MSK PROTOCOL COVER SHEET

Sequential Chemotherapy and Lenalidomide Followed by Rituximab and Lenalidomide Maintenance for Untreated Mantle Cell Lymphoma: A Phase II Study

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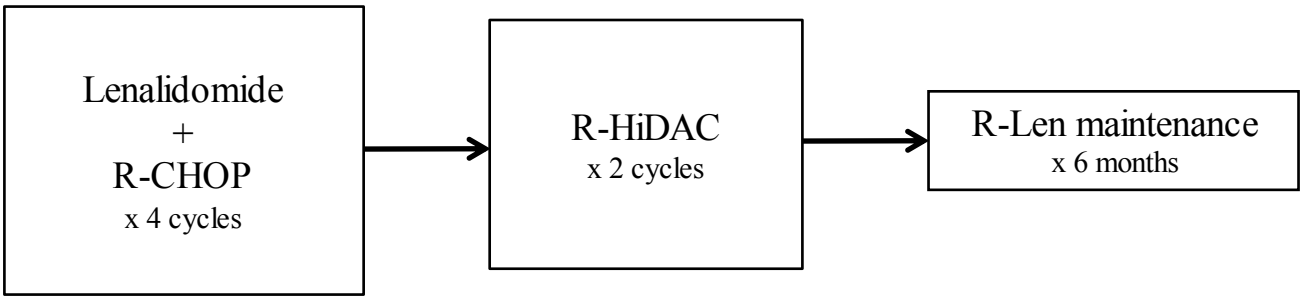
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

In this phase II study, we aim to improve outcomes for untreated mantle cell lymphoma (MCL) patients by incorporating the highly active agent, lenalidomide, to a standard induction chemotherapy backbone including RCHOP and high-dose cytarabine. Traditionally, patients with MCL have been treated based upon age or transplant-eligibility status with "younger" patients receiving multi-agent chemotherapy followed by high-dose therapy and autologous stem cell transplant (HDT-ASCT) while "older" patients typically receive less toxic chemotherapy combinations, like bendamustine and rituximab. However, this paradigm may no longer be applicable in MCL with the advent of highly active, biologically-targeted therapies, such as lenalidomide, and emerging data that suggests an unclear benefit of consolidation with HDT-ASCT. In this study, we will enroll both "younger" and "older" patients with untreated MCL. Lenalidomide has known clinical activity in both untreated and relapsed/refractory MCL. With increasing data demonstrating the benefit of maintenance after initial therapy, in this study, patients will receive 6 months of rituximab and lenalidomide maintenance therapy. In addition, we will assess early biomarkers for response, including PET/CT and minimal residual disease assessment using a novel deep-sequencing platform, and correlate these biomarkers with clinical outcomes. In particular, we are interested in assessing what proportion of patients convert to MRD- and PET-negativity after each phase of therapy, Len-RCHOP, R-HiDAC, and after Len-R maintenance, to assess the kinetics and depth of response with the three phases of treatment. The primary outcome in the study will be 3-year progression-free survival and the study will enroll a total of 45 patients.



2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective

- Determine the 3-year progression-free survival (PFS) of the primary treatment program (Len-RCHOP→R-HiDAC→R-Len maintenance)

Secondary Objectives

- Assess the 3-year PFS in different clinical risk subgroups, specified below:

- Low Risk: Ki-67<10%
- Intermediate Risk: Ki-67 10-30%
- High Risk: Ki-67≥30% or blastic/blastoid/pleomorphic morphology

- Assess if the mantle cell international prognostic index (M-IPI) is prognostically significant (correlated with PFS and OS) with this treatment program.
- Assess the rate of PET-negativity (Deauville 1, 2, or 3) at various time points and correlate with outcome (PFS). Time points include after lenalidomide-RCHOP chemotherapy, after R-HiDAC therapy, and at the conclusion of maintenance therapy.
- Evaluate MRD status using a novel deep-sequencing platform at various time points and correlate with outcome (PFS). Time points include baseline, after lenalidomide-RCHOP chemotherapy, after R-HiDAC therapy, at the conclusion of maintenance therapy, and 6 months after completion of Len-R maintenance.
- Assess the 3-year overall survival (OS)

Exploratory Objectives

- Collect serum and peripheral blood mononuclear cells to store in MSKCC tissue bank for future correlative studies. Time points will be the same as MRD collection time points (baseline, after lenalidomide-RCHOP chemotherapy, after R-HiDAC therapy, at the conclusion of maintenance therapy, and 6 months after completion of Len-R maintenance).

3.0 BACKGROUND AND RATIONALE

Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is an uncommon B-cell Non-Hodgkin lymphoma, comprising approximately 6-8% of all Non-Hodgkin lymphomas.[1] Mantle cell lymphoma often presents with advanced stage disease and common sites of extranodal involvement include the bone marrow or GI tract. The median age of presentation for mantle cell lymphoma is 68 years and more commonly presents in men versus women.

Morphologically, MCL is comprised of small to intermediate sized cells with a characteristic immunophenotype of CD5+, CD10-, BCL6-, CD20+, CD23-, CD43+, and cyclin D1+. There are different morphologic variants of MCL including blastoid, pleomorphic, small cell, and marginal zone-like variants. Blastoid and pleomorphic variants are composed of larger cells, similar to lymphoblasts, and are associated with poor clinical outcomes.[2] Mantle cell lymphoma is classically characterized by the presence of the reciprocal chromosomal translocation t(11;14) between the proto-oncogene CCND1 and the immunoglobulin heavy chain (IgH) locus.[3] This translocation leads to the deregulation of the gene CCND1 and to the overexpression of its protein product cyclin D1, an important regulator of the G1-S phase transition of the cell cycle. There are rare cases of cyclin D1and t(11;14) negative MCL.

These cases typically over express cyclin D2 or D3 and can be associated with rearrangements involving the CCND2 gene.[4,5] Recently, expression of the transcription factor SOX11 has been described to be present in the majority of cases of conventional MCL, as compared to indolent MCL which lacks SOX11 expression, and the presence of SOX11 expression can be a useful diagnostic tool in cyclin D1 negative cases.[6,7]

Prognostic Impact of Proliferative Index

The clinical behavior of mantle cell lymphoma is highly variable. A clinical prognostic score called the mantle cell international prognostic index (M-IPI) comprised of four clinical baseline characteristics including age, performance status, lactate dehydrogenase level, and white blood cell count is an effective risk stratification tool in MCL, recently validated demonstrating the 5-year overall survival rates in low, intermediate, an high-risk groups to be 83, 63, and 34%.[8,9] An important biologic prognostic marker in MCL is increased cell proliferation. Gene expression profiling defined a "proliferation signature" that is associated with inferior survival in MCL.[10] Immunohistochemistry tests that are routinely applicable in the clinical setting for MIB-1 expression or Ki-67 proliferative index can also provide an estimate of the cell proliferation and have been shown to have prognostic impact in multiple studies.[11,12] For example, in the 2nd Nordic MCL trial (MCL-2) of rituximab-maxi-CHOP alternating with rituximab-high-dose cytarabine followed by high dose therapy and stem cell transplant, event-free survival was significantly different when comparing groups of patients defined by Ki-67 index <10%, 10-29%, and >29%, see figure below.[11] Visual estimation of Ki-67 is subject to interobserver variability and a study determining the proliferative index by quantitative analysis also found that Ki-67 was a powerful prognostic tool with a Ki-67 cut-off of 30% defining risk groups with statistically significant differences in PFS and OS.[12]

Based on these data, we will plan to compare outcomes with our novel treatment program across prognostically significant clinical risk groups including 1) low risk: Ki-67<10%, 2) intermediate risk: Ki-67 10-30%, and 3) high risk: Ki-67≥30% or blastic/blastoid/pleomorphic morphology. In particular, we are interested in assessing whether the addition of lenalidomide will improve outcomes for the poor-risk group defined by elevated proliferative index.

Induction chemotherapy for MCL

Traditionally, patients with MCL have been separated into two groups “younger” or “transplant-eligible” versus “older” or “transplant-ineligible.” These two groups have been treated differently with “younger” patients receiving multi-agent chemotherapy followed by HDT-ASCT while “older” patients typically receive less toxic chemotherapy combinations, like R-CHOP followed by maintenance rituximab or bendamustine and rituximab. However, this paradigm may no longer be applicable in MCL, particularly with the development of novel therapies and with growing evidence that maintenance therapy may be equivalent to HDT-ASCT.

Cytarabine is a highly active drug in MCL and for the proposed treatment program it was important to ensure that high-dose cytarabine was included in the induction chemotherapy program. The addition of cytarabine to induction chemotherapy for younger mantle cell

lymphoma patients has been associated with improvements in progression free and overall survival in multiple studies. The R-HyperCVAD regimen with alternating high dose cytarabine and methotrexate demonstrated a high CR rate of 87% and with median follow up of 8.3 years, the median time to treatment failure among patients younger than 65 years was 5.9 years and median OS not yet reached.[13,14] Another treatment program including high dose cytarabine was the Nordic MCL-2 trial that treated patients with augmented RCHOP alternating with R-high-dose cytarabine followed by HDT-ASCT in responding patients.[11] The 6-year OS, EFS, and PFS were 70%, 56%, and 66% respectively. Updated results with median observation time of 6.5 years, yielded a median EFS of 7.4 years and median OS was not reached.[15] A similar phase II trial from the Groupe d'Etude des Lymphomes de l'Adulte utilized R-DHAP instead of R-high-dose cytarabine in an induction chemotherapy regimen consisting of sequential R-CHOP/R-DHAP followed by HDT-ASCT.[16] This study reported an ORR of 95% with median EFS of 6.9 years and a 75% survival rate at 5 years. Finally, a randomized study from the EU MCL Younger Network reported at American Society of Hematology (ASH) 2012 conference, definitively compared RCHOPx6 cycles induction chemotherapy to cytarabine-containing alternating RCHOPx3 cycles and RDHAPx3 cycles induction chemotherapy and found that the RDHAP induction chemotherapy arm was associated with improved CR rate, TTF, and OS.[17] In this study, responding patients in both arms received consolidation with HDT-ASCT. After a median of 51 months, time to treatment failure (TTF) was longer in the DHAP-containing arm (46 vs 88 months; p=0.038, HR 0.68) and OS was also superior (not reached vs 82 months, p=0.045). A recent MSKCC trial (11-095) utilized a cytarabine-containing induction chemotherapy backbone with 4 cycles of dose-dense RCHOP followed by 2 cycles of R-high-dose-cytarabine with excellent preliminary results. For the current study, we plan to add lenalidomide to a cytarabine-containing induction chemotherapy backbone consisting of 4 cycles of RCHOP chemotherapy followed by 2 cycles of high-dose cytarabine.

Lenalidomide in Mantle Cell Lymphoma

Lenalidomide is a proprietary IMiD® compound of Celgene Corporation. IMiD® compounds have both immunomodulatory and anti-angiogenic properties which could confer antitumor and antimetastatic effects. Lenalidomide has been demonstrated to possess anti-angiogenic activity through inhibition of bFGF, VEGF and TNF-alpha induced endothelial cell migration, due at least in part to inhibition of Akt phosphorylation response to bFGF.[18] In addition, lenalidomide has a variety of immunomodulatory effects. Lenalidomide stimulates T cell proliferation, and the production of IL-2, IL-10 and IFN-gamma, inhibits IL-1 beta and IL-6 and modulates IL-12 production.[19]

Although the exact antitumor mechanism of action of lenalidomide is unknown, a number of mechanisms are postulated to be responsible for lenalidomide's activity against multiple myeloma. Lenalidomide has been shown to increase T cell proliferation, which leads to an increase in IL-2 and IFN-gamma secretion. The increased level of these circulating cytokines augment natural killer cell number and function, and enhance natural killer cell activity to yield an increase in multiple myeloma cell lysis.[20] In addition, lenalidomide has direct activity against cancer cells and induces apoptosis or G1growth arrest in multiple myeloma cell lines.[21]

Lenalidomide is an immunomodulatory agent demonstrating antiproliferative effects in MCL. Several studies demonstrated promising activity with single-agent oral lenalidomide as well as lenalidomide and rituximab for the treatment of relapsed/refractory MCL. Lenalidomide was administered at a dose of 25 mg daily in a subset of 57 relapsed/refractory MCL patients included in the NHL-003 study and was associated with an ORR of 35% with a median duration of response of 16.3 months after approximately 20 months median follow up.[22] The larger international, multi-center, phase II EMERGE study of single-agent lenalidomide in patients who relapsed after or were refractory to bortezomib demonstrated an ORR of 28% (7.5% CR/CRu) with a similar median duration of response of 16.6 months.[23] This study led to the FDA approval of lenalidomide in MCL patients whose disease relapsed or progressed after two prior therapies, one of which included bortezomib. In combination with rituximab, lenalidomide was well-tolerated and associated with improved response rates, ORR 57% (36% CR/CRu).[24]

Lenalidomide has also been used for the upfront treatment of mantle cell lymphoma. A recent study reported by Ruan *et al* at the ASH 2014 conference included data from 38 previously untreated advanced stage MCL patients treated with induction and maintenance lenalidomide and rituximab.[25,26] During the induction phase, lenalidomide was administered at 20 mg daily on days 1-21 of a 28-day cycle for a total of 12 cycles, with dose escalation to 25 mg daily if tolerated. Rituximab was administered weekly x 4 during cycle 1, then once every 2 months, for a total of 9 doses. During the maintenance phase which starts with cycle 13, lenalidomide is administered at 15 mg daily on days 1-21 of a 28-day cycle, with rituximab maintenance every 2 months until progression of disease. The majority of patients had favorable disease biology with Ki67 index of <30% in 68% of patients (26/38). The ORR for all patients was 84.2% with 52.6% achieving a CR. With median follow up of 24 months, the estimated 2-year PFS rate is 83.9% and median PFS was not reached. The depth of responses improved over time with an increased number of patients achieving a complete response by 12 months compared with 3 months. In this study, neither MIPI score nor Ki67 index correlated with response. The preliminary data from this study is very promising, showing high response rates and an excellent 2-year PFS with the combination of lenalidomide and rituximab for the initial treatment of mantle cell lymphoma.

Lenalidomide-RCHOP

Given the excellent activity of lenalidomide in mantle cell lymphoma both for newly diagnosed patients as well as in relapsed, refractory patients, incorporation of lenalidomide into a standard chemotherapy backbone for untreated mantle cell lymphoma is likely to result in the increased efficacy of the induction program. We hypothesize that the induction regimen of Len-RCHOP followed by R-HIDAC will result in a higher complete response rate and higher proportion of patients with absence of minimal residual disease, as well as improvements in PFS and OS.

Lenalidomide has been safely combined with RCHOP in a phase 1 studies of B-cell Non-Hodgkin lymphomas and in two large phase 2 trials in diffuse large B-cell lymphoma (DLBCL).[27-30] Two different dosing schedules for the lenalidomide have been used in DLBCL: 1) lenalidomide 15mg orally daily on days 1-14 and 2) lenalidomide 25 mg orally daily on days 1-10. Although both were safe, the lenalidomide dose of 15 mg days 1-14 versus 25 mg

days 1-10 was associated lesser myelosuppression (22% vs. 75% grade 4 neutropenia; 13% vs. 44% grade 3 and 4 thrombocytopenia; 4% vs. 9.4% febrile neutropenia, respectively).[29] The VTE rates were low in both studies, range 1.6 – 4%. Therefore, we plan to use the dosing schedule of lenalidomide 15mg orally daily on days 1-14 in conjunction with standard RCHOP. In addition, all patients with receive pegfilgrastim support and aspirin VTE prophylaxis.

Maintenance therapy in MCL

In the current study, after completion of induction chemotherapy, patients will receive maintenance therapy with lenalidomide and rituximab. Lenalidomide and rituximab maintenance therapy was effectively applied in the aforementioned study by Ruan *et al* and there are a growing number of studies that underscore the important of maintenance therapy in MCL. Although several phase II studies that have supported the role of HDT-ASCT after induction chemotherapy in younger patients with MCL, there is no phase III randomized trial data to support the use of HDT-ASCT in first remission in MCL. Furthermore, there is data to suggest that HDT-ASCT may be deferred to a later time point in the disease course of MCL. A recent registry study from the Center for International Blood and Marrow Transplant Research demonstrated that HDT-ASCT performed at a later time point, not after first remission, is an effective strategy resulting in a 5-year overall survival of 44%.[31] A recent study reported at ASH 2014 of the first interim analysis of the phase III randomized Lyma Trial showed a significantly improved EFS and PFS after rituximab maintenance versus observation. In this study, patients were treated with R-DHAP x 4 cycles and if CR/PR, then patients received HDT-ASCT with subsequent randomization to rituximab maintenance versus observation. Finally, there are several studies that have demonstrated the efficacy of maintenance therapy after induction chemotherapy in mantle cell lymphoma. In the EU MCL Elderly phase III study, patients ≥ 60 years of age underwent two randomizations: first to R-FC versus R-CHOP chemotherapy and next to maintenance therapy with rituximab or interferon alpha until progression.[32] Overall survival was significantly improved in the RCHOP versus R-FC arm, and among responding patients who received RCHOP, administration of maintenance rituximab was associated with improved overall survival with a 4-year overall survival of 87%. These results for RCHOP followed by maintenance rituximab are among the best outcomes reported for the upfront treatment of MCL in the elderly and suggest that the maintenance phase is important for prolonging PFS and OS and likely improves the depth of response after initial therapy. Another study including maintenance therapy for untreated MCL is the Eastern Cooperative Oncology Group phase 2 study of rituximab, bortezomib, modified hyper-cyclophosphamide, doxorubicin, vincristine, dexamethasone (VcR-CVAD) induction chemo immunotherapy with maintenance rituximab for 2 years.[33] Seventy-five patients were included and transplant-eligible patients had the option of HDT-ASCT consolidation instead of maintenance rituximab. The primary end point was the CR rate to VcR-CVAD. The ORR was 95% and a CR was achieved in 68% of patients. After a median follow-up of 4.5 years, 3-year PFS and OS were 72% and 88%, respectively. No substantial difference in PFS or OS was observed between patients treated with maintenance rituximab (n = 44) vs HDT-ASCT (n = 22). Although the study was not designed or powered to compare maintenance rituximab and HDT-ASCT, these data raise the possibility that a maintenance phase post-induction may be equivalent to HDT-ASCT.[34] Taken together, these data suggest that maintenance therapy is highly efficacious in MCL and that HDT-ASCT,

particularly in light of its associated toxicities, may not be a necessary component of initial therapy for MCL patients.

The lenalidomide maintenance dose of 15 mg day on days 1-21 of 28-day cycle with rituximab every 2 months is the same maintenance dose used in the Weill Cornell Medical College study of untreated advanced stage MCL patients with induction and maintenance lenalidomide and rituximab.[25] Lenalidomide maintenance has been extensively studied in multiple myeloma and the maintenance dose ranges from 10-15 mg days 1-21 of a 28-day cycle continued indefinitely post-ASCT and is generally well-tolerated and associated with prolonged time to disease progression.[35,36] The optimal duration of maintenance therapy is unclear in MCL, and, therefore, we are interested in studying an abbreviated maintenance period of 6 months and utilizing MRD assessments to gain insight into the optimal duration of lenalidomide-rituximab based upon conversion from MRD-positivity to negativity.

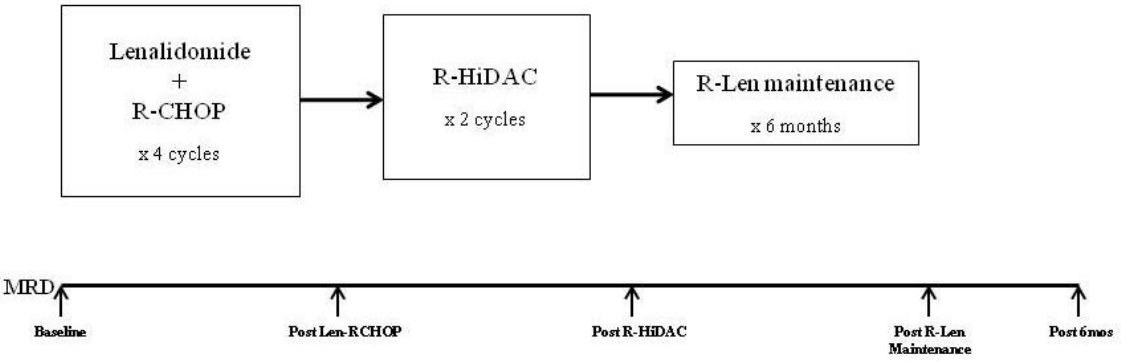
Minimal Residual Disease in MCL

Several strategies for the detection of minimal residual disease in lymphoid malignancies have been developed. A molecular marker for MRD in B-cell lymphomas is the presence of a unique immunoglobulin heavy chain gene rearrangement associated with a malignant clone (clonotypic DNA sequence). Allele-specific oligonucleotide PCR (ASO-PCR) amplification of immunoglobulin genes has been previously employed, however, a novel DNA sequencing-based technique for detecting MRD has been developed with advantages over ASO-PCR. The Sequenta LymphoSIGHT™ platform is a high-throughput DNA sequencing method that can detect minimal residual disease (MRD) of lymphoid malignancies in peripheral blood that has a higher sensitivity of one lymphoma cell per million leukocytes, efficient turn-around time, and the ability to detect and monitor multiple clones.[37,38]

MRD detection has been found to be prognostically significant in MCL.[39,40] Using the ASO-PCR technique, MCL patients treated on 2 randomized trials (MCL Younger and Elderly) had MRD status assessed after induction therapy and after HDT/ASCT (MCL Younger) or during maintenance therapy (MCL Elderly).[39] Achievement of molecular remission (MRD-negative) after induction therapy and HDT/ASCT was associated with significantly improved progression-free survival.

In this study, we plan to test MRD status using the Sequenta LymphoSIGHT™ platform after lenalidomide-RCHOP chemotherapy, after R-HiDAC therapy, at the conclusion of maintenance therapy, and 6 months after completion of Len-R maintenance.

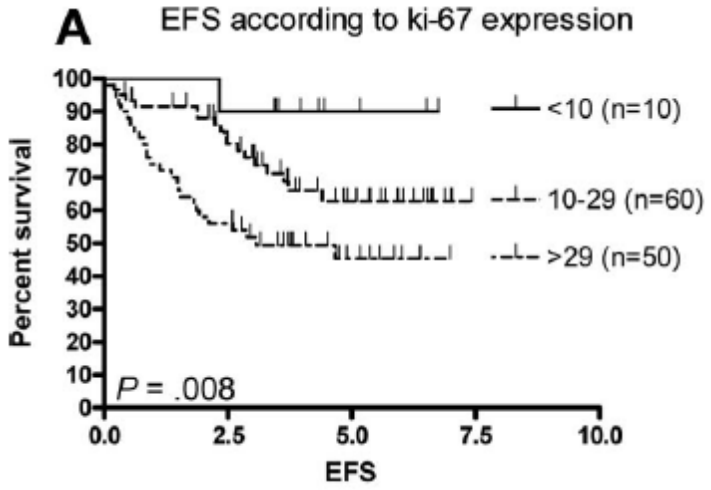
Adaptive Biotechnologies will be using the data to seek regulatory approval and development of the assay for treatment purposes.



Interim PET-CT in MCL

Achievement of a negative PET-scan after induction chemotherapy prior to consolidation with HDT/ASCR has been shown to be prognostically significant. In the MCL-3 study of R-maxi-CHOP alternating with R-high-dose Ara-C followed by Zevalin-ASCT, 77% of patients had a PET-CT scan performed after induction chemotherapy and interpreted using the Deauville 5-point scale with Deauville 1-3 defined as negative. In this study, 85.6% (107/125) patients achieved a negative PET-scan and these patients had significantly improved PFS compared to patients with an interim PET-positive scan, 4- year PFS of 78% versus 27%, respectively ($p<0.001$).

In this study, we plan to obtain PET-CT at baseline, after lenalidomide-RCHOP chemotherapy, after R-HIDAC therapy, and at the conclusion of Len-R maintenance therapy. The PET-CT scans will be interpreted using the Deauville 5-point scale.

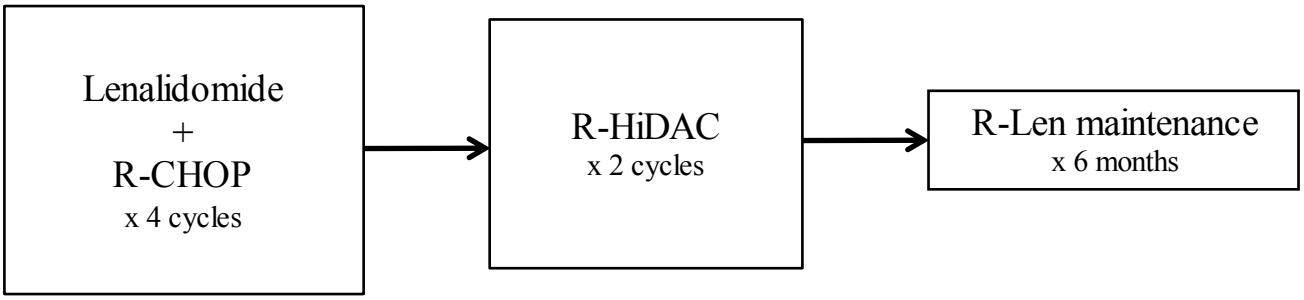


Based on these data, we will plan to compare outcomes with our novel treatment program across prognostically significant clinical risk groups including 1) low risk:Ki-67<10%, 2) intermediate risk: Ki-67 10-30%, and 3) high risk: Ki-67≥30% or blastic/blastoid/pleomorphic morphology. In particular, we are interested in assessing whether the addition of lenalidomide will improve outcomes for the poor-risk group defined by elevated proliferative index.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a phase II clinical trial at MSKCC for mantle cell lymphoma patients previously untreated with systemic therapy. This will include both "younger" / transplant-eligible patients as well as "older" / transplant-ineligible patients. Patients will be treated with three phases of treatment: lenalidomide + RCHOP, rituximab + high-dose cytarabine, and lenalidomide + rituximab maintenance. The treatment schema is shown below:



4.2 Intervention

R-CHOP

Patients will receive lenalidomide 15 mg orally daily on days 1-14 with standard-dose R-CHOP (375 mg/m^2 intravenous rituximab, 750 mg/m^2 intravenous cyclophosphamide, 50 mg/m^2 intravenous doxorubicin, and 1.4 mg/m^2 intravenous vincristine on day 1, and 100 mg prednisone days 1-5 or days 2-6) every 21 days for four cycles.

All patients will receive pegfilgrastim on day 2 of each cycle and aspirin 81 mg orally daily for venous thromboembolism prophylaxis throughout the four cycles.

After four cycles of Len-RCHOP, the patients will undergo restaging PET/CT scans. Patients with evidence of disease progression will be treated off study.

R-HIDAC

After lenalidomide-RCHOP phase, patients without evidence of progressive disease will receive rituximab 375 mg/m^2 day 1 and then patients will be admitted for high-dose cytarabine (HIDAC). Recommended age-adjusted HIDAC doses are as follows: ≤70 years: 2 g/m^2 every12 hours X 4 doses and >70 years: 1 g/m^2 every12 hours X 4 doses. Physician discretion will dictate the choice of HIDAC dose, ranging from 1 g/m^2 – 2 g/m^2 every 12 hours X 4 doses.

Patients will receive two cycles of rituximab-HIDAC every 3 weeks. After two cycles of R-HIDAC, the patients will undergo restaging PET/CT scans. Patients with evidence of disease progression will be treated off study.

Len-Rituximab Maintenance

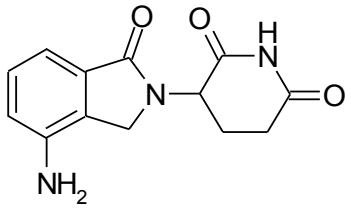
After completion of induction chemotherapy with Len-RCHOP and R-HIDAC, patients will begin maintenance phase with lenalidomide and rituximab for 6 months. Lenalidomide will be administered at 15 mg orally daily on days 1-21 of a 28-day cycle for a total of 6 cycles and rituximab maintenance every 8 weeks for a total of 3 treatments.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 REVLIMID®

REVLIMID® (lenalidomide), a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2*H*-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:

Chemical Structure of Lenalidomide



3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione

The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3.

Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

5.1.1 Clinical Pharmacology:

Mechanism of Action:

The mechanism of action of lenalidomide remains to be fully characterized. Lenalidomide possesses immunomodulatory and antiangiogenic properties. Lenalidomide inhibited the secretion of pro-inflammatory cytokines and increased the secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells. Lenalidomide inhibited cell proliferation with varying effectiveness (IC50s) in some but not all cell lines. Of cell lines tested, lenalidomide was effective in inhibiting growth of Namalwa cells (a human B cell lymphoma cell line with a deletion of one chromosome 5) but was much less effective in inhibiting growth of KG-1 cells (human myeloblastic cell line, also with a deletion of one chromosome 5) and other cell lines without chromosome 5 deletions. Lenalidomide inhibited the expression of cyclooxygenase-2 (COX-2) but not COX-1 in vitro.

5.1.2 Pharmacokinetics and Drug Metabolism

Absorption:

Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. Co-administration with food does not alter the extent of absorption (AUC) but does reduce the maximal plasma concentration (Cmax) by 36%. The pharmacokinetic disposition of lenalidomide is linear. Cmax and AUC increase proportionately with increases in dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.

Pharmacokinetic analyses were performed on 15 multiple myeloma patients treated in the phase I studies. Absorption was found to be rapid on both Day 1 and Day 28 with time to maximum blood levels ranging from 0.7 to 2.0 hours at all dose levels (5mg, 10mg, 25mg, and 50mg). No plasma accumulation was observed with multiple daily dosing. Plasma lenalidomide declined in a monophasic manner with elimination half-life ranging from 2.8 to 6.1 hours on both Day 1 and 28 at all 4 doses. Peak and overall plasma concentrations were dose proportional over the dosing range of 5mg to 50mg.[21] Exposure (AUC) in multiple myeloma patients is 57% higher than in healthy male volunteers.

Pharmacokinetic Parameters

Distribution

In vitro (14C)-lenalidomide binding to plasma proteins is approximately 30%.

Metabolism and Excretion

The metabolic profile of lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore is partially or entirely active. Half-life of elimination is approximately 3 hours. Supplier(s)Celgene Corporation will supply Revlimid® (lenalidomide) to study participants at no charge through Celgene's Revlimid Risk Evaluation and Mitigation Strategy™ (REMS) (formerly known as RevAssist® Program). Dosage formLenalidomide will be supplied as capsules for oral administration. PackagingLenalidomide will be shipped directly to patients or to the clinic site for IND studies. Bottles will contain a sufficient number of capsules for one cycle of dosing.

Labeling

Lenalidomide supplies are dispensed in individual bottles of capsules. Each bottle will identify the contents as study medication. In addition, the label will bear Celgene's name, quantity contained and the standard caution statement as follows: "Caution: New drug - Limited by Federal law to investigational use." Lenalidomide should not be handled by FCBP unless wearing gloves.

The study drug label must be clearly visible. Additional labels must not cover the Celgene label.

Receipt of study drug

The Investigator or designee is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug accountability form. The Investigator will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Celgene or its representative.

Storage

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access.

Lenalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

Unused study drug supplies

Celgene will instruct the Investigator on the return or destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the source documents. Study drug supplies will be retained at the clinical site pending instructions for disposition by Celgene. Patients will be instructed to return empty bottles or unused capsules to the clinic site.

Special Handling Instructions

Females of childbearing potential should not handle or administer lenalidomide unless they are wearing gloves.

5.1.3 Prescribing Information

Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with the Celgene Corporation's Revlimid REMS® program. Per standard Revlimid REMS® program requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in, and must comply with, all requirements of the Revlimid REMS® program.

Drug will be shipped on a per patient basis by the contract pharmacy to the clinic site for IND studies. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

Pregnancy Testing

Must follow pregnancy testing requirements as outlined in the Revlimid REMS® program material.

5.2 CYCLOPHOSPHAMIDE

Mechanism of action: a nitrogen mustard derivative, is converted to polyfunctional alkylating metabolites by hepatic microsomal enzymes. It interferes with DNA replication and RNA transcription, and possesses potent immunosuppressive activity.

Formulation: The drug is supplied as a lyophilized powder in 100 mg, 200 mg, 500 mg, l g, and 2 g vials.

Preparation/Storage: It is reconstituted to result in a concentration of 20 mg/mL. It is stable for 24 hours at room temperature or for 6 days refrigerated (2°-8° C).

5.3 DOXORUBICIN

Mechanism of action: An anthracycline antibiotic derived as a fermentation product of Streptomyces peucetius (caesius). The drug is tightly bound to DNA, preventing DNA-directed DNA and RNA synthesis. The drug may also act via a free radical mechanism. It appears to be active in all phases of the cell cycle.

Formulation: The drug is supplied reconstituted in 10, 50 and 200 mg vials.

Storage: Reconstituted solutions are stable at room temperature for 24 hours and under refrigeration for 48 hours.

Administration: The drug is administered via a freely-flowing intravenous line over 15 minutes. Care must be taken to avoid extravasation.

5.4 VINCRISTINE

Mechanism of action: Vincristine is a member of the vinca alkaloid class of natural product anti-tumor agents. It exerts its antineoplastic effects by binding to tubulin, resulting in inhibition of microtubule assembly. This, in turn, blocks formation of the mitotic spindle resulting in the accumulation of cells in mitosis.

Formulation: The drug is supplied reconstituted to a concentration of 1 mg/ Ml

Preparation/Storage: The drug is administered via a freely-flowing intravenous line over 1-2 minutes, with care taken to avoid extravasation.

5.5 PREDNISONE

Mechanism of action: Prednisone is a synthetic glucocorticoid. It is often used to enhance the effects of other cancer agents when used in combination. Given in pharmacologic doses, prednisone exerts anti-inflammatory and immunosuppressive effects on the blood and lymphatic system. At the cellular level, prednisone appears to halt DNA synthesis by mediating the inhibition of glucose transport or phosphorylation. In consequence, this causes a decrease in available intracellular energy and thus, impedes mitotic division. Prednisone is rapidly absorbed from the gastrointestinal tract when administered orally and

has a short duration (304 hours) of pharmacologic effects. Animal studies demonstrate that it is rapidly distributed to muscles, liver, skin, intestines, and kidneys upon ingestion.

Formulation: Supplied as tablets ranging from 1 to 50mg

Storage: Store at controlled room temperature 15º to 30ºC (59º to 86º F).

5.6 RITUXIMAB(Rituxan®, C2B8)

Mechanism of action: Rituximab binds to the CD20 antigen expressed on B-cells and causes cell death by complement mediated lysis and ADCC.

Formulation: Rituximab is supplied as 100 mg and 500 mg sterile, preservative-free, single-use vials.

Preparation: The appropriate dose is withdrawn and diluted to a final concentration of 1-4 mg/ml in either 0.9% sodium chloride or 5% dextrose solution. The solution is then stable at 2° to 8°C for 24 hours and at room temperature for an additional 12 hours.

Storage: Vials can be stored at 2o to 8oC. They should be protected from sunlight.

Administration: Rituximab to be given intravenously per institiutional policy.

Supplier: Genentech, Inc., IDEC Pharmaceuticals Corp.

5.7 CYTARABINE (HIDAC, Cytosine Arabinoside, Cytosar-U®)

Mechanism of action: Cytarabine is a cell cycle-specific (S phase) antimetabolite that inhibits cell development from the G1 to the S phase.

Formulation: Cytarabine is supplied in a powder for reconstitution at 100 mg, 500 mg, 1 g, and 2 g. It is also present as an injection, and solution concentrations are 20 mg/mL (5 mL, 25 mL, 50 mL) and 100 mg/mL (20 mL).

Preparation: Cytarabine must be reconstituted from a 100-mg vial with 5 mL bacteriostatic water for injection, yielding 20 mg/mL.

Storage: Cytarabine must be protected from light. Retain in carton until time of use. Store the product at controlled room temperature 15° to 30°C (59° to 86°F).

Administration: May be administered I.M., I.T., or Subcutaneously at a concentration not to exceed 100 mg/mL. When administered via I.V. infusion, infuse over 1-3 hours or as a continuous infusion. GI effects may be more pronounced with divided I.V. bolus doses than with continuous infusion.

Supplier: UpJohn

5.8 NEUPOGEN® (Filgrastim, G-CSF) or NEULASTA® (Pegfilgrastim)

Mechanism of action: NEUPOGEN® is a human protein, which is involved in the promotion of the growth and maturation of granulocytic progenitors and the stimulation of functional activity.

Formulation: Available as a recombinant DNA product supplied as 1 or 2 ml vials containing clear colorless sterile protein solution.

Storage: It can be stored at 2-6°C and is stable for at least 30 months.

Supplier: Amgen, Inc.

Mechanism of action: NEULASTA® is a covalent conjugate of filgrastim and monomethoxypolyethylene glycol. It stimulates the production, maturation, and activation of neutrophils to increase both their migration and cytotoxicity. Pegfilgrastim has reduced renal clearance and prolonged persistence in vivo when compared with filgrastim.

Formulation: Neulasta® 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

Storage: Neulasta® should be stored refrigerated at 2° to 8°C (36° to 46°F); syringes should be kept in their carton to protect from light until time of use. Shaking should be avoided. Before

Neulasta® (pegfilgrastim) injection, Neulasta® may be allowed to reach room temperature for a maximum of 48 hours but should be protected from light. Neulasta® left at room temperature for more than 48 hours should be discarded. Freezing should be avoided; however, if accidentally

frozen, Neulasta® should be allowed to thaw in the refrigerator before administration. If

frozen a second time, Neulasta® should be discarded. It can be stored at 2-6°C and is stable for at least 30 months.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

This study will include previously untreated mantle cell lymphoma patients.

6.1 Subject Inclusion Criteria

- Previously untreated mantle cell lymphoma patients (at least clinical stage 2)
- Histologic diagnosis confirmed by MSKCC pathologist as mantle cell lymphoma.
- Presence of evaluable disease
- Age ≥18 years KPS ≥ 70%
- Adequate organ function: ANC ≥1500 and platelet count ≥100,000, unless felt to be secondary to underlying mantle cell lymphoma
- Renal function assessed by calculated creatinine clearance as follows (see Appendix: Cockcroft-Gault estimation of CrCl):

  - Calculated creatinine clearance ≥ 30ml/min by Cockcroft-Gault formula. See section below, "Dosing Regimen", regarding lenalidomide dose adjustment for calculated creatinine clearance ≥ 30ml/min and < 60ml/min.
- Adequate hepatic function as determined by
  - Total bilirubin <1.5X upper limit of normal (ULN) (unless known Gilbert syndrome)
  - AST (SGOT) and ALT (SGPT) ≤ 3 x ULN
- All study participants must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of the REMS® program.
- Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.
- Each subject must sign an informed consent form indicating that he or she understand the purpose of and procedures required for the study and are willing to participate.
- Short course systemic corticosteroids is permissible for disease control, improvement of performance status or non-cancer indication if ≤ 10 days and must be discontinued prior to study treatment.

6.2 Subject Exclusion Criteria

- Known central nervous system (CNS) lymphoma
- Uncontrolled or severe cardiovascular disease or left ventricular ejection fraction <50% as determined by echocardiogram or MUGA.
- Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.
- Pregnant or breast-feeding. Pre-menopausal patients must have a negative serum HCG within 14 days of enrollment.
- Patients using ≥20 mg/day of prednisone (or steroid equivalent dose) for any chronic medical condition.
- Known seropositive, requiring anti-viral therapy, and with detectable viral load by PCR for human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV).
- Known hypersensitivity to thalidomide or lenalidomide
- The development of erythema nodosum if characterized by a desquamating rash while taking thalidomide or similar drugs.
- Patients planned for upfront consolidation with high-dose therapy and autologous stem cell transplant.

7.0 RECRUITMENT PLAN

Patients seen in the inpatient or outpatient setting who meet eligibility criteria will be recruited to this study. An attending physician will evaluate all patients. Participation is voluntary. The consenting physician will inform patients of their diagnosis, current treatment options, including standard treatment, and the risks, benefits and experimental nature of this treatment program. All patients will be required to sign a statement of informed consent that conforms to FDA and IRB guidelines.

8.0 PRETREATMENT EVALUATION

- **Prior to initiating treatment:**
    - Adequate material is required to confirm the diagnosis of mantle cell lymphoma (if pathologic material is not available a repeat biopsy is necessary). The immunohistochemistry studies may include: CD20, CD3, CD5, cyclin D1, Ki-67, SOX-11, p53, p27, p16, cyclin D2, or cyclin D3. FISH demonstrating the CCDN1 translocation [t(11;14)] provides further support of diagnosis, but is not required for making the diagnosis.
    - If possible, obtain tissue block or 15-20 unstained slides from initial diagnostic biopsy for correlative studies.
    - Baseline tumor biopsy to identify tumor-specific clonotype. The specimen can be from lymph node, GI tract, bone marrow, or blood. The ID Test Specimen Recommendations are detailed in Appendix 1.
- **Within 16 weeks:**
    - Gastrointestinal evaluation with upper endoscopy and colonoscopy with blind biopsy is advisable when clinically indicated and acceptable from a risk-benefit standpoint.. This is a recommended, not mandatory, evaluation and should be completed at the discretion of the treating physician.
- **Within 6 weeks prior to initiating treatment:**
    - CT scans of chest, abdomen, and pelvis and FDG-PET scan for pretreatment staging (can include CT neck if appropriate per physician discretion)
    - **Unilateral** bone marrow biopsy and aspirate, unless the patient has evidence of leukemic phase disease (confirmed presence of circulating mantle cell lymphoma cells in the peripheral blood).
    - Electrocardiogram
    - Echocardiogram or MUGA scan
    - Hepatitis B surface antigen and core antibody
    - Hepatitis C antibody
    - HIV 1/2 antibodies

- **2 weeks prior to initiating treatment:**
    - History and physical including height, weight, and vital signs
    - Karnofsky or Eastern Cooperative Oncology Group (ECOG) performance status
    - Complete blood count with differential
    - Serum lactate dehydrogenase
    - Comprehensive Metabolic Panel
    - Serum pregnancy test in pre-menopausal women
    - Baseline peripheral blood test for potential clone identification and MRD analysis (1 EDTA tube with 10cc of fresh peripheral blood). See Appendix 1 for detailed recommendations for MRD test specimen collection.
    - Research blood tests (2 Cell Preparation Tube (CPT) tubes with 8cc of peripheral blood and 1 serum separator tube (SST) with 8.5 cc of peripheral blood)

9.0 TREATMENT/INTERVENTION PLAN

9.1 INDUCTION: Lenalidomide + R-CHOP CHEMOTHERAPY: 4 cycles every 3 weeks ± 3 days

- **Lenalidomide-R-CHOP will be administered every 3 weeks (+/- 3 days) as an outpatient per institution policy at the following doses:**
    - Rituximab 375 mg/m^2 IVPB with premedications Day 1
    - Cyclophosphamide 750 mg/m2 IVPB Day 1
    - Doxorubicin 50 mg/m^2 IVP Day 1
    - Vincristine 1.4 mg/m^2 IVP (capped at 2 mg) Day 1
    - Prednisone 100 mg PO Daily on Days 1-5 or Days 2-6
    - Lenalidomide 15 mg PO Daily on Days 1-14

Per physician discretion, rituximab can be administered as a “split dose” over days 1 and 2 to reduce the likelihood of a rituximab-related injection reaction in patients with leukemic phase disease.

Lenalidomide Dosing:

Patients with moderate renal insufficiency (creatinine clearance ≥30 mL/min but <60 mL/min) will receive a lower dose of lenalidomide of 10 mg PO Daily on Days 1-14.

At investigator discretion, patients started with a reduced lenalidomide dose due to baseline calculated creatinine clearance ≥ 30ml/min but < 60ml/min, may have their lenalidomide dose gradually increased in a step-wise manner at the start of Cycle 2 or at the start of subsequent treatment cycles, if they tolerated the prior treatment cycle without requiring dose modifications, interruptions or delays due to toxicity. Lenalidomide dose titrations are

permitted in 5mg increments on the same dosing schedule up to the maximum allowable target dose.

Dosing will be at approximately the same time each day. Prescriptions must be filled within 7 days for females of child bearing potential and 14 days for all other risk categories.

Swallow lenalidomide capsules whole with water at the same time each day. Do not break, chew or open the capsules.

If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.

Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

- **Supportive care:**
    - Premedication will be given per institutional guidelines
    - Anti-emetics will be given per institutional guidelines
    - Aspirin 81 mg PO Days 1-21 (daily throughout every cycle) for venous thromboembolism prophylaxis. If aspirin is contraindicated, alternate anticoagulant agent for prophylaxis of VTE should be initiated per physician discretion and tailored to the patient's individual risk/benefit profile by taking into account the patient's thrombotic risk, bleeding risk, and other relevant factors. Aspirin can be deferred if the patient is already on prophylactic or therapeutic dose anticoagulation.
    - Mandatory growth factor support will be provided after each cycle of Lenalidomide-R-CHOP with either pegfilgrastim, filgrastim, or alternate growth factor per physician discretion.

- **Prophylactic antibiotics (all)**:
    - Acyclovir 400 mg PO BID or Valacyclovir 500 mg PO QD
    - Sulfamethoxazole/trimethoprim double-strength 1 tab PO three times per week OR single-strength 1 tab daily.

  Note: Patients allergic or intolerant to sulfa drugs can receive either dapsone 100 mg PO daily if not G6PD deficient, atovaquone 750 mg PO BID, or pentamidine 300 mg by nebulizer every 4 weeks as an alternative.

- **Dose delays/reductions**
    - Patients with absolute neutrophil count < 1000 cells/ul or platelet count < 50,000 cells/ul on the scheduled day of treatment may be delayed up to 2 weeks.
    - Patients experiencing ≥ grade 2 neurotoxicity will have their vincristine dose-reduced by 50%.
    - Any dose reduction that is made will be applied to all subsequent cycles.

  Dose Reduction Steps

Table 1: LENALIDOMIDE Dose Reduction Steps	
Starting Dose	**15 mg daily on Days 1-14every 21days**

Dose Level – 1	10 mg daily on Days 1-14 every 21 days
Dose Level – 2	5 mg daily on Days 1-14 every 21 days

* Lenalidomide 5 mg daily on Days 1-14 every 21 days is the minimum lenalidomide dose. Lenalidomide will be discontinued in patients who cannot tolerate this dose. However, patients who experience toxicity requiring dose reduction while receiving lenalidomide 5 mg daily on Days 1-14 every 21 days may, at the discretion of their physician, have their dose held until toxicity resolves and then restart lenalidomide 5 mg daily. If the same toxicity recurs at lenalidomide 5 mg daily, consideration should be given to discontinuing lenalidomide.

Instructions for initiation of a New Cycle

A new course of treatment may begin on the scheduled Day 1 of a new cycle if:

- The ANC is ≥1,000 cells/ul;
- The platelet count is ≥ 50,000 cells/ul;
- Any drug-related rash or neuropathy that may have occurred has resolved to ≤ grade 1 severity;
- Any other drug-related adverse events that may have occurred have resolved to ≤ grade 2 severity.

Same day results are not required from the comprehensive metabolic panel (including renal function and liver function testing) to assess for non-hematologic laboratory toxicity prior to treatment on day 1 of each new cycle. It is acceptable to review the comprehensive metabolic panel results that were obtained within 23 days prior to day 1 of each cycle.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated within a week and a new cycle of treatment will not be initiated until the toxicity has resolved as described above. If the cycle is delayed > 4 weeks, then the patient will be removed from study.

Instructions for dose modifications or interruption during a cycle

Table 2: Dose Modifications	
NCI CTC Toxicity Grade	**Dose Modification Instructions**
Grade 3 or 4 neutropenia associated with fever (temperature ≥ 38.5º C)	• Hold (interrupt) lenalidomide dose. • Follow CBC at least weekly. • If neutropenia has resolved to ≤ grade 2 (ANC ≥ 1000/mm^3) prior to Day 14 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 14 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up
Grade 3 or 4 neutropenia without fever	• Continue lenalidomide dosing, no interruptions or reductions required.

Table 2: Dose Modifications	
NCI CTC Toxicity Grade	**Dose Modification Instructions**
Thrombocytopenia ≥Grade 3 (platelet count < 50,000/mm³)	• Continue lenalidomide dosing, no interruptions or reductions required. •
Thrombocytopenia ≥Grade 3 (platelet count < 50,000/mm³) with associated bleeding	• Hold (interrupt) lenalidomide dose. • Follow CBC at least weekly. • If thrombocytopenia resolves to ≤ grade 2 (platelet count ≥ 50,000/mm^3) prior to Day 14 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 14 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up.
Non-blistering rash	• See Table 3 for management
Desquamating (blistering) rash- any Grade	• Discontinue lenalidomide.
Neuropathy **Grade 3** **Grade 4**	• If Grade 3, hold (interrupt) lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 14 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 14 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. • If Grade 4, discontinue lenalidomide. Remove patient from study.
Venous thrombosis/embolism ≥ Grade 3	• Hold (interrupt) lenalidomide and start therapeutic anticoagulation, if appropriate. • Restart lenalidomide at investigator's discretion (maintain dose level).
Hyperthyroidism or hypothyroidism	• Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. • If toxicity has resolved to ≤ grade 2 severity, restart for the next cycle and reduce the dose of lenalidomide by 1 dose level.

Table 2: Dose Modifications	
NCI CTC Toxicity Grade	**Dose Modification Instructions**
Other non-hematologic toxicity ≥ Grade 3	• Hold (interrupt) lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 2 prior to Day 14 of the current cycle, restart lenalidomide and continue through the scheduled Day 14 of the current cycle. Otherwise, omit for remainder of cycle. Omitted doses are not made up. For toxicity attributed to lenalidomide, reduce the lenalidomide dose by 1 dose level when restarting lenalidomide.

Table 3: Management of lenalidomide-related rash (non-blistering)			
Grade	**Description (CTCAE)**	**Lenalidomide management**	**Recommended rash management**
1	**<10% of BSA**	**No action required**	**Treat with topical corticosteroids and oral antihistamines until resolution of rash/symptoms** • Short course of low-dose oral steroid (prednisone 10mg or equivalent) is allowed
2	**10-30% of BSA**	**Consider interruption (holding) lenalidomide** • If the rash resolves to ≤ grade 1 prior to Day 14 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 14 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up.	**Treat with topical corticosteroids and oral antihistamines until resolution of rash/symptoms or ≤grade 1** • Short course of low-dose oral steroid (prednisone 10mg or equivalent) is allowed
3	**>30% of BSA**	**Hold lenalidomide** • If the toxicity resolves to ≤ grade 1 prior to Day 14 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 14 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up.	**Treat with topical corticosteroids and oral antihistamines until resolution of rash/symptoms or ≤grade 1** • Short course of low-dose oral steroid (prednisone 10mg or equivalent) is allowed

4	**Life threatening**	**Discontinue lenalidomide. Remove patient from study.**	**Medical intervention as appropriate**

Abbreviations: BSA = body surface area; CTCAE = Common Terminology Criteria for Adverse Events

Restaging after Lenalidomide-RCHOP cycle 4:

- Restaging FDG-PET scans 17 to 28 days after day 1 of the 4th cycle of Lenalidomide-RCHOP. Patients without evidence of progressive disease (Deauville 5) may proceed to consolidation with R-HIDAC.

9.2 CONSOLIDATION: R- HIDAC CHEMOTHERAPY: 2 cycles every 3 weeks ± 3 days

- R-HIDAC will be administered within 21-28days of completing the last cycle of Lenalidomide-R-CHOP.
- R-HIDAC will be administered once every 3 weeks ± 3 days for 2 cycles.
- R- HIDAC will be administered in the following manner: **Rituximab 375mg/m²** will be administered as an outpatient on day 1, where the patient will be seen by a study investigator. Patients will then be admitted for HIDAC on day 2 (+/- 2 days). Patients will be allowed admission at Overlook Hospital, a local hospital that is affiliated with Memorial Sloan Kettering. All research assessments and tests will be performed at the outpatient visit on day 1, and there will be no assessments done during their inpatient stay for HIDAC. All follow-up notes from the affiliated hospitals will be submitted to our Electronic Medical Records to account for any adverse events that may occur while in-patient. Patient will be discharged at the completion of HIDAC administration.
- Inpatient HIDAC will be administered as follows:
  - Cytarabine [DOSE] IVPB over 3 hours every 12 hours x 4 doses
  - The DOSE of cytarabine will be determined at the discretion of the treating physician. We recommend the cytarabine dose is adjusted based upon age. Suggested guidelines are shown in chart below.

Age	DOSE	Regimen
≤70	2,000 mg/m2	Every 12 hours X 4 doses
>70 years	1,000 mg/m2	Every 12 hours X 4 doses

Supportive care:

- Premedications, anti-emetics, and hematopoietic growth factors will be administered per institutional guidelines.
- Patients will continue to receive prophylactic antibiotics as outlined in section 9.1.
- Patients will receive growth factor support after each cycle with pegfilgrastim, filgrastim, or alternate growth factor per physician discretion. After cycle 2, per physician discretion, patients can undergo optional stem cell collection. In this case, standard growth factor support is not required.

- Steroid eyedrops may be used at the discretion of the investigator.

Dose delays/reductions:

- Patients with absolute neutrophil count < 1000 cells/ul or platelet count < 50,000 cells/ul may be delayed for up to 5 weeks following their last cycle of chemotherapy.
- Patients with serum creatinine ≥1.5 mg/dL or creatinine clearance ≤ 50 ml/hr on the scheduled day of HIDAC will be delayed for up to two weeks.

Optional stem cell collection after cycle 2 of HIDAC:

- At the treating physician's discretion, patients can undergo stem cell collection after cycle 2 of R-HIDAC for future use. Stem cell mobilization would be carried out per physician discretion.

Restaging after R-HIDAC Cycle 2:

Restaging FDG-PET scans should be completed prior to cycle 1 of rituximab and lenalidomide maintenance.. Patients without evidence of progressive disease (Deauville 5) may proceed to lenalidomide-rituximab maintenance.

9.3 MAINTENANCE: Lenalidomide + Rituximab for 6 months

- **Lenalidomide and rituximab maintenance will begin within 3-5 weeks after day 1 of the 2nd cycle of RHIDAC.**
- **Lenalidomide will be administered on days 1-21 of a 28-day cycle for a total of 6 cycles (total 6 months) at the following dose:**
    - Lenalidomide 15 mg PO Daily on Days 1-21

Patients with moderate renal insufficiency (creatinine clearance ≥30 mL/min but <60 mL/min) will receive a lower dose of lenalidomide of 10 mg PO Daily on Days 1-21.

- **Rituximab will be administered on day 1 every 8 weeks for (+/- 3 days) for a total of 3 cycles (total 6 months) at the following dose:**
    - Rituximab 375 mg/m^2 IVPB Day 1

Lenalidomide and rituximab maintenance is continued for 6 months or until disease progression, unacceptable toxicity, or voluntary withdrawal.

- **Supportive care:**
    - Premedication will be given per institutional guidelines
    - Anti-emetics will be given per institutional guidelines

- Aspirin 81 mg PO Daily throughout 6 months of lenalidomide maintenance therapy for venous thromboembolism prophylaxis. If aspirin is contraindicated, alternate anticoagulant agent for prophylaxis of VTE should be initiated per physician discretion and tailored to the patient's individual risk/benefit profile by taking into account the patient's thrombotic risk, bleeding risk, and other relevant factors. Aspirin can be deferred if the patient is already on prophylactic or therapeutic dose anticoagulation.

- **Prophylactic antibiotics**:
  - Acyclovir 400 mg PO BID

- **Dose delays/reductions**

The lenalidomide starting dose will be based on baseline calculated creatinine clearance as follows:

Lenalidomide Starting Dose Based on Renal Function at Study Entry	
Baseline Calculated Creatinine Clearance (by Cockcroft-Gault)	**Starting Lenalidomide Dose**
≥ 60 ml/min	15 mg daily on Days 1 - 21 of each 28-day cycle
≥ 30 and < 60 ml/min	10mg daily on Days 1 - 21 of each 28-day cycle

At investigator discretion, patients started with a reduced lenalidomide dose due to baseline calculated creatinine clearance ≥ 30ml/min but < 60ml/min, may have their lenalidomide dose gradually increased in a step-wise manner at the start of Cycle 2 or at the start of subsequent treatment cycles, if they tolerated the prior treatment cycle without requiring dose modifications, interruptions or delays due to toxicity. Lenalidomide dose titrations are permitted in 5mg increments on the same dosing schedule up to the maximum allowable target dose.

The lenalidomide dose may only be increased once every 28 days (or less frequently), and may only be increased if the prior treatment cycle was completed without requiring dose modifications, interruptions or delays due to toxicity.

Dosing will be at approximately the same time each day. Prescriptions must be filled within 7 days for females of child bearing potential and 14 days for all other risk categories.

Swallow lenalidomide capsules whole with water at the same time each day. Do not break, chew or open the capsules. If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up. Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

Dose Reduction Steps

Table 1: LENALIDOMIDE Dose Reduction Steps	
Starting Dose	**15 mg daily on Days 1-21 every 28 days**

Dose Level – 1	10 mg daily on Days 1-21 every 28 days
Dose Level – 2	5 mg daily on Days 1-21 every 28 days

* Lenalidomide 5 mg daily on Days 1-21 every 28 days is the minimum lenalidomide dose. Lenalidomide will be discontinued in patients who cannot tolerate this dose. However, patients who experience toxicity requiring dose reduction while receiving lenalidomide 5 mg daily on Days 1-21 every 28 days may, at the discretion of their physician, have their dose held until toxicity resolves and then restart lenalidomide 5 mg daily on Days 1-21 every 28 days. If the same toxicity recurs at lenalidomide 5 mg daily on Days 1-21 every 28 days, consideration should be given to discontinuing lenalidomide.

Instructions for initiation of a New Cycle
A new course of treatment may begin on the scheduled Day 1 of a new cycle if:

- The ANC is ≥1,000 cells/ul;
- The platelet count is ≥ 50,000 cells/ul;
- Any drug-related rash or neuropathy that may have occurred has resolved to ≤ grade 1 severity;
- Any other drug-related adverse events that may have occurred have resolved to ≤ grade 2 severity.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated within a week and a new cycle of treatment will not be initiated until the toxicity has resolved as described above.

Instructions for dose modifications or interruption during a cycle

Table 2: Dose Modifications	
NCI CTC Toxicity Grade	**Dose Modification Instructions**
Grade 3 neutropenia associated with fever (temperature ≥ 38.5º C) or Grade 4 neutropenia	• Hold (interrupt) lenalidomide dose. • Follow CBC weekly. • If neutropenia has resolved to ≤ grade 2 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. • If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the lenalidomide dose maintained.

Table 2: Dose Modifications	
NCI CTC Toxicity Grade	**Dose Modification Instructions**
Thrombocytopenia ≥Grade 3 (platelet count < 50,000/mm^3)	• Hold (interrupt) lenalidomide dose. • Follow CBC weekly. • If thrombocytopenia resolves to ≤ grade 2 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up.
Non-blistering rash	• See Table 3 for management
Desquamating (blistering) rash- any Grade	• Discontinue lenalidomide.
Neuropathy **Grade 3** **Grade 4**	• If Grade 3, hold (interrupt) lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. • If Grade 4, discontinue lenalidomide. Remove patient from study.
Venous thrombosis/embolism ≥ Grade 3	• Hold (interrupt) lenalidomide and start therapeutic anticoagulation, if appropriate. • Restart lenalidomide at investigator's discretion (maintain dose level).
Hyperthyroidism or hypothyroidism	• Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. • If toxicity has resolved to ≤ grade 2 severity, restart for the next cycle and reduce the dose of lenalidomide by 1 dose level.
Other non-hematologic toxicity ≥ Grade 3	• Hold (interrupt) lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 2 prior to Day 21 of the current cycle, restart lenalidomide and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle. Omitted doses are not made up. • For toxicity attributed to lenalidomide, reduce the lenalidomide dose by 1 dose level when restarting lenalidomide.

Table 3: Management of lenalidomide-related rash (non-blistering)			
Grade	**Description (CTCAE)**	**Lenalidomide management**	**Recommended rash management**
1	**<10% of BSA**	**No action required**	**Treat with topical corticosteroids and oral antihistamines until resolution of rash/symptoms** • Short course of low-dose oral steroid (prednisone 10mg or equivalent) is allowed
2	**10-30% of BSA**	**Consider interruption (holding) lenalidomide** • If the rash resolves to ≤ grade 1 prior to Day 14 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 14 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up.	**Treat with topical corticosteroids and oral antihistamines until resolution of rash/symptoms or ≤grade 1** • Short course of low-dose oral steroid (prednisone 10mg or equivalent) is allowed
3	**>30% of BSA**	**Hold lenalidomide** • If the toxicity resolves to ≤ grade 1 prior to Day 14 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 14 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up.	**Treat with topical corticosteroids and oral antihistamines until resolution of rash/symptoms or ≤grade 1** • Short course of low-dose oral steroid (prednisone 10mg or equivalent) is allowed
4	**Life threatening**	**Discontinue lenalidomide. Remove patient from study.**	**Medical intervention as appropriate**

Abbreviations: BSA = body surface area; CTCAE = Common Terminology Criteria for Adverse Events

Prior to administration of treatment during any phase (RCHOP, RHIDAC, or R-Lenalidomide), a complete blood count (CBC) obtained within 3 days of day 1 is required. However, a comprehensive metabolic panel obtained within 30 days of day 1 of treatment can be used to determine dosing, including delays and reductions.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

- **Tests to be performed within 3 days of day 1 of each cycle of lenalidomide and RCHOP:**
    - History and physical exam (MD, PA, or NP evaluation)
    - KPS or ECOG performance Status
    - Adverse event and toxiticy review
    - CBC
    - Comprehensive metabolic panel (includes: Electrolytes [Na, K, Cl, CO2], BUN, Creatinine, bilirubin, total protein, albumin, AST, ALT, alkaline phosphatase)

- **Tests to be performed after completion of 4 cycles of lenalidomide and RCHOP:**
    - Restaging FDG-PET scans 17 to 28 days after 4th cycle of Lenalidomide-RCHOP.
    - Peripheral blood test for MRD analysis (1 EDTA tube with 10cc of fresh peripheral blood). See Appendix 1 for detailed recommendations for MRD test specimen collection. To be performed 17 to 28 days after 4th cycle of Lenalidomide-RCHOP.
    - Research blood tests (2 Cell Preparation Tube (CPT) tubes with 8cc of peripheral blood and 1 serum separator tube (SST) with 8.5 cc of peripheral blood). To be performed 17 to 28 days after 4th cycle of Lenalidomide-RCHOP.

- **Tests to be performed within 3 days of each cycle of R-HIDAC:**
    - History and physical exam (MD, PA, or NP evaluation)
    - Adverse event and toxicity review
    - CBC
    - Comprehensive metabolic panel ((includes: Electrolytes [Na, K, Cl, CO2], BUN, Creatinine, bilirubin, total protein, albumin, AST, ALT, alkaline phosphatase)

- **Tests to be performed after completion of 2 cycles of R-HIDAC:**
    - Restaging FDG-PET scans 17 to 35 days after cycle 2 of R-HIDAC.
    - Peripheral blood test for MRD analysis (1 EDTA tube with 10cc of fresh peripheral blood). See Appendix 1 for detailed recommendations for MRD test specimen collection. To be performed 17 to 35 days after cycle 2 of R-HIDAC.
    - Research blood tests (2 Cell Preparation Tube (CPT) tubes with 8cc of peripheral blood and 1 serum separator tube (SST) with 8.5 cc of peripheral blood). To be performed 17 to 35 days after cycle 2 of R-HIDAC.

- **Tests to be performed within 3 days of each 28-cycle of lenalidomide and rituximab maintenance**
    - History and physical exam (MD, PA, or NP evaluation)
    - Adverse event and toxicity review
    - CBC
    - Comprehensive metabolic panel ((includes: Electrolytes [Na, K, Cl, CO2], BUN, Creatinine, bilirubin, total protein, albumin, AST, ALT, alkaline phosphatase)

- **Tests to be performed 6 weeks (+/- 2 weeks) after completion of maintenance lenalidomide and rituximab:**
    - History and physical exam (MD, PA, or NP evaluation)
    - Adverse event and toxicity review
    - CBC
    - Comprehensive metabolic panel (includes: Electrolytes [Na, K, Cl, CO2], BUN, Creatinine, bilirubin, total protein, albumin, AST, ALT, alkaline phosphatase)
    - LDH
    - FDG-PET scan
    - CT of chest, abdomen, and pelvisUnilateral bone marrow biopsy and aspirate (if previously involved)
    - Upper and lower GI tract evaluation (if previously involved)
    - Peripheral blood test for MRD analysis (1 EDTA tube with 10cc of fresh peripheral blood). See Appendix 1 for detailed recommendations for MRD test specimen collection.
    - Research blood tests (2 Cell Preparation Tube (CPT) tubes with 8cc of peripheral blood and 1 serum separator tube (SST) with 8.5 cc of peripheral blood)

- **Tests to be performed 6 months (+/- 1 month) after completion of maintenance lenalidomide and rituximab:**
    - Peripheral blood test for MRD analysis (1 EDTA tube with 10cc of fresh peripheral blood). See Appendix 1 for detailed recommendations for MRD test specimen collection.
    - Research blood tests (2 Cell Preparation Tube (CPT) tubes with 8cc of peripheral blood and 1 serum separator tube (SST) with 8.5 cc of peripheral blood)

- **Long Term Follow Up**
    - Clinical evaluation (including H&P, CBC, CMP, and LDH) every 3 months (+/- 1 month) for three years after end-of-treatment evaluation..
    - CT chest, abdomen, pelvis every 6 months (+/- 1 month) for three years after end-of-treatment evaluation.

After 3 years post-long term follow up, patients will be seen at the treating physician's discretion.

Interventions

Procedures	**Screen**	**Treatment**														**EOT**
		Induction								**Maintenance**						
		Len-RCHOP (outpatient)				Restage 17-28 days post C4D1	**R-HiDAC** (inpatient) Within 3-4 weeks of completion of C4D1		Restage 17-35 days post C2D1	**Len-R** (3-5 weeks of induction C2D1)						
		C1	C2	C3	C4		C1	C2		C1	C2	C3	C4	C5	C6	6 wks post-tx

																(+/- 2 weeks)
History and Physical	X	X	X	X	X		X	X		X	X	X	X	X	X	X
Performance Status	X	X	X	X	X		X	X		X	X	X	X	X	X	
Adverse Events		X	X	X	X		X	X		X	X	X	X	X	X	X
Toxicity Review		X	X	X	X		X	X		X	X	X	X	X	X	X
CBC	X	X	X	X	X		X	X		X	X	X	X	X	X	X
Comprehensive Metabolic Panel*	X	X	X	X	X		X	X		X	X	X	X	X	X	X
Lactate dehydrogenase	X															X
Serum β-HCG**	X															
Hep B, C, HIV	X															
Tumor specimen for tumor-specific clonotype analysis	X															
MRD blood test	X					X			X							X***
Research blood test	X					X			X							X***
GI tract evaluation	X															X****
BM Bx	X															X****
FDG-PET/CT	X					X			X							X
CT CAP	X															X
EKG	X															
Echo or MUGA	X															

- *Includes: Electrolytes (Na, K, Cl, CO2), BUN, Creatinine, bilirubin, total protein, albumin, AST, ALT, alkaline phosphatase
- **premenopausal females
- ***MRD and research blood test also performed 6 months after conclusion of Len-Maintenance therapy
- ****If previously involved at baseline

11.0 TOXICITIES/SIDE EFFECTS

Doxorubicin:

Nausea, vomiting, itching, hives or red rash at the injection site. Urine can be pink or red in color for as long as 48 hours after the treatment. Alopecia, stomatitis, and reversible myelosuppression can occur. Extravasation may occur if leakage around the intravenous site occurs. Cardiomyopathy has been reported with this compound, usually in patients who have received total doses in excess of 500 mg/m^2.

Cyclophosphamide:

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

Vincristine:

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

Prednisone:

Prednisone exerts numerous effects on the body: euphoria, mood swings, fluid retention, adrenocortical insufficiency, muscle pain or weakness, muscle wasting, increased susceptibility to infections, hypokalemia, hypercorticism, amenorrhea, decreased glucose tolerance, hyperglycemia, nausea, vomiting, anorexia, increased appetite, weight gain, gastric ulceration, ulcerative esophagitis, insomnia, headache, restlessness, increased motor activity, impaired wound healing, skin atrophy and thinning, acne, and increased sweating.

Lenalidomide:

Adverse Events

Most frequently reported adverse events reported during clinical studies with lenalidomide in oncologic and non-oncologic indications, regardless of presumed relationship to study medication include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting and diarrhea, dehydration, rash, itching, infections, sepsis, pneumonia, UTI, Upper respiratory infection, atrial fibrillation, congestive heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, CVA, convulsions, dizziness, spinal cord compression, syncope, disease progression, death not specified and fractures.

The following events have been reported during the use of lenalidomide in clinical studies and in the post-marketing setting:

The rare adverse event of angioedema and serious skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. These events have the potential to result in death. Medical journals have reported patients with allergic skin reaction with thalidomide who also developed the same type of reaction with lenalidomide. The rare adverse event of rhabdomyolysis has been observed with lenalidomide.

Tumor lysis syndrome and tumor flare reaction have commonly been observed in patients with Chronic Lymphocytic Leukemia (CLL), and uncommonly in patients with other lymphomas, who were treated with lenalidomide. Fatal instances of TLS have been reported during treatment with lenalidomide. There have been rare reports of TLS in patients with multiple myeloma treated with lenalidomide, and no reports in patients with myelodysplastic syndrome treated with lenalidomide.

Second New Cancers

According to researchers, patients with cancer have a higher risk of developing a second new cancer when compared to people without cancer. In clinical studies of newly diagnosed multiple myeloma, a higher number of second cancers were reported in patients treated with lenalidomide as induction therapy (treatment for several cycles to reduce number of cancer cells) and/or bone marrow transplant followed by lenalidomide for a long period of time compared to patients treated with induction therapy and/or bone marrow transplant then placebo (a capsule containing no lenalidomide). Patients should make their doctors aware of their medical history and any concerns they may have regarding their own increased risk of other cancers.

Complete and updated adverse events are available in the Investigational Drug Brochure and the IND Safety Letters.

Other Risks

Patients should be instructed that if any physician other than the study doctor prescribes medication for another condition, or patients start to take any over-the-counter medications or vitamins, they must inform the study staff. This is important because the interaction of some medications may cause serious side effects.

- Patients taking lenalidomide and dexamethasone for multiple myeloma should be careful taking drugs that may increase chance of having blood clots.
- Cases of transient liver laboratory abnormalities were reported in patients treated with lenalidomide.
- Lenalidomide has been shown to increase the level of digoxin in the blood in some patients.

Risks Associated with Pregnancy

Pregnancy Risk:

Lenalidomide is related to thalidomide. Thalidomide is known to cause severe life-threatening human birth defects. Findings from a monkey study indicate that lenalidomide caused birth defects in the offspring of female monkeys who received the drug during pregnancy. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females must not become pregnant while taking lenalidomide. Patients with multiple myeloma who take lenalidomide and dexamethasone have a greater chance of having blood clots. Because of this, it is recommended patients not take birth control pills or hormone replacement therapy before discussing with the investigator and considering the risks and benefits of these choices.

When taking lenalidomide, the drug is present in semen of healthy men at very low levels for three days after stopping the drug. For patients who may not break down the drug normally, such as patients who do not have normal kidney function, lenalidomide may be present for more than three days. To be safe, all male patients should use condoms when engaging in sexual intercourse while taking lenalidomide, when temporarily stopping lenalidomide, and for 28 days after permanently stopping lenalidomide treatment if their partner is either pregnant or able to have children.

Patients should not donate blood during treatment therapy or for 28 days following discontinuation of lenalidomide.

Reproductive risks:

Patients should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. A woman should NOT CONCEIVE A BABY while she or her partner is receiving lenalidomide. A man should NOT DONATE SPERM OR IMPREGNATE HIS PARTNER while he is on lenalidomide.

Women should not breastfeed a baby while on this study. It is important that the patient understand that they will need to use birth control while on this study. A list of acceptable

forms of birth control methods to use and how long to use them is listed below. Pregnancy testing will be required as per Table 7.

Pregnancy Risk – Females:

If a patient is a female of childbearing potential*, she will be required to have two negative pregnancy tests: the first test within 10-14 days before lenalidomide is prescribed and the second test within 24 hours before lenalidomide is prescribed.

> * For the purposes of this study, a female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time during the preceding 24 consecutive months).

The female patient will be required to use **TWO** reliable forms of birth control, one highly effective method and one additional effective method at the same time or practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) throughout lenalidomide therapy, including interruptions in therapy; and 3) for at least 28 days after discontinuation of lenalidomide. The following are the acceptable birth control methods:

Highly Effective Method:

- Intrauterine device (IUD)
- Hormonal (birth control pills, injections, implants)
- Tubal ligation

Male partner's vasectomyAdditional Effective Methods:

- Latex condom
- Diaphragm
- Cervical cap

A female patient must not breastfeed a baby while participating in this study and for at least 28 days after the discontinuation of lenalidomide.

Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days and then every 28 days while taking lenalidomide, at the time lenalidomide is discontinued, and at day 28 following discontinuation of lenalidomide. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while taking lenalidomide, at discontinuation of lenalidomide, and at days 14 and 28 following discontinuation of lenalidomide.

If the patient has any reason to suspect that they are pregnant, the patient must IMMEDIATELY stop taking lenalidomide and contact the physician investigator.

All Patients:

Patients must **NEVER** share lenalidomide with someone else. The patient must receive counseling and complete phone surveys as required by the **RevAssist®** program.

The patient should be instructed to swallow lenalidomide capsules whole with water at the same time each day. They should not break, chew or open the capsules.

If the patient misses a dose of lenalidomide, they should take it as soon as they remember on the same day.

If they miss taking the dose for the entire day, they should take the regular dose the next scheduled day (they should NOT take a double regular dose to make up for the missed dose).

If they take more than the prescribed dose of lenalidomide they should seek emergency medical care if needed and contact the study staff immediately.

Females of childbearing potential that might be caring for you should not touch the lenalidomide capsules or bottles unless they are wearing gloves.

Any unused Revlimid® (lenalidomide) should be returned as instructed through the RevAssist® program.

Rituximab:

Common: Fever, chills, fatigue, headache; less common: nausea, vomiting, rhinitis, pruritus, hypotension; rare: neutropenia, thrombocytopenia, asthenia, arrhythmia, tumor lysis syndrome, shock, angioedema, acute respiratory distress, arthritis, vasculitis, lupus-like syndrome, pleuritis, bronchiolitis obliterans, uveitis, optic neuritis, and skin reactions such as toxic epidermal necrolysis and pemphigus.

Hematologic Events: In clinical trials, Grade 3 and 4 cytopenias were reported in 48% of patients treated with RITUXIMAB; these include: lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1 to 588 days) and of neutropenia was 13 days (range, 2 to 116 days). A single

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

hepatitis was approximately 4 months after the initiation of rituximab and approximately one month after the last dose. Progressive Multifocal Leukoencephalopathy (PML) associated with JC virus infection has been reported in patients treated with rituximab with hematologic malignancies or with systemic lupus erythematosus (SLE). PML needs to be considered in any patient presenting with new onset neurologic manifestations including confusion, dizziness or loss of balance, difficulty talking or walking, and visual changes.

Cytarabine :

Cytarabine syndrome, characterized by fever, myalgia, bone pain, chest pain, maculopapular rash, conjunctivitis, and malaise. May occur 6-12 hours following administration; may be managed with corticosteroids. Myelosuppression (Potent myelosuppressive agent; use with caution in patients with prior bone marrow suppression), pancreatitis, tumor lysis syndrome, Hepatic impairment: Use with caution in patients with hepatic impairment; may be at higher risk for CNS toxicities and dosage adjustments may be required. Can cause renal impairment and must be used with caution in patients with impaired renal function. Can cause CNS toxicities and dosage adjustments may be required. May also lead to pancreatitis: There have been reports of acute pancreatitis in patients receiving continuous infusion and in patients previously treated with L-asparaginase. Tumor lysis syndrome has been described as well. With high dose therapy, tumor lysis syndrome and subsequent hyperuricemia may occur; consider allopurinol and hydrate accordingly.

Neupogen or Neulasta:

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

11. 1 ADVERSE EVENTS

Definition:

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

Toxicities will be graded on a scale of 0-5 as described by the NCI- Common Terminology for Adverse Events (CTCAE), version 4.0. Only grade 3-5 laboratory toxicities will be reported and attributed with regard to relationship to the investigational treatment.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Criteria for interim FDG-PET/CT assessment

A five-point scale for visually assessing response on the interim and end-of-treatment FDG-PET/CT scans, referred to as the "Deauville criteria", was developed by international experts in the field at the First International Workshop on interim-PET in Lymphoma in Deauville in 2009.[42] The 5-point scale is displayed in the following table.

Score	FDG-PET/CT scan result
1	No residual uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately > liver
5	Markedly increased uptake at any site or progression

A positive or abnormal interim FDG-PET/CT scan will be defined as a score of 4 or 5. All scores (1 through 5) will be recorded for each FDG-PET/CT scan and scans will be reviewed by Dr. Schöder.

End of treatment FDG-PET/CT assessment

The updated response criteria entitled "The Lugano Classification" system will be applied to define end-of-treatment complete response, partial response, and progression of disease in this study.[38] The definitions are detailed in the table below:

Table 3. Revised Criteria for Response Assessment

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

(continued on following page)

Table 3. Revised Criteria for Response Assessment (continued)

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Progression free survival (PFS) will be calculated from the time of initiation of therapy.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients will be followed on active follow up for three years after completion of therapy. After the active followup period, survival, relapse, and new anti-lymphoma therapy information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 6 months until death, loss to follow up or consent withdrawal, whichever comes first.

The following patients will be removed from study:

• Patients who have progression of disease while on treatment. These patients may be offered alternate treatments.

• Patients who develop unacceptable toxicity.

• Patients who request that they be removed from study. This will not compromise the care they receive at this institution.

• Patients who are non-compliant with treatment or follow-up.

14.0 BIOSTATISTICS

Primary Objective: The primary efficacy endpoint of this study is to determine the 3-year progression-free survival (PFS) for patients treated with induction chemotherapy consisting of lenalidomide with RCHOP and rituximab and high-dose cytarabine followed by maintenance therapy with rituximab and lenalidomide. The defining interval for PFS starts at enrollment date, and progression of disease or death from any cause will be counted as failures. Our past experience suggests that very few patients who have completed the induction chemotherapy will be lost to follow-up or withdraw from the study by the end of the third year (about 5%). If such rare situations occur, however, they will also be counted as failures as well in this study. For this cohort of patients, we will set acceptable 3-yr PFS as 75% or higher, and unacceptable rate as 60% or lower.

To this end we will employ a one-stage design. Fourty-seven newly diagnosed MCL patients treated with induction chemotherapy followed by maintenance will be enrolled for this study. If 33 or more patients are being followed, alive and progression free at the end of the 3rd year, this treatment regimen will be declared effective. This decision rule has a type I error (declaring the new treatment regimen promising while it is actually not) less than 0.1 and a type II error (declaring the new treatment regimen not promising while it actually is) rate less than 0.2.

The above decision rule is based upon an expected proportion of high-risk and low-risk patients of 65% and 35%, respectively. “High risk” patients are defined by Ki-67≥30% or blastic/blastoid/pleomorphic morphology. “Low risk” patients are those with Ki-67<30% and lack of blastic/blastoid/pleomorphic morphology. Of note, the “low risk” category defined here includes a combination of low and intermediate risk groups that were previously discussed in Section 2.0. Historical data predicts that the expected 3-year PFS of high-risk patients is approximately 50% whereas the expected 3-year PFS of low-risk patients is 75-80%. To ensure enrollment of the expected proportion of high-risk and low-risk patients and, therefore, ensure that the decision rule is appropriate, we will fix the number of high risk patients as 31 and the number of low risk patients as 16. If the maximum number of patients has been enrolled for either the high risk group or low risk group, enrollment will continue only for group in which enrollment has not yet been met.

If a patient is enrolled and unable to complete induction treatment, that patient will be replaced.

We aim to enroll 47 patients in 1.5 years (accrual rate is 2-3 patients per month).

Secondary Objectives: PFS and OS of treated patients (overall and in different clinical risk subgroups) will be evaluated by survival analysis tools such as Kaplan-Meier and compared by the log-rank test. The prognostic value of M-IPI on PFS and OS will be evaluated by survival regression models such as the Cox model. The rate of PET-negativity at various time points will be estimated by sample proportions and their confidence intervals will be computed. Their correlate with PFS will be evaluated by landmark Cox regression). MRD status at various time points will also be correlated with PFS using landmark Cox model.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

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

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

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

All participants must be registered through the Clinical Trials Management System (CTMS) Office at Memorial Sloan Kettering Cancer Center. Registrations must be submitted via the CTMS Electronic Registraiton System (https://ctms.mskcc.org/forte-platform-web/login).

15.2 Randomization

This is not a randomized trial.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team.

The data collected for this study will be entered into the Clinical Research Database (CRDB). Source documentation will be available to support the computerized patient record.

Data to be collected will include:

1. Patient demographics and related features:

- age

- sex

2. Disease related features:

- staging

- disease risk classification (for example, international prognostic index)

- disease status at follow-up

- description of relapse

3. Treatment related

- type of treatment

- duration of treatment

- response to treatment

16.1 Quality Assurance

Registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://inside2/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf

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

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

17.0 PROTECTION OF HUMAN SUBJECTS

MSKCC affirms the subject's right to protection against invasion of privacy. In compliance with United States federal regulations, Celgene requires the Investigator to permit representatives of Celgene Corporation and, when necessary, representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

17.1 Privacy

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

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

17.2 Serious Adverse Event (SAE) Reporting

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

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

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

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following o An explanation of how the AE was handled
- A description of the participant's condition
- Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

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

17.2.1

Not applicable

18.0 INFORMED CONSENT PROCEDURES

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

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

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

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

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20.0 APPENDICES

Appendix 1. Sequenta Specimen Recommendation Sheet

Appendix 2. Lenalidomide Pill Diary

Appendix 3. Cockcroft-Gault estimation of creatinine clearance (CrCl)

Cockcroft-Gault estimation of CrCl:[43,44]

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})}$$

(**Males**)

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})} \times 0.85$$

(**Females**)