TITLE: Ofatumumab (O) in Combination With Chemotherapy: Hyper-Fractionated Cyclophosphamide, Doxorubicin, Vincristine and Dexamethasone (O-HyperCVAD) Alternating With Ofatumumab High-Dose Cytarabine and Methotrexate (O-MA) for Patients With Newly Diagnosed Mantle Cell Lymphoma

Roswell Park Cancer Institute Study Number:	**I 201611**
Initial Date:	**July 8, 2011**
Amendment #1:	**December 1, 2011**
Amendment #2:	**August 1, 2012**
Amendment #3:	**October 19, 2012**
Amendment #4:	**January 22, 2013**
Amendment #5:	**August 7, 2013**
Amendment #6:	**February 4, 2014**
Amendment #7:	**March 9, 2015**
Amendment #8:	**August 11, 2015**
Amendment#9:	**July 27, 2016**
Amendment #10:	**March 2, 2017**
Amendment #11:	**July 17, 2017**
Amendment #12	**March 19, 2018**
IND Number/Holder:	**Exempt**
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Network Site(s):	**Vanderbilt-Ingram Cancer Center**

NCT#01527149

Funding Organization: **National Comprehensive Cancer Network**

Industry/Other Supporter: **Novartis**

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RPCI Study Contacts

Study personnel outside of RPCI's-CRS Team who will be
housing essential study documents or receiving, analyzing or storing biological samples.
This contact list is to include all internal and external RPCI laboratories and their primary laboratory contacts.

NOTE:
Personnel from any potential network site
are NOT to be included on this contact page.

FOR NETWORK SITES:
Please contact the RPCI Network Monitor for any study-related questions regarding sample handling, processing or shipping.

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SYNOPSIS

Title / Phase	Ofatumumab (O) in Combination With Chemotherapy: Hyper-Fractionated Cyclophosphamide, Doxorubicin, Vincristine and Dexamethasone (O-HyperCVAD) Alternating With Ofatumumab High-Dose Cytarabine and Methotrexate (O-MA) for Patients With Newly Diagnosed Mantle Cell Lymphoma
Roswell Park Cancer Institute Study Number:	I 201611
Roswell Park Cancer Institute Investigator	Francisco J. Hernandez-Ilizaliturri, MD
Funding Organization	National Comprehensive Cancer Network
Study Drug(S)	Ofatumumab
Objectives	**Primary:** • To determine the overall response rate (ORR), and in particular, the complete remission rate (CRR) in previously untreated MCL treated with ofatumumab in combination with aggressive chemo-immunotherapy. **Secondary:** • To determine the High Sensitivity Flow Cytometry (HSFCM) complete remission rate (HSFCM-CRR) in previously untreated MCL treated with ofatumumab in combination with aggressive chemo-immunotherapy +/- high dose chemotherapy and autologous stem cell transplant (HDC-ASCT). • To determine the time-to-progression (TTP), progression-free survival (PFS) and overall survival (OS) of patients with previously untreated MCL treated with ofatumumab and aggressive chemoimmunotherapy +/- HDC-ASCT. • To determine the toxicity profiles of ofatumumab in combination with high dose cytarabine chemoimmunotherapy +/- HDC-ASCT. • To correlate minimal residual disease (MRD) at different time intervals with TTP, PFS, and OS. • To correlate surface CD20 levels, Ki67, and additional cytogenetic abnormalities in pretreatment tumor biopsies with respect to ORR, CRR, TTP, PFS, or OS. • To determine the relationship between proliferation signature and clinical outcome using quantitative real-time reverse-transcriptase polymerase chain reaction (RT-PCR). • To determine changes in surface CD20 levels, Ki67, or gain of additional cytogenetic abnormalities in relapsed/refractory tumor specimens. • To correlate serum C3, C4, and CH50 levels measured at baseline and at the end of first ofatumumab infusion with ORR, CRR, MRR, TTP, PFS and OS. • Evaluate the ability of the induction and consolidation therapy to get 70% of patients to

<table>
<tr><td></td><td>autologous stem cell transplantation.
• Evaluate the tolerability and CD34+ cell yield following therapy with patient and HyperCVAD/HD-MA.
• To compare differences in response rate in patients with MCL treated with ofatumumab + HyperCVAD/HD-MA according to the Cheson and Modified Cheson Criteria.[45,46]</td></tr>
<tr><td>Study Design</td><td>This open-label, single-arm, multi-center Phase II study evaluating efficacy, the safety, and tolerability of ofatumumab antibody in combination alternating doses of HyperCVAD and MA in previously untreated MCL administered at every 3 week intervals for 6 cycles followed by HDC-ASCT in eligible patients.
Patients achieving a high sensitivity flow cytometry complete remission (HSFCM-CR) after 2 cycles can proceed to autologous stem cell transplant after completing 4 cycles.</td></tr>
<tr><td>Target Accrual and Study Duration</td><td>A maximum of 37 patients at 2 sites (RPCI and Vanderbilt-Ingram Cancer Center) will be enrolled. Accrual is expected to take up to 7 years.
It is expected that patients will be receiving treatment on this study for approximately 6 months, after which if eligible, patients will receive an autologous stem cell transplant.</td></tr>
<tr><td>Study Procedures</td><td>All chemotherapy and immunotherapy drug doses are based on a corrected body weight as follows: ideal + 25% of the difference between ideal and actual weight. If the actual weight is less than ideal, use actual weight. For patients whose actual weight is >150% of ideal weight, use 150% of ideal weight as the "actual" weight (i.e., the corrected weight is 112.5% of ideal).

<table>
<tr><th colspan="14">Cycles 1, 3, and 5</th></tr>
<tr><th colspan="14">Allopurinol 600 mg/day PO on Day 0, then 300 mg/day for Days 1 - 10 only for Cycle 1</th></tr>
<tr><th>Day 0</th><th>Day 1</th><th>Day 2</th><th>Day 3</th><th>Day 4</th><th>Day 5</th><th>Day 6</th><th>Day 7</th><th>Day 8</th><th>Day 9-12</th><th>Day 13</th><th>Day 14</th><th>Day 15</th><th>Day 16</th></tr>
<tr><td></td><td>OFA</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
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<tr><td></td><td></td><td></td><td>MES</td><td>MES</td><td>MES</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="5">Growth factor support→</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="5">Levo→</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="5">Fluc→</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="5">Acv→</td></tr>
</table>
OFA: Ofatumumab will be administered every 21 days at a 1000 mg dose 48 hours prior to each cycle of chemotherapy. In patients with high risk for tumor lysis syndrome (TLS) (e.g. patients with high tumor burden, malignant pleural effusion, ascites, or patients in leukemic phase), the first dose of ofatumumab may be given for a “split dose”: (300 mg day 1 and 700 mg Day 2) at discretion of the investigator.
CTX: Cyclophosphamide 300 mg/m^2 IV over 2 hours every 12 hours for 6 doses on Days 3 – 5.
DOX: Doxorubicin 16.6 mg/m^2 daily for 3 days administered as a continuous intravenous infusion (CIVI) on Days 6-8
VCR: Vincristine 1.4 mg/m^2 (maximum dose 2 mg) IV on Day 6 and Day 13.
DEX: Dexamethasone 40 mg IV or orally on Days 3 - 6 and Days 13 - 16.
MES: Mesna, to be started 1 hour before the start of CTX. Mesna will be started at 600 mg/m^2 per dose IV over 24 hours daily on days 3 - 5 and completed 12 hours after the administration of the last dose of CTX
Levo: Levofloxacin 500 mg/day PO or other IV or oral antibiotic of institutional preference beginning on Day 9 until ANC ≥ 1500/μL.
Fluc: Fluconazole 400 mg/day PO or other IV or oral antifungal of institutional preference beginning on Day 9 until ANC ≥ 1500/μL.
Acv: Acyclovir 400 mg/bid PO beginning on Day 9 until ANC ≥ 1500/μL.
Growth Factor Support: G-CSF (Dose will be rounded according to Section 8.3.8 guidelines) SQ administered within 48 hours after the last dose of chemotherapy until post nadir ANC ≥ 10,000/μL x 1 or ANC ≥ 5000/μL twice or Peg-G-CSF 6 mg sq within 48 hours after the last dose of chemotherapy (See Section 8.3.8).</td></tr>
</table>

Cycles 2, 4, and 6

Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9-12	Day 13	Day 14	Day 15	Day 16
	OFA												
			MTX										
				ARAC	ARAC								
				Dopt*	Dopt*	Dopt*	Dopt**	Dopt*	Dopt*				
				Leuc*	Leuc*	Leuc*							
									Growth factor support→				
								Levo→					
								Fluc→					
								Acv→					

OFA: Ofatumumab will be administered every 21 days at a 1000 mg dose 48 hours prior to each cycle of chemotherapy.

MTX: Methotrexate 1,000 mg/m2 CIVI over 24 hours on Day 3. Alkalinization of the urine is mandatory (See Section 8.4.2). Serum methotrexate levels will be monitored at 24, 48, and 72 hours after the end of the infusion. If the patient meets the institutional standard levels for MTX serum, subsequent MTX serum levels need not be performed.

ARAC: Cytarabine at 3,000 mg/m2 (≤ 60 years) or 1,000 mg/m2 (> 60 years) IV over 2 hours every 12 hours for 4 doses on Days 4 – 5.

Leuc*: Leucovorin (Folinic acid) rescue therapy (50 mg loading dose) will be administered IV x1 dose beginning 12 hours after the infusion of methotrexate is completed, followed by 15mg IV/PO Q 6 hours for 8 doses or continuing until the serum methotrexate level is < 0.1 μM. In the event leucovorin is not available due to national shortage, levoleucovorin may be substituted at 50% of the leucovorin dose. MTX serum levels can be +/- 2 hours from the end of infusion. Folinic acid doses may be adjusted according to methotrexate levels (see Sections 8.4.2 and 8.4.5)

Dopt*: Dexamethasone 0.1% ophthalmic solution (Dopt) or equivalent, two drops in each eye four times daily, will be started on the day of cytarabine and will continued for 7 days to prevent chemical conjunctivitis.

Levo: Levofloxacin 500 mg/day PO or other IV or oral antibiotic of institutional preference beginning on Day 8 until ANC ≥ 1500/μL.

Fluc: Fluconazole 400 mg/day PO or other IV or oral antifungal of institutional preference beginning on Day 8 until ANC ≥ 1500/μL.

Acv: Acyclovir 400 mg/bid PO beginning on Day 8 until ANC ≥ 1500/μL.

Growth Factor support: G-CSF (Dose will be rounded according to Section 8.4.7 guidelines) SQ administered within 48 hours after the last dose of chemotherapy until post nadir ANC ≥ 10,000/μL x 1 or ANC ≥ 5000/μL twice or Peg-G-CSF 6 mg sq administered within 48 hours after the last dose of chemotherapy (See Section 8.4.7)

NOTE: Prophylactic central nervous system (CNS) prophylactic should be considered for MCL patients with blastoid or pleomorphic variants only (See Section 8.5)

Statistical Analysis

Sample Size Justification: The sample size calculation is based on testing the hypotheses concerning the proportion of the population with a response to the treatment:

$$H_0 : p \le 50\%,$$

$$H_a : p > 50\%.$$

This two-stage design requires a potential total of 37 patients in order to achieve approximately 80% power to detect differences of 20 percentage points (50% versus 70%).

Analysis:

Stage 1: If 12 or less of the first 23 evaluable patients achieves a complete response as measured by standard response criteria reported by Cheson et al in 199945, it will be concluded that the therapy is not promising and the study will end. Otherwise, the study will progress to the second stage. Depending on the current complete response rate at the time the last patient in Stage 1 is enrolled, study enrollment may be halted until complete response status is evaluated in all 23 patients.

	Stage 2: This study will accrue 14 additional evaluable patients. If 24 or more of the total of 37 evaluable patients achieve a complete response, it will be concluded that p exceeds 50% and that the therapy is efficacious and worthy of further study; otherwise, it will be concluded that there is no evidence to suggest that the therapy is associated with acceptable efficacy and is not promising. With this design, the probability is 4.8% of falsely concluding that the proportion of objective responders exceeds 50% and 80% is the probability of correctly concluding efficacy when the true proportion of objective responders is 70% or higher.

INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM

Patient Name: _____

Medical Record No.: _____

Title: Ofatumumab in Combination With Chemotherapy: Hyper-Fractionated Cyclophosphamide, Doxorubicin, Vincristine and Dexamethasone (O-HyperCVAD) Alternating With Ofatumumab High-Dose Cytarabine and Methotrexate (O-MA) for Patients With Newly Diagnosed Mantle Cell Lymphoma

			INCLUSION CRITERIA	
Y	**N**	**N/A**	**All answers must be "YES or "N/A" for patient enrollment.**	**DATE**
☐	☐	☐	1. Histologically documented mantle cell lymphoma with co-expression of CD20 and CD5 and lack of CD23 expression by immunophenotyping and at least one of the following confirmatory tests: 1.) Positive immunostaining for cyclin D1; 2.) The presence of t(11;14) on cytogenetic analysis; OR 3) Molecular evidence of bcl-1/IgH rearrangement. • Cases that are CD5-negative and/or CD23-positive will be eligible provided that the histopathology is consistent with mantle cell lymphoma AND positive for cyclin D1, t(11;14), or bcl-1/IgH rearrangement. • A tissue block or unstained slides (10 - 20 slides) will be submitted to the RPCI Pathology Department for central pathology review. • A diagnosis based on peripheral blood or bone marrow is allowed. • If the diagnosis is based only on blood, in addition to the immunophenotype and molecular confirmation above, a peripheral blood smear must be available for central pathology review. • If the diagnosis is based on a bone marrow, the bone marrow core biopsy or aspirate clot tissue block will be submitted to the RPCI Pathology Department; if the tissue block is not available please submit the diagnostic smears for review.	
☐	☐	☐	2. Extent of Disease • Stage I - IV. Patients with nodular histology mantle cell lymphoma must have Ann Arbor Stage III or IV disease to be eligible. • Patients with mantle zone type histology will not be eligible because of their relatively favorable prognosis. • Patients with other mantle cell histologies are eligible regardless of stage. • Measurable or assessable disease is required. Measurable tumor size (at least one node measuring 2.25 cm^2 in bidimensional measurement). • No active CNS disease defined as symptomatic meningeal lymphoma or known CNS parenchymal lymphoma. A lumbar puncture demonstrating mantle cell lymphoma at the time of registration to this study is not an exclusion for study enrollment.	
☐	☐	☐	3. Age $\geq$ 18 years and $\leq$ 70 years.	
☐	☐	☐	4. Prior Treatment • Patients must be previously untreated. • No prior radiation therapy for mantle cell lymphoma. • $\geq$ 2 weeks since major surgery.	
☐	☐	☐	5. No known hypersensitivity to murine products.	

			INCLUSION CRITERIA	
Y	**N**	**N/A**	**All answers must be "YES or "N/A" for patient enrollment.**	**DATE**
☐	☐	☐	6. No medical condition requiring chronic use of high dose systemic corticosteroids (i.e., doses of prednisone higher than 10 mg/day or equivalent).	
☐	☐	☐	7. No HIV infection. Patients with a history of intravenous drug abuse or any behavior associated with an increased risk of HIV infection should be tested for exposure to the HIV virus. Patients who test positive or who are known to be infected are not eligible. An HIV test is not required for entry on this protocol, but is required if the patient is perceived to be at risk.	
☐	☐	☐	8. Non-pregnant and non-nursing. Treatment under this protocol would expose an unborn child to significant risks. Women and men of reproductive potential should agree to use an effective means of birth control. Refer to Appendix G for definition of women of childbearing potential.	
☐	☐	☐	9. Patients who test positive for Hepatitis C Ab are eligible provided all of the following criteria are met: 1) total bilirubin ≤ 2 x upper limit of normal; 2) AND AST ≤ 3 x upper limit of normal; AND 3) liver biopsy (pathology) demonstrates ≤ Grade 2 fibrosis and no cirrhosis.	

☐	☐	☐	10. Specific guidelines will be followed regarding inclusion of MCL based on Hepatitis B serological testing as follow:
			• HBsAg negative, HBcAb negative, HBsAb positive MCL patients are eligible.
			  ○ Positive serology for Hepatitis B (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBcAb positive, a HB DNA test will be performed and if positive the subject will be excluded.
			• Patients who test positive for HBsAg are ineligible (regardless of other Hepatitis B serologies).
			• For MCL patients with HBsAg negative, but HBcAb positive (regardless of HBsAb status) should have a HBV DNA testing done and protocol eligibility determined as follows:
			  ○ If HBV DNA is positive the patient is excluded.
			  ○ If HBV DNA is negative, patient may be included but must undergo at least every 2 months HBV DNA PCR testing from the start of treatment throughout the duration the study.
			  ○ Monitoring during the study is required at least every 2 months and during follow-up at a minimum of every 2 - 3 months up to 6 months after the last dose.
			  ○ Prophylactic antiviral therapy with lamivudine (3TC) or investigator's preferred antiviral regimen throughout protocol therapy and for 6 – 12 months thereafter may be initiated at the discretion of the investigator.
			  ○ If the patients' HBV DNA becomes positive during the study, the investigator should manage the clinical situation as per the standard of care of participating institution. The investigator should weigh the r risks and benefits of continuing ofatumumab or discontinuing ofatumumab before appropriate treatment decisions are made for that individual patient.	

			INCLUSION CRITERIA	
Y	**N**	**N/A**	**All answers must be "YES or "N/A" for patient enrollment.**	**DATE**
☐	☐	☐	11. Patients must not have a history of cardiac disease, defined as New York Heart Association Class II or greater or clinical evidence of congestive heart failure.	
☐	☐	☐	12. No known hypersensitivity to ofatumumab, humanized antibodies or chemotherapy agents throughout the protocol.	
☐	☐	☐	13. Initial Required Laboratory/Test Values: • LVEF by MUGA or ECHO ≥ 45%. • Neutrophils > 1000/µL platelets ≥ 75,000/µL (Unless significant bone marrow involvement with MCL). • Creatinine ≤ 2.0 mg/dL. • Total Bilirubin ≤ 2.0 mg/dL (Unless MCL related or attributable to Gilbert's disease). If Total bilirubin is > 5 mg/dL. See Table 8. • Urine or serum β-HCG or serum HCG = Negative (If female patient of childbearing potential).	
☐	☐	☐	14. Patient or legal representative must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.	
☐	☐	☐	15. Consult with a physician experienced in care and management of subjects with hepatitis B to manage/treat subjects who are anti-HBc positive.	

Investigator Signature: _____ Date: _____

INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM

Patient Name: _____

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			EXCLUSION CRITERIA	
Y	**N**	**N/A**	**All answers must be "NO" or "N/A" for patient enrollment**	**DATE**
☐	☐	☐	1. Prior history of HIV-positivity (Routine HIV testing is not required pretreatment).	
☐	☐	☐	2. Positive serology for Hepatitis B (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBcAb positive (regardless of HBsAb status), a Hepatitis B DNA test will be performed and if positive the patient will be excluded.	
☐	☐	☐	3. Serious non-malignant disease (e.g., active uncontrolled bacterial, viral, or fungal infections) or other medical conditions (including psychiatric) which, in the opinion of the Principal Investigator would compromise other protocol objectives.	
☐	☐	☐	4. Presence of symptomatic CNS lymphoma.	
☐	☐	☐	5. Pregnant or lactating females.	
☐	☐	☐	6. Prior history of radiation or chemotherapy for MCL.	
☐	☐	☐	7. History of allergic reactions attributed to compounds of similar chemical or biologic composition to ofatumumab or other agents used in study.	
☐	☐	☐	8. Patients with a "currently active" second malignancy, other than non-melanoma skin cancer or in situ carcinoma of the cervix or breast. Patients are not considered to have a "currently active" malignancy if they have completed anti-cancer therapy, are considered by their physician to be at less than 30% risk of relapse and at least 2 – 5 years have lapsed.	
☐	☐	☐	9. Major surgery, other than diagnostic surgery, within 2 weeks.	
☐	☐	☐	10. Patients with NHL other than MCL.	
☐	☐	☐	11. Patients must not have a history of cardiac disease, defined as New York Heart Association Class II or greater or clinical evidence of congestive heart failure. All patients must have a MUGA scan or 2-D echocardiogram indicating an ejection fraction of ≥ 45% within 42 days prior to registration. The method used at baseline must be used for later monitoring.	

			EXCLUSION CRITERIA	
Y	**N**	**N/A**	**All answers must be "NO" or "N/A" for patient enrollment**	**DATE**
☐	☐	☐	12. Unwilling or unable to follow protocol requirements.	
☐	☐	☐	13. Any condition which in the Investigator's opinion deems the patient an unsuitable candidate to receive study drug.	
☐	☐	☐	14. Received an investigational agent within 30 days prior to enrollment.	

Study participant meets all entry criteria: ☐ **Yes** ☐ **No**

Investigator Signature: _____ Date: _____

TABLE OF CONTENTS

TABLES

FIGURES

APPENDICES

1 INTRODUCTION

1.1 Biology of Mantle Cell Lymphoma

According to last year's published cancer statistics, approximately 74,030 new cases were diagnosed and 21,530 patients died from lymphoma despite currently available treatment.[1] Lymphomas are a heterogeneous group of malignancies with diverse biology, clinical behavior, and prognosis. Mantle Cell Lymphoma (MCL) were defined as a distinct biological and clinical entity in early 1990 and while MCL represents only 6% of the cases of non-Hodgkin lymphoma (NHL) diagnosed in the United States every year, it continues to be a therapeutic challenge for the practicing oncologist.[2]

Pathologically, MCL is a mature B-cell lymphoma originating from the mantle zone that surrounds the germinal centers in the lymph nodes.[3] Morphologically, MCL are characterized by the monomorphic proliferation of small to medium-sized lymphoid cells with irregular nuclei and concealed nucleoli. Four pathological variants had been recognized: small cell variant, marginal-zone like, blastoid and pleomorphic.[3] The histological diagnosis of MCL can be difficult and often requires the use of immunophenotyping and cytogenetic studies. MCL cell are characterized by the expression of mature B-cell markers. Immunophenotypically, MCL is characterized by expression of CD19, CD20, CD22, CD79a, CD5 and CD43; and the absence of CD10, CD23 and Bcl-6.[4]

At the molecular level, MCL is characterized by the deregulation of Bcl-2 family members (Mcl-1, BIM) altering apoptosis, as well as, cell cycle (cyclin D1) regulated in part by the ubiquitin-proteasome system (UPS). Mcl-1 or cyclin D1 upregulation is the result of the chromosomal translocation t(11:14)(q13:q32), the hallmark cytogenetic abnormality of MCL[5,6]. Deregulation of cyclin D1 is considered the primary molecular event involved in the pathogenesis of MCL progression. Recent studies using comparative genomic hybridization and array-based genomic studies had demonstrated additional chromosomal changes with genomic loses of tumor suppression genes (i.e., ATM, CDKN2A, TP53) or gains of oncogenic genes (i.e., MYC. SYK or BCL2). Such findings lead investigators to postulate a model of multistep genetic alterations which leads to molecular pathogenesis and progression (i.e., clonal evolution) in MCL.[7]

1.2 Clinical Behavior and Management of Mantle Cell Lymphoma

The median age at diagnosis of MCL patients is 63 years with a 2 - 3:1 predominance of males to females. Extranodal disease is common and frequently involves bone marrow and gastrointestinal tract.[8] Overall, MCL is associated with a poor prognosis.[8,9] MCL is typically characterized by an aggressive clinical course and inevitable development of refractory disease despite early intervention that often includes: immunotherapy (e.g., rituximab), multi-agent induction chemotherapy and consolidation with high dose chemotherapy and autologous stem cell transplant (HDC-ASCT) in first remission.[10]

Three therapeutic interventions have improved the clinical outcomes of patients with MCL: 1) the addition of rituximab to standard chemotherapy; 2) the use of HDC-ASCT for

eligible patients; and recently; and 3) the incorporation of high dose cytarabine in the front-line treatment of MCL.[10]

1.2.1 The Use of Rituximab in the Management of Mantle Cell Lymphoma

In contrast to what has been observed in other subtypes of CD20+ B-cell lymphomas, rituximab has a somewhat less impressive activity in MCL. As a single agent, the response rate in both untreated and pretreated MCL patients is approximately 30% and the median duration of response was reported to be only 6 months.[11,12] Lenz *et al*, demonstrated that the addition of rituximab to standard doses of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) prior to HDC-ASCT (< 65 years of age) or interferon maintenance (> 65 year of age) improved the (CRR) (34% vs. 7%), but did not translate into a longer PFS or OS.[13] Other investigators have demonstrated higher response rates by adding rituximab to systemic chemotherapy in previously untreated MCL patients.[14,15] A comprehensive systematic review and meta-analysis indicated that rituximab plus chemotherapy may be superior to chemotherapy alone with respect to OS in MCL (hazard ratio for mortality, 0.60; 95% confidence interval, 0.37 - 0.98)[16]. However, given significant differences between each clinical trial analyzed in the meta-analysis regarding the type of induction chemotherapy, consolidation with HD-ASCT and/or maintenance therapy with biological agents (e.g., interferon); the survival benefit observed by the addition of rituximab might be underestimated.[16] Recently, a retrospective study suggested that the use of rituximab in combination with systemic chemotherapy prior to HDC-ASCT resulted in an improved PFS and OS.[17]

1.2.2 The Role of High Dose Chemotherapy and Autologous Stem Cell Transplant (HDC-ASCT)

In an attempt to increase the clinical outcomes of younger MCL patients responding to first line chemotherapy/chemo-immunotherapy, consolidation with HDC-ASCT had been utilized by several academic Institutions. Higher event free survival (EFS) and OS had been observed in MCL patients treated with HDC-ASCT following induction therapy when compared to historical controls in prospective Phase II studies.[18-20] The potential clinical benefit of HDC-ASCT consolidation following induction therapy in MCL patients was evaluated in a phase III clinical trial. Dreyling et al randomized 122 MCL patients to HDC-ASCT versus interferon maintenance following induction therapy with CHOP chemotherapy.[21] The use of early consolidation with HDC-ASCT resulted in a higher PFS (39 months vs. 17 months) but minimal improvement in OS at 3 years of follow up (83% vs. 77%).[21] Long-term follow-up of patients treated with chemotherapy and with/without rituximab follow by HDC-ASCT failed to show a disease-free plateau, suggesting that all patients will eventually relapse.

The Nordic group reported excellent outcomes in MCL patients treated with rituximab-maxi-CHOP alternating with rituximab high dose cytarabine followed by HDC-ASCT. In this particular study, *ex vivo* purging of the stem cells were performed with rituximab.[21,22] The 6-year OS, EFS, and PFS were 70%, 56%, and 66% respectively, with no patient relapsing after 5 years.[22] Of interest, correlative studies conducted in this particular trial demonstrated a higher number of patients achieving a complete remission by standard pathological and molecular studies (i.e., PCR) prior to HDC-ASCT. This study highlighted the importance of: 1) achieving a

complete remission at the end of induction chemotherapy; 2) clearing stem cells of contamination by malignant B-cells by in vivo or ex vivo "purging"; and 3) incorporating high dose cytarabine in the induction therapy of MCL.[22] Similar findings were observed in 63 patients transplanted in complete remission included in bone marrow transplantation registries.[23]

1.2.3 The Role of High Dose Cytarabine in the Management of HDC-ASCT Eligible MCL Patients

Various chemotherapy regimens had been used in the front-line management of patients with MCL. In general those regimens follow into 3 categories: 1) multi-agent anthracycline-based regimens (i.e., CHOP); 2) purine analog-based regimens (studied only in non-transplant eligible patients); or 3) dose-intense regimens alternating anthracycline- and cytarabine-based regimens. In general, non-dose-intense regimens had clinical outcomes with complete response rates (CRR) ranging from 7% to 48%, PFS/EFS ranging from 7 months – 21 months and 2 years OS ranging from 45% to 85%.[10]

Dose-intense regimens result in higher CRR and longer PFS/OS when compared to historical controls. One of the most highly studied dose-intense regimens is rituximab +/- hyper-fractionated cyclophosphamide, doxorubicin, vincristine and dexamethasone (R-HyperCVAD) alternating with rituximab and high-dose cytarabine and methotrexate (R-MA). Prior to rituximab, Romaguera et al, demonstrated that 4 cycles of HyperCVAD/MA (without rituximab) therapy for in previously untreated (25 points) or relapsed/refractory MCL resulted in an CRR of 38% prior to HDC-ASCT. More importantly, in the subset of previously untreated patients, the EFS following 4 cycles of HyperCVAD/MA and HDC-ASCT consolidation at 3 years was 72%.[18] Subsequently, the same group of investigators evaluated the efficacy and safety of rituximab in combination with HyperCVAD/R-MA in previously untreated MCL patients. Eligible patients received up to 8 cycles of R-HyperCVAD/R-MA. Early responder patients (i.e., those patients achieving a CR after 2 cycles) received a total of 6 cycles. The response rate to such intense regimen was remarkable, with 87% of the patients achieving a CR by standard Cheson criteria after 6 cycles of therapy and 64% of the patients were free of disease at 3-year follow up. On the other hand, hematological toxicity was significant including five deaths due to treatment-related toxicity. In addition, 29% of the patients did not completed the planned therapy, 80% of those patients were scheduled to receive 8 cycles of therapy based on response (This is one of the reasons, we propose to administer only 6 cycles of chemo-immunotherapy in this clinical protocol).[14] An updated analysis after 10 years of follow up (median 8 years), demonstrated that the median OS for all patients had not been reached and the median time to treatment failure (TTF) for all patients was 4.6 years, without a plateau in the curves stressing the need for novel therapeutic strategies.[24]

The initial results from the Nordic group were validated in a randomized Phase III clinical study evaluating the role of high-dose cytarabine in MCL patients. Recently, Dr. Hermine on behalf of the EU-MCL network presented the updated results of a clinical trial that enrolled younger MCL patients. In this particular study, MCL patients randomized to receive a high-dose cytarabine-containing induction and pre-ASCT conditioning chemo-immunotherapy regimen had a higher CRR (60% vs. 41%, P = 0.0003) and longer time to treatment failure (TTF; not reached vs. 49 months) than patients treated with standard R-CHOP for 6 cycles followed by

cyclophosphamide based pre-ASCT conditioning regimen. This data further supports the use of high-dose cytarabine in the treatment of MCL patients.[25]

In general, the addition of high dose cytarabine improves the rate and quality of remissions as well as the duration of response. Notably, this is usually associated with higher toxicity (5% of toxic deaths, 15% severe infections and 30% severe thrombocytopenia).

In summary, the incorporation of rituximab, HDCT-ASCT and/or high dose cytarabine in the management of MCL has prolonged the median overall survival from 3 – 4 years to 5 - 6 years[14,20,24,26,27]. However despite dose intense regimens such as rituximab in combination with hyper fractionated cyclophosphamide, doxorubicin, vincristine and dexamethasone (R-HyperCVAD) alternating with rituximab and high dose cytarabine and methotrexate (R-MA) +/- HDC-ASCT used in the front-line setting, the median time to treatment failure is 4.6 years for all patients and 5.9 years for those younger than 65 years (without a plateau in the curves with the exception of those patients achieving a molecular remission).[14,24]

Relapsed/refractory MCL is usually associated with a significant degree of chemo-resistance, low response rate and/or short duration of response to salvage chemotherapy (including targeted agents). There is a clinical need to incorporate promising agents into the upfront therapy of MCL in an attempt to further improve clinical outcomes.

There is a growing need to further characterize MCL cells at the molecular level in an attempt to: identify biomarkers predictive of response to front-line and salvage therapies; better understand the mechanisms associated with acquired resistance to immunochemotherapy; and identify and develop therapeutic strategies against novel targets and/or pathways.

1.3 Predictors of Clinical Outcome in Mantle Cell Lymphoma: The Importance of Achieving a Complete Remission

Several clinical and biological factors predicting the clinical outcome of MCL patients have been studied and are included in **Section 1.3.1**, **Section 1.3.2**, and **Section 1.3.3**.

1.3.1 Clinical Markers of Response

A variety of important clinical prognostic features have been identified including poor performance status, splenomegaly, anemia and age at diagnosis. The international prognostic index score initially developed for patients with diffuse large B-cell lymphoma (DLBCL) has been used to predict the clinical outcome in MCL patients with conflicting results. A specific MCL prognostic score (Mantle Cell International Prognostic Index = MIPI) has been proposed. This score, based on the study of 455 MCL patients, identified 4 independent prognostic factors of clinical outcome (age, performance status, lactic dehydrogenase levels, and leukocyte count). Based in this score, MCL patients can be stratified into 3 distinct risk groups with an OS of approximately 2 (high risk), 4 (intermediate) and 6 years (low risk).[28]

1.3.2 Biological Poor Prognostic Features

Biological Poor Prognostic Features include histological subtypes (blastoid variants), the presence of p53 mutations, and the proliferation rate as determined by Ki-67 staining (< 30% vs. > 30%).[29-32]

The importance of cell proliferation rate in the clinical outcome of MCL was recently confirmed by Rosenwald et al.[33] In a retrospective analysis, this group of investigators identified, using gene expression profiling (GEP) studies, a "cell proliferation" gene signature as being the most powerful prognostic tool in MCL. Patients in the highest quartile for this gene expression signature had a median survival of 0.83 years while those in the lowest expression quartile had a median survival of 6.7 years.[33]

This study will study the prognostic significance of abnormalities of cell cycle regulatory members at the time of diagnosis in patients with MCL treated with ofatumumab chemoimmunotherapy with/without HDC-ASCT. In addition, if genetic abnormalities in regulators of the cell cycle occur at the time of relapse following aggressive chemo-immunotherapy.

1.3.3 Kinetics of Response to Therapy as a Surrogate Marker of Clinical Outcome in Mantle Cell Lymphoma

Recent observations in clinical trials with dose-intense chemo-immunotherapy have suggested that achievement of a complete remission correlates with improve PFS and OS in MCL. Assessment of complete remission using ultrasensitive techniques had shown promising results in identifying patients who are now expected to sustain long term remission following induction and consolidation therapy for MCL.

Polymerase chain reaction (PCR) using primers directed to the breakpoint regions on 11q13 and 14q32 was evaluated to detect and monitor MRD disease post-treatment in MCL.[34] While detection of MRD by PCR in MCL had been associated with a poor clinical outcome; the high false-negative rate (40% - 60%), cost, and its labor-intensiveness are likely reasons explaining why this assay has not been incorporated into clinical practice.[10]

Immunophenotypically, MCL is characterized by expression of CD19, CD20, CD22, CD79a, CD5 and CD43; and the absence of CD10, CD23 and Bcl-6.[4] Flow cytometry (FC) analysis had been used to detect and monitor MRD in MCL.[35,36] Bottcher et al. developed and validated a four-color FC assay (also known as high sensitivity flow-cytometry = HSFCM) in MCL capable to detect MRD with similar sensitivity and specificity than IGH-PCR.[35] Using this 4-color FC assay, Pott et al. demonstrated that a "molecular" complete remission (mCR) as determined by FC analysis (HSFCM), was an independent predictor of clinical outcomes in MCL patients treated with rituximab-chemotherapy regimens followed by either HDC-ASCT (< 65 years) or rituximab vs. interferon maintenance (> 65 years).[36] Patients that achieved a mCR had a significantly improved duration of remission at 2 years (DR; 87% vs. 61%, P = 0.004). In a multivariate analysis, achievement of a mCR was found to be an independent factor predicting for prolonged DR regardless the type of induction, consolidation or maintenance therapy used.

The overall response (ORR) or complete response (CRR) rates in elderly and younger MCL patients were similar (99% vs. 96% and 32% vs. 31%, respectively).

More importantly, at the end of the induction therapy, mCR was only achieved in 67% and 48% of the elderly and younger patients respectively.[36] This finding suggests that sub-clinical disease persists in 43% to 52% of MCL patients at the end of induction chemo-immunotherapy and may play a significant role in treatment failure observed following HDC-ASCT. The use of new anti-CD20 monoclonal antibodies (mAbs) and/or novel targeted agents may lead to higher "molecular" remissions and higher cure rates in patients with MCL.

In summary, the incorporation of: 1) rituximab, 2) early HDC-ASCS, and 3) high-dose cytarabine in the management of MCL results in improved clinical outcomes (i.e., ORR, CRR, TTF, PFS or OS). But failure to eliminate MRD may be associated with relapses observed in long-term follow up of MCL treated in clinical trials and stresses the scientific need to evaluated promising novel agents (e.g., ofatumumab). These findings are the basis for the design of this clinical protocol.

1.4 Pre-Clinical Development of Ofatumumab in B-Cell Lymphoma

Ofatumumab, a novel monoclonal antibody targeting CD20, is a human IgG antibody that binds to an epitope including the smaller, more membrane proximal loop of the CD20 antigen.[37,38] In addition to binding to a different epitope, ofatumumab appears to bind with a stronger affinity due to a slower off-rate.[37] Pre-clinical studies have shown ofatumumab to have similar antibody-dependent cellular cytotoxicity (ADCC) and improved complement-mediated cytotoxicity (CMC) in comparison to rituximab[37]. Ofatumumab also prolongs B-cell depletion in comparison to rituximab and, slows lymphoma tumor cell growth in murine xenograft models.[39]

Figure 1. Ofatumumab Induced a Significantly Higher Level of Cell Lysis by CMC than Rituximab

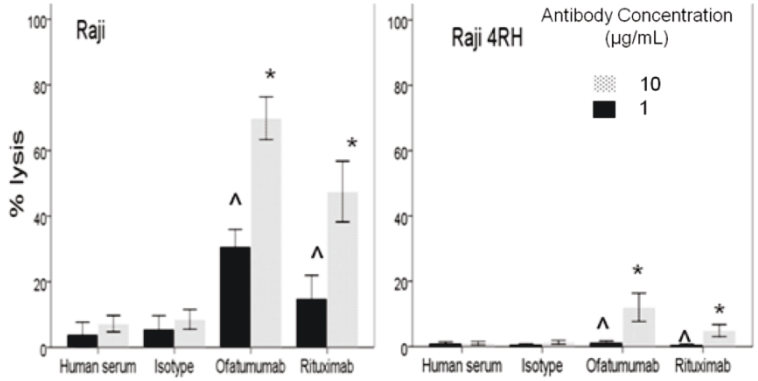


Figure 1. Ofatumumab induced a significantly higher level of cell lysis by CMC than rituximab. NHL tumor cell lines were tested for CMC cell lysis using a 51Cr release assay. In lymphoma cell lines Raji (Rituximab sensitive), and Raji 4RH (Rituximab resistant), ofatumumab was more effective than rituximab at inducing CMC lysis at doses of 10 µg/mL and 1 µg/mL. (^: $P < 0.05$, *: $P < 0.006$).

To better define ofatumumab's activity, pre-clinical studies were conducted in rituximab-sensitive (RSCL) including MCL cell lines, rituximab-resistant (RRCL), ofatumumab-resistant cells (ORCL), primary lymphoma cells, and in a lymphoma xenograft model. Rituximab or ofatumumab resistant cell lines were generated as previously described.[40]

Ofatumumab was more potent than rituximab in elucidating effective complement mediated cytotoxicity (CMC) in RSCL, RRCL, MCL (**Figure 1** and **Figure 2**) and primary tumor cells derived from patients with de novo or relapsed B-cell lymphoma (data not shown).

Figure 2. Ofatumumab Induced a Significantly Higher Level of Cell Lysis by CMC Than Rituximab in Mantle Cell Lymphoma Cell Lines

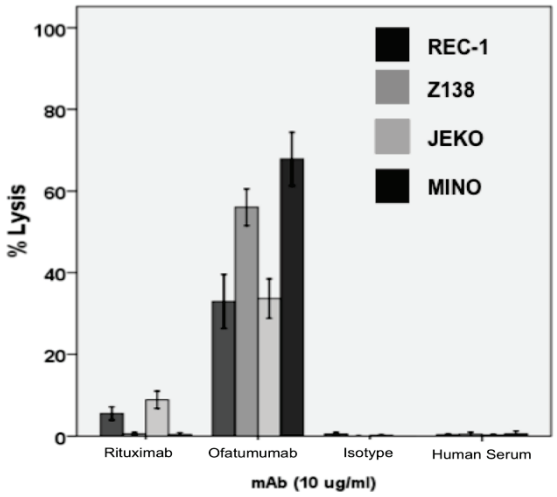


Figure 2. Ofatumumab induced a significantly higher level of cell lysis by CMC than rituximab in mantle cell lymphoma cell lines.

Of interest, the repeated exposure of lymphoma cells to ofatumumab resulted in rituximab but not ofatumumab resistance. While the activity of rituximab diminished with CD20 down-regulation in RRCL passages, ofatumumab activity was preserved even at low CD20 levels (**Figure 3**).

Figure 3. Ofatumumab Anti-Tumor Effects in RSCL and RRCL and Its relationship With CD20 Levels

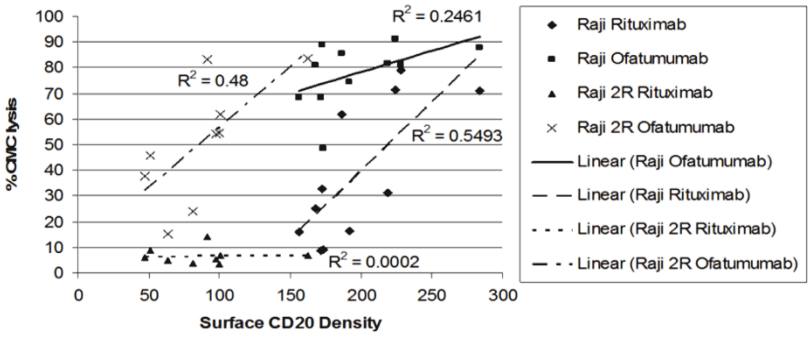


Figure 3. Single cells were isolated from Raji and Raji 2R cell lines. After expanding individual cell clones, surface CD20 density determined by ImageStream Technology and cell lysis by CMC determined by 51Cr release assay were measured.

Using quantitative flow cytometry studies, we found that the CD20 threshold to elucidate mAb-associated CMC in RSCLs and RRCLs was two-fold lower for ofatumumab than rituximab. The

slope of a best-fit line shows a higher rate of decrease for rituximab ($R^2 = 0.5514$) compared to ofatumumab ($R^2 = 0.2525$). In the RRCL Raji 2R, the best-fit line for rituximab is essentially a flat slope ($R^2 = 0.0002$) demonstrating resistance to rituximab-induced CMC lysis in all cell clones at the lowest levels of CD20 density while ofatumumab maintained higher levels of CMC lysis even at the lowest CD20 density with a continued decrease in CMC as CD20 diminished ($R^2 = 0.48$). Together, this data suggests that in both RSCLs and RRCLs ofatumumab is capable of killing lymphoma cells at lower CD20 levels more effectively than rituximab.

Finally, ofatumumab was more effective in controlling *in vivo* lymphoma growth than rituximab in a SCID mouse xenograft model. The median survival for animals treated with ofatumumab (10mg/kg/dose) [77 days] was longer than those treated with rituximab [50 days] (**Figure 4**).

Figure 4. Ofatumumab Was More Effective in Controlling Lymphoma Growth Than Rituximab in Lymphoma Xenographs

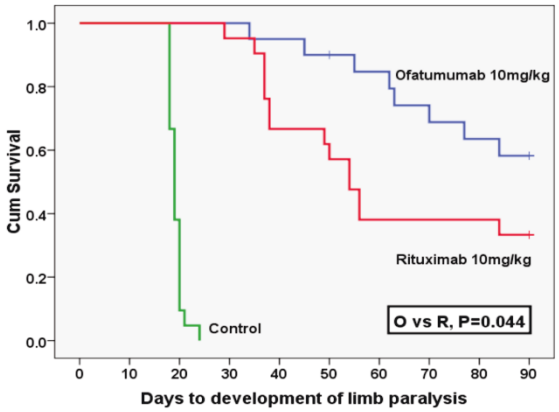


Figure 4. Ofatumumab was more effective in controlling lymphoma growth than rituximab in lymphoma xenographs. SCID mice were inoculated via tail vein with 1 x 10^6 Raji cells on Day 0 and treated via tail vein injection with either ofatumumab or rituximab at a dose of 10 mg/kg on Days 3, 7, 10 and 14. Mice were observed for up to 90 days.

Similar findings were observed when ofatumumab was compared to rituximab at 1 mg/kg/dose (data not shown).

Our data suggest that ofatumumab is more potent than rituximab in rituximab-sensitive (including MCL cell lines) or rituximab-resistant models and is less likely to induce biologic resistance to mAbs targeting CD20.

1.5 Clinical Experience with Ofatumumab in B-Cell Malignancies

Ofatumumab had been evaluated in several clinical trials enrolling CD20+ B-cell lymphoproliferative disorders. In a Phase I/II dose escalation study in CLL, ofatumumab demonstrated a relatively high objective response rate of up to 50% in a heavily pretreated population and was well tolerated.[41] Similar response rates were noted in a Phase II trial in CLL patients when combined with fludarabine and cyclophosphamide.[42] Results of a Phase III trial in

CLL patients refractory to fludarabine and alemtuzumab were promising at an interim analysis, and the FDA approved ofatumumab for use in this population based on these results [43]. In NHL, early phase clinical trials are currently underway. A Phase I/II trial of ofatumumab in FL patients showed an ORR of 43% and evidence of a dose response relationship with the highest dose group achieving an ORR up to 60%.[39] However, a Phase II trial of ofatumumab in a heavily pre-treated rituximab-refractory follicular lymphoma patient population was associated with limited anti-tumor activity.[44] Additional Phase II trials of ofatumumab in combination with CHOP and other agents in various histologies of B-cell NHL and CLL have been completed or are ongoing.

2 RATIONALE

Up to date clinical data suggests that the clinical outcome of MCL continues to be poor despite aggressive therapeutic intervention. TTF, PFS and OS curves do not demonstrate plateaus with currently available treatment (including rituximab and HDC-ASCT). Residual disease at the time of stem cell collection is an important cause for treatment failure. On the other hand, achievement of complete remission, and in particular, complete remission by high sensitivity flow cytometric analysis has been associated with sustained remissions beyond 5 years in a prospective clinical trial. This suggests that achievement of complete remission by HS-FCM may be a surrogate marker for long term survival. Rituximab-based therapy results in a HS-FCM CRR of 48%, therefore, stressing the need to test novel and more potent monoclonal antibodies targeting CD20 (i.e., ofatumumab).

In pre-clinical studies we have demonstrated that ofatumumab was more potent than rituximab in eliciting complement-mediated cytotoxicity (CMC) at the doses tested in RSCLs, RRCLs and MCL cell lines. In addition, we have shown that ofatumumab was more active than rituximab in killing primary tumor cells derived from patients with B-cell lymphoma and was more effective in controlling in vivo lymphoma growth in a murine xenograft model. This clinical trial will test if ofatumumab when combined with the most potent chemotherapy regimen available for MCL (i.e., HyperCVAD/alternating with HD-MA) leads to higher CRR, HS-FCM CRR and better clinical outcome post-HDC-ASCT in MCL patients. Ofatumumab will be used at the standard dose/schedule used in prior clinical trials as single agent or in combination with systemic chemotherapy in various subtypes of hematological malignancies.

3 OBJECTIVES

3.1 Primary Objective

- To determine the overall response rate (ORR), and in particular, the complete remission rate (CRR) in previously untreated MCL treated with ofatumumab in combination with aggressive chemo-immunotherapy.

3.2 Secondary Objectives

- To determine the High Sensitivity Flow Cytometry (HSFCM) complete remission rate (HSFCM-CRR) in previously untreated MCL treated with ofatumumab in combination

with aggressive chemo-immunotherapy +/- high dose chemotherapy and autologous stem cell transplant (HDC-ASCT).

- To determine the time-to-progression (TTP), progression-free survival (PFS) and overall survival (OS) of patients with previously untreated MCL treated with ofatumumab and aggressive chemoimmunotherapy +/- HDC-ASCT.
- To determine the toxicity profiles of ofatumumab in combination with high dose cytarabine chemoimmunotherapy +/- HDC-ASCT.
- To correlate minimal residual disease (MRD) at different time intervals with TTP, PFS, and OS.
- To correlate surface CD20 levels, Ki67, and additional cytogenetic abnormalities in pre-treatment tumor biopsies with respect to ORR, CRR, TTP, PFS, or OS.
- To determine the relationship between proliferation signature and clinical outcome using quantitative real-time reverse-transcriptase polymerase chain reaction (RT-PCR).
- To determine changes in surface CD20 levels, Ki67, or gain of additional cytogenetic abnormalities in relapsed/refractory tumor specimens.
- To correlate serum C3, C4, and CH50 levels measured at baseline and at the end of first ofatumumab infusion with ORR, CRR, MRR, TTP, PFS and OS.
- Evaluate the ability of the induction and consolidation therapy to get 70% of patients to autologous stem cell transplantation.
- Evaluate the tolerability and CD34+ cell yield following therapy with patient and HyperCVAD/HD-MA.
- To compare differences in response rate in patients with MCL treated with ofatumumab + HyperCVAD/HD-MA according to Cheson and Modified Cheson Criteria.[45,46]

4 METHODOLOGY

4.1 Study Design

This open-label, single-arm, multi-center Phase II study evaluating efficacy, the safety, and tolerability of ofatumumab antibody in combination alternating doses of HyperCVAD and MA in previously untreated MCL administered at every 3 week intervals for 6 cycles followed by HDC-ASCT in eligible patients.

Patients achieving a high sensitivity flow cytometry complete remission (HSFCM-CR) after 2 cycles can proceed to autologous stem cell transplant after completing 4 cycles.

All participants will sign an informed consent prior to study related tests. All patients will meet the inclusion and exclusion criteria summarized in **Section 5.1** and **Section 5.2** prior to treatment.

4.2 Target Accrual and Study Duration

A maximum of 37 patients at 2 sites (RPCI and Vanderbilt-Ingram Cancer Center) will be enrolled. Accrual is expected to take up to 7 years.

It is expected that patients will be receiving treatment on this study for approximately 6 months, after which if eligible, patients will receive an autologous stem cell transplant.

5 PATIENT SELECTION

This clinical trial can fulfill its objectives only if patients appropriate for the trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. To maximize eligibility for study entry patient safety, patients will be treated on this protocol only at NCCN-members/approved autologous transplant centers. Physicians should consider the risks and benefits of any therapy and, therefore, only enroll patients for which the agents administered are appropriate. Although they will not be considered as formal eligibility criteria, as part of this decision-making process, physicians should recognize that the following might increase the risk to the patient entering this protocol:

- Other serious illnesses which would limit survival to less than 2 years, or psychiatric condition which would prevent compliance with treatment or informed consent.
- Uncontrolled or severe cardiovascular disease, pulmonary disease, or infection, which in the opinion of the treating physician would make this protocol unreasonably hazardous for the patient.
- Known peripheral or autonomic neuropathy which, in the opinion of the treating physician, would make the administration of vincristine unreasonably hazardous for the patient.

All patients must be screened for hepatitis B infection before starting treatment Those patients who test negative for hepatitis B surface antigen, but HepBc antibody positive + HBV DNA negative should be closely monitored for evidence of active HBV infection and hepatitis during and for several months after ofatumumab treatment, and should be managed as clinically indicated (see **Section 5.1**: bullet 5.1.10.3, and **Error! Reference source not found.**).

5.1 Inclusion Criteria

To be included in this study, patients must meet the following criteria:

5.1.1 Histologically documented mantle cell lymphoma with co-expression of CD20 and CD5 and lack of CD23 expression by immunophenotyping and at least one of the following confirmatory tests: 1.) Positive immunostaining for cyclin D1; 2.) The presence of t(11;14) on cytogenetic analysis; OR 3.) Molecular evidence of bcl-1/IgH rearrangement.

5.1.1.1 Cases that are CD5-negative and/or CD23-positive will be eligible provided that the histopathology is consistent with mantle cell lymphoma AND positive for cyclin D1, t(11;14), or bcl-1/IgH rearrangement.

5.1.1.2 A tissue block or unstained slides (10 – 20 slides) will be submitted to the RPCI Pathology Department for central pathology review.

5.1.1.3 A diagnosis based on peripheral blood or bone marrow is allowed. If the diagnosis is based only on blood, in addition to the immunophenotype and molecular confirmation above, a peripheral blood smear must be available for central pathology review. If the diagnosis is based on a bone marrow, the bone marrow core biopsy or aspirate clot tissue block will be submitted to the RPCI Pathology Department; if the tissue block is not available please submit the diagnostic smears for review.

5.1.2 Extent of Disease:

5.1.2.1 Stage I - IV. Patients with nodular histology mantle cell lymphoma must have Ann Arbor Stage III or IV disease to be eligible.

5.1.2.2 Patients with mantle zone type histology will not be eligible because of their relatively favorable prognosis.

5.1.2.3 Patients with other mantle cell histologies are eligible regardless of stage.

5.1.2.4 Measurable or assessable disease is required. Measurable tumor size (at least one node measuring 2.25 cm^2 in bidimensional measurement).

5.1.2.5 No active CNS disease defined as symptomatic meningeal lymphoma or known CNS parenchymal lymphoma. A lumbar puncture demonstrating mantle cell lymphoma at the time of registration to this study is not an exclusion for study enrollment.

5.1.3 Age ≥ 18 years and ≤70 years.

5.1.4 Prior Treatment:

5.1.4.1 Patients must be previously **untreated**.

5.1.4.2 No prior radiation therapy for mantle cell lymphoma.

5.1.4.3. ≥ 2 weeks since major surgery.

5.1.5 No known hypersensitivity to murine products.

5.1.6 No medical condition requiring chronic use of high dose systemic corticosteroids (i.e., doses of prednisone higher than 10 mg/day or equivalent).

5.1.7 No HIV infection. Patients with a history of intravenous drug abuse or any behavior associated with an increased risk of HIV infection should be tested for exposure to the HIV virus. Patients who test positive or who are known to be infected are not eligible. An HIV test is not required for entry on this protocol, but is required if the patient is perceived to be at risk.

5.1.8 Non-pregnant and non-nursing. Treatment under this protocol would expose an unborn child to significant risks. Women and men of reproductive potential should

agree to use an effective means of birth control. Refer to Appendix G for definition of women of childbearing potential.

5.1.9 Patients who test positive for Hepatitis C Ab are eligible provided all of the following criteria are met: 1.) total bilirubin ≤ 2 x upper limit of normal; 2.) AND AST ≤ 3 x upper limit of normal; AND 3.) liver biopsy (pathology) demonstrates ≤ Grade 2 fibrosis and no cirrhosis.

5.1.10 Specific guidelines will be followed regarding inclusion of MCL based on Hepatitis B serological testing as follow:

5.1.10.1 HBsAg negative, HBcAb negative, HBsAb positive MCL patients are eligible.

5.1.10.2 Patients who test positive for HBsAg are ineligible (regardless of other Hepatitis B serologies).

5.1.10.3 For MCL patients with HBsAg negative, but HBcAb positive (regardless of HBsAb status) should have a HBV DNA testing **done and protocol eligibility determined as follows**:

- If HBV DNA is positive the subject is excluded.
- If HBV DNA is negative, patient may be included but must undergo at least every 2 months HBV DNA PCR testing from the start of treatment throughout the duration the study.
- Monitoring during the study is required at least every 2 months and during follow-up at a minimum of every 2 - 3 months up to 6 months after the last dose.
- Prophylactic antiviral therapy with lamivudine (3TC) or investigator's preferred antiviral regimen throughout protocol therapy and for 6 - 12 months thereafter may be initiated at the discretion of the investigator.
- If the patients' HBV DNA becomes positive during the study, the investigator should manage the clinical situation as per the standard of care of participating institution. The investigator should weigh the risks and benefits of continuing ofatumumab or discontinuing ofatumumab before appropriate treatment decisions are made for that individual patient.

5.1.11 Patients must not have a history of cardiac disease, defined as New York Heart Association Class II or greater or clinical evidence of congestive heart failure.

5.1.12 No known hypersensitivity to ofatumumab, humanized antibodies or chemotherapy agents throughout the protocol.

5.1.13 Initial Required Laboratory/Test Values:

5.1.13.1 LVEF by MUGA or ECHO ≥ 45%.

5.1.13.2 Neutrophils > 1000/μL platelets ≥ 75,000/μL (Unless significant bone marrow involvement with MCL).

5.1.13.3 Creatinine ≤ 2.0 mg/dL.

5.1.13.4 Total bilirubin ≤ 2.0 mg/dL (Unless MCL related or attributable to Gilbert's disease). If Total bilirubin is > 5 mg/dL see **Table 8**.

5.1.13.5 Urine or serum β-HCG or serum HCG = Negative (If female patient of childbearing potential).

5.1.14 Patient or legal representative must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.

5.1.15 Consult with a physician experienced in care and management of subjects with hepatitis B to manage / treat subjects who are anti-HBc positive.

5.2 Exclusion Criteria

Patients will be excluded from this study for the following:

5.2.1 Prior history of HIV-positivity (Routine HIV testing is not required pre-treatment).

5.2.2 Positive serology for Hepatitis B (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBcAb positive (regardless of HBsAb status), a Hepatitis B DNA test will be performed and if positive the patient will be excluded.

5.2.3 Serious non-malignant disease (e.g., active uncontrolled bacterial, viral, or fungal infections) or other medical conditions (including psychiatric) which, in the opinion of the Principal Investigator would compromise other protocol objectives.

5.2.4 Presence of symptomatic CNS lymphoma.

5.2.5 Pregnant or lactating females.

5.2.6 Prior history of radiation or chemotherapy for MCL.

5.2.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to ofatumumab or other agents used in study.

5.2.8 Patients with a "currently active" second malignancy, other than non-melanoma skin cancer or in situ carcinoma of the cervix or breast. Patients are not considered to have a "currently active" malignancy if they have completed anti-cancer therapy, are considered by their physician to be at less than 30% risk of relapse and at least 2 - 5 years have lapsed.

5.2.9 Major surgery, other than diagnostic surgery, within 2 weeks.

5.2.10 Patients with NHL other than MCL

5.2.11 Patients must not have a history of cardiac disease, defined as New York Heart Association Class II or greater or clinical evidence of congestive heart failure. All

patients must have a MUGA scan or 2-D echocardiogram indicating an ejection fraction of ≥ 45% within 42 days prior to registration. The method used at baseline must be used for later monitoring.

5.2.12 Unwilling or unable to follow protocol requirements

5.2.13 Any condition which in the Investigator's opinion deems the patient an unsuitable candidate to receive study drug.

5.2.14 Received an investigational agent within 30 days prior to enrollment

5.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this study.

For Network Sites refer to **Error! Reference source not found.** for site specific instructions.

6 INVESTIGATIONAL PRODUCT

6.1 Ofatumumab

6.1.1 Availability

Novartis will supply ofatumumab to the investigator as content-labeled 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.

The investigational medical product, ofatumumab, is a liquid concentrate for solution for infusion presented in glass vials. Ofatumumab will be infused intravenously.

Ofatumumab open-labeled product will be for intravenous infusion. The site is responsible for labeling individual vials for investigational use.

All items required for administration of study medication (e.g., infusion bags, filters, etc.) are to be provided by the site.

6.1.2 Storage and Stability

Ofatumumab vials must be stored at 2°C - 8°C. Protect from light and do not freeze. No special packaging components, other than the outer white cardboard carton in which the vials are placed, will be used to afford light protection.

6.1.3 Formulation / Composition of Ofatumumab Injection 20 mg/mL

The quantitative composition of acetate formulation 20 mg/mL: this is available in 2 fill volumes, 5 mL/vial (100 mg/vial) and 50 mL/vial (1000 mg/vial).

Table 1. Formulation / Composition of Ofatumumab Injection 20 mg/mL

Ingredient	Quantity/mL
Ofatumumab	20.0 mg
Sodium Acetate, Trihydrate	6.80 mg
Edetate Disodium, Dihydrate (EDTA)	0.019 mg
Polysorbate 80	0.20 mg
L-Arginine	10.0 mg
Sodium Chloride	2.98 mg
Hydrochloric Acid	to give pH 5.5
Water for Injection	*q.s.* to 1.0 mL

6.1.4 Drug Shipment

Ofatumumab will be provided by NOVARTIS and shipped to the participating sites.

The date of receipt and the amount of drug received will be documented. Drug shipment records will be retained by the investigational pharmacist or designee.

6.1.5 Preparation

Ofatumumab will be prepared as 1000 mL dilution of ofatumumab in sterile, pyrogen-free 0.9% NaCl to yield a 0.3 mg/mL, 1 mg/mL, or 2 mg/mL ofatumumab concentration for infusions of 300 mg, 1000 mg, or 2000 mg, respectively.

Once diluted into saline, the product is stable for up to 24 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 (Refer to **Table 2**).

Used vials will be disposed of per Institute policy. Unused vials will be disposed of at the end of the study as directed by the study sponsor.

Table 2. 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).

6.1.6 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 48 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 NOVARTIS.
- Needles and syringes (50 mL sterile syringe), not supplied by NOVARTIS.
- Intravenous (IV) cannula not required if patient has central venous access. Not supplied by NOVARTIS.
- Infusion pump and infusion tubing set, not supplied by NOVARTIS.
- In-line low protein binding, polyether sulfone filter 0.2 μm (Note that a spare filter is available in case the filter needs to be changed), not supplied by NOVARTIS. Note that the commercial filters are sterilizing-grade (0.22 μm) hydrophilic Durapore by Millipore.

6.1.7 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 3** or **Table 4** below.
- Draw the required amount of ofatumumab according to **Table 3** (100 mg vials) or **Table 4** (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

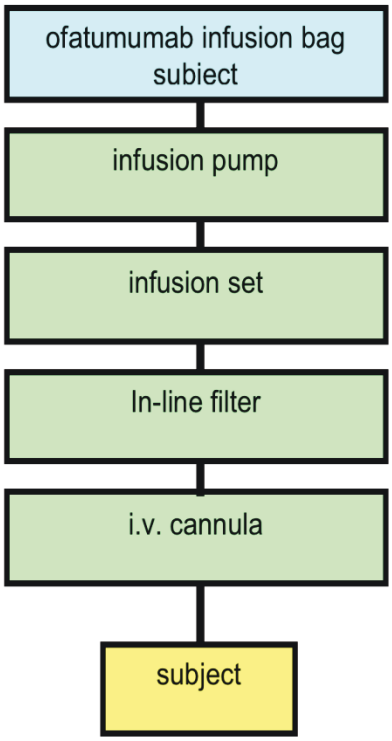
Dose of Ofatumumab	Infusion Bag Size	Volume of NaCl to Be Removed From Infusion Bag	Volume Ofatumumab (Number of Ofatumumab Vials)
300 mg	1000 mL	15 mL	15 mL (3 vials, 5 mL/vial)
700 mg	1000 mL	35 mL	35 mL (7 vials, 5 mL/vial)
1000 mg	1000 mL	50 mL	50 mL (10 vials, 5 mL/vial)

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)

6.1.8 Ofatumumab Infusion Set-Up

Figure 5. Ofatumumab Infusion Set-Up Schema



- Ofatumumab must be administered by IV infusion through an in-line filter and through a well-functioning IV catheter (IV cannula) into a vein in the arm (or other venous access) by an infusion pump.
- 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.
- NOTE: 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 pre-dose blood samples.

- Check patient 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 patient within 48 hours from time of preparation.
- Attach the 1000 mL infusion bag to the infusion set (if not done at the pharmacy).
- Attach the in-line filter to the infusion set. *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 IV cannula according to routine practice at site
- Set the pump at the initial infusion rate 12 mL/hr for the first infusion and 25 mL/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).

Table 5. Infusion Rate at First Ofatumumab Infusion (300 mg or 1000 mg)

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

Table 6. Infusion Rate at Subsequent Ofatumumab Infusion (700 mg or 1000 mg)

No ofatumumab dose modifications are permitted.

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

6.1.9 Toxicity

The most common or serious adverse events associated with ofatumumab include:

- **Infusion Reactions:** Infusion reactions occurred in 44% of patients on the day of the first infusion (300 mg), 29% on the day of the second infusion (2,000 mg), and less frequently during subsequent infusions. 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.
- **Tumor Lysis Syndrome:** Tumor lysis syndrome resulting in renal failure has been described, and occasional fatalities noted. Tumor lysis syndrome is more likely in patients with high numbers of circulating malignant cells. In patients with circulating mantle cells ≥ 10,000/μL, the first ofatumumab infusion should be reduced or omitted.
- **Cytopenias: Neutropenia:** Of 108 patients with normal neutrophil counts at baseline, 45 (42%) developed ≥ Grade 3 neutropenia. Nineteen (18%) developed Grade 4 neutropenia. Some patients experienced new onset Grade 4 neutropenia > 2 weeks in duration.
- **Intestinal Obstruction:** Obstruction of the small intestine can occur in patients receiving ofatumumab. Perform a diagnostic evaluation if obstruction is suspected.
- **Infections:** A total of 108 patients (70%) experienced bacterial, viral, or fungal infections. A total of 45 patients (29%) experienced ≥ Grade 3 infections, of which 19 (12%) were fatal. The proportion of fatal infections in the fludarabine- and alemtuzumab-refractory group was 17%.
- **Fulminant and Fatal Hepatitis B Virus (HBV):** Fulminant and fatal hepatitis B virus (HBV) infection can occur in patients newly exposed to HBV following treatment with ofatumumab. In addition, hepatitis B reactivation, including fulminant hepatitis and death, occurs with other monoclonal antibodies directed against CD20. Screen patients at high risk of HBV infection before initiation of ofatumumab. Closely monitor carriers of hepatitis B for clinical and laboratory signs of active HBV infection during treatment with ofatumumab and for 6 months to 12 months following the last infusion of ofatumumab. Discontinue ofatumumab in patients who develop viral hepatitis or reactivation of viral hepatitis, and institute appropriate treatment. Insufficient data exist regarding the safety of administration of ofatumumab in patients with active hepatitis.
- Exacerbation or reactivation of other viral infections has also been reported with ofatumumab. Recent reports describe JC virus reactivation leading to progressive multifocal leukoencephalopathy (PML) in patients who were receiving ofatumumab. Patients presenting with new neurologic findings (e.g., major changes in vision, unusual eye movements, loss of balance or coordination, confusion) should be evaluated for PML (see **APPENDIX B**).
- A report in the literature described an increase in fatal infection in HIV-related lymphoma patients when rituximab was used in combination with CHOP chemotherapy, as compared to

CHOP alone. Similar effects could be seen with ofatumumab. Patients with HIV infection are not eligible for entry on this research study.

Other rare serious adverse events are:

- Brain damage (possible headache, confusion, seizures, weakness on one side and/or vision loss), also called PRES or posterior reversible encephalopathy syndrome.
- Very severe blistering skin disease; loss of large portions of skin, also called toxic epidermal necrolysis (TENS).
- Another antibody treatment similar to ofatumumab has caused severe skin rashes, including the lining of the mouth, gut and lungs. In some cases this was fatal. Severe skin reactions may also be observed in association with ofatumumab, particularly in the setting of cancer.

6.2 Cyclophosphamide (Cytoxan®, CTX)

6.2.1 Availability

Commercially available as a powder in 100 mg, 200 mg, 500 mg, 1000 mg, and 2000 mg vials.

6.2.2 Storage and Stability

Reconstituted solutions are stable for 6 days in a refrigerator.

6.2.3 Preparation

Reconstitute 100 mg, 200 mg, 500 mg, 1 g and 2 g vials with 5 mL, 10 mL, 25 mL, 50 mL, or 100 mL of NS to give a final concentration of 20 mg/mL. Vigorous shaking, gentle warming may be necessary for non-lyophilized preparation.

6.2.4 Administration

Infuse IV over 2 hours.

6.2.5 Toxicity

Hemorrhagic cystitis, nausea, vomiting, alopecia, bone marrow suppression, stomatitis/enteritis, skin darkening, abnormal nails, SIADH, cardiac necrosis (usually doses > 200 mg/kg ideal body weight).

6.3 Mesna (Mesnex®)

6.3.1 Availability

Mesna is commercially available in 2 mL, 4 mL, and 10 mL ampoules containing 200 mg, 400 mg, and 1000 mg, respectively (100 mg/mL).

6.3.2 Storage and Stability

Mesna is stable at room temperature, but should be administered within 6 hours of opening the vial to assure sterility. Diluted solutions are stable for 24 hours at 25°C.

6.3.3 Preparation

Dilute dose in 100 mL - 1000 mL D5W of NS to a final concentration of 1 mg/mL – 20 mg/mL.

6.3.4 Administration

Give as an IV bolus or as a continuous IV infusion diluted in D5W, D5NS, NR, or LR.

6.3.5 Toxicity

Skin rash or hives, pruritus, nausea, vomiting, dysgeusia, fatigue, headache, hematuria, hypotension, and diarrhea.

6.4 Doxorubicin (Adriamycin®, Rubex®, Adriamycin RDF™, Adriamycin PFS™)

6.4.1 Availability

Commercially available in 10 mg, 20 mg, and 50 mg vials as a red-orange, lyophilized powder which has a storage stability of at least 2 years. Refer to the expiration date on vial.

6.4.2 Storage and Stability

Reconstituted doxorubicin is stable for 7 days if stored at room temperature and under normal room light and 5 days under refrigeration (2°C - 8°C). It should be protected from exposure to sunlight. To prevent bacterial growth, however, the solution should be used within eight hours. Discard any unused solution from the 10 mg, 20 mg, and 50 mg vials. Bacteriostatic diluents with preservatives are NOT recommended as they might possibly worsen the reaction to extravasated drug.

6.4.3 Preparation

The 10 mg, 20 mg and 50 mg vials should be reconstituted with 5 mL, 10 mL, and 25 mL, respectively, of sodium chloride injection, USP (0.9%) to give a final concentration of 2 mg/mL.

6.4.4 Administration

Intravenous infusions should be diluted in NS. If the solution is not to be used within 8 hours, it should be protected from light. Push or bolus administration should be done over 5 – 10 minutes through the side arm of a free flowing IV line. Care must be taken not to infiltrate doxorubicin as it is a tissue vesicant. If extravasation occurs: stop the infusion; aspirate blood/solution from the injection site; disconnect the syringe/IV infusion bag from the catheter; inject 0.5 mL of hydrocortisone phosphate mixed in 2 mL NS into the catheter; remove the catheter/needle; apply ice packs 30 minutes QID to the area for one day. Doxorubicin is not compatible with heparin so it should not be administered through a heparin-lock.

6.4.5 Toxicity

Myelosuppression, soft tissue vesicant, cardiomyopathy (dose-related), darkening of the skin and nail beds, nausea, emesis, stomatitis, alopecia, red urine.

6.5 Vincristine (Oncovin®)

6.5.1 Availability

Vincristine is commercially available in 1 mg, 2 mg, and 5 mg vials (1 mg/mL).

6.5.2 Storage and Stability

Vials should be refrigerated.

6.5.3 Administration

Administer without further dilution by rapid IV bolus in the side arm of a newly started IV line or rapid IV bolus or continuous infusion through a central venous catheter. Care must be taken not to infiltrate vincristine as it is a tissue vesicant. If extravasation occurs: stop the infusion; aspirate blood/solution from the injection site; disconnect the syringe/IV infusion bag from the catheter; inject 1 mL of hyaluronidase (150 units/mL) into the catheter; remove the catheter/needle; apply dry heat 30 minutes QID to the area for 1 day.

6.5.4 Toxicity

Abdominal pain, agitation, alopecia, anorexia, blurred vision, constipation, cranial nerve palsies, depression, diplopia, dysuria, erythema, fatigue, fever, hallucinations, hypertension, ileus, injection site reaction, nausea/vomiting, neuropathic pain, night blindness, ocular irritation, optic atrophy, orthostatic hypotension, peripheral neuropathy, phlebitis, polyuria, ptosis, rash, seizures, SIADH, skin ulcer, thrombocytopenia, tissue necrosis, urinary incontinence, urinary retention. Avoid extravasation as VCR is irritating to tissues.

6.6 Dexamethasone

6.6.1 Availability

Commercially available in 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 4 mg, and 6 mg scored tablets and in an intravenous solution containing 0.5 mg/5 mL or 1 mL of dexamethasone.

6.6.2 Storage and Stability

All forms are stable at room temperature.

6.6.3 Administration

Administer orally with meals to minimize indigestion or GI irritation.

6.6.4 Toxicity

Abdominal pain, acne vulgaris, adrenocortical insufficiency, amenorrhea, angioedema, anorexia, anxiety, appetite stimulation, arthralgia, avascular necrosis, bone fractures, cataracts, constipation, Cushing's syndrome, depression, diabetes mellitus, diaphoresis, diarrhea, dysmenorrhea, ecchymosis, edema, EEG changes, emotional liability, erythema, esophageal ulceration, euphoria, exfoliative dermatitis, exophthalmos, fever, fluid retention, gastritis, headache, heart failure, hirsutism, hypercholesterolemia, hyperglycemia, hypernatremia, hypertension, hypocalcemia, hypokalemia, hypotension, immunosuppression, infection, insomnia, lethargy, menstrual irregularity, mood lability, myalgia, myopathy, nausea/vomiting, ocular hypertension, optic neuritis, osteoporosis, palpitations, pancreatitis, papilledema, peptic ulcer, peripheral neuropathy, petechiae, phlebitis, pseudotumor cerebri, psychosis, restlessness, retinopathy, seizures, sinus tachycardia, skin atrophy, thrombocytopenia, thrombosis, urinary incontinence, urinary urgency, urticaria, vertigo, visual impairment, weakness, weight gain or loss.

6.7 Methotrexate (Folex®; Mexate®)

6.7.1 Availability

Commercially available as powder in single use vials of 20 mg and 1000 mg or as liquid vials of 50 mg and 250 mg.

6.7.2 Storage and Stability

Once diluted, methotrexate is stable for 24 hours at 21°C - 25°C.

6.7.3 Preparation

Reconstitute in D5W or NS to a concentration of 50 mg/mL.

6.7.4 Administration

Intravenous administration is permitted. This protocol will use IV high dose methotrexate over 24 hours.

6.7.5 Toxicity

Bone marrow suppression, stomatitis/enteritis, transaminitis, cutaneous reaction, renal failure, and pneumonitis.

6.8 Leucovorin (Citrovorum factor; Folinic Acid; Wellcovorin)

6.8.1 Availability

Leucovorin is commercially available in 1 mL vials containing 3 mg/mL (Lederle); 5 mL vials containing 5 mg/mL; and in 50 mg, 100 mg, and 350 mg vials of lyophilized powder for reconstitution. Follow the manufacturer's labeling for reconstitution of vials containing powders. Leucovorin is also available in 5 mg, 10 mg, 15 mg, and 25 mg tablets.

6.8.2 Storage and Stability

Store vials between 15°C - 25°C (59°F - 77°F). Protect from light and moisture.

6.8.3 Preparation

Reconstitute the 50 mg or 100 mg vial with 5 mL or 10 mL, respectively, of bacteriostatic or sterile water for injection. The resultant injection solution has a concentration of 10 mg/mL. Reconstitute the 350 mg vial with 17 mL of bacteriostatic or sterile water for injection. The resultant injection solution has a concentration of 20 mg/mL. If reconstituted with sterile water for injection, use immediately. If bacteriostatic water for injection was used, the solution is stable for 7 days. Visually inspect parenteral products for particulate matter and discoloration prior to administration whenever solution and container permit.

6.8.4 Administration

Administration route for leucovorin is IV injection by bolus or short infusion. Oral administration allowed for 10 mg/m^2 doses.

6.8.5 Toxicity

Toxicities include anaphylactoid reactions, nausea, vomiting, seizures, syncope, and urticaria.

6.9 Cytarabine (Cytosar-U®; Ara-C; Cytosine Arabinoside)

6.9.1 Availability

Commercially available as 100 mg, 500 mg, 1,000 mg, and 2,000 mg vials.

6.9.2 Storage and Stability

Diluted solutions are stable for at least 192 hours at room temperature.

6.9.3 Preparation

Dilute with 0.9% benzyl alcohol (5 mL for 100 mg – 1000 mg cytarabine; 20 mL for 2000 mg cytarabine) plus 50-100 mL D5W or NS for 1-2 hour IV infusions or in 500 mL - 1000 mL D5W or NS for longer IV infusions. May be given SQ (10 mg – 30 mg) in 1 mL NS.

6.9.4 Administration

Infuse IV over 2 hours.

6.9.5 Toxicity

Myelosuppression, central nervous system toxicity (doses $\geq$ 500 mg/m^2, especially when creatinine clearance is < 60 cc/min; (see **Section 8.7**), stomatitis, nausea, emesis, non-cardiogenic pulmonary edema, keratoconjunctivitis, cutaneous toxicity, alopecia, hepatic dysfunction.

6.10 Filgrastim (G-CSF; r-met HuG-CSF; Granulocyte Colony Stimulating Factor; Neupogen®)

6.10.1 Availability

Filgrastim is commercially available in 1 mL and 1.6 mL vials at a concentration of 300 mcg/mL. Discard unused portions. Use only 1 dose per vial; do not reenter the vial. Do not save unused drug for later administration. Filgrastim is also available as single-dose, preservative-free, prefilled syringes with 26 gauge, 5/8 inch needles containing 300 mcg (0.5 mL) or 480 mcg (0.8 mL) of filgrastim (600 mcg/mL).

6.10.2 Storage and Stability

Filgrastim should be stored in the refrigerator at 2°C - 8°C (36°F - 46°F). Do not freeze. Avoid shaking. Prior to injection, filgrastim may be allowed to reach room temperature for a maximum of 24 hours. Any vial left at room temperature for greater than 24 hours should be discarded.

6.10.3 Administration

Only SQ administration is permitted. Use only one dose per vial; do not re-enter the vial. Do not save unused drug for later administration. Filgrastim is contraindicated in patients with known hypersensitivity to E. Coli-derived products, filgrastim, or any component of the product. Rounding of doses is appropriate; follow the dose rounding instructions below:

If actual weight is < 60 kg use 300 mcg/dose; if actual weight is 60 kg – 99 kg, use 480 mcg/dose; if actual weight is 100 kg – 130 kg use 600 mcg/dose; if actual weight is > 130 kg use 780 mcg/dose.

6.10.4 Toxicity

The only consistently observed clinical toxicity described with filgrastim is medullary bone pain. Other clinical toxicities that have been described include skin rash, and cutaneous vasculitis. Since commercial introduction of filgrastim, there have been rare reports of allergic-type reactions. Biochemical abnormalities that may occur include increases in alkaline phosphatase, uric acid, and lactate dehydrogenase.

6.11 Pegfilgrastim (Neulasta)

6.11.1 Availability

Pegfilgrastim is manufactured and packaged and distributed by Amgen Inc. Pegfilgrastim is supplied as a preservative-free solution containing 6 mg (0.6 mL) of pegfilgrastim (10 mg/mL) in a single-dose syringe with a 27 gauge, ½ inch needle with an UltraSafe® Needle Guard. Pegfilgrastim is supplied in 0.6 mL prefilled syringes for subcutaneous injection. Each syringe contains 6 mg pegfilgrastim (based on protein weight), in a sterile, clear, colorless, preservative-free solution (pH 4.0) containing acetate (0.35 mg), sorbitol (30.0 mg), polysorbate 20 (0.02 mg), and sodium (0.02 mg) in water for injection, USP.

6.11.2 Storage and Stability

Peg-filgrastim should be stored refrigerated at 2°C to 8°C (36°F to 46°F); syringes should be kept in their carton to protect from light until time of use. Shaking should be avoided. Before injection, pegfilgrastim may be allowed to reach room temperature for a maximum of 48 hours but should be protected from light. Pegfilgrastim left at room temperature for more than 48 hours should be discarded. Freezing should be avoided; however, if accidentally frozen, pegfilgrastim should be allowed to thaw in the refrigerator before administration. If frozen a second time, pegfilgrastim should be discarded. Pegfilgrastim should be visually inspected for discoloration and particulate matter before administration. Pegfilgrastim should not be administered if discoloration or particulates are observed.

6.11.3 Administration

Each patient will receive a fixed dose of 6 mg of pegfilgrastim. The entire contents of the 0.6 mL prefilled syringe should be administered irrespective of the patient's actual weight.

6.11.4 Toxicity

In a placebo-controlled trial, bone pain occurred at a higher incidence in pegfilgrastim-treated patients as compared to placebo-treated patients (pegfilgrastim, n = 467; placebo, n = 461). The incidence of other commonly reported adverse events were similar in the pegfilgrastim and placebo-treated patients, and were consistent with the underlying cancer diagnosis and its treatment with chemotherapy. Those adverse events occurred at rates between 48% and 10% in the pegfilgrastim treated patients and included: alopecia, bone pain, diarrhea, pyrexia (not including febrile neutropenia), myalgia, headache, arthralgia, vomiting, asthenia, edema peripheral, and constipation.

In the active controlled studies, common adverse events occurred at similar rates and severities in both treatment arms (pegfilgrastim, n = 465; filgrastim, n = 331). These adverse experiences occurred at rates between 72% and 15% and included: nausea, fatigue, alopecia, diarrhea, vomiting, constipation, fever, anorexia, skeletal pain, headache, taste perversion, dyspepsia, myalgia, insomnia, abdominal pain, arthralgia, generalized weakness, peripheral edema, dizziness, granulocytopenia, stomatitis, mucositis, and neutropenic fever.

6.11.5 Laboratory Abnormalities

In clinical studies, leukocytosis (WBC counts > 100 x 10^9/L) was observed in less than 1% of 932 patients with non-myeloid malignancies receiving pegfilgrastim. Leukocytosis was not associated with any adverse effects. In the placebo-controlled study, reversible elevations in LDH, alkaline phosphatase, and uric acid that did not require treatment occurred at similar rates in pegfilgrastim- and placebo-treated patients.

6.11.6 Toxicity/Warnings

Pegfilgrastim is contraindicated in patients with known hypersensitivity to E. coli-derived proteins, pegfilgrastim, Filgrastim, or any other component of the product.

Rare cases of splenic rupture have been reported following the administration of pegfilgrastim. Splenic rupture, in some cases resulting in death, has also been associated with filgrastim, the parent compound of pegfilgrastim. Patients receiving pegfilgrastim who report left upper abdominal and/or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Adult respiratory distress syndrome (ARDS) has been reported in neutropenic patients with sepsis receiving Filgrastim, the parent compound of pegfilgrastim, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Neutropenic patients receiving pegfilgrastim who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, pegfilgrastim should be discontinued and/or withheld until resolution of ARDS and patients should receive appropriate medical management for this condition.

Severe sickle cell crises have been associated with the use of pegfilgrastim in patients with sickle cell disease. Severe sickle cell crises, in some cases resulting in death, have also been associated with Filgrastim, the parent compound of pegfilgrastim. Only physicians qualified by specialized training or experience in the treatment of patients with sickle cell disease should prescribe pegfilgrastim for such patients, and only after careful consideration of the potential risks and benefits.

7 STUDY PROCEDURES

7.1 Patient Registration

All data management will be conducted at RPCI. For information on Network Site patient registration, refer to **Appendix A**.

Informed consent ***MUST*** be completed prior to receiving any study related procedures.

Following registration, patients should begin protocol treatment within 10 days or sooner if clinically necessary. Issues that would cause treatment delays should be discussed with the Principal Investigator.

The following will be completed within 10 DAYS prior to registration:

- Medical history
- Physical examination
- Vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, body weight, and height)
- Hematology (complete blood count (CBC) with automated differentials): WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, % neutrophils, absolute neutrophils, % monocytes, absolute monocytes, % eosinophils, absolute eosinophils, % basophils, absolute basophils, % lymphocyte (*designated as % lymphocyte total in RPCI lab system*), absolute lymphocyte (*designated as absolute lymphocyte total in RPCI lab system*), platelet confirmation (*as clinically indicated*), and differential confirmation (*as clinically indicated)*.

- Chemistry (i.e., complete metabolic panel (CMP): chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap).
- Pregnancy test (serum) in females of childbearing potential
- Concomitant Medications: List any medications that are ongoing, or that will be discontinued, within 1 week prior to first dose of study drug.

The following will be completed within 28 DAYS prior to registration:

- Blood work other than CBC with auto diff and CMP, and any X-ray, scans of any type or ultrasound, lumbar puncture, and bone marrow biopsy which is utilized for tumor measurement.

7.2 Schedule of Procedures and Observations

The schedule of procedures and observations for this study is summarized in below. Unless otherwise defined in the written protocol text, all procedures/assessments will be conducted in accordance with RPCI Clinical Research Services Standard Operating Procedures.

Table 7 Schedule of Procedures and Observations

Evaluations	Prior to Study	Day 1* of Each Cycle	At Time of Restaging**	Prior to Stem Cell Collection HDC-ASCS	Day 100 (±1 week) If HDC-SCT Eligible	Post Treatment Follow-Up‡
Test and Observations						
History and Physical Exam[6]	X	X	X	X	X	X
Pulse, Blood Pressure	X	X		X	X	
Height/Weight/Body Surface Area†	X	X		X		
Performance Status	X	X	X	X	X	X
Tumor Measurements	X		X	X	X	PRN
Drug Toxicity Assessment		X	X			PRN
Laboratory Studies						
CBC, Differential, Platelets	X	XΩ	X	X	X	X
Serum Creatinine, BUN	X	X	X	X	X	X
Creatinine Clearance	X			X		
Serum Electrolytes	X	X	X	X	X	X
Ca^{++}	X	X	X	X	X	PRN
AST, Alk.Phos., Bilirubin	X	X	X	X	X	PRN
LDH	X	X	X	X	X	X
EKG	X			X		
PFTs	X			X		
MUGA or ECHO	X			X		
Hepatitis BSAg, Hepatitis BcAb	X		XΔ	XΔ	XΔ	XΔ
Hepatitis B DNA	XΔ					
Hepatitis C Ab	XΦ					
HIV (If risk factors present)	X			X		
Beta-2-microglobuline (B2M)	X			X	X	
Albumin	X	X	X	X	X	X
Urine or serumβHCG (female patients)	Xϖ					Xϖ
Concomitant Medications		X[a]				

Evaluations	Prior to Study	Day 1* of Each Cycle	At Time of Restaging**	Prior to Stem Cell Collection HDC-ASCS	Day 100 (±1 week) If HDC-SCT Eligible	Post Treatment Follow-Up‡
Staging						
Chest X-ray, PA, and Lateral	**X**			**X**		
Lumbar Puncture* **	**X**	**A**	**PRN**			**F**
CT Scan Neck/Chest/Abdomen/Pelvis	**X**		**J**	**J**	**J**	**J**
PET	**X**		**X**	**X**	**X**	**K**
Bone Marrow Aspirate						**D**
Bone Marrow Biopsy and Aspirate	**X**		**F**	**X**	**X**	
GI endoscopic evaluation (i.e., upper GI endoscopy and colonoscopy)**	**X**			**B**	**B**	**D**
Histologic Review	**X**					**D**
Cytogenetics	**X**		**D**	**D**	**D**	**D**
Sample Submission and Correlative Studies						
Lymph Node Biopsy (Repeat)	E					D
Bone Marrow Aspirate (for MRD)	G		G	G	G	G
Peripheral Stem Cells				X		
Peripheral Blood (for MRD)	H		H	H	H	H
Complement Activation Studies		I				

*	Within 72 hours prior to Day 1 of each induction treatment cycle.
**	Prior to Cycles 3 and 5
***	Base-line lumbar puncture will only be required in patients with unexplained neurological symptoms to rule out lymphomatous meningitis.
****	GI evaluation at baseline may be waived in emergent situations per PI discretion.
†	Although doses are recalculated prior to each treatment; actual dose to be given need not change unless the difference in BSA from baseline is ≥ 10%.
‡	As long as the patient remains on study, after the Day 100 post stem cell visit date, follow-up will occur every 4 months for 2 years(± 2 weeks), then every 6 months per 3 years(± 2 weeks), then as clinically instructed. If the patient does not proceed to transplant they will be followed annually for survival.
A	Within 2 weeks of starting Cycle 3 and Cycle 5 only if positive at baseline.
B	Prior to HDC-SCT and on Day 100 only if positive at baseline.

C	Footnote "C" was removed from table and not replaced.
D	At the time of relapsed/refractory disease diagnosis.
E	Repeat diagnostic lymph node/tumor biopsy if initial biopsy was not diagnostic.
F	Document absence of disease at least once in CR if previously involved.
G	Bone marrow biopsy/aspiration will be submitted for flow cytometry analysis for minimal residual disease (MRD) analysis (see Section 7.4) at baseline, before Cycle 3, before Cycle 5, end of therapy/prior to stem cell collection (if transplant eligible), and on Day 100 (if HDC-ASCT eligible).
H	Peripheral blood will be submitted for flow cytometry analysis for minimal residual disease (MRD) analysis (see Section 7.4) at baseline, before Cycle 3, before Cycle 5, end of therapy/prior to stem cell collection (if transplant eligible), on Day 100 (if HDC-ASCT eligible) and then every 6 months for 3 years or until disease progression.
I	Refer to Section 7.4.5.
J	CT of the neck as clinically indicated.
K	In follow up, PET scan should be performed as clinically indicated.
6	Neurological exams need to be performed prior to each dose of high dose cytarabine during Cycle 2, Cycle 4 and Cycle 6.
Ω	CBC with differential and platelet counts will be monitored three times per week in between cycles of Ofatumumab-HyperCVAD/Ofatumumab-HD-MA and during the first post 30 days after HDC-ASCT for eligible patients.
Φ	All patients must be screened for hepatitis C infection before starting treatment. Patients who test positive for Hepatitis C antibody (Ab) must have a liver biopsy performed and other evaluations prior to enrollment (See Section 5.1.9).
Δ	All patients must be screened for hepatitis B infection (Hepatitis Bs Ag/Hepatitis Bc Ab) before starting treatment. Patients tested positive for Hepatitis B surface antigen are ineligible. Patients tested Hepatitis Bs Ag negative/Hepatitis Bc Ab positive should have Hepatitis B DNA PCR testing (see Section 5.1, Bullet 5.1.10.3). If HBV DNA is positive the patient is excluded. If HBV DNA is negative, patient may be included but must undergo at least every 2 months HBV DNA PCR testing from the start of treatment throughout the duration the study. Monitoring during the study is required at least every 2 months and during follow-up at a minimum of every 2 - 3 months up to 6 months after the last dose. Prophylactic antiviral may be initiated at the discretion of the investigator (see Section 5.1, Bullet 5.1.10.3).
ϖ	Pregnancy testing prior to first dose if last test was more than 30 days prior and at 6 months post-therapy.
PRN	When clinically appropriate
a	Medications ongoing, or discontinued, within 1 week prior to first dose of study drug.

7.3 Histologic Review

Submission of a tissue block is critical for MCL diagnosis confirmation. High quality hematoxylin and eosin-stained sections and any required confirmatory studies (i.e., immunohistochemistry and in situ hybridization) may be done most efficiently from the tissue block in laboratories of the RPCI pathology and cytogenetic departments. In this study, additional analysis will include baseline Ki-67, cyclin D1 expression as well as the existence or acquisition of additional cytogenetic abnormalities besides the t(11;14)(q13;q32) (i.e., as P53 deletion, 13q (RB1 and D13S25), 9p (CDKN2A)(p16) loss, ATM deletion, MYC rearrangement).Within 30 days of registration, send a formalin-fixed, paraffin-embedded block of well-fixed lymphoma tissue containing adequate material for histologic confirmation of MCL and for additional studies described above. A block at least 1 cm x 1 cm x 2 cm is preferable, although smaller is acceptable if no other block is suitable. If only 1 block exists, and the tissue is sufficiently large, it is acceptable to split the block into 2 blocks and submit 1 block. Failure to submit pathology materials within 30 days of patient registration will be considered a major protocol violation.

7.4 Correlative Science Sample Submission

All investigator- or analyzing-research laboratories housing research samples are required to maintain current Temperature Logs and study-specific Sample Tracking and Shipping Logs. The Principal Investigator/Laboratory Manager must ensure that the stated lab(s) have a process in place which documents the receipt/processing/storage/shipping of study-related sample/specimens.

See also section 13 and Appendix D

7.4.1 Minimal Residual Disease (MRD) by Flow Cytometric Analysis (Mandatory)

Samples will be required at the following time points:

Peripheral blood in heparin will be evaluated for MRD and collected at baseline, prior to Cycle 3, Cycle 5, prior to HDC-ASCT in transplant-eligible patients, and during the post-transplant/therapy surveillance period (on Day 100 and every 6 months for 3 additional years or until disease progression).

Bone marrow aspiration in heparin will be submitted for flow cytometry analysis for minimal residual disease (MRD) analysis (see Section 7.4) at baseline, before Cycle 3, Cycle 5, end of therapy/prior to stem cell collection (if transplant eligible), and on Day 100 (if HDC-ASCT eligible).

For RPCI patients, peripheral blood and bone marrow aspirate MRD samples will be performed as standard of care at baseline, prior to HDC-ASCT and on Day 100.

7.4.2 Cytogenetic Abnormalities in the Prognosis of Mantle Cell Lymphoma

Cytogenetic Abnormalities in the Prognosis of Mantle Cell Lymphoma at initial diagnosis and/or at time of relapse (when applicable for relapsing/primary refractory patients):

The prognostic significance of pre-treatment cytogenetic abnormalities in MCL treated with ofatumumab + HyperCVAD/HD-MA will be studied. In addition, the gain or loss of cytogenetic abnormalities in those MCL patients with refractory/relapsed disease will be studied. Tissue and/or

bone marrow aspirate specimens will be submitted for cytogenetic studies to the RPCI Cytogenetics Department.

This study will do a cytogenetic study at the time of diagnosis, as well as at the time of relapse utilizing the fluorescent in-situ hybridization (FISH) technique to determine the presence and/or acquisition of abnormalities involving P53, ATM, CDKN2A (p16), del(13q), and MYC. This study will subsequently correlate the cytogenetic findings with clinical outcomes.

7.4.3 Surface CD20 Density Analysis by ImageStream

Surface CD20 Density will be analyzed by the ImageStream Technology from Amnis Inc., which combines the quantitative power of flow cytometry with high content image analysis, giving the visual information obtained from a microscope integrated with population statistics. Fresh primary tumor cells (**if patients are undergoing initial or repeat lymph node biopsy/tumor biopsy for diagnostic purposes at participating Institutions**) will be collected prior to therapy and submitted for staining and fixation. Flow cytometric analysis will be performed at RPCI Flow Cytometry Department.

7.4.4 Ex vivo Activity of Ofatumumab in Primary Mantle Cell Lymphoma Cells

The capacity of ofatumumab to elucidate complement-mediated cytotoxicity (CMC) will be measured by standard Chromium-51 (51Cr) release assay as previously described.[47] MCL cell isolated from baseline tumor biopsy if patients are undergoing initial or repeat lymph node biopsy/tumor biopsy for diagnostic purposes at participating Institutions. Material will be processed in the RPCI Department of Medicine Lymphoma/Myeloma Laboratory.

7.4.5 Degree of *In Vivo* Complement Activation and Clinical or Molecular Responses to Ofatumumab-Based Therapy in Mantle Cell Lymphoma

Ofatumumab has been demonstrated to elucidate better complement activation and cell lysis when compared to rituximab in pre-clinical studies. Complement activation will be measured by: a) Total hemolytic complement (CH50), and b) serum C3 and C4 levels prior to the first ofatumumab infusion and at the end of the first ofatumumab infusion. CH50 and C3/C4 levels will be performed locally per institute standards.

7.4.6 Sample Procurement (At Each Time Interval Required)

- MRD
  - 10 mL of peripheral or central venous blood in sodium heparin green top tube.
  - 5 mL of bone marrow aspirate in a sodium heparin green top tube.
- Diagnosis
  - Diagnostic or refractory/relapsed (when applicable) fresh lymph node biopsy is strongly encouraged if available. If a diagnostic lymph node specimen/tumor specimen is available, it should be submitted fresh in RPMI-10%. A minimum of 1 mm3 is required for analysis.
- Cytogenetic Studies
  - 5 mL of bone marrow aspirate in a sodium heparin green top tube.

- CD20 Surface Antigen Quantification and Ex Vivo Testing
  - Fresh lymph node biopsy/tumor biopsy (when available) submitted fresh in sterile RPMI-10%.
- Complement Activation Studies will be performed locally per institute standards prior to first ofatumumab infusion and at the end of the first ofatumumab infusion.

7.4.7 Sample Shipment Instructions (Network Site Only)

- Samples should be logged and shipped via FedEx.
- Label the tubes with the RPCI study number, patient initials, the subject's study number, the date of collection, source and intended use of material (e.g., blood for MRD, etc.) and the sample collection period (i.e., prior to initiation of therapy, etc.).
- Required blood and bone marrow samples will be obtained, as indicated below.
- Submit the fresh tumor specimen prior to initiation of therapy as indicated below.

Complete the RPCI-MCL-OFA-1 form (Error! Reference source not found. – the form that is to accompany the specimens); and fax the form to notify the technician of the impending sample arrival.

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8 TREATMENT PLAN

8.1 Dosing and Administration

Treatment will be administered in an inpatient/outpatient basis. Reported adverse events (AEs) and potential risks are described in **Section** 6. Appropriate dose modifications are described in **Section 8.7**. No other investigational or commercial drugs or therapies other that those described below may be administered with the intent to treat the patient.

8.2 General Guidelines

Prior to initiating therapy, placement of a mediport or a multi-lumen indwelling Silastic catheter is required.

All patients will be given allopurinol 600 mg/day PO the day prior to Treatment 1 (Day 0) and then 300 mg/day PO for Day 1 through Day 10 of the first cycle. Allopurinol length of therapy may be extended at discretion of the investigator in the presence of tumor lysis syndrome.

All chemotherapy drug doses in Treatments 1 - 6 are based on a corrected body weight as follows: ideal + 25% of the difference between ide al and actual weight. If the actual weight is less than ideal, use actual weight. For patients whose actual weight is > 150% of ideal weight, use 150% of ideal weight as the "actual" weight (i.e., the corrected weight is 112.5% of ideal). Ofatumumab will be administered at a fix dose of 1000 mg unless the patient is at risk for tumor lysis syndrome (first cycle only).

Ofatumumab + HyperCVAD (Cycles 1, 3 and 5) alternating with ofatumumab + HD-MA (Cycles 2, 4 and 6) will be administered every 21 days.

The following laboratory parameters must be met before starting Cycles 2 to 6:

- Begin subsequent cycles no sooner than Day 22 but no later than Day 29. If treatment is delayed for more than 7 days, please contact the Principal Investigator at RPCI.
- ANC ≥ 1000/μL without G-CSF
- Platelets ≥ 75,000/μL or investigator discretion
- Serum creatinine ≤ 2.0 mg/dL
- Total bilirubin ≤ 2.0 mg/dL (unless due to disease involvement with MCL or Gilbert's syndrome). **If total bilirubin is > 5 mg/dL (see Table 8**).
- If there is a greater than 7 day delay because of these starting rules, please contact the Principal Investigator at RPCI.

8.3 Cycles 1, 3 and 5 (Cycles Will Be Administered Every 21 Days)

8.3.1 Ofatumumab

Pre-medications should include acetaminophen 650 mg PO and diphenhydramine 25 mg IV; 40 mg of methylprednisolone (or equivalent) should be given pre-ofatumumab and when clinically appropriate...

Administer in an outpatient setting on Day 1 of each cycle, will be administered at a fixed dose of 1000 mg IV on Day 1, titrated to a maximum infusion rate of 400 mg/hr, provided the number of circulating mantle cells ≤ 10,000/μL, otherwise split the first ofatumumab dose during Cycle 1 as described in the following sentence. Other patients at high risk for TLS as determined by the investigator **may** also have the first dose of ofatumumab divided as following: 300 mg Day 1 and 700 mg on Day 2.

Guidelines regarding preparation of ofatumumab and infusion protocol are described in **Section 6.1.5and Section 6.1.8.**

8.3.2 Cyclophosphamide

Administer in an inpatient setting, dosed at 300 mg/m^2 IV over 2 hours every 12 hours for 6 doses on Days 3 – 5.

8.3.3 Doxorubicin

Administer in an inpatient setting, dosed at 16.6 mg/m^2 daily for 3 days administered as a continuous intravenous infusion (CIVI) on Days 6-8.

8.3.4 Vincristine

Administer in an inpatient setting, dosed at 1.4 mg/m^2 (maximum dose 2 mg) IV on Day 6. Administer in an outpatient setting, dosed at 1.4 mg/m^2 (maximum dose 2 mg) IV on Day 13.

8.3.5 Dexamethasone

Administer in an inpatient setting, dosed at 40 mg IV or orally on Days 3 – 6. Administer in an outpatient setting, dosed at 40 mg IV or orally on Days 13 - 16.

8.3.6 MESNA

Administered 1 hour before the start of cyclophosphamide, MESNA will be started at 600 mg/m^2 per dose IV over 24 hours daily on Days 3 - 5 and completed 12 hours after the administration of the last dose of cyclophosphamide.

8.3.7 Intravenous Hydration

For Cycle 1, administer hydration with D_5W + 100mEq sodium bicarbonate per liter at 150 cc/hr on Day 3. Chemotherapy infusion should not begin until urine pH is ≥ 7. Continue adequate hydration until Day 9. Check urine pH with every void and adjust bicarbonate to maintain urine pH ≥ 7.

For Cycles 3 and 5, administer hydration with normal saline at 150cc/hr.

8.3.8 Prophylactic Granulocyte Growth Factor Use

Selection of agent is at investigator discretion.

- **G-CSF:** SQ beginning within 48 hours after the last dose of chemotherapy until post nadir ANC ≥ 10,000/μL x 1 or ANC ≥ 5000/μL twice (as per ASCO guidelines). Dose reduction for bone pain is allowed. If actual weight is < 60 kg use 300 mcg/dose; if actual weight is 60 kg – 99 kg, use 480 mcg/dose; if actual weight is 100 kg - 130 kg, use 600 mcg/dose; if actual weight is > 130 kg, use 780 mcg/dose.
- **Pegfilgrastim (Neulasta):** may be used instead of G-CSF, but will be administered within 48 hours after the last dose of chemotherapy.

8.3.9 Levofloxacin

Administer 500 mg PO daily or other IV or oral antibiotic institutional preference beginning on Day 9 until ANC ≥ 1,500/μL.

8.3.10 Fluconazole

Administer 400 mg/day PO or other IV or oral antifungal of institutional preference beginning on Day 9 until ANC ≥ 1500/μL.

8.3.11 Acyclovir

Administer 400 mg/bid PO beginning on Day 9 until ANC ≥ 1500/μL.

8.4 Cycles 2, 4, and 6 (Cycles Will Be Administered Every 21 Days)

8.4.1 Ofatumumab

Pre-medications should include acetaminophen 650 mg PO and diphenhydramine 25 mg IV; 40 mg of methylprednisolone (or equivalent) should be given pre-patient and when clinically appropriate.

Administer in an outpatient setting on Day 1 of each cycle), will be administered at a dose of 1000 mg IV on Day 1 (titrated to a maximum infusion rate of 400 mg/hr).

Guidelines regarding preparation of ofatumumab and infusion protocol are described in **Section 6.1**.

8.4.2 Methotrexate (MTX)

Administer in inpatient setting at 1000 mg/m^2 CIVI over 24 hours on Day 3.

Monitor MTX serum levels at the end of the MTX infusion and every 24, 48 and 72 hours after the completion of MTX infusion. If the patient meets the institutional standard levels for MTX serum, subsequent serum levels need not be performed. MTX serum levels can be +/- 2 hours from the end of infusion.

Continue adequate hydration until methotrexate serum level is < 0.1 μM. Check urine pH with every void and adjust bicarbonate to maintain urine pH ≥ 7.

For patients with an estimated creatinine clearance between 10 to 50ml/min, the dose of methotrexate should be decreased by 50%.

In patients with evidence of third spacing of fluids (i.e., pleural effusion or ascites), the fluid should be tapped completely prior to the administration of systemic methotrexate.

8.4.3 Cytarabine

Administer in an inpatient setting at 3,000 mg/m^2 (≤ 60 years) or 1,000 mg/m^2 (> 60 years) IV over 2 hours every 12 hours for 4 doses on Days 4 - 5.

The serum creatinine should be checked on Day 3 of Cycles 2, 4 and 6. If serum creatinine ≥ 1.5 mg/dL, then reduce the cytarabine dose by 50%.

If cytarabine neurotoxicity develops or is suspected during administration in Treatment 3 (dysmetria, dysdiadochokinesis, truncal/gait ataxia, dysarthria, and/or cerebral/psychiatric abnormalities not explainable by other medications), stop cytarabine immediately (see **Section 8.7.3.)**

8.4.4 Intravenous Hydration

For Cycles 2, 4 and 6, administer hydrate with D5W + 100mEq sodium bicarbonate per liter at 150 cc/hr on Day 3. MTX infusion should not begin until urine pH is ≥ 7. Continue adequate hydration until Day 9. Check urine pH with every void and adjust bicarbonate to maintain urine pH ≥ 7.

8.4.5 Leucovorin

Administer at 50 mg IV x 1 dose beginning 12 hours after completing the methotrexate infusion and then 15 mg IV/PO q6 hours for 8 doses or continuing until the serum methotrexate level is < 0.1 μM. In the event leucovorin is not available due to national shortage, levoleucovorin may be substituted at 50% of the leucovorin dose.

Additionally, leucovorin doses may be adjusted at treating physician clinical judgment for the following MTX levels at different time periods:

- Immediate end of infusion MTX level > 20 μM
- 24 hour post MTX level > 1 μM
- 48 hour post MTX level > 0.1 μM

8.4.6 Dexamethasone 0.1% Ophthalmic Solution (or equivalent)

Administer 2 drops in each eye 4 times daily, will be started on the day of cytarabine and will continued for 7 days to prevent chemical conjunctivitis.

8.4.7 Prophylactic Granulocyte Growth Factor Use

Selection of agent is at investigator discretion.

- **G-CSF:** SQ beginning within 48 hours after the last dose of chemotherapy until post nadir ANC ≥ 10,000/μL x 1 or ANC ≥ 5000/μL twice (as per ASCO guidelines). Dose reduction for bone pain as follow: Dose reduction for bone pain is allowed. If actual weight is < 60 kg use 300 mcg/dose; if actual weight is 60 kg - 99 kg, use 480 mcg/dose; if actual weight is 100 kg – 130 kg, use 600 mcg/dose; if actual weight is > 130 kg, use 780 mcg/dose.
- **Pegfilgrastim (Neulasta):** may be used instead of G-CSF, but will be administered within 48 hours after the last dose of chemotherapy.

8.4.8 Levofloxacin

Administer 500 mg PO daily or other IV or oral antibiotic institutional preference beginning on Day 8 until ANC ≥ 1,500/μL.

8.4.9 Fluconazole

Administer 400 mg/day PO or other IV or oral antifungal of institutional preference beginning on Day 8 until ANC ≥ 1500/μL.

8.4.10 Acyclovir

Administer 400 mg/bid PO beginning on Day 8 until ANC ≥ 1500/μL.

8.5 Treatment of CNS Disease (If Present at Diagnosis) and CNS Prophylaxis

- Patients with symptomatic CNS involvement are not eligible.
- A lumbar puncture demonstrating lymphoma at the time of initial staging in a neurologically asymptomatic patient should be treated with 10 doses of intrathecal (IT) methotrexate (12 mg in non-preserved NS) spread over Cycles 1 - 6.
    - Do not give IT methotrexate until leucovorin rescue is completed or during the days of high-dose cytarabine administration in Cycle 2.
    - If the patient's platelet count is < 50,000/μL on the day of a planned IT methotrexate, transfuse platelets just before the procedure. All blood products should be leukofiltered and irradiated to reduce/prevent alloimmunization and transfusion graft-vs-host disease.
- CNS prophylaxis: The administration of IT prophylactic chemotherapy should be performed according to the individual institution's standard of care guidelines. It should be considered in all MCL patients with blastoid or pleomorphic variants. The following prophylactic regimens are suggested, but not required:
    - IT methotrexate 12 mg in non-preserved NS on Day 3 of 4 or more cycles.
    - IT methotrexate 12 mg in non-preserved NS on Day 3 and cytarabine 100 mg in non-reserved NS on Day 7 of 4 or more cycles.

8.6 Stem Cell Collection and HDC-ASCT and Rituximab Maintenance.

- In eligible patients, HDC-ASCT will be performed at the participating NCCN institution following the individual institution's standard of care guidelines.
- Eligibility for HDC-ASCT will be assessed according to the Individual Institution's guidelines.
- The following information will be collected for each patient undergoing HDC-ASCT:
  - Stem cell mobilization agent utilized.
  - Feasibility of stem cell collection following ofatumumab-based chemoimmunotherapy (i.e., total of number of stem cell collected and length of time to successful stem cell collection).
  - Detection of MCL cells in the final stem cell product by HS-FCM and molecular diagnostics.
  - Disease status following HDC-ASCT at Day 100.
- Timeline for stem cell collection and HDC-ASCT
  - Stem cell collection should be attempted within 4 – 6 weeks after the last dose of ofatumumab-chemotherapy (after Cycle 6; or, after Cycle 4 for patients who achieve an HSFCM-CR after 2 cycles). Delayed stem cell collections beyond 6 weeks are allowed in those patients experiencing significant treatment related toxicities and/or unsuccessful stem cell collection attempts.
  - HDC-ASCT should be performed within 2 – 6 weeks following stem cell collection.

- Recently, the use of rituximab maintenance following HDC-ASCT was found to improve not only the progression free survival (PFS) but also the overall survival (OS) of patients with Mantle cell lymphoma (MCL).[1]. Because of that, the standard of care for patients with MCL changed recently. The protocol has been modified to reflect changes in clinical practice.
  - *Lymphoma Study Association group reported last year the results of an important randomized phase III study. A total of 299 MCL patients younger than 66 years of age were randomly assigned rituximab maintenance therapy (N=240) or to undergo observation (N=120) after autologous stem-cell transplantation; 59 patients did not undergo randomization. All patients received the same front line therapy and the same conditioning regimen prior to the autologous stem cell support. Rituximab maintenance was started 3 months after HDC-ASCT. The primary end point was event-free survival (with an event defined as disease progression, relapse, death, allergy to rituximab, or severe infection) after transplantation among patients who underwent randomization. The median follow-up from randomization after HDC-ASCT was 50.2 months (range, 46.4 to 54.2). The rate of event-free survival at 4 years was 79% (95% confidence interval [CI], 70 to 86) in the rituximab maintenance group versus 61% (95% CI,*

51 to 70) in the observation group (P=0.001). The rate of PFS at 4 years was 83% (95% CI, 73 to 88) in the rituximab maintenance group versus 64% (95% CI, 55 to 73) in the observation group (P<0.001). The rate of overall survival was 89% (95% CI, 81 to 94) in the rituximab maintenance group versus 80% (95% CI, 72 to 88) in the observation group (P=0.04). This study confirmed prospectively the clinical benefit of rituximab maintenance.[1]

- Rituximab maintenance will be offered to those patients on active treatment after these changes in clinical practice. It will be offered as standard of care for patients who completed their day 100 workup or are on active therapy on 12/01/2017 and beyond.
- Rituximab maintenance will be administered at the standard dose-schedule of 375mg/m^2 every 2 months for 3 years. [1]

8.7 Dose Modifications and Management of Toxicity

8.7.1 Hematologic Toxicity

Febrile Neutropenia: is expected with Cycles 1 - 6. Prophylactic antibiotics and G-CSF/Peg-GCSF are utilized during these cycles. No dose modifications are made in subsequent cycles following an episode of febrile neutropenia.

Monitoring Blood Counts During Cycles 1 - 6: Anemia and thrombocytopenia are expected from the agents utilized in this regimen. The use of erythrocyte growth factors (i.e., epogen) is not allowed. Routine blood counts will be performed 3 times per week between Day 9 and Day 20 of each cycle. Blood product support will be provided at discretion of the primary investigator. All blood products should be leukofiltered and irradiated to reduce/prevent alloimmunization and transfusion graft-vs-host disease.

Blood Counts on Day 1 of Cycles 2 - 6: The following modification will be made based on blood counts obtained within 3 days prior to each subsequent cycle (Cycles 2 - 6). Delay treatment until ANC count ≥ 1000/μL and platelet count ≥ 75,000/μL, then begin treatment at full dose. If treatment is delayed for more than 7 days, please contact the Principal Investigator at RPCI.

8.7.2 Hepatic Dysfunction

Table 8. Percent of Full Dose, Based on Laboratory Values Obtained Within 3 Days Prior to Cycles 2 - 6

Bilirubin (mg/dL)	Vincristine	Doxorubicin	Methotrexate
< 1.5	100	100	100
≥ 1.5 but < 3.0	50	50	75
≥ 3.0 but < 5.0	25	25	50
> 5*	0	0	0

*If bilirubin is ≥ 5.0 mg/dL due to any cause other than disease (i.e., hepatic obstruction due to tumor), all therapy (including ofatumumab) should be held until bilirubin < 5.0 mg/dL. If ≥ 5.0 mg/dL is due to disease, full dose cyclophosphamide should be given along with ofatumumab and dexamethasone (Cycles 1, 3, and 5) or ofatumumab along with cytarabine (Cycles 2, 4, and 6) according to the treatment plan.

Ofatumumab stopping criteria for liver dysfunction (see **Error! Reference source not found.**).

If liver toxicity develops during therapy with Ofatumumab + HyperCVAD/HD-MA that is not due to disease progression, stopping criteria (any of 3) had been formulated as below:

CRITERIA 1: ALT > 3 x upper limit of normal (ULN) and bilirubin > 2 x ULN (> 35% direct bilirubin; bilirubin fractionation required‡).

CRITERIA 2: ALT > 8 x ULN.

CRITERIA 3: ALT > 5 x ULN for more than 2 weeks.

8.7.3 Neurotoxicity

8.7.3.1 Vincristine - Associated Sensory and Motor Neuropathy

The dose of vincristine should only be reduced if the patient develops neuropathy that interferes with activities of daily living (see below). Most vincristine associated neuropathy resolves after completion of treatment.

- **Sensory Neuropathy:** If Grade 3 toxicity develops, reduce vincristine 25%. If symptoms improve to < Grade 2, doses may be increased to previous levels (i.e., 25% for Grade 2 and full dose for < Grade 1). If a patient experiences Grade 4 toxicity, discontinue vincristine.
- **Motor Neuropathy:** If Grade 2 toxicity develops, reduce vincristine 25%. If a patient experiences Grade 3 toxicity, reduce vincristine 50%. If symptoms improve, doses may be increased to previous levels. If a patient experiences Grade 4 toxicity, discontinue vincristine.
- **Vincristine May Produce GI Hypomotility with Constipation or Ileus:** Prophylactic laxatives according to institutional policies are recommended. Decrease vincristine dose 50% for Grade 3, severe constipation with ileus despite aggressive medical management. Discontinue vincristine for severe persistent GI hypomotility following dose adjustment.

8.7.3.2 Cytarabine Neurotoxicity

If cytarabine neurotoxicity develops or is suspected during Cycles 2, 4 or 6 (dysmetria, dysdiadochokinesis, truncal/gait ataxia, dysarthria, and/or cerebral/psychiatric abnormalities not explainable by other medications), stop cytarabine immediately.

8.7.3.3 Dexamethasone Neurotoxicity

Table 9. Dose Adjustment for Dexamethasone

Toxicity	Percent of Dexamethasone Dose
Slowed ability to think, depression, insomnia.	100%*
Confusion, severe depression, difficulty functioning.	50%
Delirium, suicidal.	0%

*If the disability persists or worsens, hold and re-institute at 50% dose once toxicity clears.

8.7.4 Gastrointestinal Toxicity

Mucositis, Dysphagia, and Diarrhea: For severe oral ulceration or diarrhea (Grade 3) occurring during chemo-immunotherapy, delay subsequent cycle until mucositis or diarrhea clears (≤ Grade 1).

Activation of peptic ulcer will warrant discontinuation of corticosteroid treatment.

8.7.5 Cardiotoxicity

Anthracyclines may result in congestive heart failure (CHF) with fluid retention and shortness of breath that may be controllable with medications. Discontinue anthracycline if:

- Persistent arrhythmia Grade > 3 (including, sinus tachycardia with no demonstrable cause).
- CHF appears.
- Decrease in ejection fraction (by > 15% from baseline) as measured by MUGA scan or 2D-echo.

8.7.6 Genitourinary/Renal Toxicity

8.7.6.1 Cystitis

Cyclophosphamide-related gross or microscopic hematuria correlates with the concentration of drug metabolites in the bladder. Adequately hydrate patients and ensure frequent voiding. Should hemorrhagic cystitis occur following Cycle 1, delay subsequent therapy until macroscopic hematuria has completely cleared. Then give cyclophosphamide for the next patient-HyperCVAD (Cycle 3) cycle at full dose and also administer MESNA (2400 mg/m^2 IV over 24 hours). If hemorrhagic cystitis occurs with Cycle 1 and Cycle 3 then also add bladder irrigation to the cyclophosphamide given during Cycle 5 (500 cc/hour sterile urologic saline via a 3-way Foley catheter during and for 48 hours after cyclophosphamide administration).

8.7.6.2 Renal Dysfunction/Cytarabine Dose Modifications

Give the following cytarabine dose for renal dysfunction based on serum creatinine and/or creatinine clearance (CrCl) within 3 days prior to Cycles 2, 4 and 6 and on any day of high-dose cytarabine administration (Refer to **Table 10**).

Table 10. Cytarabine Dose Adjustments Based on Renal Function

Serum Creatinine	Cytarabine Dose
< 1.5 mg/dL and/or CrCl ≥ 60 cc/min	Full dose according to age
1.5 mg/dL - 1.9 mg/dL or an increase of 0.5 mg/dL - 1.2 mg/dL and/or CrCl 20 - 59 cc/min	50% reduction
≥ 2.0 mg/dL or an increase of ≥ 1.3 mg/dL and/or CrCl < 20 cc/min	Hold and call Chair study

8.7.6.3 Renal Dysfunction / Methotrexate Dose Modifications

If the estimated creatinine clearance is between 10 to 50ml/min, the methotrexate dose should be modified to be 50% of the full dose (500 mg/m^2). Please contact the Principal Investigator at RPCI with any questions regarding dose modifications.

8.8 Ancillary Therapy

Patients should receive full supportive care, including transfusions of blood and blood products, some growth factors (see below), antibiotics, antiemetics, etc., when appropriate. The reason(s) for treatment, dosage, and the dates of treatment should be recorded on the flow sheets.

Treatment with hormones or other chemotherapeutic agents may not be administered except for corticosteroids given for adrenal failure, as an antiemetic or part of a pre-medication for ofatumumab. Other hormones administered for non-lymphoma-related conditions (e.g., insulin for diabetes) are allowed.

Use of growth factors.

The following guidelines are applicable unless otherwise specified in the protocol:

- The use of EPO is not permitted in this protocol.
- Prophylactic G-CSF or peg-G-CSF is required by this protocol due to the intense nature of protocol treatments.

Subjects who are HBAg negative, anti-HBc positive and HVB DNA negative may be included in the study but must undergo HVB DNA monitoring. Consult with a physician experienced in care and management of subjects with hepatitis B to manage/treat subjects who are anti-HBc positive. Initiate anti-viral therapy if required. If a subject's HVB DNA becomes positive during the study, notify the NOVARTIS medical monitor. For subjects who have not completed planned ofatumumab therapy, discuss with the medical monitor the risks and benefits of continuing or discontinuing ofatumumab before appropriate treatment decisions are made for that individual subject.

8.9 Treatment Discontinuation

- **Duration of Treatment:** Remove from protocol therapy any patient with rapid disease progression. Because protocol-designated, complete restaging is not performed until three months post-stem cell transplant, patients should proceed with all protocol treatment unless clinical events warrant an investigation and subsequent unequivocal documentation of progression. When in doubt as to whether progression has occurred, evaluate with appropriate scans and biopsies and consult the Principal Investigator at RPCI. Document details, including tumor measurements, on flow sheets.
- **Extraordinary Medical Circumstances:** If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:
  - Notify the Principal Investigator at RPCI.
  - Document the reason(s) for discontinuation of therapy on flow sheets.
  - Follow the patient for survival, progression, late toxicity, and secondary malignancies.

9 EFFICACY EVALUATIONS

9.1 Objectives

The primary objective of this clinical study is to evaluate the overall response rate and complete response rate to ofatumumab+HyperCVAD/HD-MA in MCL. It is important to evaluate response to therapy using standardized response criteria utilized in previous clinical studies in MCL patients so direct comparisons can be performed with historical controls (i.e., rituximab+HyperCVAD/HD-MA). For this reason response to therapy will be evaluated using the response criteria reported by Cheson et al in 1999 (see **Section 9.3**).[45] However, as medical imaging technology advances it is imperative to evaluate prospective differences in response rates when patients treated with a given regimen are evaluated using criteria incorporating novel imaging studies (i.e., PET scan). For this reason this study will also assess response to ofatumumab+HyperCVAD/HD-MA using the modified Cheson criteria published in 2007 (**Section 3.2**, last bullet) (see **Section 9.4**).[46]

9.2 Imaging, Laboratory and Pathological Studies

Imaging, laboratory and pathological studies will be conducted for staging and response evaluation at baseline, before Cycle 3, and Cycle 5, within 3 weeks after Cycle 6 (or within 3 weeks after Cycle 4 for patients who achieve an HSFCM-CR after 2 cycles), and in those eligible, on Day 100 post HDC-ASCT. Response to treatment will be evaluated according to: the International Working Group Response criteria as reported by Cheson et al. and the revised Cheson criteria (**Section 3.2**, last bullet).

Each investigator- or analyzing-research laboratory housing research samples will maintain current Temperature Logs and study-specific Sample Tracking and Shipping Logs. Each such laboratory will have a process in place to document the receipt, storage, shipping and handling of study-related samples and specimens.

9.3 International Working Group Response Criteria (Original Cheson Criteria)

9.3.1 Complete Response (CR)

Complete disappearance of all detectable clinical and radiographic evidence of target lesions and disappearance of all disease-related symptoms if present prior to therapy, as well as normalization of those biochemical abnormalities (e.g., LDH, etc.) definitely assignable to MCL.

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 prior to therapy). Previously involved nodes that were 1.1 cm to 1.5 cm in their greatest transverse diameter prior to 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 their greatest transverse diameters (SPD).

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. (No normal size can be specified, however, because of the difficulties in evaluating splenic and hepatic size.) Any macroscopic nodules in any organs detectable on imaging studies should no longer be present. Similarly, other organs considered to be enlarged prior to therapy due to involvement of lymphoma (i.e., kidneys, liver, etc.) must have decreased in size.

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

9.3.2 Complete Response/Unconfirmed (CRu)

Complete response/unconfirmed will include those patients who have met the criteria in **Section 9.3** (complete response, paragraphs 1 and 3), but with 1 or more of the following:

A residual node > 1.5 cm in greatest transverse diameter that has regressed more than 75% in the product of its diameters. Individual nodes that were previously confluent must have regressed more than 75% in the product of their diameters compared with the size of the original mass.

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

9.3.3 Partial Response (PR)

A decrease of ≥ 50% in the 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 measurements; 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.

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

Splenic and hepatic nodules must regress by at least 50% in SPD. With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease.

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 (e.g., large-cell lymphoma).

No new sites of disease.

9.3.4 Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest SPD since the treatment started.

9.3.5 Progression (PD) or Relapse

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

Appearance of any new lesion during or after completion of therapy.

9.4 Modified Cheson Criteria

9.4.1 Complete Response (CR)

Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.

Typically FDG-avid lymphoma: in patients with PET scan positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

Variably FDG-avid lymphomas/FDG avidity unknown: in patients with a negative pretreatment PET scan, all lymph nodes and nodal masses must have regressed on CT 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 cm to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to 1.0 cm in their short axis after treatment.

The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

If the bone marrow was involved by lymphoma before treatment the infiltrate must have cleared on repeat bone marrow biopsy.

The biopsy sample on which this determination is made must be adequate (with a goal of 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

HIGH SENSITIVITY FLOW CYTOMETRY (HSFCM) COMPLETE REMISSION (HSFCM-CR)

All CR criteria are met and negative flow cytometry examination of peripheral blood and bone marrow biopsy/aspiration.

9.4.2 Partial Response (PR)

A decrease of ≥ 50% in the in the sum of the products of their greatest transverse diameters (SPD) of the 6 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 measurements; 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.

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

Spleen and hepatic nodules must regress by at least 50% in SPD.

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

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 (e.g., large-cell lymphoma).

Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders.

When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.

No new sites of disease should be observed.

Typically FDG-avid lymphoma: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.

Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used.

9.4.3 Stable Disease (SD)

A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]).

Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.

Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

9.4.4 Progression (PD) or Relapse

Lymph nodes should be considered abnormal if the long axis in more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 cm to 1.5 cm, it should only be considered abnormal if its short axis is more than 1 cm. Lymph nodes 1 cm x 1 cm will not be considered as abnormal for relapse or progressive disease.

Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1 cm must increase by 50% and to a size of 1.5 cm or more than 1.5 cm in the long axis.

At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.

Lesions should be PET positive if observed in a typical FDG avid

Lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (1.5 cm in its long axis by CT).

9.4.5 Duration of Overall Response

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

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

9.4.6 Duration of Stable Disease

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

10 SAFETY EVALUATION

Given the expected hematological and non-hematological toxicities from rituximab-HyperCVAD alternating with rituximab and high dose Methotrexate/Cytarabine (MA) regimen, close monitoring will be conducted for this proposed ofatumumab-HyperCVAD alternating with ofatumumab-Methotrexate/Cytarabine regimen.

The description and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse events (AE) evaluation and reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://evs.nci.nih.gov/ftp1/CTCAE/About.html). All reactions determined to be “reportable" in an expedited manner must be reported to the local Institutional Review Board (IRB) of the participating Institution, the Principal Investigator at RPCI, RPCI CRS, and to the funding organization (National Comprehensive Cancer Network) and agent provider Novartis. (Reporting of cases of secondary acute myeloid leukemia/myelodysplastic syndrome (AML/MDS) should also be done as described above.

10.1 Adverse Events

10.1.1 Definition

An adverse event or adverse experience (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of ‘unrelated’, ‘unlikely’, ‘possible’, ‘probable’, or ‘definite’).

An AE is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan in other study-related documents.

Events meeting the definition of an AE include:

- Any abnormal laboratory test results (e.g., hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., EKGs, 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.
- 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 a 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

For the purpose of this study, AE reporting will not be required during the HFC-ASCT portion that will follow after the completion of chemo-immunotherapy in eligible patients. After the completion of all therapy, including HDC-ASCT for those eligible, subjects will be followed for disease response, progression and survival only, and research samples and re-staging studies will be done at the defined time points.

10.1.1.1 Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be clinically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

10.1.1.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the CRF.

However, clinically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

10.1.1.3 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 x the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the CRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7 mEq/L should be recorded as "hyperkalemia"

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the CRF, unless their severity, seriousness, or etiology changes.

10.1.1.4 Preexisting Medical Conditions (Baseline Signs and Symptoms)

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

10.1.2 Grading and Relationship to Drug

The descriptions and grading scales found in the CTEP Version 4 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. CTEP Version 4 of the CTCAE is identified and located at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.html.

AEs not covered by specific terminology listed should be reported with common medical terminology, and documented according to the grading scales provided in the CTCAE Version 4.

The relationship of event to study drug will be documented by the Investigator as follows:

- **Unrelated:** The event is clearly related to other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs administered to the participant.
- **Unlikely:** The event is doubtfully related to investigational agent(s). The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible:** The event follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs.
- **Probable:** The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions or concomitant drugs.
- **Definite:** The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions or concomitant drugs; AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

10.1.3 Reporting Adverse Events

Table 11 Guidelines for Routine Adverse Event Reporting for Pilot, Phase 2, and Phase 3 Studies (Regardless of Expectedness)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4
Unrelated			X	X
Unlikely			X	X
Possible	X	X	X	X
Probable	X	X	X	X
Definite	X	X	X	X

Routine AEs occurring between the start date of intervention until 30 days after the last intervention or until the event has resolved, the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible, will be reported. New information will be reported after it is received.

10.2 Serious Adverse Events

10.2.1 Definition

A serious adverse event (SAE) is any adverse event (experience) that in the opinion of either the investigator or sponsor results in **ANY** of the following:

- Death.
- A life-threatening adverse event (experience). Any AE that places a participant or participant, in the view of the Investigator or sponsor, at immediate risk of death from the reaction as it occurred. It does **NOT** include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.
- Important Medical Event (IME) that, based upon medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

10.2.2 Reporting Serious Adverse Events

All new SAEs occurring from the date the participant signs the study consent until 2 months after the last intervention or a new treatment is started, whichever comes first, will be reported. The RPCI SAE Source Form is to be completed with all available information, including a brief narrative describing the SAE and any other relevant information. All SAE's assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to Novartis concomitant medication, will be reported promptly to the Local IRB, NCCN, and Novartis.

SAEs occurring after the 2 month follow-up period that the investigator determines to be possibly, probably or definitely related to the study intervention should be reported to NCCN and Novartis. All related SAEs should be followed to their resolution, until the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible. New information will be reported when it is received.

SAEs identified as an Unanticipated Problem by the Investigator must be reported. Please refer to **Section 10.5** for details on reporting Unanticipated Problems.

- For this study, myelosuppression and its associated complications due to this protocol therapy are expected events during treatment. Hospitalizations for the treatment of the following events do not require reporting for SAE's but should be documented as AEs:
  - Fatigue, weakness and/or shortness of breath associated with anemia.
  - Febrile neutropenia.
  - Bleeding due to thrombocytopenia.
  - Neutropenic colitis.

10.2.3 Laboratory and Other Safety Assessment Abnormalities Reported as Adverse Events and Serious Adverse Events

- Any abnormal laboratory test results (e.g., hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., EKGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant (> Grade 3) 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, lymphopenia, 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.
- Reactivation of hepatitis B or PML (see **APPENDIX B** and **Error! Reference source not found.**).

10.2.4 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as Serious Adverse Events

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.

10.2.5 Adverse Event Characteristics

- CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).
- 'Expectedness': AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only.
- Attribution of the AE:
  - Definite – The AE is clearly related to the study treatment.
  - Probable – The AE is likely related to the study treatment.
  - Possible – The AE may be related to the study treatment.

- Unlikely – The AE is doubtfully related to the study treatment.
- Unrelated – The AE is clearly NOT related to the study treatment.

10.3 Pregnancy

Any pregnancy that occurs during study participation must be reported to NCCN and Novartis. To ensure subject safety, each pregnancy must be reported to NCCN and Novartis 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 NCCN and Novartis representative. (Appendix G).

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 NCCN and Novartis as described above.

10.4 Additional Instructions or Exclusions to Expedited Reporting Requirements.

- Deaths occurring greater than 30 days after the last dose of treatment that are due to disease progression do not require expedited reporting.
- All Grade 4 events that are unexpected and that are at least possibly related to treatment must be reported within 24 hours of learning of the event, followed by a complete report within 5 calendar days of the initial 24-hour report. Grade 4 events that are expected do not require expedited reporting.
- Any unexpected medical event equivalent to CTCAE Grade 4 that precipitates hospitalization (or prolongation of existing hospitalization) and that is at least possibly due to treatment must be reported.
- A list of specific expected adverse events can be found in Section 6.1.9 (Toxicity).
- For the purposes of expedited adverse event reporting, the CAEPR for ofatumumab will be similar to what has been used in rituximab-clinical studies
- Exacerbation or reactivation of serious viral infections (e.g., hepatitis, JC) as described in Section 5.1 (bullet 5.1.10.3), **APPENDIX B**, and **Error! Reference source not found.** should be reported within 10 calendar days of the investigator learning of the event.
- Grade 3 or Grade 4 myelosuppression and hospitalization resulting from Grade 3 or Grade 4 myelosuppression do not require reporting, but should be submitted as part of study results.
- Grade 4 neurotoxicity and hospitalization from Grade 3 or Grade 4 neurotoxicity do not require reporting, but should be submitted as part of study results.

10.5 Unanticipated Problems

10.5.1 Definition

An Unanticipated Problem (UP) is any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given:
  a) The research procedures that are described in the study-related documents, including study deviations, as well as issues related to compromise of participant privacy or confidentiality of data.
  b) The characteristics of the participant population being studied.
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized and if in relation to an AE is also deemed **Serious** per **Section 10.2**.

10.5.2 Reporting Unanticipated Problems

Unanticipated problem reporting will begin at the time of participant consent.

An Unanticipated Problem shall be submitted to the CRS Compliance Office as "Reportable New Information" in the Click system within 1 business day of becoming aware of the Unanticipated Problem. After review, CRS Compliance will submit the UP to the IRB.

When becoming aware of new information about an Unanticipated Problem, submit the updated information to CRS Compliance as "Reportable New Information" in the Click system.

10.6 FDA Reporting

If the protocol is being conducted under a RPCI IND it is the responsibility of the study IND holder to report certain AEs or Unanticipated Problems to the FDA.

RPCI's Compliance Office will report Network Site reports to the FDA.

The following describes the FDA reporting requirements by timeline for AEs and new safety findings that meet the criteria outlined below:

Within 7 Calendar Days

Any adverse event that meets **ALL** the following criteria:

- Related or possibly related to the use of the study drug;
- Unexpected; and
- Fatal or life-threatening.

Within 15 Calendar Days

Any adverse event that meets **ALL** the following criteria:

- Related or possibly related to the use of the study drug;
- Unexpected; and
- Serious but not fatal or life-threatening.

Or meets **ANY** of the following criteria:

- A previous adverse event that is not initially deemed reportable but is later found to fit the criteria for reporting (report within 15 days from when event was deemed reportable).
- Any findings from other studies, including epidemiological studies, pooled analysis of multiple studies, or other clinical studies conducted with the study drug that suggest a significant risk in humans exposed to the drug.
- Any findings from animal or in vitro testing that suggest a significant risk for human patients including reports of mutagenicity, teratogenicity, or carcinogenicity or reports of significant organ toxicity at or near the expected human exposure.

- Any clinically important increase in the rate of occurrence of a serious, related or possibly related adverse event over that listed in the protocol or investigator brochure.

Sponsors are also required to identify in IND safety reports, all previous reports concerning similar adverse events and to analyze the significance of the current event in the light of the previous reports.

Reporting Process

The principal investigator or designee will complete and submit a FDA Form 3500A for any event that meets the above criteria. Forms will be submitted to the CRS Compliance Office via email to CRS Compliance@Roswellpark.org. The Compliance office will send the form to the FDA.

11 DATA AND SAFETY MONITORING

The RPCI Data and Safety Monitoring Board will assess the progress of the study, the safety data, and critical efficacy endpoints. The DSMB will review the study annually and will make recommendations that include but not limited to; (a) continuation of the study, (b) modifications to the design (c) or termination of the study.

12 STATISTICAL METHODOLOGY

The primary objective of this one-arm Phase II trial is to assess the efficacy of the study treatment as compared to historical control. Let p represent the proportion of the evaluable population of interest who experience a complete response within $18-22$ weeks of the beginning of treatment. A true complete response rate of less than 50% is considered unacceptable. A complete response rate of more than 70% is considered promising and evidence of such will deem the treatment worthy of further study. The null and alternative hypotheses corresponding to the design are

$$H_0 : p \leq 50\%,$$
$$H_a : p > 50\%.$$

A total of up to 37 evaluable patients will be accrued. The evaluable population is defined as patients who meet eligibility requirements and complete at least once cycle of treatment. Unevaluable patients will be replaced. The study design will be a Simon (1989) minimax design that proceeds in two stages and stops early only for futility. At the end of the first stage of accrual (23 evaluable patients), data will be reviewed to decide if the study should be terminated due to inactivity of therapy.

12.1 Primary Analysis

Stage 1: If 12 or less of the first 23 evaluable patients achieves a complete response as measured by standard response criteria reported by Cheson et al in 1999[45], it will be concluded that the therapy is not promising and the study will end. Otherwise, the study will progress to the second stage. Depending on the current complete response rate at the time the last patient in Stage 1 is

enrolled, study enrollment may be halted until complete response status is evaluated in all 23 patients.

Stage 2: This study will accrue 14 additional evaluable patients. If 24 or more of the total of 37evaluable patients achieve a complete response, it will be concluded that p exceeds 50% and that the therapy is efficacious and worthy of further study; otherwise, it will be concluded that there is no evidence to suggest that the therapy is associated with acceptable efficacy and is not promising.

With this design, the probability is 4.8% of falsely concluding that the proportion of objective responders exceeds 50% and 80% is the probability of correctly concluding efficacy when the true proportion of objective responders is 70% or higher.

12.2 Sample Size Justification

The sample size calculation is based on testing the hypotheses concerning the proportion of the population with a response to the treatment:

$$H_0 : p \leq 50\%,$$
$$H_a : p > 50\%.$$

This two-stage design requires a potential total of 37 patients in order to achieve approximately 80% power to detect differences of 20 percentage points (50% versus 70%).

12.3 Secondary Analyses

Both activity and toxicity rates will be estimated using simple relative frequencies. The corresponding 95% confidence intervals for the estimated probabilities will be computed using the method proposed in Clopper and Pearson.[48] The association between the endpoints and collected predictors, such as surface CD20 levels, Ki67, and additional cytogenetic abnormalities, will be statistically assessed using logistic regression. Wald tests of the model effects will be performed to assess statistical significance. See Hosmer and Lemeshow (2000) for a discussion of such techniques.[49] Alternative parametric models will be considered if model fit is found to be inadequate.

The estimated distributions of TTP, PFS, and OS will be obtained using the Kaplan-Meier method. Estimates of quantities such as median survival will be obtained. Corresponding confidence intervals using the methodology of Brookmeyer and Crowley will be computed.[50] It is assumed a priori that any drop out times will be non-informative in terms of the censoring mechanism. Groups defined by levels of categorical or dichotomized predictors, ex. minimal residual disease, will be compared in regards to time-to-event distributions using the log-rank test. Cox proportional hazards model regression will be utilized for multivariate analyses.

Longitudinal analyses such as those used to determine changes in surface CD20 levels, Ki67, or gain of additional cytogenetic abnormalities in relapsed/refractory tumor specimens, will be based on standard techniques. A series of graphical analyses will initially take place including individual subject-level profile plots and overall mean plots used to examining the mean structure. Formal statistical examination of longitudinal patterns will be done through the use of

a mixed model. Each endpoint will be fit as a function of the fixed effect of time treated as a categorical variable. Since repeated measurements will be obtained from each patient, a random subject effect will be added to the model to incorporate the subject-specific dependence, which may exist. Restricted maximum likelihood estimation will be utilized in the model fitting procedures as implemented by SAS PROC MIXED (version 9.2). Once the model is fit, specific linear contrasts based on the estimated model parameters will be constructed and used to test hypotheses concerning between time point comparisons.

All tests performed during the secondary analyses will be two-sided and tested at a 0.05 nominal significance level. Standard diagnostic plots will be used to assess model fit and transformations of variables may be considered in order to meet statistical assumptions.

13 CORRELATIVE STUDIES

13.1 Central Hypothesis

Based on pre-clinical data, we postulate that the incorporation of ofatumumab into aggressive induction chemotherapy in patients with mantle cell lymphoma (MCL) will yield higher complete and HSFCM remission rates at the end of induction chemotherapy and prior to stem cell collection in those patients scheduled to undergo HDC-ASCT. This study will determine if achievement of HSFCM remission translates into improved clinical outcomes. In addition, we propose to study biomarkers that may predict clinical response and/or biological response to ofatumumab.

Specifically, this study will study: 1) the relationship between surface CD20 antigen density in MCL and the ex vivo activity of ofatumumab vs. rituximab; 2) if complement activation in vivo can be used as a surrogate marker for the activity of ofatumumab in combination with chemotherapy in patients with MCL; and 3) finally, as complementary data, this study will determine at diagnosis and at relapse, whether changes occur in known predictors of clinical outcome of MCL (i.e., Ki67 proliferation index and the acquisition of additional cytogenetic abnormalities besides the t(11:14) (i.e. as P53, 13q (RB and D13S25), 9p (CDKN2A), ATM, MYC).

13.2 STUDY Material To Be Studied

Correlative samples will be collected for patients enrolled into the clinical trial. Tissue, bone marrow (BM), and peripheral blood (PB) will be collected at different time intervals (S**ection 7.4**).

- **Tissue:** Pretreatment and at the time of disease progression excisional (preferable) or core biopsy material from either lymph node or any accessible extranodal mass will be submitted for pathological confirmation of MCL, cytogenetic studies, quantification of CD20 levels, ex vivo testing and measurement of biomarkers. Central review of MCL will be performed at RPCI.
- **Bone Marrow Aspirate at Diagnosis and if Positive for Involvement By Lymphoma: Before Cycle 3,** before Cycle 5 and prior to stem cell collection or at the end or therapy for non-transplant eligible will be evaluated by standard pathological evaluation, cytogenetic

analysis for the t(11:14) or additional genetic abnormalities, and flow cytometry analysis for MRD detection.

- Peripheral blood will be evaluated for MRD and collected at baseline, prior to Cycle 3, Cycle 5, prior to HDC-ASCT in transplant-eligible patients, and during the post-transplant/therapy surveillance period (on Day 100 and every 6 months for 3 additional years).

13.3 Methodology

13.3.1 Correlation Between Baseline Surface CD20 in Mantle Cell Lymphoma Isolated From Patients Enrolled in the Clinical Trial and *Ex Vivo* Ofatumumab Anti-Tumor Activity and Clinical Endpoints

Isolation of Malignant Cells: Malignant B-cells will be isolated by MACS sorting (negative selection) from pretreatment biopsy tissue and bone marrow biopsy obtained from enrolled patients with MCL. Samples from patient biopsy specimens will be procured under Institutional Review Board (IRB) RPCI protocols I42804 and I42904 Tissue biopsies will be disrupted by mechanical disruption. Samples will be then diluted with RPMI 1640-containing 10% fetal bovine serum (FBS) and the cell suspension filtered through a 100 µm cell strainer to remove large clumps. Mononuclear cells (lymphocytes) will be isolated from either tumor cell suspension or bone marrow aspirates by Histopaque-1077 density centrifugation. MCL cells will be then isolated from normal lymphocytes by MACS separation using a human B-cell Isolation Kit II (Miltenyi Biotec, Gladbach, Germany). B-cell purity was assessed by flow cytometry using antibodies to CD19, CD5 and CD20 (Becton Dickenson, San Jose, CA). Collected cells re-suspended in media and used in corresponding experiments.

13.3.2 Surface CD20 Density Analysis by ImageStream

Surface CD20 density analysis by ImageStream will be analyzed by the ImageStream Technology from Amnis Inc., which combines the quantitative power of flow cytometry with high content image analysis, giving the visual information obtained from microscope integrated with population statistics. In brief, 2 x 10^6 cells will be stained with a mouse anti-human CD19 fluorescein isothiocyanate (FITC) labeled monoclonal antibody (mAb), a mouse an anti-human CD20 allophycocyanin (APC) labeled mAb, or proper isotype control(s) and then fixed by 2% paraformaldehyde. Cells will be then illuminated in the ImageStream system by a bright field lamp and the proper wavelength excitation laser for APC. Data will be analyzed by ImageStream IDEAS image analysis software. Cells will be gated for single, focused populations, which will then analyzed for the mean cell size (by mean surface area) and mean surface CD20 expression (by mean CD20-FITC intensity). Mean surface CD20 density will be calculated based on the following formula: Surface CD20 density = mean surface CD20-APC intensity/mean surface area (CD20-APC per μm^2).

13.3.3 Ex vivo Activity of Ofatumumab in Primary Mantle Cell Lymphoma Cells

The capacity of ofatumumab to elucidate complement-mediated cytotoxicity (CMC) will be measured by standard by Chromium-51 (51Cr) release assay as previously described.[47] MCL cell

isolated from baseline tumor biopsy will be labeled with 51Cr at 37°C, 5% CO_2 for 2 hours. ^{51}Cr-labeled cells will be then placed in 96-well plates at a cell concentration of 1 x 10^5 cells/well and then exposed to ofatumumab (10 µg/mL), rituximab (10 µg/mL) or isotype (10 µg/mL) and human serum (1:4 dilution) for 6 hours at 37°C and 5% CO_2 (final volume adjusted to 200 µL/well). ^{51}Cr release will be measured from the supernatant by standard gamma counter and the percentage of lysis will be calculated as following:

%Lysis = [Test cpm – Background cpm] / [Maximumcpm – Background cpm]

Individual human serum from each patient will be used as source of complement for CMC assays.

13.3.4 Degree of *In Vivo* Complement Activation and Clinical or Molecular Responses to Ofatumumab-Based Therapy in Mantle Cell Lymphoma

Ofatumumab has been demonstrated to elucidate better complement activation and cell lysis when compared to rituximab in pre-clinical studies. Complement activation will be measured by a) Total hemolytic complement (CH50); and b) serum C3 and C4 levels at different time intervals (before and after the first and last ofatumumab infusion) as previously described by Byrd et al.[51] CH50, and C3/C4 levels will be performed locally per institute standards.

13.3.5 Measurement of Minimal Residual Disease (MRD) by Eight-Color Flow Cytometric Analysis

Peripheral blood and/or bone marrow aspirate specimens will be collected at different time intervals to measure MRD as previously described.[35] Briefly, washed samples will be adjusted to 10,000 leukocytes/µL, incubated with mouse IgG to block Fc receptors and stained with the a panel of directly conjugated monoclonal antibodies against κ, λ, CD5, CD19, CD20, CD23, CD22, and CD79b for 30 minutes followed by incubation with ammonium chloride lysing solution and 2 washing steps. After an incubation with fixable live dead yellow to exclude dead cells the cells will be fixed in 2% formaldehyde and analyzed within 24 hours. Isotope and autofluorescent controls will be included. Data will be collected by a FACSCanto II using DivA software v4.6. Instrument sensitivity and intensity settings will be standardized daily with Cytometer Setup and Tracking beads (CS&T) and compensations will be adjusted using single color controls with automated DiVa routines.

13.3.6 Clonal Evolution in Mantle Cell Lymphoma

The spectrum of clinical behavior observed in MCL patients suggests differences exist at the molecular level that impact clinical outcomes. Mantle cell lymphoma histologically has a spectrum of variants, including blastoid and pleomorphic variants with high proliferation rates and more aggressive clinical behavior. Aberrant over expression of cyclin D1 is characteristic of MCL and is the result of the t(11;14) (q13;q32). Cyclin D1 binds with CDK4, CDK6 and phosphorylates RB1 ultimately leading to cell cycle dysregulation at G1-S phase transition.[52] Apart from this hallmark translocation few other lymphogenesis phenomena have been described to be responsible for MCL including ATM, CHK2 and p53, which are important in cellular DNA damage response. On the other hand, it is unclear if emergence of resistant disease is associated

with cytogenetic abnormalities or loss or gain of cell surface receptors. The most common loci previously reported that are genetically altered in MCL are P53, ATM, CDKN2A (p16), del(q13), MYC, among the others.[53] This study will do a cytogenetic/FISH study at the time of diagnosis, as well as at the time of relapse utilizing the fluorescent in-situ hybridization (FISH) technique to determine the presence and/or acquisition of the above listed cytogenetic abnormalities. This study will subsequently correlate the cytogenetic findings with clinical outcomes.

14 ETHICAL AND REGULATORY STANDARDS

14.1 Ethical Principles

This study will not be initiated until the protocol and informed consent document(s) have been reviewed and approved by a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Each patient (or legal guardian) shall read, understand, and sign an instrument of informed consent prior to performance of any study-specific procedure. It is the responsibility of the investigator to ensure that the patient is made aware of the investigational nature of the treatment and that informed consent is given.

The Investigator is responsible for the retention of the patient log and patient records; although personal information may be reviewed by authorized persons, that information will be treated as strictly confidential and will not be made publicly available. The investigator is also responsible for obtaining patient authorization to access medical records and other applicable study specific information according to Health Insurance Portability and Accountability Act regulations (where applicable).

This study will be conducted in compliance with all applicable laws and regulations of the state and/or country and institution where the patient is treated, in accordance with the Declaration of Helsinki, Good Clinical Practice, and according to the guidelines in this protocol, including attached appendices.

14.2 Informed Consent

The Investigator (or IRB specified designee) is responsible for obtaining written consent from each patient or the patient's legally authorized representative in accordance with ICH-GCP guidelines using the approved informed consent form, before any study specific procedures (including screening procedures) are performed. The informed consent form acknowledges all information that must be given to the patient according to ICH-GCP, including the purpose and nature of the study, the expected efficacy and possible side effects of the treatment(s), and specifying that refusal to participate will not influence further options for therapy. Any additional information that is applicable to the study must also be included. Additional national or institutionally mandated requirements for informed consent must also be adhered to. The patient should also be made aware that by signing the consent form, processing of sensitive clinical trial data and transfer to other countries for further processing is allowed.

The Investigator shall provide a copy of the information sheet and of the signed consent form to the patient and the signed original shall be maintained in the Investigator File. A copy of the

signed consent form must be filed in the patient file. At any stage, the patient may withdraw from the study and such a decision will not affect any further treatment options.

15 STUDY RESPONSIBILITIES

15.1 Data Collection

Data entry into the database is to be completed in a timely fashion (within 30 days) after the patient's clinic visit. If an AE is considered serious it is captured on both the Adverse Event page and the Serious Adverse Event Form, which is handled in an expedited fashion (see **Section 10**).

Data management activities will be performed using eClinical. eClinical is a suite of software tools that enables the collection, cleaning and viewing of clinical trial data. CRS data management will design the study-specific database and facilitate its development by the eClinical Information Technology team. Once the database design is approved by the Investigator, Statistician, and Clinical Research Coordinator, the database will be put into production and data entry can begin. Data can be entered and changed only by those with the rights to do so into the eCRFs via the EXPeRT Module). eClinical is compliant with all relevant technical aspects of relevant GCP guidelines.

- The system can generate accurate copies of stored data and audit trail information in human readable form.
- System access is limited to authorized individuals through the controlled assignment of unique ID and password combinations.
- The system is designed to periodically force users to change their passwords and verifies that user ID and password combinations remain unique.
- The system automatically generates a permanent time-stamped audit trail of all user interactions.

When data entry is complete, data management will review the data and will query any missing, incomplete, or invalid data points for resolution by the Clinical Research Coordinator and Investigator. Once all queries have been resolved, the data can be released to the statistician for analysis.

15.2 Maintenance of Study Documents

Essential documents should be retained per RPCI's policy for 6 years from the study termination date. These documents could be retained for a longer period, however, if required by the applicable local regulatory requirements or by an agreement with RPCI.

16 ADMINISTRATIVE RULES

16.1 Revisions to the Protocol

RPCI may make such changes to the protocol as it deems necessary for safety reasons or as may be required by the U.S. FDA or other regulatory agencies. Revisions will be submitted to the IRB/ERC for written approval before implementation.

16.2 Termination of the Study

It is agreed that, for reasonable cause, either the RPCI Investigators or the Sponsor may terminate this study, provided a written notice is submitted within the time period provided for in the Clinical Trial Agreement. In addition, RPCI may terminate the study at any time upon immediate notice if it believes termination is necessary for the safety of patients enrolled in the study.

16.3 Confidentiality

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

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18 APPENDICES

APPENDIX A INSTRUCTIONS FOR NETWORK SITE

1. CONTACT INFORMATION

All questions related to the protocol or study implementation should be directed to:

Roswell Park Cancer Institute
CRS Network Office
ASB K 104
Buffalo, New York 14263

Telephone:
Monday-Friday; 8:00 AM to 5:30 PM EST
716-845-3155 or 716-845-1203

After hours, weekends, and holidays request the **RPCI Investigator** 716-845-2300

Fax: 716-845-8743

2. INFORMED CONSENT

- Informed Consent must be obtained by the **Site Investigator/designee** from any patients wishing to participate, **prior to any procedures or change in their treatment.**
- An informed consent template is provided by RPCI and can be amended to reflect institutional requirements.
- All consent changes **must** be reviewed by RPCI Network Office prior to submission to the site IRB.
- The informed consent must be IRB approved.
- Always check that you are using the correct date and version of the IRB approved consent.
- Within 5 business days, notify the RPCI Network Office of all participant withdrawals or consent to limited study participation and appropriately document the discontinuation and the reason(s) why.

3. SUBJECT REGISTRATION

The patient completes the **Gender, Race, and Ethnicity Form** and this is placed in the study binder.

RPCI does not grant exceptions to eligibility criteria.

Phase 2 Protocol Registration Instructions

The Subject Screening and Enrollment Log must be faxed to the RPCI Network Office within 1 business day of the date the participant is consented. Once the Investigator has determined that

eligibility has been met, complete the eligibility check list and fax the Subject Registration form to the RPCI Network Monitor at 716-845-8743.

4. STUDY DEVIATIONS

- If a deviation has occurred to eliminate hazard, this should be reported to the RPCI Network, site IRB and any other regulatory authority involved in the trial.
- ALL study deviations will be recorded on the **Study Deviation Log**.

5. STUDY DOCUMENTATION

- Study documents must be filled out completely and correctly. Ditto marks are not allowed.
- If an entry has been documented in error put a single line through the entry and initial and date the change. The RPCI Network Monitor must be able to read what has been deleted.
- Do **NOT** use white-out, magic marker, scratch-outs.
- Do **NOT** erase entries.
- Use only black ink for documentation on the accountability form and any other study forms.
- It is the responsibility of RPCI to inform the Investigator/ institution as to when these documents no longer need to be retained. If, for any reason, the Investigator desires to no longer maintain the study records, they may be transferred to another institution, another investigator, or to RPCI upon written agreement between the Investigator and RPCI.

6. DRUG ACCOUNTABILITY

Drug accountability must be strictly maintained.

- Responsibility rests solely with the Investigator but can be delegated as appropriate (e.g., to pharmacy personnel).
- A drug accountability record form (DARF) will record quantities of study drug received, dispensed to subjects and wasted, lot number, date dispensed, subject ID number and initials, quantity returned, balance remaining, manufacturer, expiration date, and the initials of the person dispensing the medication.
- Study drug supply should only be used in accordance with the IRB approved study.
- Drug accountability forms are protocol and agent specific, they are study source documents and will be used to verify compliance with the study.
- An inventory count must be performed with each transaction. Any discrepancies shall be documented and explained.
- An inventory count should be performed with each transaction. Any discrepancies shall be documented and explained.

- Drug accountability forms shall be stored with study related documents.
- Each medication provided for this study and each dosage form and strength must have its own DARF.
- Dispensing the wrong study supply is considered a **medication error**.
    - **Never** replace investigational agents with commercial product.
    - Do **NOT** "transfer", "borrow" or "replace" supplies between studies.

7. SERIOUS ADVERSE EVENT REPORTING

The site Investigator or designated research personnel will report all SAEs whether related or unrelated to the investigational agent(s) to the site's **IRB in accordance with their local institutional guidelines**.

The site will notify the RPCI Network Monitor within 1 business day of being made aware of the SAE. Follow protocol Section 10.2.2 Reporting Serious Adverse Event. Report promptly to local IRB, NCCN, and Novartis

A preliminary written report must follow within 1 business day of the first notification using the following forms:

- RPCI SAE Source form
- MedWatch 3500A

SAEs and pregnancies should also be reported to Novartis representative (**Appendix F**)

SAE reports are to be submitted to the NCCN: Email ORPReports@NCCN.org or fax SAEs to: 215-358-7699

A complete follow-up report must be filed within 10 working days.

A complete follow-up report must be sent to the RPCI Network Monitor when new information becomes available.

8. UNANTICIPATED PROBLEM REPORTING

An unanticipated problem (UP) is any incident, experience, or outcome that meets all of the criteria in **Section 10.5.**

For all adverse events occurring that are unanticipated and related or possibly related to the research drug, biologic or intervention, the participating physician or delegated research staff from each site will notify **their local IRB in accordance with their local institutional guidelines**. The site must also notify the RPCI Network Monitor within 1 business day of being made aware of the Unanticipated Problem by completing the **RPCI Unanticipated Problem Report Form** and faxing it to the RPCI CRS Network Office FAX # 716-845-8743

APPENDIX B Screening for Progressive Multifocal Leukoencephalopathy During Ofatumumab Treatment in B-Cell Lymphoma Patients

Progressive multifocal leukoencephalopathy (PML) is a viral-induced demyelinating disease of the central nervous system usually occurring in the immunocompromised individual. JC virus infection resulting in PML and death has been reported in rituximab-treated patients with hematologic malignancies or with systemic lupus erythematosus (SLE), an indication for which rituximab has not been approved. In the literature, PML has been reported to occur in 0.52% of CLL patients and in approximately 5% of fludarabine-treated B-CLL patients. One case of PML was reported in a very ill CLL patient treated with ofatumumab, previously treated with alemtuzumab and fludarabine and with very low CD4 cell count.

Investigators and nurses should pay careful attention for signs and symptoms consistent with a diagnosis of PML. Signs and symptoms of PML include visual disturbances, ocular movements, ataxia, and changes in mental status such as disorientation or confusion. These symptoms are not an exhaustive list and the investigator should exercise judgment in deciding to report signs and symptoms to sponsor promptly.

If a patient develops neurological signs or symptoms consistent with PML treatment should be halted and the patient referred to a neurologist for evaluation. At a minimum, blood JCV PCR and/or MRI will be performed and if either is positive perform Cerebrospinal Fluid (CSF) JCV PCR. If blood JCV PCR and MRI are negative, the investigator will contact the NCCN for appropriate action to be taken. If blood JCV PCR and/or MRI are positive, the patient should proceed to the Follow-Up Period. All such patients will be followed until resolution. Any patient with a diagnosis of PML will be withdrawn from ofatumumab. There are no known tests that can reliably determine who is at increased risk for developing PML. There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs.

	Neurological Symptoms Questions	YES	NO
1.	Does the patient report any new weakness?		
2.	Does the patient report any new difficulty with coordination or walking?		
3.	Does the patient report any new signs of confusion, impaired memory or attention?		
4.	Does the patient appear apathetic compared to previous contacts?		
5.	Does the patient report any new visual disturbances?		
6.	Has the patient had any new trouble speaking, either slurring speech, difficulty getting out words, difficulty understanding words, or difficulty comprehending spoken language?		
7.	Does the patient have any other new neurological symptoms, including but not limited to: New onset seizure. New sensory loss. New emotional liability.		

If any of the above are answered “Yes” at any visit, the investigator will refer the patient to a neurologist.

APPENDIX C Ofatumumab Liver Interruption/Stopping Criteria for Oncology Studies (Updated May 2011)

Based upon SRT discussion and agreement on 16 February 2011 and 03 March 2011, the following Liver Interruption/Stopping criteria were established for use in all ofatumumab oncology trials including CRTs. These criteria were initially discussed with Novartis for OMB110911. The criteria are required for all future ofatumumab oncology protocols (including this clinical trial).

CRITERIA 1: ALT > 3 x upper limit of normal (ULN) **and** bilirubin > 2 x ULN (> 35% direct bilirubin; bilirubin fractionation required‡). ‡ *NOTE: If serum bilirubin fractionation not immediately available, study drug should be discontinued if ALT > 3 x ULN and bilirubin > 2 x ULN. Serum bilirubin fractionation should be performed if testing is available. If testing unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.*

CRITERIA 2: ALT > 8 x ULN.

CRITERIA 3: ALT > 5 x ULN for more than 2 weeks.

Liver Chemistry Interruption/Stopping and Follow- up Criteria have been designed to assure patient safety and evaluate liver event etiology. The site investigator in conjunction with the Principal Investigator at RPCI will review all events which meet liver chemistry stopping criteria to determine if the event was due to tumor lysis, disease related liver involvement, concomitant chemotherapy or other identified cause and to exclude drug induced liver injury (DILI) due to ofatumumab. If the event is determined to be due to causes other than ofatumumab DILI and improvement is observed after withdrawal of ofatumumab, rechallenge may be attempted if deemed appropriate by the principal investigator and in addition to consent of the patient.

When any of the liver chemistry stopping criteria is met, do the following:

Immediately stop study treatment.

Report the event to NCCN within 24 hours of learning its occurrence.

Hold ofatumumab for 2 weeks, repeat liver chemistry testing at least twice weekly, and call the Principal Investigator at RPCI to discuss the possibility of re-challenging with ofatumumab. *Note: The 2 week time point for stopping medication was chosen because it will distinguish from LFT elevations due to tumor lysis, which should have resolved within this time period. Medication is interrupted and it is a clinical and patient decision if ofatumumab may be re-started. The risk:benefit ratio is different in an oncology setting and an efficacious therapy may be life-saving.*

Report SAE to NOVARTIS within 24 hours.

All events of ALT > 3 x ULN and bilirubin > 2 x ULN (> 35% direct bilirubin) (or ALT > 3 x ULN and INR > 1.5, if INR measured; INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants), termed 'Hy's Law', must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

NOTE: if serum bilirubin fractionation is not immediately available, study treatment should be discontinued if ALT > 3 x ULN and bilirubin > 2 x ULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.

Liver chemistry follow-up assessments are to be followed until liver chemistries resolve, stabilize or return to baseline values.

Liver Chemistry Follow-up Assessments: (these chemistry tests/ assessments below are to be performed at the time of the event and then continued and/or discontinued at the discretion/judgment of the sponsor-investigator; please refer to stopping criteria within this document below).

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

Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).

Fractionate bilirubin, if total bilirubin > 2 x ULN.

Obtain complete blood count with differential to assess eosinophilia.

Record the appearance or worsening clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash.

Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins.

Increased alcohol use.

The following assessments are required for patients with ALT > 3 x ULN and bilirubin > 2 x ULN (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.

Stopping Criteria:

For patients meeting liver Criteria 1:

A repeat of liver chemistries within 24 hours, liver event follow-up assessments and close monitoring.

A specialist or hepatology consultation is recommended.

Monitor patients twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

For patients meeting Criteria 2 or 3:

A repeat of liver chemistries within 24 hours to 72 hours for repeat liver chemistries and liver event follow-up assessments.

Monitor patients weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

After holding ofatumumab for 2 weeks:

If the treatment is exhibiting efficacy and the patient wants to continue therapy after being informed of the results of liver chemistry testing, then the ofatumumab may be re-started.

Liver chemistries and follow-up assessments should be monitored at a minimum of every 2 weeks until resolution, stabilization, or a return to baseline values, at which point monitoring should be continued per protocol.

Patients with ALT > 3 x ULN but ALT < 5 x ULN and bilirubin < 2 x ULN without hepatitis symptoms or rash, and who may be monitored weekly for at least 4 weeks, then the following actions should be taken:

Patients can continue ofatumumab.

Weekly repeat of liver chemistries until they resolve, stabilize, or return to baseline values, then monitor liver chemistries as per protocol assessment schedule.

If at any time the patient meets any of the liver chemistry stopping criteria, then proceed as described above.

If after 4 weeks of monitoring, ALT < 3 x ULN and bilirubin < 2 x ULN monitor twice monthly until liver chemistries normalize or return to within baseline values.

APPENDIX D Schema of Pathology Tissue Processing

A3.1 For processing a fresh lymph node or extra-nodal mass biopsy material for pathological diagnosis and correlative science experiments.

A3.1.1 Applicable to:

- To be performed in patients that the original biopsy was not sufficient for complete diagnosis or patients with accessible lymph nodes consenting for a repeat biopsy to complete correlative studies (i.e. ex vivo testing, as all other studies can be performed from archived material).
- To be performed in all patients with suspected relapsed/refractory disease after ofatumumab-hyper-CVAD/ofatumumab-HD-MA or during the follow up period (including after HDC-ASCT if eligible).

A3.2.1 Procedure(s):

The pathologist will first make 6 touch preparations to confirm the presence of representative tissue adequate for evaluation. Tissue will then be divided as follows:

1. Sufficient tissue to clinical pathology to be formalin-fixed and paraffin-embedded for morphology and immunohistochemistry
2. Fresh tissue in RPMI 10%FCS for ex vivo studies to the RPCI Lymphoma/Myeloma Laboratory CCC Bldg. 3rd Floor, Rm 304 [RPCI patients only]
3. If sufficient tissue remains, submit fresh in % RPMI 10%FCS to the RPCI Cytogenetics Lab.

To isolate B-cells by negative selection for ex vivo *studies (RPCI patients only)* *Fresh tissue in RPMI-10% to Lymphoma/Myeloma Lab*	***Clinical Pathology***	*Cytogenetics studies* *If tissue remains, submit fresh in RPMI-10% to RPCI Cytogenetics Lab*

A3.2 For processing archived lymph node or extra-nodal mass biopsy material for pathological diagnosis and correlative science experiments

A3.2.2 Applicable to:

- To be performed in all patients during the registration period (See **Section 7.1**).
- Material to be submitted: tissue block (preferable) or 10 – 20 unstained slides cut at 4 μm on positively charged slides for pathological examination.
- If nodal/extranodal fresh tissue is not available, but involved bone marrow at diagnosis with MCL specimen had been procured, cytogenetic studies can be performed from such material and must be submitted. FISH can also be performed on unstained FFPE sections from diagnostic sample, cut at 4 μm and placed on positively charged slides.

APPENDIX E Roswell Park Cancer Institute MCL-OFA-1 Form

Specimen Shipment Form MCL-OFA-1 **Study Number: I 201611**			
Patient ID: **2016VU_ _**			**Fax a copy to:** **Cory Mavis** **716-845-7188**
Date Collected:	Sex:	Age:	
Specimen Type:			
Specimen Site:			

Note: Specimen must be shipped between Mondays to Thursdays
Please schedule surgical procedures accordingly to adhere to shipment days.
Ship via overnight mail (check AM delivery)

FedEx the Original form with the specimen to:

Roswell Park Cancer Institute
Department of Medicine Lymphoma/Myeloma Laboratory
CCC Bldg. 3rd Floor, Rm 304
Attn: Study Number – I 201611
Elm & Carlton Streets
Buffalo, NY 14263
Tel: 716-845--3464
Fax: 716-845-7188

Contact: cory.mavis@RoswellPark.org

PLEASE CIRCLE THE APPROPRIATE SAMPLE BEING SHIPPED

Baseline:

A mandatory tissue block or unstained slides (10-20) are to be submitted to Cory Mavis who will deliver to RPCI Pathology Department for central pathology review

10mL green top – Blood (MRD)

5mL green top - Bone marrow aspirate (MRD)

5mL green top – Bone marrow aspirate (cyto)

Restaging Visits (prior to C3, prior to C5, prior to transplant) and D100 post-transplant:

10mL green top – Blood (MRD)

5mL green top – Bone marrow aspirate (MRD)

Follow-up Visits – every 6 months for 3 yrs. or until PD:

10mL green top – Blood (MRD)

At relapse or diagnosed refractory disease:

5mL green top – Bone marrow aspirate (cyto)

APPENDIX F Serious Adverse Event Report Fax Coversheets

NOVARTIS

Interventional Clinical Trial SAE Fax Cover Sheet

To: Local Novartis Patient Safety via **1-877-778-9739**

If you experience difficulty faxing this form, please email the SAE & Cover Sheet to clinicalsafetyop.phuseh@novartis.com

Investigator contact details:

Fax number: _____

Phone number: _____

Study Name	I 201611: Ofatumumab (O) in Combination With Chemotherapy: Hyper-Fractionated Cyclophosphamide, Doxorubicin, Vincristine and Dexamethasone (O-HyperCVAD) Alternating With Ofatumumab High-Dose Cytarabine and Methotrexate (O-MA) for Patients With Newly Diagnosed Mantle Cell Lymphoma
Centre Number	
Patient Number	

NVS STUDY #: COMB157DUS12T

Relationship between study treatment and event(s) is:

Suspected/Unknown

This document contains important safety information.
If fax is received in error, please forward to 1-877-778-9739

Version 3.0, 14 Mar 2017

NOVARTIS

Interventional Clinical Trial SAE Fax Cover Sheet

To: Local Novartis Patient Safety via **1-877-778-9739**

If you experience difficulty faxing this form, please email the SAE & Cover Sheet to clinicalsafetyop.phuseh@novartis.com

Investigator contact details:

Fax number: _____

Phone number: _____

Study Name	I 201611: Ofatumumab (O) in Combination With Chemotherapy: Hyper-Fractionated Cyclophosphamide, Doxorubicin, Vincristine and Dexamethasone (O-HyperCVAD) Alternating With Ofatumumab High-Dose Cytarabine and Methotrexate (O-MA) for Patients With Newly Diagnosed Mantle Cell Lymphoma
Centre Number	
Patient Number	

NVS STUDY #: COMB157DUS12T

Relationship between study treatment and event(s) is:

Not Suspected

This document contains important safety information.
If fax is received in error, please forward to 1-877-778-9739

Version 3.0_14 Mar 2017

APPENDIX G Reproductive Potential and Contraceptive Methods

Women of child-bearing potential (WOCBP) is defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception throughout the study and for 6 months after study drug discontinuation. Highly effective contraception methods include:

- Total abstinence when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.
- Combination of any of the two following (a+b or a+c or b+c)
    a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
    b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
    c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository

In case of use of oral contraception, women should have been stable on the same pill before taking study treatment.

Note: Oral contraceptives are allowed but should be used in conjunction with a barrier method of contraception due to unknown effect of drug-drug interaction.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

Sexually active males should not father a child unless they use a condom during intercourse while taking the drug and 3 months after stopping treatment. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. Sexually active mails should not donate sperm while taking the drug and 3 months after stopping treatment.