSKCC, they will not be asked to repeat this procedure for correlative purposes. Instead these patients will be asked for a peripheral blood specimen (5 cc of blood in a purple top tube). For patients in whom a bone marrow biopsy/aspirate is required at MSKCC for staging purposes, a bone marrow aspirate specimen will be obtained, as well as one sample of peripheral blood for research purposes will be obtained following informed consent.

Handling of Research Specimens:

Once samples of bone marrow aspirate and peripheral blood are obtained, they will be placed in a biohazard specimen storage bag. The consenting physician will page the lymphoma clinic RSA (pg. x6265) who will arrange for the delivery of the specimens from 205 E. 64th St to the laboratory of Dr. Christopher Y. Park in the Human Oncology and Pathogenesis Program at Memorial Sloan-Kettering Cancer Center in the Zuckerman Research Building, 410 East 69th Street Room 502. The delivery will be arranged by the same mechanisms as all HOTB samples that are sent from 205 E 64th St. Kristina Knapp, the HOTB coordinator can be contacted at 646-888-3227. If the RSA is not immediately available, or the specimen is collected after-hours the bone marrow specimen may be refrigerated temporarily) until they can be delivered the following day.

miRNA Analysis

For the purposes of miRNA analysis, the Park lab will first begin identifying candidate miRNAs in MCL that mediate chemoresistance in cell lines. Utilizing near-diploid MCL cell lines harboring the pathognomonic MCL t(11:14) translocation (e.g. REC-1, MAVER-1), we will identify miRNAs potentially regulating chemoresistance. MCL cell lines will be treated with CHOP chemotherapy *in vitro.* After establishing doses of CHOP that induce >95% cell death, miRNAs will be measured using TaqMan based RT-PCR in emerging/residual chemoresistant cells and mock treated control cells, similar to that recently described for non-small cell lung cancer cell lines [27]. miRNAs will be measured at two time points following initiation of therapy: 1) at the nadir of cell survival following CHOP (reflecting early responses to CHOP); and 2) after continued maintenance of resistant cells grown in the presence of CHOP, which would represent changes associated with long-term maintenance therapy.

Subsequently, we will then evaluate the role of miRNAs in MCL chemoresistance and biology. Once candidate miRNA mediators of chemoresistance are identified in cell lines, it will be necessary to characterize the functional role of such miRNAs in multiple aspects of MCL biology. We will test candidate miRNAs identified in AIM 1 for their effects on cellular growth, apoptosis, and chemoresistance using MCL cell lines stably expressing miRNAs or their “antagomirs” after transduction with lentiviral vectors. Cell counts will be taken and apoptosis measured by flow cytometry by staining for annexin V at predetermined time points. Similar measurements will be taken following CHOP as well, both in acutely treated cells as well as chemoresistant clones.

Lastly we will identify miRNAs that provide enhanced prognostic information in MCL. As previously noted, the most robust predictor of clinical outcomes in MCL is the PI. However, even within groups of patients stratified on this basis, individual outcomes are difficult to predict. Thus, it is important to

identify additional molecular markers that can be measured to better prognosticate clinical outcomes. We will initially characterize miRNA expression profiles in MCL samples drawn from formalin fixed, paraffin embedded tissue (FFPE) previously characterized at MSKCC with respect to PI and clinical outcomes [16]. miRNA profiles will be generated using our TaqMan based human miRNA RT-PCR platform, which can generate robust miRNA profiles *from as few as 500 cells.* These results will allow us to generate a predictive algorithm for MCL outcomes (e.g. OS, EFS). Following the identification of miRNAs that further stratify MCL patients after taking PI into account, we will evaluate a validation set of MCL cases collected prospectively from patients enrolled on this clinical trial. miRNA expression profiles will be determined in at least 30 MCL samples using our TaqMan RT-PCR method, and the prognostic utility of the miRNAs evaluated will be assessed by correlation with the PI as measured by Ki-67.

SOX11 analysis:

Immunohistochemical staining for SOX11 would be performed at MSKCC by the Department of Pathology, Dr Julie-Teruya Feldstein. Patients would be requested to donate 2 unstained slides from the subset of diagnostic slides made available to MSKCC for confirmation of diagnosis. For biopsies performed at MSKCC, we would request 2 unstained slides from the tissue block for SOX11 staining. SOX11 analysis will be performed following validation/QA of the immunohistochemistry test at MSKCC.