A Phase Ib/IIa Study of Combination therapy with Carfilzomib, Romidepsin, Lenalidomide in Patients with Relapsed or Refractory B- and T-cell Lymphomas

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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

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Participating Institutions – If multicenter study coordinated by MSK:	**PI's Name**	**Site's Role**
University of Nebraska	Matthew A Lunning, M.D.	Data Collection

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1.1 PROTOCOL SUMMARY AND/OR SCHEMA

Title: A Phase Ib/IIa Study of Combination therapy with Carfilzomib, Romidepsin, Lenalidomide in Patients with Relapsed or Refractory B- and T-cell Lymphomas

Objectives: The primary endpoint of the phase Ib and IIa portion of the study is to determine the MTD (phase Ib) and characterize the safety and toxicity profile of extended treatment with the combination carfilzomib, romidepsin, lenalidomide in patients with relapsed and refractory B- and T-cell lymphomas. The secondary objectives of this study are to a) assess the overall response rate (ORR) of carfilzomib, romidepsin, and lenalidomide in B- and T-cell lymphoma; b) to assess the complete response (CR) and partial response (PR) rate; c) to assess the time to response (TTR), duration of response (DOR) and event free survival (EFS).

Patient Population: Patients with relapsed or refractory B-cell and T-cell lymphomas.

Expected Number of Patients: 30

Study Design and Methodology: This will be a multicenter, open label, phase Ib/IIa trial carfilzomib, romidepsin and lenalidomide in patients with relapsed or refractory lymphomas.

Treatments Administered: Romidepsin will be administered intravenously on days 1 and 8 of a 21-day cycle. Lenalidomide will be taken orally daily for days 1-14 of a 21-day cycle. Carfilzomib will be given intravenously weekly on days 1 and 8, of a 21 day cycle. Maximum tolerated dose (MTD) to be determined in the phase Ib portion. A cycle of carfilzomib, romidepsin, and lenalidomide will be 21-days.

Safety Data Collected: The following evaluations will be conducted to assess the safety of the combination of romidepsin, carfilzomib, and lenalidomide:

Phase Ib: Determine the MTD by NCI-CTCAE v4.0.

Phase IIa: Further assess the combination"s toxicity profile by NCI-CTCAE v4.0.

Efficacy Data Collected: Disease specific evaluations will be conducted to assess the efficacy of the combination of carfilzomib, romidepsin, and lenalidomide:

- Phase IIa portion (including phase Ib treated at MTD) - overall response rate, complete response rate, partial response rate, time to response, duration of response, and event-free survival.

2.1 OBJECTIVES AND SCIENTIFIC AIMS

We hypothesize that therapy with carfilzomib in combination with romidepsin and lenalidomide will be a well-tolerated and active regimen for subjects with relapsed or refractory B-cell and T-cell (PTCL) lymphoma.

a. The primary endpoint of the phase Ib and IIa portion of the study is to determine the MTD (phase Ib) and characterize the safety and toxicity profile of extended use with the combination carfilzomib, romidepsin, lenalidomide in patients with B- and T-cell lymphomas.
b. Preliminary efficacy secondary endpoints in the phase IIa portion (including those treated in the phase Ib at MTD) of the study will also be assessed:
    i. Overall response rate (ORR) of carfilzomib romidepsin, and lenalidomide collectively as well as by disease subtype
    ii. Complete response (CR) and partial response (PR) rate;
    iii. Time to response (TTR), duration of response (DOR) and event free survival (EFS).
    iv. Based on safety and preliminary secondary endpoints further study could include:
        1. Addition of monoclonal antibodies or other agents to regimen
        2. Randomization against standard therapies in the relapsed and refractory setting
        3. Up-front therapy (PTCL only or indolent B-cell lymphoma)

3.0 BACKGROUND AND RATIONALE

3.1 Relapsed and Refractory B- and T-cell lymphomas

Relapsed and refractory B- and T-cell lymphomas remain an ongoing challenge with repeated courses of cytotoxic chemotherapy often yielding diminishing returns. The 5-year overall survival (OS) in transplant ineligible patients with B- and T-cell lymphomas was 32%, and 20% respectively [Phillip, 1995; Vose J, 2008]. There remains significant need for more active therapies and combinations with many newer approaches now looking to long-term or maintenance treatments employing drugs without cumulative toxicity.

As T-cell lymphomas have been traditionally difficult to treat, single agent overall response rates have generally been in the 20-35% range. Additionally, durations of response have been generally short lived. Therefore, combination therapy of well tolerated agents may be the best approach to therapy.

3.2 Proteasome Inhibitors in B- and T-cell Lymphomas

Proteasome inhibitors were initially approved for use in relapsed and/or refractory multiple myeloma and have been subsequently found to be effective in mantle cell lymphomas as well as indolent B-cell lymphomas [Goy et al. 2005, O"Connor et al

2005]. In follicular lymphoma, bortezomib, a proteasome inhibitor, carries a 55-70% response rate in combination with rituximab [Zinzani et al. 2012, Coiffer et al. 2011]. Additionally, in previously untreated diffuse large B-cell lymphoma, patients treated with R-CHOP plus bortezomib carried a 100% response rate [Ruan et al. 2011].

Bortezomib has also shown efficacy in T-cell lymphomas with a response rate of 67% as a single agent. Responses with bortezomib in these patients were durable lasting 7 to 14 months in a phase II study [Zinzani et al. 2007]. Furthermore, a phase I study of CHOP with bortezomib as first line treatment for aggressive T-cell lymphomas demonstrated a 61% response rate [Lee et al. 2008]. Therefore, proteasome inhibitors such as bortezomib have demonstrated efficacy in these difficult to treat disorders.

3.2.1 Carfilzomib

Carfilzomib is a next-generation proteasome inhibitor that exhibits a high degree of specificity for the catalytic domain in proteolytic active sites within the proteasome. Compared to bortezomib which is a slowly reversible inhibitor of the proteasome, carfilzomib is mechanistically irreversible.[Demo et al 2007; O"Connor et al. 2009] Carfilzomib has been studied in hematologic malignancies, including multiple myeloma, non-Hodgkin"s lymphomas. [O"Connor et al. 2009] With regards to its use in multiple myeloma, carfilzomib was studied in a multicenter single arm study of 266 patients with relapsed multiple myeloma who had received at least two prior therapies including bortezomib and an iMID. It was administered for two consecutive days weekly for 3 weeks of a 28 day cycle. This study demonstrated an overall response rate of 23.7% with a median duration of response of 7.8 months. The most common side effects included fatigue, anemia, nausea and thrombocytopenia. [Seigel et al. 2012] A similar study in bortezomib naïve patients demonstrated an overall response rate of 64.2% and the median duration of response was not reached. [Vij et al. 2012] It was based on these studies that carfilzomib gained fast track FDA approval for the treatment of relapsed/refractory multiple myeloma in 2012. Carfilzomib has also been studied in combination with dexamethasone using a weekly dosing schedule at ≥45mg/m2 in patients with relapsed/refractory multiple myeloma. In these studies, half-life was found to be comparable and AUC was found to be higher than on the traditional schedule. The overall response rate was found to be 67%. [Berenson et al. 2013]

3.3. Histone Deacetylase Inhibitors in B- and T-cell lymphomas: Romidepsin

Romidepsin is a potent histone deacetylase (HDAC) inhibitor which causes arrest of the cell cycle at both G1 and G2/M phases, induces the internucleosomal breakdown of chromatin, and inhibits intracellular HDAC activity resulting in an accumulation of marked amounts of acetylated histone species within M-8 cells [Nakajima Y, 1998]. The proposed mechanism of action in B-cell lymphomas is through the proto-oncogene BCL6 that is highly active as a transcriptional repressor within the germinal B cell. Uncurbed activity of BCL6 lends to suppression of genes involved in lymphocyte activation, differentiation, cell cycle arrest, and apoptosis. Moreover, accumulation of acetylated BCL6 is known to

down regulate the transcriptional repressive function allowing gene transcription of beneficial pro-apoptotic cellular products in the otherwise malignant cell. [Boreschenko O, 2002]

Romidepsin has not been clinically studied as a single agent in B-cell lymphomas, but is undergoing evaluation in combination with lenalidomide in a phase Ia/IIb study in hematologic malignancies [NCTG: 01755975] However, other HDAC inhibitors (vorinostat, belinostat, and panobinostat) have demonstrated cli nical activity in early phase studies. For example, in a combined analysis of two consecutive phase I trials in hematologic malignancies performed at MSK utilizing vorinostat, an HDAC inhibitor, of those enrolled 32 had a B-cell non-Hodgkin lymphoma (NHL). Three of these patients responded with one achieving a CR. [O"Connor O, 2005] Furthermore, the HDAC inhibitor panobinostat was employed in a phase II single agent study with 13 patients having relapse or refractory Hodgkin lymphoma. In this subgroup , 5 or 13 achieved a partial response. [Ottman O, 2008] In a more recent study the same drug was employed specifically for relapsed disease after autologous stem cell transplantation with an ORR of 13%. [Younes, 2009]

The demonstrated clinical activity of romidepsin in T-cell lymphoma is more robust. Romidepsin first demonstrated activity in a National Cancer Institute (NCI) phase I study. [Sandor V, 2002] Three patients with cutaneous T-cell lymphoma (CTCL) and 1 with significant cutaneous involvement of peripheral T-cell lymphoma (PTCL) all demonstrated a response to romidepsin at varying dose levels (12.7 to 17.8 mg/m2). The patient with PTCL experienced a complete remission after 8 cycles of romidepsin. Subsequently, romidepsin was further evaluated in 135 evaluable subjects with CTCL in Study GPI-04-0001 and NCI Study 1312. [Rasheed W, 2008] Across all 135 evaluable subjects with CTCL, the overall response rate (ORR) was 41% (55/135) and the complete response (CR) rate was 7% (10/135). Subjects with advanced disease had a similar ORR as subjects with earlier stage disease: 42% for ≥ stage IIB and 38% for stage I or IIA disease. Romidepsin was active in all sites of disease, including skin, lymph nodes, viscera, and blood. The median duration of response was 454 days (14.9 months). Although the median time to response was 57 days (1.9 months), in some cases an objective response to romidepsin was achieved after ≥6 months. Across all 135 subjects included in the pooled evaluable subjects analysis set, median time to disease progression was 252 days (8.3 months). These data led to FDA approval of romidepsin for CTCL in September 2009.

In the initial Phase 2 NCI-sponsored study in 48 subjects with PTCL or other T-cell lymphomas were enrolled in addition to the CTCL patients listed above. [Piekarz R, 2005] Among all 48 subjects, the ORR (CR+PR) was 31% (15/48). The CR and PR rates were 8% (4/48) and 23% (11/48), respectively. When response was evaluated among the 34 subjects who received ≥2 cycles of therapy, the ORR was 44% (15/34) and the CR and PR rates were 12% (4/34) and 32% (7/34), respectively.

This activity of romidepsin in PTCL was confirmed in the multi-center Phase 2 study of 131 patients with relapsed PTCL. [Coiffier B, 2011] The objective

response rate was 25% (33/130), including 15% (19/130) with CR/CRu. Response rates were not impacted by patient characteristics, prior stem-cell transplant, number or type of prior therapies, or response to last prior therapy. The median duration of response was 17 months, with the longest response ongoing at 34+ months. Of the 19 patients who achieved CR/CRu, 17 (89%) had not progressed at a median follow-up of 13.4 months. The most common grade ≥ 3 adverse events were thrombocytopenia (24%), neutropenia (20%), and infections (all types, 19%). This data led to FDA approval of romidepsin for PTCL in June of 2011.

3.4 Lenalidomide in B- and T-cell Lymphomas

Lenalidomide is an IMiD® compound that has become a commonly used agent as a partner with rituximab or in multi-agent approaches in the treatment of B-cell malignancies. IMiD® compounds have both immunomodulatory and anti-angiogenic properties which confer antitumor effects. 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 B- and T-cell lymphoid malignancies. 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. [Dredge K, 2005] 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. [Corral L, 1999] 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 cell lysis. [Davies F, 2001] Upregulation of T cell derived IL-2 production is achieved at least in part through increased AP-1 activity. [Schafer P, 2003]

Lenalidomide has been investigated in both relapsed and refractory indolent and aggressive non-Hodgkins lymphoma as well as Hodgkin lymphoma. In aggressive B-cell lymphomas, 49 patients were treated with the standard 25 mg dose taken orally for 21 days with 1 week rest. [Wiernik P, 2008] An ORR of 35% was seen with a complete response rate of 13%. Interestingly, a quarter of those who achieved a partial response at the time of first response assessment achieved further response with subsequent cycles. The toxicities were similar with a grade 4 neutropenia and thrombocytopenia of 8.2%. In indolent B-cell lymphoma lenalidomide has been studied in a similar dosing and duration strategy. The outcomes in 43 patients yielded an ORR of 23% with 7% achieving a complete response. Importantly, at the time of publication the median duration of response had not been met, but was longer than 16.5 months. Toxicities were again predictable to include grade 4 neutropenia and thrombocytopenia of 16% and 5% respectively. [Witzig T, 2009] Lastly, lenalidomide has been studied in refractory and heavily pretreated cohort of 12 patients with Hodgkin lymphoma. [Boll B, 2009] While the main objective of the study was to characterize the toxicity in this cohort 50% of the patient did achieve an objective response. Interestingly, no grade 3 or 4 toxicities were reported in this study.

Lenalidomide has also been studied in PTCL as a single agent. A multicenter phase II study in relapsed PTCL lenalidomide when dosed at 25 mg orally for 21 days of a 28-day cycle achieved an ORR of 30% with all responses being partial responses. [Deuck G, 2010] Grade 4 thrombocytopenia was seen in 33% of patients while grade 3 neutropenia was seen in 21%. Interestingly, development of a skin rash was correlated with those who obtained a response. A smaller study of lenalidomide in PTCL, also showed a 30% ORR at the same dose and schedule. [Zinzani P, 2011]

A small phase 2 study of lenalidomide in CTCL yielded a similar degree of activity. Among the 24 patients reported by Querfeld et al., the ORR was 32%. However, in these patients dose-limiting skin toxicity was seen at the 25 mg dose and dose de-escalation to 10 mg was performed. [Querfeld, 2011] In this study significant skin tumor flare may have confounded disease assessment among the CTCL patients resulting in premature withdrawal from study due to spurious progression.

3.5 Rationale for Combination Therapy

Relapsed and refractory B- and T-cell lymphoid malignancies are a challenge faced daily. Current paradigms approaches led many patients down a path of multiple cytotoxic combination therapies in the hopes of long-term disease free control or used as a strategy towards chemosensitivity for stem cell transplantation. However, treatment limiting toxicities are often encountered and repeated courses of cytotoxic chemotherapy often yield diminishing returns. There remains significant need for more active therapies and combinations with many newer approaches investigating regimens that shift the paradigm to long term or maintenance treatment employing drugs without cumulative toxicity.

In preclinical studies of Namalwa cells (derived from a Burkitt lymphoma), lenalidomide had synergistic effects with valproic acid (a known histone deacetylase inhibitor) by increasing apoptosis without adverse and potentially even beneficial effects on CD34+ progenitor cells. [Verhelle D, 2007] Furthermore, in multiple myeloma cells, a combination of lenalidomide with panobinostat, another HDAC inhibitor, has shown additive or greater activity in both *in vitro* and *in vivo* models. [Ocio E, 2007; Ocio E, 2010] The study of the combination of a HDAC inhibitor and lenalidomide are ongoing in patients with relapsed and refractory multiple myeloma. In two phase I dose finding studies, the oral HDAC inhibitor vorinostat has been safely combined with lenalidomide at the MTD and full standard approved doses (400 mg of vorinostat and 25 mg lenalidomide) of each drug alone without significant dose limiting toxicities [Siegel D 2009; Kaufman J 2010; Richardson P, 2010].

Among novel, non-chemotherapeutic agents, lenalidomide and romidepsin have shown significant activity in a broad range of lymphoid malignancies with good safety profiles, absence of cumulative toxicities, and fundamentally different mechanisms of action than the chemotherapies to which most patients are initially exposed. Among the HDAC inhibitors, romidepsin has shown the most potent clinical activity when similar diseases have been studied.

We have been conducting a phase Ib/IIa study of lenalidomide with romidepsin among patients with B - and T-cell lymphomas. While the MTD has not been determined in this study (currently enrolling into the last cohort; full dose romidepsin with full dose lenalidomide), overall response rate among the patients evaluable for response (n=13) patients accrued in this study is 54% (n=7) with 39% PR (n=5) and 15% CR (n=2). Responses by subtypes include 67% in T-cell lymphomas, 50% in B-cell lymphomas, and 33% in Hodgkin lymphoma with responses ongoing at >1 year. Thus far, patients have tolerated doses of lenalidomide 25mg with romidepsin 10mg/m^2. Only one patient experienced dose limiting toxicity with pneumococcal bacteremia. Therefore, this combination appears to be a promising strategy for patients with relapsed/refractory B- and T-cell lymphomas.

Additionally, there is evidence for the combination of HDAC with proteasome inhibitors. Studies in pancreatic cancer, ovarian cancer, melanoma, pancreatic cancer, lung cancer, multiple myeloma, acute lymphoblastic leukemia, primary effusion lymphoma have all shown in vivo, in vitro and early clinical synergy between HDAC and proteasome inhibitors. [Kikuchi et al 2013, Bhatt et al 2013, Bastian et al 2013, Huang et al 2012, Gatti et al 2012, Millward et al 2012] The synergy between HDAC and proteasome inhibitors is most likely dependent on a number of mechanisms. In multiple myeloma cell lines, the use of romidepsin in particular enhanced in vitro and in vivo activity of bortezomib. [Kikuchi et al 2010]. One proposed mechanism for this synergy was enhanced inhibition of the proteasome. In multiple myeloma cells previously exposed to a proteasome inhibitor, the addition of an HDAC inhibitor resulted in apoptosis through mitochondrial dysfunction and caspase mobilization [Pei et al. 2004]. Manipulation of the aggresome, an analogous protein degradation pathway, by HDAC and proteasome inhibitors may also disrupt protein folding leading to more defective protein production [Hideshima, Richardson, Anderson 2011]. In combi nation, these pathways may disrupt cellular or microenvironment communication and result in apoptosis. However it is unlikely that these are the sole mechanisms for synergy between these classes of agents, which remains an area of intense investigation.

It has been established in multiple myeloma that IMiDs and proteasome inhibitors are synergistic and the combination can often overcome refractory clones that have been previously been exposed to either class as a single agent. In hopes to expand on this synergy, a phase I study was conducted in patients with newly diagnosed multiple myeloma were treated with lenalidomide, bortezomib, dexamethasone with the addition of the HDAC inhibitor vorinostat. This study demonstrated that the regimen was efficacious with an overall response rate of 100% amongst the evaluable patients (n=29) [Kaufman et al 2012]. In this study, the most common toxicities included thrombocytopenia, constipation, diarrhea, fatigue, nausea and neuropathy. Grade 3 or higher toxicity that occurred in 10% or greater patients was thrombocytopenia, fatigue, neutropenia, neuropathy or cardiovascular toxicity denoting a well tolerated up-front strategy.

Given the need for better tolerated and more active therapy for patients with relapsed and refractory B- and T-cell malignancies we propose a phase Ib/IIa study of carfilzomib, romidepsin, lenalidomide. This would be a strategy to build upon the data the will be produced from the currently accruing phase Ib/IIa with romidepsin and lenalidomide (not yet published). We believe that the addition of carfilzomib to romidepsin and lenalidomide will improve response rates and will be well tolerated.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

We plan to perform an open label phase Ib/IIa study of patients with relapsed/refractory B- and T-cell lymphomas who are treated with carfilzomib, lenalidomide and romidepsin in a 3+3 design (see section 9.2). The phase IIa portion of the study will involve a dose expansion at the MTD to better characterize the efficacy and to inform further disease specific studies.

Phase Ib: The phase Ib portion of the study is designed to determine the MTD of carfilzomib, romidepsin and lenalidomide. All patients must have a relapsed or refractory B-cell or T-cell lymphoma. The design is a standard 3+3 dose escalation (**Table 3**) of carfilzomib, romidepsin and lenalidomide. The first cohort will enter at dose level 1. For details please see section 9.2.

Three patients will be initially treated in each cohort until the MTD is determined. If dose level 4 is achieved without DLT after 1 cycle that dose level will be deemed the optimal dose and the study will proceed to a phase IIa expansion cohort. Patients treated at MTD in the phase Ib portion will be counted towards the phase IIa accrual by disease subtype and also for all efficacy and toxicity endpoints unless they did not have measurable disease at point of study entry as allowed in the phase Ib portion.

Phase IIa: The phase IIa portion will further assess the toxicity and safety and allow a preliminary assessment of the efficacy of the combination to provide background for a potential future subtype specific phase II study. The assessment of efficacy will be descriptive. At the time of enrollment the patients will be identified as representing two cohorts based upon disease subtype: 1) B-cell lymphoma 2) T-cell lymphoma. Each cohort will enroll 10 patients including those treated at the MTD of the phase Ib portion. The assessment of toxicity and efficacy will be performed within the entire cohort evaluable at MTD. A preplanned exploratory analysis of the toxicity and efficacy of the disease specific cohorts will also be performed. Efficacy measures which will be determined include ORR , TTR, DOR,

and EFS. ORR is defined as the percentage of patients achieving a best response of CR/Cru or PR at any disease assessment time point. TTR is defined as the time or number of cycles between study registration and documentation of first response (CR/Cru or PR). DOR is defined as the time or number of cycles between documentation of first response and progression, change of therapy, death, or date of last contact (if still alive without progression). EFS is defined as the time between study registration and documented progression, change in therapy, or death if no progression was observed.

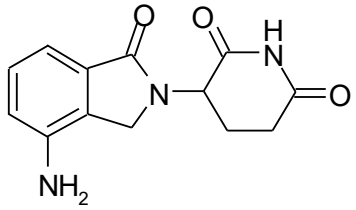
4.3 Intervention

All patients will be treated with romidepsin administered intravenously on days 1 and 8 of a 21-day cycle. Lenalidomide will be taken orally daily for days 1-14 of a 21-day cycle. The carfilzomib will be given weekly on days 1, and 8 of a 21-day cycle. Once a MTD is determined this dosing level will be used for the phase IIa portion. Cycles will be continued as above until the patient‟s wishes to be removed from the study, unacceptable toxicity develops, disease progression, treating physician recommends removal, or termination of study occurs.

5.1 THERAPEUTIC/DIAGNOSTIC AGENTS

5.2 REVLIMID®

REVLIMID® (lenalidomide), a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic properties. The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3. 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:



Lenalidomide is 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.

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*.

5.1.1 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. Exposure (AUC) in multiple myeloma patients is 57% higher than in healthy male volunteers.

5.1.2 Pharmacokinetic Parameters:

Distribution:

In vitro (^{14}C)-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).

***Revlimid REMS* Dosage form**

Lenalidomide will be supplied as capsules for oral administration.

Packaging

Lenalidomide will be delivered to the center where the prescription will be filled and dispensed. 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.

Storage

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

Special Handling Instructions

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

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.

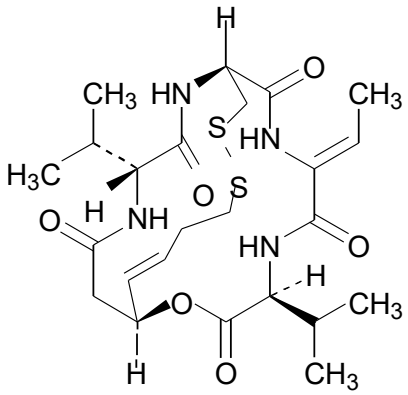
5.1.3 Prescribing Information

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 Revlimid REMS® program of Celgene Corporation. Lenalidomide will be delivered to the center

where the prescription will be filled and dispensed. Per standard Revlimid REMS® 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. Prescriptions must be filled within 14 days, unless the patient is a female of childbearing potential, in which case the prescription must be filled within 7 days. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

5.2 Romidepsin

Romidepsin (ISTODAX®) is a unique bicyclic depsipeptide originally isolated from *Chromobacterium violaceum* strain 968. [Ueda H, 1994] Romidepsin is an antineoplastic agent that has been identified as a novel HDAC inhibitor. Romidepsin has been shown to induce hyperacetylation of histones and other nonhistone protein species resulting in a variety of phenotypic changes, induction of the upregulation of gene transcription, G1 and G2/M arrest of the cell cycle, morphological reversion of transformed cells, cell growth inhibition, apoptotic cell death, and inhibition of angiogenesis.



The molecular formula of romidepsin is $C_{24}H_{36}N_4O_6S_2$, its molecular weight is 540.71, and its chemical name is: (1S,4S,7Z,10S,16E,21R)-7-ethylidene-4,21-bis(1-methyletheyl)-2-oxa12,13-dithia-5,8,20,23-tetraazabicyclo[8.7.6]tricos-16-ene-3,6,9,19,22-pentone.

In both *in vitro* and *in vivo* systems, romidepsin has been shown to elicit a range of biological activities, including HDAC inhibition, induction or repression of gene expression, cell cycle arrest, differentiation, cell growth inhibition, apoptotic cell death, morphological reversion of transformed cells, and inhibition of angiogenesis. The manner in which romidepsin and other HDAC inhibitors exert their biological effects has not been fully elucidated. The current view is that these agents inhibit, to a greater or lesser extent, the activity of Class I (HDACs 1, 2, 3, 8), Class II (HDACs 4, 5, 6, 7, 9, 10), and Class IV (HDAC 11) HDACs, causing chromatin remodeling and altered gene expression, which results in biological effects that are deleterious to tumor cell growth and survival. There is a growing body of evidence that HDAC

inhibitors can also target substrates other than histones and that the posttranslational modification of cellular proteins by acetylation may play an important role in the biological activities of HDAC inhibitors.

5.2.1 Dosage Form

The lyophilized, sterile finished product contains romidepsin, 10 mg/vial and 20 mg/single use vial Povidone, USP, and hydrochloric acid to adjust pH. Romidepsin (for infusion) is supplied in a dual-pack configuration with a single use diluent for romidepsin vial that contai ns 2 mL of 80% Propylene Glycol, USP, and 20% Dehydrated Alcohol (ethanol), USP; sterile for use in reconstitution of romidepsin (for Infusion).

5.2.2 Storage and Handling

The dual pack is to be stored at 20 to 25ºC (68 to 77°F), excursions permitted between 15 to 30°C (59 to 86°F) [USP controlled room temperature]. Romidepsin (for infusion) is stable for at least 36 months at 25°C/60% relative humidity (RH) as well as for 6 months at 40°C/75% RH and is stable against heat (for 3 months at 50°C) and humidity (for 3 months at 25°C/83% RH). Appropriately trained personnel using aseptic technique should reconstitute the drug. A volume of 2 mL of reconstitution diluent is added to the lyophilized powder and swirled until contents of the vial are free from visible particles. The reconstituted product stock solution at 5 mg/mL is chemically stable for at least 8 hours at room temperature. However, whenever possible, drug should be prepared within 4 hours of dose administration. A volume of the 5 mg/mL stock solution containing the appropriate dose for the patient will be diluted in 0.9% Sodium Chloride Injection, USP (0.9% saline) for intravenous infusion, as directed by the protocol. This dilution should result in a final drug concentration within the demonstrated stability range of 0.02 to 0.16 mg/mL for reconstituted romidepsin, that is compatible with polyvinyl chloride (PVC), ethylene vinyl acetate (EVA), and polyethylene (PE) intravenous infusion bags; glass bottles may also be used. The romidepsin infusion solution is chemically stable for at least 24 hours at room temperature. However, whenever possible, drug should be prepared within 4 hours of dose administration.

Supplier(s)

Celgene Corporation will supply ISTODAX® (romidepsin) to study participants at no charge.

5.2.3 DRUGS DISPENSATION AND ACCOUNTABILITY

The clinical trial supplies of romidepsin will be provided in a dual pack containing one vial of romidepsin for injection and one vial of diluent. The drug vial will contain a lyophilized powder of 10 mg of lyophilized romidepsin and 20 mg of povidone, USP (used as a bulking agent). The diluent vial will contain 2 mL of a 4:1 mixture of propylene glycol and ethanol. Appropriately trained personnel using an aseptic

technique should reconstitute the drug. A volume of 2 mL of diluent should be added to the lyophilized powder and swirled until contents of the vial are free from visible particles. This provides a stock solution at 5 mg/mL. The stock solution will be diluted using aseptic technique in 500 mL 0.9% Sodium Chloride Injection, USP (0.9% saline) for patients with a body surface area (BSA) ranging from 1.35 to 2.79 m² and in 1000 mL 0.9% saline for patients with a BSA of 2.8 m². Reconstituted drug in saline is compatible with PVC, EVA, and PE IV infusion bags as well as glass bottles. The vials containing the investigational product and the kits they are packaged in will be labeled according to the Good Manufacturing Practice guidelines and the local requirements

Special Handling Instructions

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

Record of Administration

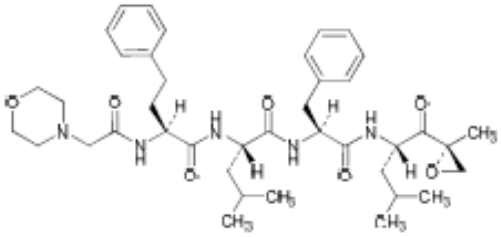
Accurate records will be kept in the source documents of all drug administration (including prescribing and dosing).

5.3 Carfilzomib

Carfilzomib (trade name Kyprolis®) is an analog of epoxomicin and eponemycin, a pair of related natural products that were initially discovered as antitumor agents in animals, and later shown to inhibit the chymotrypsin-like (CT-L) activity of the 20S proteasome.

Carfilzomib, atetrapeptide epoxyketone proteasome inhibitor, was FDA approved for the treatment of relapsed and refractory multiple myeloma. Carfilzomib is a potent, selective, and irreversible inhibitor of the CT-L activity of the constitutive proteasome (the form of proteasome found in most cell types) and the immunoproteasome (the form of proteasome found in many hematopoietic cells). In studies comparing carfilzomib to bortezomib, both were found to inhibit the CT-L activity of the proteasome with comparable potency [Demo 2007].

Incubation of tumor cells in culture with carfilzomib results in rapid and sustained inhibition of proteasome activity, accumulation of polyubiquitinated proteins, and induction of apoptosis [Demo 2007]. The period of time required to induce apoptosis varies among tumor cell types and is a function of the depth and duration of proteasome inhibition, with cells derived from hematological tumors being the most sensitive to brief periods of proteasome inhibition.



The molecular formula of carfilzomib is $C_{40}H_{57}N_5O_7$ and its molecular weight is 719.9. It"s chemical name is (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4-methylpentanamide..

Intravenous administration of carfilzomib in humans over 2 to 10 minutes results in suppression of proteasome CT-L activity when measured in blood 1 hour after the first dose. Inhibition of proteasome CT-L activity was comparable in whole blood and PBMCs. Proteasome inhibition was maintained in whole blood following the first dose of carfilzomib for each week of dosing, with 30-minute and bolus infusions.

5.3.1 Pharmacokinetic Parameters

Following intravenous administration of doses ≥ 15 mg/m2, carfilzomib was rapidly cleared from the systemic circulation with a half-life of ≤ 1 hour on Day 1 of Cycle 1. The systemic clearance ranged from 151 to 263 L/hour, and exceeded hepatic blood flow, suggesting that carfilzomib was largely cleared extrahepatically. The pathways of carfilzomib elimination have not been characterized in humans. [Onyx 2013]

5.3.2 Dose Administration

- Carfilzomib will be diluted in 100 mL D5W and administered over approximately 30 minutes.

- The dose is calculated using the patient"s actual body surface area (BSA) at baseline. Patients with a BSA greater than 2.2 m^2 should receive a dose based upon a BSA of 2.2 m^2. Dose adjustments do not need to be made for weight changes of less than or equal to 10%. Carfilzomib may be rounded according to local institutional rounding guidelines.

- Prior to each dose of carfilzomib in Cycle 1, give 250 IV normal saline or other appropriate IV fluid before and after carfilzomib administration. At the discretion of the treating physician, give an additional 250 mL to 500 mL of IV fluids as needed following carfilzomib administration. Fluids associated with Romidepsin infusion count toward the 250 mL to 500 mL total volume and may be used as prehydration for carfilzomib . Continue IV hydration, as needed, in subsequent cycles. In patients with chronic kidney disease or history of congestive heart failure, one may consider holding hydration in addition to the romidepsin volume.

- With cycle 1, pre-medicate with dexamethasone 4 mg PO or IV prior to all doses of carfilzomib. Additionally, if dose escalating, please also plan to premedicate with dexamethasone 4mg PO or IV to reduce the incidence and severity of infusion reactions. Reinstate dexamethasone premedication (4 mg PO or IV) if these symptoms develop or reappear during subsequent cycles. Dexamethasone premedication dosing has been increased to 8 mg PO or IV in clinical trials where the carfilzomib dose has exceeded 45 mg/m^2.
- It is preferred that carfilzomib is given after romidepsin.
- The Initial dose of carfilzomib given to any given patient (cycle 1, day 1) will be 20mg/m^2 regardless of the dose level. Subsequent doses will be based on the patient"s dose level.

5.3.3 Storage and Handling

Carfilzomib for Injection is supplied as single-use vials containing a dose of 60 mg of carfilzomib as a white to off-white lyophilized cake or powder. Carfilzomib vials contain no antimicrobial preservatives and are intended only for single use.

Unopened vials of carfilzomib are stable until the date indicated on the package when stored in the original package at 2°C to 8°C (36°F to 46°F). Retain carfilzomib in the original package to protect from light. The reconstituted solution contains carfilzomib at a concentration of 2 mg/mL.

5.3.4 Supplier

Onyx will supply carfilzomib to patients at no additional charge.

5.3.5 DRUGS DISPENSATION AND ACCOUNTABILITY

Special Handling Instructions

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

Record of Administration/Accountability

Accurate records will be kept in the source documents of all drug administration (including prescribing and dosing).

Each site will also maintain records of each shipment of investigational product. The records will document shipment dates, method of shipment, batch numbers, and quantity of vials contained in the shipment. Upon receipt of the investigational product, the designated recipient at the study site will inspect the shipment, verify the number and condition of the vials, and prepare an inventory or drug accountability record.

Empty and partially used vials should be accounted for and destroyed at the study site in accordance with the internal standard operating procedures. Drug destruction records must be readily available for inspection by representatives of Onyx and by regulatory authorities.

Only sites that cannot destroy unused drug on-site will be required to return their unused supply of investigational product.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

a) Pathologically confirmed B- or T-cell lymphomas at the enrolling institution, including stage ≥ Ib CTCL, which has relapsed or progressed after at least one systemic therapy.
   - Hodgkin lymphoma is allowed and will be classified as a B-cell lymphoma in the phase IIA portion.

b) Age ≥ 18,

c) Previous systemic anti-cancer therapy must have been discontinued at least 3 weeks prior to treatment and adverse effects must have resolved to ≤Grade 1 or baseline. In the phase IIa portion, in progressing subjects a 2 week washout may be allowed after discussion with the MSK Principal Investigator.

d) Previous radiation, hormonal therapy, and/or surgery must have been discontinued or completed at least 2 weeks prior to treatment in this study and adverse effects must have resolved. Lymph node or other diagnostic biopsies within 2 weeks are not considered exclusionary.

e) ECOG ≤ 2

f) Meet the following laboratory criteria:
   - Absolute neutrophil count ≥ 1.0/mm³,
   - Platelet count ≥ 80 K/μ (in the Phase IIa portion, if thrombocytopenia is due to bone marrow involvement platelet count must be ≥ 50 K/μL),
   - Phase Ib subjects must have calculated creatinine clearance ≥ 50ml/min by Cockcroft-Gault formula, phase IIa subjects must have calculated creatinine clearance ≥ 40ml4/min by Cockcroft-Gault formula.
   - Total bilirubin ≤ 1.5 x upper limit of normal (ULN). AST (SGOT) and ALT (SGPT) ≤ 3 x ULN.

g) Measurable disease for phase IIa portion only.
   - Lymphoma (includes CTCL patients who are without evidence of the disease in the skin): CT or PET/CT by modified Cheson criteria with incorporation of PET.
   - CTCL: mSWAT >0, or absolute Sezary count ≥ 1000 cells/μL.

h) 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.

i) Short course systemic corticosteroids for disease control, improvement of performance status or non-cancer indication (≤ 7 days) must have been discontinued at least 6 days prior to study treatment. Stable ongoing corticosteroid use (≥ 30 days) up to an equivalent dose of 15 mg of prednisone is permissible.
   - Topical steroids that have been used for > 3 weeks may be continued (CTCL only).

j) Women of reproductive potential† must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. See Appendix A: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

† A female of reproductive potential is a sexually mature female who:
1) has not undergone a hysterectomy or bilateral oophorectomy; or has not been naturally postmenopausal for at least 24 consecutive months (i.e. has had menses at any time in the preceding 24 consecutive months).

6.3 Subject Exclusion Criteria

a) Patients who have a standard curative option for their lymphoid malignancy at current state of disease are excluded. For eligibility on this trial, allogeneic stem cell transplantation is not to be considered a standard curative option.

b) Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.

c) Pregnant females. (Lactating females must agree not to breast feed while taking carfilzomib, lenalidomide or romidepsin).

d) Known hypersensitivity to thalidomide.

e) The development of erythema multiforme if characterized by a desquamating rash while taking thalidomide or similar drugs.

f) Prior use of lenalidomide if discontinued due to toxicity.

g) Prior therapy with romidepsin if discontinued due to toxicity.

h) Prior therapy with carfilzomib if discontinued due to toxicity.

i) Prior therapy with a proteasome inhibitor if discontinued due to toxicity.

j) Concurrent use of other anti-cancer agents or treatments.

k) Known seropositive and requiring anti-viral therapy for human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV).

l) Concurrent malignancy requiring active therapy.
- Patients with more than one type of lymphoma may be enrolled after discussion with the MSK Principal Investigator.

m) Known central nervous system or meningeal involvement (in the absence of symptoms investigation into central nervous system involvement is not required).

n) The following known cardiac abnormalities:
1. Congenital long QT syndrome.
2. QTc/QTf interval ≥ 480 milliseconds; unless secondary to pacemaker or bundle branch block.
3. Myocardial infarction within 6 months of cycle one, day one (C1D1). Subjects with a history of myocardial infarction between 6 and 12 months prior to C1D1 who are asymptomatic and have had a negative cardiac risk assessment (treadmill stress test, nuclear medicine stress test, or stress echocardiogram) since the event may participate.
4. Other significant ECG abnormalities including 2nd degree atrio-ventricular (AV) block type II, 3rd degree AV block.
5. Symptomatic coronary artery disease (CAD), e.g., angina Canadian Class II-IV (see Appendix B). In any patient in whom there is doubt, the patient should have a stress imaging study and, if abnormal, angiography to define whether or not CAD is present.
6. An ECG recorded at screening showing evidence of cardiac ischemia (ST depression of ≥2 mm, measured from isoelectric line to the ST segment). If in any doubt, the patient should have a stress imaging study and, if abnormal, angiography to define whether or not CAD is present.
7. Congestive heart failure (CHF) that meets New York Heart Association (NYHA) Class II to IV definitions (see Appendix C) and/or ejection fraction <45% by echocardiogram, or cardiac MRI.
8. A known history of sustained ventricular tachycardia (VT), ventricular fibrillation (VF), Torsade de Pointes, or cardiac arrest unless currently addressed with an automatic implantable cardioverter defibrillator (AICD).
9. Hypertrophic cardiomegaly or restrictive cardiomyopathy from prior treatment or other causes.
10. Uncontrolled hypertension, i.e., blood pressure (BP) of ≥170/95; patients who have a history of hypertension controlled by medication must be on a stable dose (for at least one month) and meet all other inclusion criteria.
11. Any cardiac arrhythmia requiring an anti-arrhythmic medication (excluding stable doses of beta-blockers)

12. Patients taking drugs that can cause significant QTc/QTf prolongation, unless able to be switched to non-QTc/QTf prolonging medication or on a stable dose without significant QT prolongation (>470 msec)
13. Concomitant use of significant CYP3A4 inhibitors unless able to be switched to a non-CYP3A4 inhibiting medication..

    - Caution should be used when administering study drugs to patients taking medications significantly metabolized by these enzymes refer to (http://medicine.iupui.edu/clinpharm/ddis/clinical-table/) for clinically relevant medications Particular attention should be paid to patients receiving warfarin. Patient should have coagulation paramaters monitored regularly, and warfarin dose adjusted accordingly. If these drugs cannot be discontinued or replaced, enrollment may be allowed after discussion with MSK PI.

7.0 RECRUITMENT PLAN

Potential research subjects will be identified by a member of the patient"s treatment team, the protocol investigator, or research team. If the investigator is a member of the treatment team, s/he will screen their patient"s medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study. Furthermore, eligible patients from the lymphoma or myeloma service will be identified by individual consenting physicians at the time of medical disciplinary rounds or in clinic at Memorial Sloan Kettering Cancer Center or the University of Nebraska Medical Center.

8.1 PRETREATMENT EVALUATION

8.2 Documentation of tests resulted and/or verification to be performed within 28 days of starting treatment.

1. Record prior medications and treatments
2. Record prior anti-cancer therapy
3. Physical examination
4. ECOG performance status
5. 12 lead ECG
6. ECHO or Cardiac MRI
7. Complete metabolic panel, including magnesium and phosphorus
8. Lactate dehydrogenase (LDH)
9. PET/CT or CT Chest, Abdomen, and Pelvis
10. Register patient with Revlimid REMS® program.

11. mSWAT for patient with cutaneous lymphoma.
12. Sezary panel in patients with Sezary syndrome only.
    - Sezary panel: peripheral blood flow cytometry including CD2, CD3, CD4, CD8, CD26 and or CD7
13. Phase IIa only: patients with suspected or known prior bone marrow involvement must have a bone marrow biopsy performed.
14. Pregnancy testing for females of childbearing potential within 10-14 days and again 24 hours prior to prescribing lenalidomide per the Revlimid REMS® program.

8.3 Documentation of tests resulted and/or verification to be performed within 14 days of starting treatment.

- Complete blood count (CBC)

9.1 TREATMENT/INTERVENTION PLAN

9.2 Pretreatment electrolyte assessment and drug management

Prior to initiation of each dose of romidepsin in cycle 1 and cycle 2 the patients level of potassium (K+) and magnesium (Mg) must be confirmed to be greater than or equal to the lower limit of normal for the testing laboratory, or corrected to those levels. In cycle 3 and beyond, magnesium and potassium levels may be checked up to 3 days before romidepsin. If within treatment range they do not need to be repeated prior to romidepsin administration. Intravenous (IV) supplementation with potassium chloride (KCL) and/or magnesium sulfate can be used. If supplementation is necessary, documentation of levels after IV supplementation is required. Supplementation with oral KCL or magnesium oxide (MgOX) or magnesium soy (MgSoy) can be used. These parameters apply to both the phase Ib and IIa portion of the study.

9.3 Treatment plan carfilzomib/romidepsin/lenalidomide Phase Ib

9.3.1 Lead-in Dose

The initial dose of carfilzomib (cycle 1, day 1) given to any patient regardless of dose level must be 20mg/ m^2 . All subsequent doses of carfilzomib will be based on the patient"s dose level.

9.3.2 Dose Escalation

Subjects enrolled into the phase 1b portion will enroll at dosing level 1 with three patients per dosing level (3+3 design). A cycle will be 21-days. Based on toxicity

and activity seen during the phase Ib portion, additional dose levels and/or alternate 28 day cycle may be explored through an amendment. The carfilzomib will be given intravenously weekly on days 1 and 8. The romidepsin will be given intravenously on days 1 and 8. The lenalidomide will be given as a once a day oral drug given on days 1-14. It is preferred that romidepsin be administered prior to carfilzomib.

TABLE 1: Phase I Dose Escalation			
Dose Level	Romidepsin	Lenalidomide	Carfilzomib (mg/m^2)
-1	8 mg/m^2	10 mg	20
1	8 mg/m^2	15 mg	36
2	8 mg/m^2	15 mg	45
3	10 mg/m^2	20 mg	45
4	10 mg/m^2	20mg	56

If all three patients complete one cycle of therapy without a DLT at the respective dose level then the subsequent dose level can be accrued.

A DLT is defined in cycle 1 of the phase I portion as:

- Non-hematologic toxicity of grade ≥3 (attributed to study drugs with the exception of alopecia , nausea, or grade ≥3 vomiting not responsive to antiemetics)
- Hematologic grade 4 toxicity (attributed to study drugs) defined as grade 4 thrombocytopenia of any duration; grade 4 neutropenia lasting more than 5 days; or grade 4 anemia unexplained by the underlying disease
- Grade ≥3 thrombocytopenia with clinically significant bleeding
- Febrile neutropenia of any duration (ANC <1.0K/ µL with fever 38.5^{o}C)
- Inability to receive day 1 of cycle 2 due to continued drug-related toxicity including Grade ≥ 2 toxicity that does not resolve to Grade ≤ 1 by the start of the next cycle.
- Grade 3 thrombocytopenia or neutropenia (attributed to study drug) within cycle 1 that results in a) ≥ 4 day delay in any romidepsin or carfilzomib dose or b) missing greater than 4 days of lenalidomide. (This criteria only applies to the **phase Ib portion** and does not apply to the phase IIa stopping rules).

After the MTD is determined by either DLT or accrual of six patients without DLT at dose level 4 in the first cycle accrual to the phase Ib portion will be considered closed. The MTD from the phase Ib study will be used for the phase IIa portion.

Of note, only patients who complete ≥80% of the doses of carfilzomib, romidepsin and lenalidomide during the first cycle will be evaluable for MTD. Patients who do

not meet this criteria for minimum drug exposure and do not have a dose limiting toxicity will be replaced for determination of MTD.

The treatment plan is described below for the **phase Ib portion**:

- **Romidepsin/Lenalidomide/Carfilzomib:** Romidepsin IVPB over 4 hours on days 1 and 8
- Carfilzomib IVPB administered over approximately 30 minutes on days 1 and 8**
- Lenalidomide PO q days 1-14

****1 cycle equals 21 days**

Patients will be treated until progression of disease, unacceptable toxicity, patient or physician choice or study closure. The study will remain open until all patients have discontinued therapy or 1 year from the last enrollee, whichever comes first. If a patient is respondi ng past the timeline listed above, the MSK Principal Investigator may decide to keep the trial open.

Of note, if patient"s experiences a greater than 10% change in body weight, dose of romidepsin and carfilzomib should be adjusted accordingly. Doses do not need to be adjusted for less than 10% changes in body weight.

a. Treatment Plan: carfilzomib/romidepsin/lenalidomide Phase IIa

The phase IIa portion is planned to include 20 patients. Each disease cohort, B- and T-cell lymphoma, will have 10 patients. Patients treated at MTD in the phase Ib cohort (if measurable disease at enrollment) will be included towards the 20 patient total in the phase IIa. The MTD has been determined to be dose level 1; 8 mg/m^2 romidepsin on days 1 and 8, 15 mg lenalidomide from days 1 - 14, and 36 mg/m^2 carfilzomib on days 1 and 8. The phase IIa cohort will be evaluated both collectively and by disease subtype.

> Patients that have received long-term therapy (greater than one year) with response will be allowed to have their schedule modified to allow less frequent dosing per investigator and primary investigator discretion.

b. Lenalidomide administration

In either phase of the study patients will be asked to take the lenalidomide at approximately the same time each day. 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. A medication diary will be provided to the patient and asked to be returned prior to each cycle [See Appendix G]. Any pills not used must be returned and all pills must be accounted for.

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.

9.4 Prophylactic Measures

- Subjects should receive prophylactic anti-emetics prior to romidepsin and carfilzomib administration (ondansetron preferred).
- Subjects should receive dexamethasone 4mg PO or IVPB prior to the first two cycles of carfilzomib. Dexamethasone is optional for the subsequent cycles.
- G-CSF may be given at the discretion of the treating physician.
- Subjects should be taking prophylaxis against varicella zoster per the institutional guidelines (e.g. acyclovir 400mg by mouth twice daily) while on this regimen.

9.5 Concomitant Medications

Patients will be instructed not to take any additional medications (including over-the-counter products) during the trial without prior consultation with their treating physician. All medications taken within 30 days of screening and medications and supportive therapies that are administered during the study must be recorded in the electronic Case Report Forms (eCRFs) and in the source documents. Supportive therapy, that is ongoing at baseline, will be permitted during the treatment phase of the study. If other therapy for the disease is required, continuation of the study treatment should be discussed with the MSKPrincipal Investigator. Concomitant medications for other medical conditions are permitted as clinically indicated subject to specific protocol requirements outlined below.

9.5.1 Prohibited/monitored concurrent therapy

- Any investigational agent other than lenalidomide or romidepsin.
- Any medications at high risk of causing QTc/QTf prolongation or inducing torsades de pointes (as listed in Appendix E).
- Concomitant use of CYP3A4 inhibitors with romidepsin should be avoided (excluding anti-emetics) to prevent potential increase in romidepsin exposure during concomitant treatment with these drugs. Should a patient already enrolled on this study require treatment with a drug listed in Appendix F romidepsin must be interrupted prior to starting these drugs and should not resume until a washout period of at least 5 half-lives has elapsed.

Any medications that have the potential to alter serum electrolytes (e.g., diuretics) should be monitored very closely for electrolyte abnormalities as these can contribute to the risk of QTc/QTf prolongation and ventricular arrhythmias.

9.5 Dose Continuation, Modification and Interruption

Subjects will be evaluated for AEs at each visit with the NCI CTCAE v4.0 used as a guide for the grading of severity. DLTs as defined will be tabulated in cycle 1 of phase Ib and cycles 1-4 of the phase IIa portion of the study. The toxicity decision rule for the IIa portion is described in Section 14.0. The sections below describe dose reduction steps, instructions for initiation of a new cycle of therapy and dose modifications during a cycle of therapy. Of note, if patient"s experiences a greater than 10% change in body weight, dose of romidepsin should be adjusted accordingly. Doses do not need to be adjusted for less than 10% changes in body weight.

9.5.1 Instructions for Dose Modifications or Interruption During Phase 1 Cycle 1

There will be no dose reductions in cycle 1 phase 1. Inability to meet treatment criteria will result in holding the dose.

9.5.2 Instructions for Dose Modifications or Interruption During Phase 1 Cycle 2 and beyond and phase 2 all cycles

Dose delay and dose reduction rulesare as follows and in the table below. The following dose modification criteria are applicable to adverse events related to study drugs:

- In the event of dose reduction due to toxicity all agents will be reduced as per Table 2, 3, 4. If an agent is already at its lowest dose per tables 2,3,4 then the other agents will be reduced. If the lowest doses are not tolerated the subject will be removed from the study.
- For treatment interruptions during a cycle, the 21-day schedule of each cycle will continue to be followed. Missed doses of lenalidomide, carfilzomib and romidepsin are not made up. For treatment interruptions that delay the scheduled start of a new cycle, when toxicity has resolved as required to allow the start of a new cycle, the restart day of therapy becomes Day 1 of the next cycle.
- If a patient is at the lowest dose level and deriving benefit from therapy, they may continue on protocol therapy despite ≥ grade 3 hematologic toxicity or non-clinically significant non-hematologic toxicity after discussion with the MSK principal investigator. A delay of planned study therapy of greater than 21 days with result in removal from study.

TABLE 2: Lenalidomide Dose Modification Steps	
Current Lenalidomide Dose	**One Level Dose Reduction**
20 mg daily on Days 1-14 every 21 days	15 mg daily on Days 1-14 every 21 days
15 mg daily on Days 1-14 every 21 days	10 mg daily on Days 1-14 every 21 days
10 mg daily on Days 1-14 every 21 days	5 mg daily on Days 1-14 every 21 days

TABLE 3: Romidepsin Dose Modification Steps	
Current Romidepsin Dose	**One Level Dose Reduction**
10 mg/m^2 daily on Days 1,8	8 mg/m^2 daily on Days 1,8
8 mg/m^2 daily on Days 1,8	5 mg/m^2 daily on Days 1,8
5 mg/m^2 daily on Days 1,8	5 mg/m^2 daily on Days 1
Carfilzomib Dose Modification Steps	
Current Carfilzomib Dose	**One Level Dose Reduction**
56 mg/m^2	45 mg/m^2
45 mg/m^2	36 mg/m^2
36mg/m^2	20 mg/m^2

TABLE 4: Dose Modifications for Lenalidomide, Carfilzomib and Romidepsin for Phase 1 cycle 2 and beyond/ Phase 2 all cycles	
NCI CTC Toxicity Grade	**Dose Modification Instructions (also see Instructions for Initiation of a New Cycle above)**

≥Grade 3 neutropenia not associated with fever	• If found on the day of romidepsin and/or carfilzomib treatment hold (interrupt) lenalidomide, carfilzomib and romidepsin dose.
	  ◦ Follow CBC at least weekly until recovery
	  ◦ Treatment with romidepsin/carfilzomib and lenalidomide may be resumed if ANC recovers to ≤ grade 2 neutropenia within 4 days of a planned dose (with or without G-CSF).
	  ◦ If ANC does not recover to ≤ grade 2 within 4 days, dose is missed and not made up. Reduce one dose level upon resolution of neutropenia to ≤ grade 2.
	• If found on days between romidepsin and carfilzomib dosing, lenalidomide may be held and G-CSF may be used at the discretion of the treating physician.

≥Grade 3 neutropeniaassociated with fever (temperature ≥ 38.5º C) or Grade 4 neutropenia	• Hold (interrupt) lenalidomide, carfilzomib and romidepsin dose. • Follow CBC at least weekly until recovery. • If neutropenia has resolved to ≤ grade 2 prior to Day 14 of the current cycle, restart lenalidomide, carfilzomib and romidepsin 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, carfilzomib and romidepsin by 1 dose level at the start of the next cycle. Omitted doses are not made up.

TABLE 4: Dose Modifications for Lenalidomide, Carfilzomib and Romidepsin for Phase 1 cycle 2 and beyond/ Phase 2 all cycles	
NCI CTC Toxicity Grade	**Dose Modification Instructions (also see Instructions for Initiation of a New Cycle above)**

Thrombocytopenia ≥ Grade 3 (platelet count < 50,000/mm³)	• If found on the day of romidepsin and/or carfilzomib treatment, hold (interrupt) lenalidomide, carfilzomib and romidepsin dose.
	  ◦ Follow CBC at least weekly.
	  ◦ Treatment with romidepsin/carfilzomib and lenalidomide may be resumed if thrombocytopenia recovers to ≤ grade 2 thrombocytopenia within 4 days of a planned dose.
	  ◦ If thrombocytopenia does not recover to ≤ grade 2 within 4 days, dose is missed and not made up. Reduce one dose level upon resolution of thrombocytopenia to ≤ grade 2.
	• If grade 3 thrombocytopenia found on the days between romidepsin and/or carfilzomib treatment, lenalidomide may be held at the discretion of the treating physician.
	• If grade 4 thrombocytopenia found on the days between romidepsin and/or carfilzomib treatment, hold lenalidomide
	  ◦ Follow CBC at least weekly.
	  ◦ If thrombocytopenia resolves to ≤ grade 2 prior to Day 14 of the current cycle, lenalidomide may be restarted at the same dose level. Otherwise, omit for remainder of the cycle and reduce the dose of romidepsin, carfilzomib, and lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up.
	• Hold prophylactic anti-coagulation, if applicable.
	• Restart prophylactic anti-coagulation when platelet count is ≥ 50,000/mm³.
	• Platelet transfusion solely to meet treatment criteria are discouraged but may be considered after discussion with the MSK PI.

Non-blistering rash **Grade 3** **Grade 4**	• If Grade 3, hold (interrupt) lenalidomide, romidepsin and carfilzomib dose. Follow weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 14 of the current cycle, restart lenalidomide, carfilzomib and romidepsin 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, carfilzomib and lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. • If Grade 4, discontinue lenalidomide, romidepsin and carfilzomib. Remove patient from study.
Desquamating (blistering) rash- any Grade	Discontinue lenalidomide, carfilzomib and romidepsin. Remove patient from study.

TABLE 4: Dose Modifications for Lenalidomide, Carfilzomib and Romidepsin for Phase 1 cycle 2 and beyond/ Phase 2 all cycles	
NCI CTC Toxicity Grade	**Dose Modification Instructions (also see Instructions for Initiation of a New Cycle above)**
Neuropathy **Grade 3** **Grade 4**	• If Grade 3, hold (interrupt) romidepsin, lenalidomide and carfilzomib dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 14 of the current cycle, restart lenalidomide, romidepsin and carfilzomib 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, romidepsin and carfilzomib by 1 dose level at the start of the next cycle. Omitted doses are not made up. • If Grade 4, discontinue lenalidomide and carfilzomib. Remove patient from study. Responding patients may continue on romidepsin off of study.
Venous thrombosis/embolism ≥ Grade 3	• Hold (interrupt) carfilzomib, lenalidomide and romidepsin. Start therapeutic anticoagulation, if appropriate. • Restart carfilzomib, lenalidomide and romidepsin at investigator"s discretion after discussion with the MSK PI (reduce 1 dose level of each drug). • See Anticoagulation Consideration
Hyperthyroidism or hypothyroidism	• Omit lenalidomide, carfilzomib, and romidepsin for remainder of cycle, evaluate etiology, and initiate appropriate therapy. • See Instructions for Initiation of a new cycle and reduce the dose of lenalidomide by 1 dose level.
Other related non-hematologic toxicity ≥ Grade 3 including grade 3: • **Pulmonary hypertension** • **Congestive heart failure** • **Myocardial ischemia** • **Decreased ventricular function** • **Hepatic toxicity** • **Pulmonary complications** • **Renal Failure**	• Hold (interrupt) lenalidomide, carfilzomib romidepsin dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 2 prior to Day 14 of the current cycle, restart lenalidomide, carfilzomib and romidepsin at one dose level lower and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle. Omitted doses are not made up. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide, carfilzomib and romidepsin by 1 dose level at the start of the next cycle. • For patients with ≥ grade 3 nausea or vomiting, dose reductions are only required for patients who had persistent ≥grade 3 vomiting despite use of oral and/or IV antiemetics.

9.5.2 Romidepsin Dose Modification in Case of Cardiac Toxicity

The guidelines for cardiac monitoring and timing of ECG assessments are presented in Table 5. Prolongation of QTc/QTf ≥ 500 msec is considered to be an alert associated with romidepsin administration.

Table 5: Dose alteration based on cardiac abnormalities			
Parameter/Symptoms	**Change**	**Action**	**Dosing/ Continuation**
Sinus tachycardia	Pulse >140/min after recumbency	Hold further dosing and treat appropriately. If desired, a local cardiologist may be consulted.	If resolved, restart romidepsin at reduced dose as per table 3. If not resolved, take off study.
Atrial dysrhythmia (SVT, atrial fibrillation, or atrial flutter)	New occurrence		
Prolongation of QTc/QTf compared to baseline	To ≥500 msec		
Heart rate	> 120 bpm with > 20 bpm increase from previous evaluation;		
Ventricular tachycardia	≥3 beats in a row		
Ventricular fibrillation; Torsade de Pointes	New occurrence	Hold further dosing and treat appropriately. The MSK PI should be notified immediately and local cardiologist should be consulted.	Hold further dosing until MSK PI and cardiologist evaluation is complete
A subsequent episode of any of the above, despite dose reduction		**Take off study**	
T-wave morphology	Inversion of ≥4 mm[a]	Hold further dosing and treat appropriately. If desired, a local cardiologist may be consulted.	If resolved, restart romidepsin at reduced dose of 10 mg/m² In some patients, ST segment and T-wave morphology changes may recur despite a dose reduction to 10mg/m^2. In such cases, further treatment should be held until the ECG changes resolve. If the patient experiences no concomitant clinical events, treatment may be resumed at the reduced dose of 10 mg/m^2 If not resolved, take off study
ST-segment	Depression of ≥2 mm[b]		

NOTE: Cardiac findings that require dose modification should be reported as AEs or SAEs as appropriate.

[a] Measured from isoelectric line to peak of T-wave.

[b] Measured from isoelectric line to ST segment.

9.5.3 Other Non-Hematologic and Hematologic Toxicities

All previously established or new toxicities observed any time, with the exception of those mentioned above, are to be managed as summarized in Table 5:

- Dose interruption or study discontinuation is not required for lymphopenia of any grade.
- In general, if study drug has been held and the toxicity does not resolve, as defined above, then drug must be discontinued.
- Dose reductions should not be performed for alopecia or for non-infectious diarrhea, nausea, or vomiting that was not treated with aggressive anti-diarrheal or anti-emetic support.

9.6 Treatment Adherence

Research personnel will review the dosing instructions with patients. Patients will be provided with a medication diary and asked to record the drug administration. Patients will be asked to bring any unused drug and empty drug containers to the research personnel at the beginning of each cycle. Site staff will count and record the number of used and unused drug at the beginning of each cycle and reconcile with the patient diary.

Any unused Revlimid® (lenalidomide) should be returned to the patient for disposition in accordance with the Revlimid REMS program.

9.7 Concomitant Therapy

9.7.1 Recommended Concomitant Therapy

Subjects will receive full supportive care, including transfusions of blood and blood products, antibiotics, analgesics, and antiemetics when appropriate. Subjects should take prophylaxis against varicella zoster as per their institutional guidelines while on this regimen (e.g. acyclovir 400mg by mouth twice daily).

9.7.2 Anticoagulation Consideration

Lenalidomide increases the risk of thrombotic events in patients who are at high risk or with a history a thrombosis, in particular when combined with other drugs known to cause thrombosis. When lenalidomide was combined with other agents such as steroids (e.g. dexamethasone, prednisone), anthracyclines (Doxil, Adriamycin) and erythropoietin the risk of thrombosis is increased. For information on the risk of venous thromboembolism with combined oral contraception see Appendix A: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

Consideration should be given to the optional use of aspirin (81 or 325 mg) or some other form of prophylaxis as deemed appropriate. Low molecular weight heparin may be utilized in patients that are intolerant to ASA. Coumadin should be

used with caution and close monitoring of INR. Carefully monitor prothrombin time (PT) and International Normalized Ratio (INR) in patients concurrently administered ISTODAX® and Coumadin derivatives.

If prophylactic anti-coagulation is used, it will be held for platelet counts < 50,000, and then restarted when platelet counts are above this level.

10.1 EVALUATION DURING TREATMENT/INTERVENTION

10.2 Assessments During Treatment: Phase 1, cycle 1 and cycle 2; phase 2, cycle 1

A patient may receive treatment on day 1 or day 8 of the first cycle if he or she meets the following parameters on the day of treatment:

- ANC is ≥ 1.0 K/μL Platelet count is ≥ 80 K/μL or within 10 K/μL of baseline for cycle 1 day 1 and platelet count ≥ 50 K/μL for cycle 1 day 8. (In the Phase II portion, if thrombocytopenia is due to bone marrow involvement platelet count must be ≥ 50 K/μL),
- Serum creatinine concentration ≤ 2.0 × ULN or ≤ baseline
  Serum potassium must be confirmed to be greater than or equal to the lower limit of normal for the testing laboratory, or corrected to those levels.
    - Supplements must be given to patients whose potassium and/or magnesium are below the aforementioned range.
        - Magnesium supplementation: If levels are below normal range, but within 0.5 units of the lower limit of normal, patients can receive at least 2gm magnesium IV and proceed to treatment without re-checking labs. Patients can be treated if magnesium levels are above normal range.
- Potassium supplementation: If levels are below normal range, but within 0.3 units of the lower limit of normal, patients can receive at least 20mEq potassium and proceed to treatment without re-checking labs. 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.

Within 7 days of treatment:

- AST (SGOT) and ALT (SGPT) ≤ 3.0 × ULN .
    - Liver function analysis should be assessed on the day of treatment but does not have to be resulted prior to initiating treatment if the most recent assessment meets the above criteria and was performed within the last 7 days.

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

10.2.1 Assessments During Treatment: Phase 1, cycle 3 and beyond; phase 2, cycle 2 and beyond

A patient may initiate a new cycle if he or she meets the following parameters on the day of treatment:

- ANC is ≥ 1.0 K/μL
- Platelet count is ≥ 80 K/μL or within 10 K/μL of baseline. (In the Phase II portion, if thrombocytopenia is due to bone marrow involvement platelet count must be ≥ 50 K/μL)

The following parameters may be checked within 3 days of initiating a cycle:

- Serum creatinine concentration ≤ 2.0 × ULN or ≤ baseline
- Serum potassium and magnesium is ≥ the lower limit of normal for the testing laboratory, or corrected to those levels for the testing laboratory.
- If levels are within range romidepsin may be administered without repeat testing on day of treatment unless clinically indicated (such as vomiting, diarrhea, or initiation of medications that may affect electrolytes).
- Supplements must be given to patients whose potassium and/or magnesium are below the aforementioned range:
  - Magnesium supplementation: If levels are below normal range, but within 0.5 units of the lower limit of normal, patients can receive at least 2gm magnesium IV and proceed to treatment without re-checking labs.

  Potassium supplementation: If levels are below normal range, but within 0.3 units of the lower limit of normal, patients can receive at least 20mEq potassium and proceed with treatment without re-checking labs.

- 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.
- ECG schedule as specified in Table 7.

Within 14 days of treatment:

- AST (SGOT) and ALT (SGPT) ≤ 3.0 × ULN.
  - Liver function analysis should be assessed on the day of treatment but does not have to be resulted prior to initiating treatment if the most

recent assessment meets the above criteria and was performed within the last 14 days.

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

10.3 Required Blood Parameters and Other Investigations Prior to Romidepsin Day 8

The following criteria must be fulfilled:

- ANC is ≥1.0 K/μL.
- Platelet count is ≥ 50 K/μL.
    - Serum potassium and magnesium is ≥ the lower limit of normal for the testing laboratory, or corrected to those levels for the testing laboratory.
    - If levels are within range romidepsin may be administered without repeat testing on day of treatment unless clinically indicated (such as vomiting, diarrhea, or initiation of medications that may affect electrolytes).
    - Supplements must be given to patients whose potassium and/or magnesium are below the aforementioned range.
        - Magnesium supplementation: If levels are below normal range, but within 0.5 units of the lower limit of normal, patients can receive at least 2gm magnesium IV and proceed to treatment without re-checking labs.
        - Potassium supplementation: If levels are below normal range, but within 0.3 units of the lower limit of normal, patients can receive at least 20 mEq potassium and proceed with treatment without re-checking labs.
- Recovery of any drug-related non-hematological toxicity to Grade 2 or less, unless otherwise indicated.
- ECG schedule as specified in **Table 7**.
- If any of these criteria are not fulfilled, then administration of study drugs should be delayed as detailed in Section 9.0.

Within 7 days of treatment:

- AST (SGOT) and ALT (SGPT) ≤ 3.0 × ULN.
    - Liver function analysis should be assessed on the day of treatment but does not have to be resulted prior to initiating treatment if the most recent assessment meets the above criteria and was performed within the last 7 days.

10.4 Cardiac Monitoring

Minor ECG changes are expected following romidepsin administration (refer to current Investigator"s Brochure). Cardiac assessments must be performed for all study patients. The treating investigator must perform the primary assessment and is responsible for the cardiac safety of the patients.

10.5 Cardiac Alert Findings

In the event of an alert finding, the individual decision about a delay of administration, dose reduction, or withdrawal from the study will be made by the Investigator (in association with local cardiologist, if preferred). All alerts must be confirmed via manual read of the patients ECG; the machine reading alone is not adequate. The following findings are considered to be cause for alert and if they occur, should be reported as AEs or SAEs, as appropriate:

- QTc or QTf is ≥ 500 msec:
    - Either QTc or QTf formulas can be used; the lesser of the two values will be recorded.
    - If the patient has a known incomplete or complete right bundle branch block (RBBB) or left bundle branch block (LBBB) a change in QTc/QTf of > 60 msec from the post antiemetic ECG will be used as criteria for and adverse event and would be graded as a grade 3 adverse event.
    - If the patient has a single or dual chamber pacemaker a change in QTc/QTf of > 60 msec from the post antiemetic ECG in either the native rhythm or paced rhythm will be used as a criteria for an adverse event and would be graded as a grade 3 adverse event.
- Ventricular arrhythmia: VT (≥ 3 beats in a row) or VF.
- Sinus tachycardia (pulse >140/min after recumbency).
- Heart rate is ≥ 120 bpm with ≥ 20 bpm increase from previous evaluation.
- New occurrence of atrial dysrhythmias (SVT, atrial fibrillation, or atrial flutter).
- Abnormal ST and/or T-wave changes including ST depression of ≥ 2 mm (as measured from isoelectric line to the ST segment at a point 60 msec at the end of the QRS complex); T-wave inversion of ≥ 4 mm (measured from isoelectric line to peak of T-wave) as long as the main QRS vector is positive.
- Ventricular tachycardia, including Torsade de Pointes.

See **Table 5** in Section 9 for recommended dose reductions, etc., in the above situations.

10.6 Electrocardiograms

An ECG must be performed within 1 hour (after administration of antiemetic premedication) prior to romidepsin and after completion of each romidepsin infusion for cycles 1 and 2. If no QTc/QTf value greater than 480 msec is demonstrated by auto-read or manual read then further ECGs may be omitted for

the duration of study. If a QTc/QTf value greater than 480 but less than 500 msec is encountered then ECGs should be performed within 1 hour prior to romidepsin infusion for the first dose of each subsequent cycle.

If a QTc/QTf is ≥ 500 msec is encountered, ECGs should be repeated twice more for a mean of three QTc/QTf values. If the mean is ≥ 500 msec, follow dose modification guidelines in **table 6**.

Note to Investigators: At the Investigator"s discretion, more intensive ECG monitoring can be performed for all romidepsin administrations.

10.7 Pregnancy Testing

Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e. has had menses at any time in the preceding 24 consecutive months).

Pregnancy tests will be required by the Revlimid REMS® program and will occur within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide for Cycle 1 (prescriptions must be filled within 7 days). FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see Appendix A: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).

10.8 Follow-Up

Patients, who discontinue treatment for any reason, will be followed for 1 month or until resolution of all treatment related AEs or initiation of alternate cancer therapy, whichever is longer. At treatment discontinuation, patients will undergo a safety assessment approximately 1 month after the last dose of protocol therapy. In addition, off study evaluations per the end of study assessments will be done.

11.0 TOXICITIES/SIDE EFFECTS

Side Effects of Romidepsin

Likely

- Nausea
- Vomiting
- Loss of appetite
- Fatigue
- Constipation
- Diarrhea
- Altered sensation of taste
- Fever

Side effects related to levels of substances found in the blood:

- Thrombocytopenia
- Anemia
- Leukopenia
- Hyperglycemia
- Hypocalcemia
- Hypomagnesemia
- Hypoalbuminemia

Less Likely

- Swelling
- Decreased weight
- Heart tracing irregularities
- Weakness
- Joint pain
- Itching
- Back pain
- Dizziness
- Abdominal pain
- Dehydration
- Changes in heart function
- Heartburn
- Low blood pressure
- Cough
- Skin infections
- Shortness of breath
- Headache
- Feeling of discomfort or uneasiness
- Insomnia
- Burning or tingling sensations
- Headache
- Feeling of discomfort or uneasiness

Side effects related to levels of substances found in the blood:

- Hyperbilirubinemia
- Hypokalemia
- Lymphopenia
- Hyponatremia
- Hypermagnesemia
- Increased creatinine
- Hypophosphatemia
- Elevated transaminases
- Elevated alkaline phosphatase

Rare but serious

- Anxiety
- Infections
- Bleeding
- Increased heart rate
- Hyperkalemia
- Hyperuricemia
- Pancreatitis
- Deep venous thrombosis
- Syncope

Side Effects of Lenalidomide

Likely:

- Fatigue or feeling tired
- Lack or loss of strength
- Anemia or a decrease in red blood cells that can cause tiredness
- Decrease in white blood cells that can make you more prone to infections (Neutropenia)
- Decrease in platelets which can cause you to bruise or bleed easily (Thrombocytopenia)
- Blood clot in lower extremities
- Vision blurred
- Nosebleed
- Constipation or difficulty moving your bowels
- Diarrhea or loose/frequent bowel movements
- Nausea or vomiting
- Loss of appetite
- Joint pain
- Swelling of the arms and legs
- Fever
- Cough

- Shortness of breath or difficulty catching your breath
- Upper respiratory infection (infection of nose, sinus, and throat)
- Allergic reaction
- Itching and dry skin
- Dizziness
- Headache
- Altered sense of taste
- Abnormal sense of touch
- Pain and decreased sensation in nerves
- Pneumonia

Less Likely:

- Problem with moving food through digestive system (gastrointestinal motility disorder)
- Dry mouth
- Indigestion (dyspepsia)
- Muscular weakness
- Stroke
- Tingling sensation (paresthesia)
- Fainting (syncope)
- Drowsiness
- Difficulty breathing (respiratory distress)
- Excessive sweating (hyperhidrosis)
- Fever with a decrease in white blood cells that help fight infections (febrile neutropenia)
- Shortage of all types of blood cells including red blood cells, white blood cells, and platelets (pancytopenia)
- Excessive loss of body water (dehydration)
- High blood sugar (hyperglycemia)
- Uncontrolled blood sugar (diabetes mellitus)
- Higher than normal blood uric acid (hyperuricemia)
- Higher than normal level of iron in body (iron overload)
- Lens of eye becomes cloudy (cataracts)
- High blood pressure (hypertension)
- Low blood pressure (hypotension)
- Bleeding
- Altered mood
- Depression
- Irregular heartbeat (atrial fibrillation)
- Failure of the heart (cardiac failure)
- Heart attack (acute myocardial infarction)
- Fast heartbeat (tachycardia)
- Not enough blood flow to heart muscle (myocardial ischemia)
- Secondary cancer
- Kidney damage (renal failure)

- Abnormal liver function tests
- Tumor lysis syndrome

Rare but Serious

- Fever with a decrease in white blood cells that help fight infections (Febrile neutropenia)
- Blood clot in or around the lungs (Pulmonary embolism)
- Deep vein thrombosis or blood clots in larger blood vessels
- Atrial fibrillation or irregular heartbeat
- Pneumonia or an infection of the lungs
- Sepsis or an infection of the blood
- Kidney failure or inability of the kidneys to remove waste from the body
- Muscle breakdown (rhabdomyolysis)
- Swelling of the lungs
- Severe skin rash (Stevens-Johnson syndrome)

Side Effects of Carfilzomib

Likely Side Effects:

- Fatigue (tiredness)
- Fever
- Headache
- Cough
- Cough with phlegm
- Shortness of breath (at rest or with exertion)
- Nausea
- Vomiting
- Diarrhea
- Constipation
- Decreased red blood cell count which may lead to feeling tired
- Decreased platelet counts which may lead to increase bleeding or bruising
- Decreased white blood cell count
- Upper respiratory tract infection
- Mild decreases in kidney function which are generally reversible
- Swelling of the arms or legs
- Back pain
- High blood pressure
- Pneumonia or other lower respiratory tract infections

Less Likely Side Effects:

- Flu-like symptoms such as fever, chills, or shaking that may occur at any time but are more likely to occur on the day of or the day after carfilzomib infusion.
- Loss of or decreased appetite which may lead to weight loss

- Insomnia (difficulty sleeping)
- Anxiety
- Dizziness
- Confusion or changes in mental state
- Blurred or double vision
- Numbness, tingling, or decreased sensation in hands and/or feet
- Blood chemistry and electrolyte alterations
- Rash and/or itching, or dry skin
- Pain, burning, or irritation at the infusion site
- Generalized pain
- Pain in the bones or joint pain
- Muscle spasm, pain, or weakness
- General weakness, or lack of energy or strength
- Abdominal pain, discomfort, or swelling
- Indigestion (upset stomach)
- Inflammation of the liver (mild, reversible changes in liver function tests)
- Increase or decrease in blood pressure
- Urinary tract infection
- Nosebleeds
- Dehydration
- Sore throat, inflammation of the nose and throat, runny nose or nasal congestion
- Blood clots in the leg or lungs
- Change in voice or hoarseness
- Toothache
- Low white blood cell count which may be associated with fever
- Low blood pressure

Rare and/or Potentially Serious Side Effects:

- Infusion reactions (which can occur during or shortly after carfilzomib infusion) including flushing or feeling hot, fever, shakes, nausea, vomiting, weakness, shortness of breath, swelling of the face, pain in the muscles or joints, tightness or pain in the chest, and low blood pressure
- Allergic reaction including total body rash, hives, and difficulty breathing
- Inflammation of the pancreas (pancreatitis)
- Kidney failure which can lead to dialysis
- Worsening liver function up to and including liver failure
- Decreased or worsening of heart function including chest pain, abnormal heart rhythm, heart attack, and heart failure
- Severe shortness of breath leading to hospitalization or death
- Increase in the blood pressure in the arteries of the lungs
- Infections in the blood
- Thrombotic thrombocytopenic purpura (TTP)
    - TTP is a rare blood disorder. In TTP, blood clots form in small blood vessels throughout the body. The clots can limit or block the flow of

oxygen-rich blood to the body's organs, such as the brain, kidneys, and heart.

- Hemolytic-uremic syndrome (HUS)
    - HUS is a disorder that usually occurs when an infection in the digestive system produces toxic substances that destroy red blood cells, causing kidney injury.

- Secondary cancers such as myelodysplastic syndrome (MDS) / Acute Myeloid Leukemia
    - Myelodysplastic syndromes refers to disorders that develop when the cells in the bone marrow (the soft inner part of the bones, where new blood cells are made) do not work properly and have problems making new blood cells.

- Posterior Reversible Encephalopathy Syndrome (PRES)
    - PRES is a rare, neurological disorder, which can present with seizure, headache, lethargy, confusion, blindness, altered consciousness, and other visual and neurological disturbances, along with hypertension.
- Tumor lysis syndrome (TLS)
    - Tumor lysis syndrome is caused by rapid killing of tumor cells during treatment. When the tumor cells die, they release their contents into the bloodstream. If cell killing is very rapid, this can affect blood chemistries and the kidneys. In severe cases, this can lead to shutdown of kidney function requiring dialysis.
- Pulmonary hemorrhage (bleeding in the lungs)
- Brain Hemorrhage
- Bleeding in the stomach and bowels

12.1 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Response and progression of disease will be evaluated in this study using a modification of the international criteria proposed by the modified Cheson criteria with incorporation of PET/CT. [Cheson B, 2007]. The imaging modality for evaluation will be dependent on disease subtype. For aggressive lymphomas (e.g. DLBCL, PTCL, HL), PET/CT will be used for evaluation of response. For indolent lymphomas, CT alone or PET/CT may be used at the discretion of the treating physician. For CTCL, please see Section 12.0.2.

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 15 mm with conventional techniques (PET, CT, MRI, x-ray). All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter < 15 mm), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphoma

cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

12.1.1 Extracutaneous Response Criteria

Response criteria will be based on assessment following 2 cycles and subsequent assessments will be made every 3 cycles thereafter (e.g. after cycle 5, 8, 11 etc). The criteria are as follows (GTD = Greatest Transverse Diameter; SPD = Sum of the Products of the Greatest Diameter):

Complete Remission (CR):

- No clinical, radiographic or diagnostic evidence of disease.
- No disease related symptoms.
- Abnormal biochemical values (e.g., LDH) clearly attributable to lymphoma must have normalized.
- Lymph nodes, nodal masses regressed to “normal” size:
- If > 1.5 cm before treatment regressed to ≤ 1.5 cm in GTD.
- If 1.1 to 1.5 cm before treatment, regressed to ≤ 1 cm in GTD (or >75% in SPD).
- Spleen and all previously enlarged organs decreased in size. Spleen must not be palpable on exam
- Bone marrow free of disease on repeat aspirate and biopsy if initially positive.
- Normalization of PET scan.

Complete Remission/unconfirmed (CRU):

Patients meeting the above criteria for CR with the following exceptions:

- Residual node mass of >1.5 cm in GTD regressed by > 75% in SPD.
- Individual nodes previously confluent regressed by >75% in SPD
- Indeterminate bone marrow (increased number or size of lymphoid aggregates without cytologic or architectural atypia).

Partial Remission (PR):

- Greater than or equal to 50% decrease in SPD of the six largest dominant nodes/nodal masses.
- No increase in size of other nodes, liver or spleen.
- Splenic and hepatic nodes regressed at least 50% in SPD.
- No new sites of disease.
- Bone marrow and organs other than the spleen and liver cannot be considered for evaluation for PR because involvement at these sites is considered evaluable but not measurable.

PET negative Partial Remission (PET- PR):

- Patient meets above criteria for PR with resolution of previous PET positive lesions.

Stable Disease (SD):

- Patients who have achieved less than a partial remission but who have not developed findings consistent with progressive disease.

Progressive Disease (PD):

- In patients previously CR, CRUCRU, PR or SD.
- Greater than or equal to 50% increase in SPD of any previously identified abnormal node.
- Appearance of any new lesion during or at the end of therapy

12.1.2 Cutaneous T-cell Lymphoma (CTCL) Response Criteria

Dermatologic responses will be determined by the modified Severity-Weighted Assessment Tool (mSWAT), a standardized approach to measuring the extent and severity of overall skin disease in patients with CTCL. It will be briefly described and full details are provided in Appendix D. The purpose of this description is to optimize intra-observer objectivity and to minimize the potential for intra-observer and inter-observer variability in the measurement of overall skin disease. Only physicians who received training will be permitted to conduct mSWAT assessments during the clinical study. It is essential that physicians adhere as closely as possible to the prescribed procedures so as to reduce measurement error and variability. All efficacy assessments should be performed by the same physician for each patient whenever possible. Physicians will be instructed not to examine previous mSWAT assessments and full body photographs prior to conducting the current mSWAT assessment.

13.1 CRITERIA FOR REMOVAL FROM STUDY

13.2 Discontinuation of Study Treatment

Treatment will continue until the occurrence of any of the following events.

- Disease progression
- Institution of alternate therapy or planned stem cell transplantation.
- Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of the treatment regimen.
- Discontinuation of lenalidomide, carfilzomib or romidepsin for any reason.
- Major violation of the study protocol.
- Withdrawal of consent
- Lost to follow up
- Death
- Pregnancy or a positive pregnancy test

14.0 BIOSTATISTICS

The standard dose-escalation scheme for this study is as follows. Patients will be accrued to the study in cohorts of 3. For any given dose an initial cohort of 3 patients will be treated at that dose. The dose level will be escalated if none of the 3 patients exhibits any DLT in the first cycle as defined above. If a DLT is observed in one patient, an additional cohort of 3 patients will be treated at that dose. The dose will be escalated if none of the additional 3 patients exhibits any DLT. Dose-escalation stops and the previous dose will be considered the MTD if 2 or more patients have a DLT. If the previous dose level has been administered to only 3 patients, an additional 3 patients will be enrolled to confirm the result. For this design the probability of escalation is as follows:

True toxicity rate	5%	10%	15%	20%	25%	30%	40%	50%
Probability of escalation	0.97	0.91	0.81	0.71	0.60	0.49	0.31	0.17

Dose escalation will start with dose level 1. A dose level -1 is also added to the design to ensure a minimum level of toxicity (we expect this dose level will be quite tolerable for patients based on the phase I data of romidepsin and lenalidomide). The maximum number of patients needed for this dose escalation design is 30. We estimate accrual to be 2 patients per month. Patients with measurable disease treated at MTD in the phase Ib will be analyzed in phase IIa to further characterize the toxicity of carfilzomib, romidepsin and lenalidomide in combination at the MTD determined by phase Ib. In phase IIa, we plan to enroll patients so that the total number of patients enrolled in each disease type cohort (B-cell lymphoma and T-cell lymphoma) will include 10 patients at the MTD. We estimate accrual to be 1 patient per month in each disease type cohort. To consecutively monitor the safety primary endpoint in the phase IIa portion, we will employ a sequential probability stopping rule for the predefined DLT in the phase Ib portion of cycles 1-4. This stopping rule specifies that the study will be terminated if DLT occur in: ≥3/first 6; ≥6/first 12; or if more than 10 patients when the last (20^{th}) evaluable patient has completed the trial have any DLT. This rule has the following stopping probability:

True toxicity rate	5%	10%	15%	20%	25%	30%	35%	40%	50%
Stopping prob.	0.002	0.016	0.049	0.104	0.184	0.289	0.413	0.548	0.797

Se
condary objectives of this study aim at examining many clinical endpoints (see above section for detailed definitions). Our assessment of efficacy will remain descriptive and we will evaluate the following measures. Overall response rate (ORR), complete response rate, partial response rate will be summarized using proportions and

confidence intervals will be provided. ORR will be calculated based on the best response at any time during the course of treatment on this protocol. Response rates will be calculated based on the first time point at which that degree of response was noted. Time to response, duration of response and event free survival will be analyzed by routine survival analysis tools such as Kaplan-Meier estimation or competing risks method. In this portion of the study, the disease subtypes (B-cell and T-cell lymphoma) will be grouped together including those from the phase Ib that were treated at MTD. To preliminarily collect the data, subset analyses will also be conducted to evaluate the ORR (CR +PR), TTR, DOR, and EFS for each disease subtype.

Dr. Fausto Loberiza, and Dr. Fang Yu from the University of Nebraska provided the Biostatistical plan for this trial. Dr. Fang Yu will be involved in study analysis during the study. The statistician will have access to the data in Medidata which will allow for a secure transfer of information.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. 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. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

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15.1. Registration for Participating Sites

Central registration for this study will take place at MSK.

To complete registration and enroll a participant from another institution, the site must contact the MSK study coordinator to notify him/her of the participant registration.

The following documents must be sent to the MSK study coordinator for each enrollment within 24 hours of the informed consent form being signed:

- The completed or partially completed MSK eligibility checklist
- The signed informed consent and HIPAA Authorization form
- Supporting source documentation for eligibility questions (e.g. labora tory results, pathology report, radiology reports, MD notes, physical exam sheets, medical history, prior treatment records, and EKG report).

Upon receipt, the MSK study coordinator will conduct an interim review of all documents and will associate the participant to the study in MSK"s Clinical Trials Management System (CTMS). The participant will be assigned a protocol participant number in CTMS. This number will be relayed back to the study staff at the registering participating site via e-mail and will serve as enrollment confirmation. The number is unique and must be written on all data and correspondence for the participant.

If the eligibility checklist is not complete or source documentation is missing, the participating site will be responsible for sending the completed registration documents within 30 days of the consent.

Once the external registration submission is complete, if the participating site IRB has granted approval for the protocol and the participating site is in good standing, the MSK study coordinator will fully register the participant in CTMS. The participating site will be notified by the MSK study coordinator when registration is complete.

15.3 Randomization

There is no randomization in this study.

16.1 DATA MANAGEMENT ISSUES

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

The data collected for this study will be entered into a secure electronic Case Report Forms (eCRFs) by the assigned MSK RSA (for MSK patients only). Source documentation will be available to support the computerized patient record.

16.1.1 Data and Source Documentation for Participating Sites

Data

The participating site(s) will enter data remotely into electronic Case Report Forms (eCRFs) using the internet based system, Medidata Rave. Data entry guidelines have been generated for this study and site staff will receive database training prior to enrolling its first participant. The participating site PI is responsible for ensuring these forms are completed accurately and in a timely manner. A schedule of required forms is shown in section 16.0.3.

Source Documentation
Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into eCRFs. Relevant source documentation to be submitted throughout the study includes:

- Baseline measures to assess pre–protocol disease status (ex. CT, PSA, bone marrow)
- Treatment records
- Toxicities/adverse events of grades that meet study reporting requirements and have not been previously submitted with a SAE Report
- Response designation
- Any other forms of source documentation required per protocol

Source documentation should include a minimum of two identifiers to allow for data verification. MSK will maintain the confidentiality of any subject-identifiable information it may encounter.

16.1.2 Data and Source Documentation Submission for Participating Sites

Participating sites should enter data directly into Medidata Rave. Source documentation should be sent to MSK to the contact information provided by the MSK study coordinator. Submissions should include a cover page listing relevant records enclosed per participant.

16.1.3 Data and Source Documentation Submission Timelines for Participating Site

Data and source documentation to support data should be transmitted via MediData Rave according to following chart:

Time point	Data	Source Documentation
Baseline	Within 24 hours of consent (see section 4.0)	Within 24 hours of consent (see section 4.0)

Study Visits	Within 14 days of the study visit	Within 14 days of the study visit
Serious Adverse Events	Within 3 days of event(see section 17.3); Updates to be submitted as available	Within 3 days of event (see section 16.1.1)

***Toxicities/adverse events that meet reporting requirement as outlined in section 11.**

16.1.4 Data Review and Queries for Participating Site Data

Research staff at MSK will review data and source documentation as it is submitted. Data will be monitored against source documentation and discrepancies will be sent as queries to the participating sites. Queries will be sent by MSK Research staff twice a month.

Participating sites should respond to data queries within 14 days of receipt.

16.2 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.

16.2.1 Quality Assurance for Participating Sites

Monitoring

Each data collection site will be monitored periodically by MSK. Monitoring visits will be conducted every 4-8 weeks, dependent upon the protocol and patient accrual and activity. The monitor and the participating site will identify a mutually agreeable time for each monitoring visit. At least 10 business days ahead of the visit, the monitor will send the site a notification letter that details the date and expectations of the visit. Monitoring may be conducted remotely or in-person. The monitor must be allowed access to all protocol regulatory and source documents to assess compliance with the protocol, federal regulations and GCPs. The monitor will assess all data for completeness of source documents and to confirm data being recorded in the eCRFs is accurate. If monitoring will be done remotely, sites must agree in advance to provide source documents as required. During onsite visits, the monitor will also inspect and review the facilities and investigational product storage area. The participating site will maintain accurate records of dispensing of study drugs for drug accountability. Drug accountability will be reviewed at monitoring visits. Study drug and bottles must be retained until the monitor performs drug accountability of the study drug(s).

The site Investigator(s) and/or an authorized member of the Investigator"s staff should allow sufficient time during monitoring visits to discuss findings. The Investigator(s) or an authorized member of the Investigator"s staff will make any necessary corrections during and between monitoring visits.

Auditing

Each participating site accruing participants to this protocol may be audited by MSK for protocol and regulatory compliance, data verification and source documentation. Audits of selected participant records may be conducted on-site or remotely.

Each audit will be summarized and a final report will be sent to the PI at the audited participating site within 30 days of the audit. The report will include a summary of findings, participant-specific case review, recommendations on any performance and/or shortcomings and request for corrective action, when necessary. When corrective action is required, the participating site must reply within 45 days of receipt of the audit report with their corrective action plan.

16.1.2 Response Review

Since therapeutic efficacy is a stated primary objective, all sites participant"s responses are subject to review by MSK"s Therapeutic Response Review Committee (TRRC). Radiology, additional lab reports and possibly bone marrow biopsies and/or aspirates will need to be obtained from the participating sites for MSK TRRC review and confirmation of response assessment. These materials must be sent to MSK promptly upon request.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSK were established and are monitored by the Office of Clinical Research. The MSK Data and Safety Monitoring Plans can be found on the MSK Intranet at: http://inside2/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf.

There are several different mechanisms at MSK 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.

16.3 Regulatory Documentation

Site Activation

Prior to implementing this protocol at MSK, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSK Institutional Review Board/Privacy Board (IRB/PB). There will be one protocol document and each participating site will utilize that document.

The following documents must be provided to MSK before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved informed consent form and HIPAA authorization
- Participating Site 1572
- Conflict of Interest forms for Participating Site Investigators on the 1572
- Participating Site IRB membership list
- Participating Site IRB"s Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Documentation of Good Clinical Practice (GCP) training for the PI and co-PI at each participating site.
- Participating site laboratory certifications and normals

Upon receipt of the required documents, MSK will formally contact the site and grant permission to proceed with enrollment.

16.3.1 Amendments

Each change to the protocol document must be organized and documented by MSK and approved first by the MSK IRB/PB. Protocol amendments that affect MSK only (e.g. change in MSK Co-Investigator, MSK translation, etc.) do not require IRB review at the participating site(s). All other protocol amendments will be immediately distributed to each participating site upon receipt of MSK IRB/PB approval.

Each participating site must obtain IRB approval for all amendments within 45 calendar days of MSK IRB/PB approval. If the amendment is the result of a safety issue or makes eligibility criteria more restrictive, participating sites will not be permitted to continuing enrolling new participants until site IRB approval of the revised protocol documents is granted and submitted to MSK.

16.3.2 Additional IRB Correspondence

Continuing Review Approval

The Continuing Review Approval letter from the participating site"s IRB and the most current approved version of the informed consent form should be submitted to MSK within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of new participant enrollment.

Deviations

A protocol deviation on this study is defined as any incident involving non-adherence to an IRB approved protocol. Deviations typically do not have a significant effect on the rights, safety, or welfare of research participants or on the integrity of the resultant data. Deviations that represent unanticipated problems involving risks to participants or others, or serious adverse events should be reported.

Deviations that do not adversely affect the rights and/or welfare of the participant or the scientific validity of the study and are related to protocol scheduling changes outside of the allowed window due to a holiday (e.g., New Year"s, Thanksgiving, etc.) and/or inclement weather or other natural event do not require reporting to the MSK IRB/PB. However, they must be clearly documented in the patient"s medical record.

Prospective Deviations

Deviations to the research protocol that involve an informed consent procedure change and/or treatment/pharmacy alterations that are not allowed by the protocol require prospective approval from the MSK IRB/PB prior to the change being carried out. Participating sites should contact the MSK PI who will in turn seek approval from

the MSK IRB/PB. Deviations to the research protocol that involve patient eligibility will not be permitted.

Retrospective Deviations

Deviations that include a change or departure from the research protocol without prior approval from the MSK IRB/PB are considered retrospective deviations. Retrospective deviations should be reported to the MSK PI as soon as possible, who will in turn report the deviation to the MSK IRB/PB as per MSK guidelines.

Participating Site IRB Reporting

Participating sites should report all deviations to their institution‟s IRB per local guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations should be submitted to MSK upon receipt.

Other correspondence

Participating sites should submit other correspondence to their institution‟s IRB according to local guidelines, and submit copies of official site IRB correspondence, including approvals and acknowledgements, to MSK.

16.3.4 Document maintenance

The MSK PI and participating site PI will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified.

The participating sites will ensure that all regulatory documents and participating site IRB correspondences are maintained in an on-site regulatory binder and sent to MSK as outlined within the protocol. The regulatory binder on site will be reviewed by the MSK designated study monitor at monitoring visits. A regulatory binder for each site will also be maintained at MSK; this binder may be paper or electronic.

After study closure, the participating sites will maintain all source documents, study related documents and CRFs for 7 years.

16.4 Noncompliance

If a participating site is noncompliant with the protocol document, accrual privileges may be suspended and/or contract payments may be withheld, until the outstanding issues have been resolved.

17.1 PROTECTION OF HUMAN SUBJECTS

MSK affirms the subject‟s right to protection against invasion of privacy. In compliance with United States federal regulations, Celgene requires the Investigator to permit representati ves 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.

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).

17.2 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).

17.3 Serious Adverse Event (SAE) Reporting

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

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

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

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

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

Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject"s initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

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

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

The CRDB SAE report should be completed as per above instructions. If

appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office

17.3.1 Serious Adverse Event (SAE) Definition

A serious adverse event is one that at any dose (including overdose):

- Results in death
- Is life-threatening[1]
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity[2]
- Is a congenital anomaly or birth defect
- Is an important medical event[3]
- Pregnancy

[1]"Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2]"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person"s ability to carry out normal life functions.

[3]Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

In addition, an important medical event that may not result in death, be life-threatening, or require/prolong hospitalization may be considered a SAE, when, based upon appropriate medical judgment, it may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the outcomes listed above.

Adverse Event Definition

An adverse event ("**AE**") is any untoward medical occurrence in a Study subject administered an investigational Study drug and that does not necessarily have a causal relationship with this treatment. An AE therefore can be any unfavorable and unintended sign (including laboratory finding), symptom or disease temporally associated with participation in a study, whether or not considered drug-related. In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the subject signs a consent form for participation is

considered an AE. This includes any side effect, injury, toxicity, or sensitivity reaction.

A suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of expedited safety reporting, „reasonable possibility" means there is evidence to suggest a causal relationship between the study drug and the adverse event. An adverse reaction (AR) means any adverse event caused by a study drug. This means there is reason to conclude that the study drug caused the event.

An unexpected AE is any AE, the specificity or severity of which is not consistent with the current labeling for the Study drug. „Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the Investigator Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse Event Reporting

Toxicity will be scored using CTCAE Version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov).http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each patient"s outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness. Adverse experiences (AE) should be defined with regards to the toxicity attribution scale as follows:

- Unrelated: The AE is clearly not related to the intervention.
- Unlikely: The AE is doubtfully related to the intervention.
- Possible: The AE may be related to the intervention.
- Probable: The AE is likely related to the intervention.
- Definite: The AE is clearly related to the intervention.

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient"s outcome.

AEs should be reported from the date of signed consent through 30 days post-last dose of Study drug or initiation of a new anti-cancer therapy, whichever occurs first. All AEs must be followed to resolution or to stabilization if improvement or resolution is not expected. Recording should be done in a concise manner using standard, acceptable medical terms. The AE recorded should not be a procedure or a clinical measurement (i.e., a laboratory value or vital sign) but should reflect the reason for the procedure of the diagnosis based on the abnormal measurement. Further, a

procedure or surgery is not itself an AE; rather, the event leading to the procedure or surgery is considered an AE.

If, in the Site Principal Investigator"s judgment, a clinically significant worsening from baseline is observed in any laboratory or other test parameter (e.g., electrocardiogram “ECG” or angiogram), physical exam finding, or vital sign, a corresponding clinical AE should be recorded. If a specific medical diagnosis has been made, then that diagnosis should be recorded. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, “hepatitis” and not “elevated liver function tests” should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an AE, using appropriate medical terminology (e.g., thrombocytopenia, peripheral edema, QT prolongation).

17.3.2 Pregnancies and Lactation Exposure

Pregnancies ,lactation exposure and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on lenalidomide and carfilzomib, or within 28 days of the subject"s last dose of the study drugs, are considered immediately reportable events. Lenalidomide and carfilzomib are to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile or email using the Pregnancy Initial Report Form. The pregnancy, lactation exposure, suspected pregnancy, or positive pregnancy test must be reported to Onyx within ten (10) calendar days by facsimile or email. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety and Onyx immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety and Onyx immediately by facsimile, or other appropriate method, within 24 hours of the Investigator"s knowledge of the event using the SAE Report Form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety and Onyx immediately by facsimile, or other appropriate method, within 24 hours of the Investigator"s knowledge of the event using the SAE Report Form.

Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking lenalidomide and/ or carfilzomib should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

In the case of a live "normal" birth, Celgene Drug Safety and Onyx should be advised as soon as the information is available.

17.3.3 Expedited Reporting by MSK to Celgene

Serious adverse events (SAE) are defined in Section 17.2.1. The MSK investigator must inform Celgene in writing using a Celgene SAE form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24-hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (RV-NHL-PI-637) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

Celgene Drug Safety Contact Information:

Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922

Fax: (908) 673-9115
E- mail: drugsafety@celgene.com

17.3.4 Expedited Reporting by MSK to NCCN/Onyx

Serious adverse events (SAE) are defined in Section 17.2.1. All SAEs that are judged to be unexpected according to the Investigator"s Brochure and drug related must be considered for reporting and/or reported by Onyx (an Amgen subsidiary) to the relevant Regulatory Authority (ies) in accordance to ICH E2B guidelines: Clinical Safety Data Management Data Elements for Transmission of Individual Case Safety Reports and any applicable local regulations (e.g. 21 CFR 312, EU Clinical Trial Directive). The Site Principal Investigator is also responsible for notifying the

Institutional Review Board (“IRB”) or Independent Ethics Committee (“IEC”) in accordance with local regulations, of all appropriate SAEs.

The MSK Principal Investigator must inform MSK‟s Safety Department of all expedited safety reports submitted to the relevant Regulatory Authorities via the contact information listed below. These notifications should be performed in parallel to the Regulatory Authority submissions (e.g., within seven (7) calendar days for any fatal or life-threatening SUSARs and within fifteen (15) calendar days for all other SUSARs, but in no case any later than 24 hours one (1) business day from the submission date. This report must be completed on a MSK SAE report form and provided to Onyx Drug Safety in English. All safety submissions to Onyx (via fax or email) must be accompanied by a completed **SAE Report Cover Page.**

All other SAEs shall be reported and provided to MSK‟s Safety Department as described in section 17.2. All other SAEs (non-SUSARs) will be batched and submitted to Onyx as line listings on a monthly basis. Onyx Drug Safety reserves the right to review the eCRFs or source documents in response to any inquiries by Regulatory Authorities that the Institution may receive.

The initial report must be as complete as possible, at a minimum including the serious adverse event term (s), subject identifier, date of awareness of the event, an assessment of the causal relationship between each event and the investigational Study drug(s), and name of the reporter (Principal Investigator or sub-investigator). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up MSK SAE (only for non-expedited SAEs) form, and submitted to Onyx in the same timelines as outlined above. Additional information shall also include SAE onset date, SAE stop date, outcome, date of first dose of Study drug(s), date of last dose of Study drug(s) prior to event onset, action taken with Study drug(s), Relevant history (including diagnostics, laboratory values, radiographs, concomitant medications, and event treatment and Site Principal Investigator‟s causality assessment to each event. The Institutional protocol number should be included on all reports to Onyx Drug Safety. MSK is responsible for creating an annual safety report of the overall conduct of the specific Study for distribution to the EC(s) and applicable Regulatory Authorities. Onyx, in addition, shall create an annual safety report including listings of all serious adverse drug reactions from both Onyx sponsored research and Investigator-Sponsored Trials, and Onyx will submit this report to the Regulatory Authorities in any country where there is clinical development of the Study drug or where the Study drug is marketed. Additionally, the Institution is responsible for reporting SAEs to Onyx Drug Safety as described above to the following:

To report a Serious Adverse Event or other safety related information to Onyx Drug Safety please use:

Drug Safety Hotline:	650.266.2501
Drug Safety Fax:	888-814-8653
Drug Safety E-mail:	svc-ags-in-us@amgen.com

AND

To report a Serious Adverse Event or other safety related information to the NCCN please use:

NCCN Fax:	(215) 358-7699
NCCN Email:	ORPReports@nccn.org

17.4 Serious Adverse Event (SAE) Reporting for Participating Sites

Responsibilities of Participating Sites

- Participating sites are responsible for reporting all SAEs to their local IRB per local guidelines. Site IRB approvals/acknowledgments must be sent to MSK upon receipt.
- Participating sites are responsible for submitting the SAE Report Form to MSK within 3 calendar days of learning of the event.
- When a life-threatening event or death is unforeseen and indicates participants or others are at increased risk of harm, participating sites should notify the MSK PI as soon as possible but within **24 hours** of the time the site becomes aware of the event.

SAE contact information for the Coordinating Center is listed below:

E- mail MSK Research Staff to the attention of **MSK IRB# 14-179**

AND

MSK PI: Steven Horwitz, MD Memorial Sloan Kettering Center
Email: horwitzs@mskcc.org

Responsibility of MSK

- MSK Research Staff are responsible for submitting all SAEs to the MSK IRB/PB and funding entities (if applicable) as specified in 17.2, to Celgene as specified in 17.2.3, and to Onyx/NCCN as specified in 17.2.4.
- MSK is responsible for informing all participating sites about all unexpected SAEs that are either possibly, probably or definitely related to the study intervention within 15 days of receiving the stamped SAE from the MSK IRB/PB.
- MSK is responsible for informing all participating sites within **24 hours** or on the next business day about a life-threatening event or death that is unforeseen and indicates participants or others are at increased risk of harm.

17.5 Safety Reports

MSK must submit external safety reports to the MSK IRB/PB according to institutional guidelines. All external safety reports will be made available to the participating sites. Outside safety reports that are reportable to the MSK IRB/PB will be distributed to the participating sites immediately upon receiving a stamped copy from the MSK IRB/PB. Participating sites will receive a special alert for any outside safety reports that warrant a significant change to the conduct of the study. Outside safety reports that are not reportable to the MSK IRB/PB, will be sent to the participating sites monthly.

Participating sites are responsible for submitting safety reports to their local IRB per their local IRB guidelines. All local IRB approvals/acknowledgments of safety reports must be sent to MSK upon receipt.

17.6 Unanticipated Problems

Unanticipated problems involving risks to participants or others (UPs) are defined as any incident, experience or outcome that meets all of the following criteria:

- Unanticipated (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; **and**
- Related or possibly related to participating in the research (possibly related means there is a reasonable probability that the incident, experience or outcome may have been caused by procedures involved in the research); **and**
- Suggests that the research place participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Participating sites are responsible for reporting all UPs to MSK as soon as possible but within 3 calendar days of learning of the event. UPs that are SAEs should be reported to MSK via SAE Report form as per section 17.3 of this protocol. All other UPs should be reported to MSK in a memo signed by the site PI.

MSK is responsible for submitting UPs to the MSK IRB/PB according to institutional guidelines. In addition, MSK is responsible for notifying participating sites of all non-SAE UPs that may affect the sites.

18.1 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.

18.2 Inform Consent Procedures for Participating Sites

The investigators listed on the Consenting Professionals Lists at each participating site may obtain informed consent and care for the participants according to good clinical practice and protocol guidelines.

A note will be placed in the medical record documenting that informed consent was obtained for this study, and that the participant acknowledges the risk of participation.

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20.0 APPENDICES

Appendix A – Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Risks Associated with Pregnancy

The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of the lenalidomide on human eggs and sperm. Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

All study participants must be registered into the mandatory **Revlimid REMS™**, and be willing and able to comply with the requirements of **REMS™.**.

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

The investigator must ensure that:

- Females of childbearing potential comply with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Females NOT of childbearing potential acknowledge that she understands the hazards and necessary precautions associated with the use of lenalidomide
- Male patients taking lenalidomide acknowledge that he understands that traces of lenalidomide have been found in semen, that he understands the potential teratogenic risk if engaged in sexual activity with a female of childbearing potential, and that he understands the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a female of childbearing potential.

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to 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 the entire duration of lenalidomide treatment; 3) during dose interruptions; and 4) for at least 28 days after lenalidomide discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effecti ve and additional effective methods of contraception:

- Highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants)
  - Tubal ligation
  - Partner‟s vasectomy
- Additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to one of the effective method listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 50 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting lenalidomide

Female Patients:

FCBP must have two negative pregnancy tests (sensitivity of at least 50 mIU/mL) prior to prescribing lenalidomide. The first pregnancy test must be performed within 10-14 days prior to prescribing lenalidomide and the second pregnancy test must be performed within 24 hours prior to prescribing lenalidomide. The patient may not receive lenalidomide until the Investigator has verified that the results of these pregnancy tests are negative.

Male Patients:

Must agree to practice complete abstinence or agree to use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following lenalidomide discontinuation

Female Patients:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of lenalidomide treatment, including dose interruptions and then every 28 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 28 following lenalidomide discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days of lenalidomide treatment, including dose interruptions, and then every 14 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 14 and Day 28 following lenalidomide discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control at each visit during the time that birth control is required.
- If pregnancy or a positive pregnancy test does occur in a study patient, lenalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide treatment must be temporarily discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after lenalidomide discontinuation.

Male Patients:

- Must practice complete abstinence or use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

Additional precautions

- Patients should be instructed never to give lenalidomide to another person.

- Female patients should not donate blood during therapy and for at least 28 days following discontinuation of lenalidomide.
- Male patients should not donate blood, semen or sperm during therapy or for at least 28 days following discontinuation of lenalidomide.
- Only enough lenalidomide for one cycle of therapy may be prescribed with each cycle of therapy.

Appendix B – Canadian Cardiovascular Society Angina Classification

Class I
Ordinary physical activity, (e.g., walking and climbing stairs) does not cause angina; angina occurs with strenuous, rapid, or prolonged exertion at work or recreation.
Class II
Slight limitation of ordinary activity; angina occurs on walking or climbing stairs rapidly; walking uphill; walking or stair climbing after meals, in cold, in wind, or under emotional stress; or only during the few hours after awakening; when walking > 2 blocks on level ground; or when climbing more than 1 flight of stairs at a normal pace and in normal conditions.
Class III
Marked limitation of ordinary physical activity; angina occurs on walking 1 to 2 blocks on level ground or climbing 1 flight of stairs at a normal pace in normal conditions.
Class IV
Inability to perform any physical activity without discomfort; anginal symptoms may be present at rest.

Campeau L. Grading of angina pectoris. Circulation 1975; 54:522-3.

Appendix C – New York Heart Association Classification of Cardiac Disease

NYHA Classification of Cardiac Disease

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulti ng limitations of physical activity. Ordinary physical acti vity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical acti vity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical acti vity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical acti vity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

Appendix D – Grading Scales for modified Severity-Weighted Assessment Tool mSWAT

1. Total Body Surface Area (TBSA) Involvement by Skin Disease

The body is divided into 12 regions with pre-assigned %TBSA based on the burn literature. The extent of skin disease in each region is quantified by using the patient"s palm to measure the %TBSA involvement within region: patient"s palm with 4 fingers (excluding the thumb) is 1% of TBSA. Patient"s palm without fingers is 0.5% of TBSA. The patient"s palm with 4 fingers is traced on a transparency sheet at the baseline visit, using a permanent marker that will not rub off or smear. The transparency of the patient"s palm should be used in all mSWAT assessments during the course of the clinical study. The transparency will be labeled with the patient"s study ID number kept in the patient"s study file on site. Using the baseline visit transparency of the patient"s palm, the investigator will measure and record on the electronic case report form (Example of table from eCRF is given below) the %TBSA for each lesion type within each of the 12 regions.

2. Severity Weighting Factor

The severity weighting factors will be the following:

1= patch (flat erythema or erythema with mild infiltration)
2=plaque (elevated erythema or erythema with moderate infiltration)
4= tumor or ulceration (erythema with fissuring, ulceration or tumor)

Patch is defined as abnormal skin not elevated from normal skin. A plaque is defined as abnormal skin elevated from normal skin by < 5 mm. A plaque elevated ≥ 5 mm is a tumor.

3. Calculating Skin Scores

The sum of %TBSA by lesion is derived by summing the %TBSA from all regions affected by the lesion. The sum of %TBSA across lesion types (patches, plaques and tumors) within each region cannot exceed the %TBSA for the region. For example, the %TBSA for the head region is 7%. The sum of %TBSA across lesion types from head can only range from 0-7%. The skin score subtotal by lesion type are derived by multiplying the sum of %TBSA for patches from all regions by 1, sum of %TBS of plaques from all regions by 2, and the sum of %TBSA of tumors or ulcers from all regions by 4. The skin score total is derived from summing the skin score subtotals for patches, plaques and tumors or ulcers. The skin score total is dimensionless with a scale of 0 to 400.

Region	% TBSA for the region	% TBSA Patch (or flat erythema)	% TBSA Plaque (or elevated/indurated erythema)	% TBSA Tumor/ Ulceration (or erythema w/fissuring, ulceration)
Head	7			
Neck	2			
Anterior Trunk	13			
Posterior Trunk	13			
Buttocks	5			
Genitalia	1			
Upper Arms	8			
Forearms	6			
Hands	5			
Thighs	19			
Lower Leg	14			
Feet	7			
% BSA by category	100			
Severity Weighting Factor		X 1	X 2	X 4
Skin Score Subtotal				

Responses will be determined by the criteria described in the table below. Progression of disease while on treatment should be confirmed by a second assessment 1-4 weeks later so that patients who experience a temporary flare of disease due to skin infection or other intercurrent illnesses are not removed from the study prematurely.

Assessment	Description	Status
Completely clear	No evidence of disease; 100% improvement	CR
Marked Improvement	Greater than or equal to 50% decrease in skin scores compared	PR
Slight Improvement	Less than 50% decrease in skin scores compared to baseline	SD
Worse	≥ 25% increase in skin scores compared to baseline while the patient is actively taking the study drug *or* ≥ 50% increase in the sum of the products of the greatest diameters of pathologically positive lymph nodes (should be documented by biopsy) compared to baseline while the patent is actively taking the study drug.	PD

Appendix E – Medications That May Cause QTc Prolongation

The following table presents a list of drugs that may prolong the QTc. These drugs are prohibited during the study. Romidepsin may be administered after a 5 half-life washout period elapses following the use of these drugs. Washout period is based on roughly 5 half-lives and rounded to a convenient interval. Patients taking lower risk drugs not known to interact with the study drug will be monitored and may be allowed on study.

Medications That May Cause QTc Prolongation

Compound (Brand Name)	**Compound Half-Life**	**Possible Washout Period (Hours)**	**Possible Washout Period (Days)**
Antiarrhythmics			
Amiodarone (Cordarone, Pacerone)	58 days (15-142) 36 days (active metabolite)		180
Disopyramide (Norpace, Norpace CR)	6.7 hr (4-10)	36	
Dofetilide (Tikosyn)	10 hr	48	
Flecainide (Tambocor)	20 hr (12-27)		5
Ibutilide (Corvert)	6 hr (2-12) (variable among patients)	36	
Procainamide (Pronestyl, Procanbid, Procan)	3-4 hr for PA and NAPA (active metabolite)	24	
Quinidine (Quinaglute, Cardioquin, Quinidex)	6-8 hr in adult; 3-4 hr in children	36	
Sotalol (Betapace, Sorine)	12 hr	72	
Antibiotics			
Azithromycin (Zithromax, Zithromax Tri-Pack, Zithromax Z-Pak, Zmax)	Immediate release: 68-72 hr, extended release 59 hr		12-15
Clarithromycin (Biaxin, Biaxin XL)	Nonlinear PK 3-4 hr (250 mg Q12) 5-7 hr (500 mg Q12)	36	
Erythromycin (Benzamycin, Eyrc, E-glades, Erygel, E-solve 2, Akne-Mycin, Eryderm, Sansac, Erythro-Statin, Erymax, Staticin, T-Stat, C-solve-2, Erycetter, PCE, Ery-Tab, E-Mycin, E-Base, E.E.S., Eryped, E.E.S 200, E.E.S 400, Pediamycin, Eryzole, Erythrocin)	Each salt form has different half-life		
Gatifloxacin (Tequin, Tequin Teqpaq)	7-14 hr	48	
Grepafloxacin (Raxar)	16 hr		3
Antibiotics *(cont'd)*			
Levofloxacin (Levaquin, Quixin, Elequin)	6-8 hr	48	
Moxifloxacin (Avelox, Vigamox)	12 ± 1.3 hr	72	
Sparfloxacin (Zagam)	20 hr (16-30)		4
Telithromycin (Ketex)	2-3 hr	24	
Anticonvulsants			
Felbamate (Felbatol)	20-23 hr		5
Fosphenytoin (Cerebyx)	12-29 hr		6
Antidepressants			
Venlafaxine (Effexor)	5 ± 2 hr for parent comp. 11± 2 hr for OVD (active metabolite)	60	
Antidiarrheals			
Octreotide (Sandostatin)	1.7 hr	12	
Antiemetics			
Dolasetron (Anzemet)	8.1 hr		
Droperidol (Inapsin)	2.2 hr	10	
Domperidone (Motilium)	7-8 hr	48	
Palonosetron (Aloxi)	40 hr		10
Antihypertensives			

Compound (Brand Name)	Compound Half-Life	Possible Washout Period (Hours)	Possible Washout Period (Days)
Moexipril/Hydrochlorothiazide (Uniretic)	2-9 hr(include active metabolite) for moexipril; 5.6-14.8 hr for HCTZ	48	
Antimalarials			
Halofantrine (Halfan)	6-10 days (variable among individuals)		45
Quinidine (Quinaglute, Cardioquin, Quinidex)	6-8 hr in adult; 3-4 hr in children	36	
Antimanics			
Lithium (Eskalith, Lithobid, Lithonate)	24 hr (10-50)		7
Antineoplastics			
Arsenic trioxide (Trisenox)	Not characterized		
Tamoxifen (Nolvadex)	5-7 days (biphasic)		30
Antiprotozoals			
Pentamidine (NebuPent, Pentam)	6.4 ± 1.3 hr	36	
Antipsychotic agents			
Chlorpromazine (Thorazine)	30 ± 7 hr		7
Haloperidol (Haldol)	18 ± 5 hr		5
Mesoridazine (Serentil)	24-48 hr (animal study)		10
Pimozide (Orap)	55 hr		14

(Continued from previous page)

Antipsychotic agents *(cont'd)*			
Quetiapine (Seroquel)	6 hr	36	
Risperidone (Risperdal, Risperdal Consta)	3-20 hr (extensive to poor metabolizer) 9-hydroxyrisperidone (active metabolite) T ½ = 21-30 hr (extensive to poor metabolizer)		4
Thioridazine (Mellaril)	20-40 hr (Phenothiazines)		7
Ziprasidone (Geodon, Zeldox)	7 hr	36	
Antispastics			
Tizanidine (Zanaflex)	2.5 hr	12	
Antivirals			
Amantadine (Symadine, Symmetrel)	17 ± hr (10-25)		4
Foscarnet (Foscavir)	87.5 ± 41.8 hr (distribution and release from bone)		20
Analgesics			
Levomethadyl (Orlaam)	Multiple compartment PK with active metabolite 2.6 day for LAAM, 2 day for nor-LAAM, 4 day for dinor-LAAM		20
Asthma medications			
Salmeterol (Advair Diskus, Serevent, Serevent Diskus)	5.5 hr (only one datum)	36	
Calcium channel blockers			
Bepridil (Vascor)	42 hr (26-64)		10
Isradipine (DynaCirc)	8 hr (multiple metabolites)	48	

Compound (Brand Name)	**Compound Half-Life**	**Possible Washout Period (Hours)**	**Possible Washout Period (Days)**
Nicardipine (Cardene)	~2 hr post IV infusion	12	
Cholinergic enhancers			
Cisapride (Propulsid)	6-12 hr, up to 20 hr	60	
Diuretics			
Indapamide (Lozol)	14 hr (biphasic elimination)		3
Immunosuppressants			
Tacrolimus (Prograf, Protopic)	~34 hr in healthy patients ; ~19 hr in kidney transplant		7
Migraine medications			
Naratriptan (Amerge)	6 hr	36	
Sumatriptan (Imitrex)	2.5 hr	12	
Zolmitriptan (Zomig)	2.8-3.7 hr (higher in female)	18	
Narcotic pain relievers			
Methadone (Dolophine, Methadose)	15-30 hr		7
Sedatives			
Chloral hydrate	Readily converted to Trichloroethanol (active metabolite T½= 7-10 hour)	48	

References:

Physician‟s Desk Reference 2002
Facts and Comparisons (update to June, 2000)
The Pharmacological Basis of Therapeutics 9th Edition, 1996

Appendix F – Medications That May Inhibit CYP3A4

The following table presents a list of drugs that may inhibit CYP3A4. As romidepsin is predominately metabolized by CYP3A4, inhibition of this enzyme could result in elevated plasma levels or increased exposure to romidepsin. Romidepsin may be administered after a 5 half-life washout period elapses following the use of these drugs. Washout period is based on roughly 5 half-lives and rounded to a convenient interval.

Medications That May Inhibit CYP3A4

Compound (Brand Names)	Compound Half-Life	Possible Washout Period - Hours	Possible Washout Period Days
Azole Antifungals			
Clotrimazole (Mycelex, Lotrimin, Lotrisone)	Not available		
Ketoconazole (Nizoral, Ketozole)	6 hr (2-8 hr)	30 hr	
Itraconazole (Sporanox)	21 hr		5 days
Fluconazole (Diflucan)	3 hr	15 hr	
Miconazole (Monistat)	57 hr		11 days
HIV Protease Inhibitors			
Ritonavir (Norvir, Kaletra)	4 hr	20 hr	
Indinavir (Crixivan)	2 hr	10 hr	
Saquinavir (Invirase, Fortovase)	5 hr	25 hr	
Nelfinavir (Viracept)	4 hr	20 hr	
Delavirdine (Rescriptor)	6 hr	30 hr	
Macrolide Antibiotics			
Troleandomycin (Tao)	Not available		
Erythromycin (Benzamycin, Eyrc, E-glades, Erygel, E-solve 2, Akne-Mycin, Eryderm, Sansac, Erythro-Statin, Erymax, Staticin, T-Stat, C-solve-2, Erycetter, PCE, Ery-Tab, E-Mycin, E-Base, E.E.S., Eryped, E.E.S 200, E.E.S 400, Pediamycin, Eryzole, Erythrocin)	2 hr	10 hr	
Clarithromycin (Prevpac, Biaxin)	5 hr	25 hr	
Other Antibiotics			
Chloramphenicol (Chloromycetin, Chloroptic)	4 hr	20 hr	
Ciprofloxacin (Ciprodex, Cipro, Ciloxan)	4 hr	20 hr	
Norfloxacin (Noroxin, Chibroxin)	4 hr	20 hr	
Serotonin Reuptake Inhibitors (SSRI's)			
Fluoxetine (Prozac, Sarafem, Symbyax)	Fluoxetine 5 days Norfluoxetine (active metabolite) 12 days (4-16 days)		60 days
Nefazodone (Serzone)	3 hr	15 hr	
Fluvoxamine (Luvox)	16 hr		3 days
Antiemetics			
Aprepitant (Emend)	11 hr (9-13 hr)		2 days

Compound (Brand Names)	**Compound Half-Life**	**Possible Washout Period - Hours**	**Possible Washout Period Days**
Oral Contraceptives			
Ethinyl-estradiol (Kariva, Velivet, Mircette, Desogen, Cyclessa, Ortho-Cept, Yasmin, Demulen, Zovia, NuvaRing, Seasonale, Lessina, Portia, Levlite, Nordette, Aviane, Enpresse, Trivora, Levora, Alesse, Triphasil, Ortho Evra, Ovcon, Nortrel, Gencept, Balziva, Brevicon, Norinyl, Norethin, Aranelle, Ortho-Novum, Modicon, Tri-Norinyl, Femhrt, Junel, Loestrin, Estrostep, Microgestin, Tri-Previfem, Previfem, Tri-Sprintec, Sprintec, Ortho Tri-Cyclen, Cryselle, Low-ogestrel, Ogestrel, Lo/Ovral, Ovral)	15 hr		3 days
Oral Contraceptives *(cont'd)*			
Mifepristone (Mifeprex, RU-486)	18 hr		4 days
Gestodene	20-22 hr		5 days
Histamine H2-Receptor Antagonists			
Cimetidine (Tagamet)	2 hr	10 hr	
Antiarrhythmic Drugs			
Quinidine (Quinaglute, Cardioquin, Quinidex)	7 hr	35 hr	
Amiodarone (Cordarone, Pacerone)	53 days (15-142 days)		265 days
Antihypertensives			
Diltiazem (Taztia, Cartia, Cardizem, Dilt-CD, Dilacor, Teczem, Tiamate. Trizac)	3 hr [7 hr for extended release (Trizac)]	15 hr 35 hrs	
Verapamil (Tarka, Verelan, Isoptin, Covera-HS, Calan)	8 hr	40 hr	
Calcium Channel Blocker			
Mibefradil (Posicor)	21 hr (17-25 hr)		5 days
Others			
Grapefruit juice	Not available		
Star fruit	Not available		

Appendix G – Study Calendar

Table 6: Study Evaluation Schedule

Procedure	Screening	Cycle 1			Cycle 2 and beyond				End of study
		Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	End of cycle	
Record prior medications, treatments	X								
Record prior anti-cancer therapies	X								
Physical examination[1]	X	X	X	X[10]	X				X
ECOG performance status[1]	X	X			X				X
12 Lead ECG[2]	X	X	X		X	X			
ECHO or cardiac MRI	X								
Hematology	X	X	X	X[10]	X[12]	X[12]			X
LDH[3]	X				X[12]				
Electolytes[3]	X	X	X	X[10]	X[12]	X[12]			X
Liver function analysis[3]	X	X	X	X[10]	X[12]				X
Pregnancy testing[4]	X	X	X	X[10]	X[12]				X
REMS™ program (patient enrollment)	X								
Start lenalidomide[5]		X			X				
Carfilzomib*		X	X		X	X			
Romidepsin*		X	X		X	X			
Disease/ Response assessment [6,7]	X							X[9,14]	X[11]
Record adverse events[8]		X	X	X[10]	X	X	X[13]		X
Record concomitant medications	X	X	X	X[10]	X	X	X[13]		X

Table 7 Legend

* For cycle 1, study assessments and/or romidepsin and carfilzomib dosing may be delayed a) up to 3 days in the setting of grade 3 thrombocytopenia or neutropenia that recovers or b) up to 1 day for other scheduling considerations.

*For cycle 1, labs may be performed up to 1 day prior to treatment. After completion of cycle 1, labs may be performed up to 3 days prior to treatment. For cycle 2 and beyond, romidepsin and carfilzomib dosing may be delayed up to 3 days or given up to one day ahead of the scheduled dosing. Romidepsin doses must be given at least 6 days apart.

[1]If Physical examination, vital signs, weight and ECOG performance status were done within 7 days of Day 1, they do not need to be repeated at study cycle X, Day 1 (excluding cycle 1 in the phase Ib portion). An unscheduled visit can occur at any time during the study.

[2]The schedule for ECG monitoring is found in section 10.5 and romidepsin dose modifications in Table 5. After cycle 2 the schedule can be amended as clinically indicated in section 10.5.

[3]Sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, and glucose are part of the electrolyte assessment at every time point. **Magnesium** will be added to the electrolyte panel at **screening, days 1, and 8 of the treatment cycle, and at the end of study visit. Liver function analysis** (at least total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin) **is necessary on day 1 of each cycle but does not have to be resulted to initiate treatment. Liver function analysis must be resulted within 7 days of cycle 1 day 1 and cycle 2 day 1 to proceed with treatment. Liver function analysis must be resulted within 14 days of day 1 of cycle 3 and beyond to proceed with treatment**

[4]Pregnancy tests for females of childbearing potential are required through the Revlimid REMS® program. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide for Cycle 1 (prescriptions must be filled within 7 days). FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see Appendix C: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).

[5]Lenalidomide must be prescribed through and in compliance with the **REMS™** program of Celgene Corporation. Prescriptions must be filled within 7 days. Consideration should be given to prescribing lenalidomide 5 to 7 days in advance of Day 1 of each cycle to allow time for required patient and prescriber surveys, and drug shipment to patient. Any unused Revlimid® (lenalidomide) should be returned to Biologics for disposal in accordance with the **REMS™** program.

[6]Baseline disease assessments must be performed after discontinuation of most recent anti-cancer therapy including systemic steroids. Outside scans are acceptable if performed within 28 days.

[7] The imaging modality for evaluation will be dependent on disease subtype. For aggressive lymphomas (e.g. DLBCL, PTCL, HL), PET/CT will be used for evaluation of response. For indolent lymphomas, CT alone or PET/CT may be used at the discretion of the treating physician. A bone marrow will only be repeated to confirm a complete response if previously known to be involved. Cutaneous T-cell lymphoma patients (CTCL) will have an mSWAT (Appendix D) performed at these time points and imaging at baseline. In CTCL patient"s, imaging will be repeated if appropriate (patients with known nodal or visceral disease) every other cycle. Sezary panel in patients with Sezary syndrome. Cutaneous lymphoma patients without nodal or visceral disease will have imaging repeated only to confirm a complete response.

[8] An additional safety assessment will be done 28 days (+/- 7 days) following the last dose of protocol therapy.

[9]Response assessment will be performed at the end of cycles 2. Thereafter, response assessment will occur at the end of every third cycle (5,8,11, etc..) until disease progression or removal from study.

[10] +/- 3 days

[11]if not performed within 28 days

[12]For cycle 3 and beyond, laboratory assessments performed up to three days prior to the day of treatment are adequate for treatment as long as they are within the treatment parameters.

[13] For cycles 2, 3 and 4, concomitant medications and adverse events may be performed via an assessment by telephone +/- 3 days of day 15 of the cycle. Beyond cycle 4, day 15 assessments are not required. [14] 5 days to + 3 days.