A Phase Ib/IIa Study of Romidepsin in Combination with Lenalidomide in Adults with Relapsed or Refractory Lymphomas and Myeloma

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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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Title: A Phase Ib/IIa Study of Romidepsin in Combination with Lenalidomide in Adults with Relapsed or Refractory Lymphomas and Myeloma

Objectives

The primary objective of this study is:

To define the maximum tolerated dose and characterize the safety and toxicity of the combination of lenalidomide and romidepsin.

The secondary objectives of this study are to evaluate:

1. Overall response rate and clinical benefit rate (in myeloma patients)
2. Complete response rate
3. Very good partial response/partial response rate
4. Time to response
5. Duration of response
6. Event free survival

Patient Population: Relapsed or refractory lymphomas and multiple myeloma

Number of Patients: 67

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

Treatments Administered: Romidepsin will be administered intravenously on days 1, 8, and 15 of a 28-day cycle. Lenalidomide will be taken orally daily for 21 days of a 28-day cycle. Maximum tolerated dose (MTD) to be determined in the phase Ib portion.

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

- Phase IIa portion (including phase Ib treated at MTD) - overall response rate, and clinical benefit rate (in myeloma patients), time to response, duration of response, and event-free survival.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

The primary objectives of this study are:

- To define the maximum tolerated dose and characterize the safety and toxicity of the combination of lenalidomide and romidepsin.

The secondary objectives of this study are:

- To assess the overall response rate (ORR) and the clinical benefit rate (CBr) of lenalidomide and romidepsin.
- To assess the time to response (TTR), duration of response (DOR), and event free survival (EFS).

3.0 BACKGROUND AND RATIONALE

3.1 Romidepsin

3.1.1 Romidepsin: Mechanisms of action

Romidepsin is a unique bicyclic depsipeptide originally isolated from Chromobacterium violaceum strain 968. [Ueda H, 1994] Results of early nonclinical studies showed that romidepsin inhibited the growth of the Ha-ras-transformed NIH3T3 clonal cell line, Ras-1, and induced reversion of the transformed morphology to normal within 1 day at a concentration of 2.5 ng/mL. [Ueda H, 1994] While mRNA expression of the c-myc oncogene in Ras-I cells was decreased in the presence of romidepsin, Ha-ras mRNA expression was unaffected by 24-hour exposure to 2.5 ng/mL of romidepsin. Furthermore, romidepsin blocked cell cycle transition from G0/G1 to S phase and induced nuclear quiescence. The course of c-myc suppression paralleled that of G0/G1 arrest and correlated with the morphologic reversion of the transformed cells. These results led to the proposal that the growth inhibition and G0/G1 arrest resulted from romidepsin blocking the ras-mediated signal transduction pathway. [Fecteau K, 2002] Other investigations of the effect of romidepsin on G1 to S transition of the cell cycle showed that romidepsin inhibits signal transduction through MAP kinase and causes p53- independent G1 arrest. [Sandor V, 1998; Sandor V, 2000] Romidepsin has also been identified as a potent histone deacetylase (HDAC) inhibitor similar to trichostatin A based on its ability to cause arrest of the cell cycle at both G1 and G2/M phases, to induce internucleosomal breakdown of chromatin, and to inhibit intracellular HDAC activity resulting in an accumulation of marked amounts of acetylated histone species within M-8 cells. [Nakajima Y, 1998]

3.1.2 Romidepsin: Pre-clinical Antitumor Activity

Potent antitumor effects of romidepsin have been demonstrated both *in vitro* and *in vivo*. [Ueda H, 1998; Ueda H, 1998] *In vitro*, romidepsin exerted antiproliferative activity against 12 human solid tumor cell lines (IC50 ranged from 0.5 to 5.9 nM), but was less potent against cultured normal cells. Moreover, a prolonged exposure

to romidepsin subsequently lowered the concentration of drug necessary to induce the antiproliferative activity. Similar IC50 values were found in a study of 13 lymphoid cell lines. [Murata M, 2000] More specifically, romidepsin was demonstrated to induce significant apoptosis in both a cutaneous T-cell lymphoma (CTCL) cell line, HUT78 and a multiple myeloma cell line. [Piekarz R, 2004]. In severe combined immunodeficiency disease (SCID) mice inoculated intraperitoneally (IP) with U-937, a histocytic lymphoma cell line, and treated with romidepsin (0.1 to 1 mg/kg, IP) once or twice a week survived longer [median survival times of 30.5 days (0.56 mg/kg) and 33 days (0.32 mg/kg)], than saline-treated mice (20 days). Two of 12 mice treated with 0.56 mg/kg romidepsin survived past the observation period of 60 days. [Sasakawa Y, 2002]

3.1.3 HDAC inhibitors: Clinical Activity in Lymphoid Malignancies

3.1.3.1 Cutaneous T-cell Lymphoma (CTCL)

The clinical activity of romidepsin was first demonstrated in a National Cancer Institute (NCI) phase I study. [Sandor V, 2002] Three patients with 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/m^2). 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). In Study GPI-04-0001, treatment alleviated pruritus in most subjects (48 of 52, 92%) who entered the study with this symptom. These data led to FDA approval of romidepsin for CTCL in September, 2009.

3.1.3.2 Peripheral T-cell lymphoma (PTCL)

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, where 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.

3.1.3.3 Multiple Myeloma (MM)

Recently, a phase II study of Romidepsin given at 13 mg/m^2 was performed in patients with heavily pre-treated refractory multiple myeloma. [Niesvizky, 2011] Of the 12 patients enrolled no objective responses were seen and the study was unable to meet the 30% objective response criteria. Interestingly, 4 of the 12 patient with secretory myeloma had stabilization of their paraprotein and several other patients had reduction in bone pain and/or resolution of hypercalcemia. Therefore, as a single agent romidepsin showed symptomatic activity, but overall is unlikely to be efficacious in MM.

3.1.3.4 B-cell lymphoma

Romidepsin has yet to be clinically studied as a single agent or in combination with other agents in B-cell lymphomas. However, other HDAC inhibitors (vorinostat, belinostat, and panobinostat) have demonstrated clinical activity in early phase studies. For example, in a combined analysis of two consecutive phase I trials in hematologic malignancies performed at MSKCC utilizing the HDAC inhibitor vorinostat of those enrolled 32 had a B-cell non-Hodgkin lymphoma (NHL). Three patients responded with one achieving a CR. [O'Connor O, 2006] Furthermore, the HDAC inhibitor panibinostat 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 a ORR of 13%. [Younes, 2009] 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]

3.2 Lenalidomide

3.2.1 Lenalidomide: Mechanism of action

Lenalidomide is a proprietary IMiD® compound of Celgene Corporation. IMiD® compounds have both immunomodulatory and anti-angiogenic properties which confer antitumor and antimetastatic effects. Lenalidomide has been demonstrated to possess anti-angiogenic activity through inhibition of bFGF, VEGF, and TNF-alpha induced endothelial cell migration, due at least in part to inhibition of Akt phosphorylation response to bFGF. [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] Upregulation of T cell derived IL-2 production is achieved at least in part through increased AP-1 activity. [Schafer P, 2003]

3.2.2 Lenalidomide: Pre-clinical Antitumor Activity

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 lymphoid malignancies. Lenalidomide has been shown to increase T-cell proliferation, which leads to an increase in IL-2 and IFN-gamma secretion. The increased level of these circulating cytokines augment natural killer cell number and function, and enhance natural killer cell activity to yield an increase in cell lysis. [Davies F, 2001] In addition, lenalidomide has direct activity against multiple myeloma by inducing apoptosis and/or G1growth arrest. [Hideshima T, 2000]

3.2.3 Lenalidomide: Clinical Activity in Lymphoid Malignancies

3.2.3.1 Multiple Myeloma

Lenalidomide has been extensively studied in multiple myeloma as a single agent and in combination with steroids. This activity led to the randomized phase III trial of lenalidomide and dexamethasone versus dexamethasone alone. [Dimopoulos M, 2007] This study demonstrated a significant delay in time to progression as well as a survival advantage of the lenalidomide containing arm. Of note, the grade 3 and 4 neutropenia and deep venous thrombosis rates were more common in the lenalidomide containing arm. These results led to the approval of lenalidomide in combination with dexamethasone in previously treated multiple myeloma patients.

3.2.3.2 Peripheral T-cell lymphoma

Lenalidomide has been further 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 a ORR of 30% with all responses being partial responses. [Deuke 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. [Zinzana P, 2011]

3.2.3.2 Cutaneous T-cell lymphoma (CTCL)

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 a 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.

3.2.3.3 B-cell lymphoma

Lenalidomide has been further investigated in both relapsed and refractory indolent and aggressive non-Hodgkins lymphoma as well as Hodgkin lymphoma. In aggressive B-cell lymphoma 49 patients were treated with the standard 25 mg

dose taken orally fo 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.

3.3 Rationale For Combination Therapy

Relapsed and refractory lymphoid malignancies remain an ongoing challenge with repeated courses of cytotoxic chemotherapy often yielding diminishing returns. In relapsed and refractory multiple myeloma, peripheral T cell lymphoma, and aggressive non-Hodgkin lymphoma the 5-year overall survival (OS) in transplant ineligible patients was 16%, 20%, and 32% respectively. [Kumar S, 2004; Vose J, 2008; Philip T, 1995] There remains significant need for more active therapies and combinations with many newer approaches now looking 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 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. And based on the phase I experience with vorinostat and lenalidomide, it is likely that these two agents can be safely combined at active single agent doses without excess toxicity in heavily pretreated patients. Therein lies the fundamental rationale for this research.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

Phase Ib: The phase Ib portion of the study is designed to determine the MTD of romidepsin and lenalidomide. All patients must have a relapsed or refractory B-cell lymphoma, T-cell lymphoma, or multiple myeloma. Patients will be treated on a 28-day cycle with romidepsin infused on day 1, 8, and 15, and lenalidomide taken orally on days 1-21. The design is a standard 3+3 dose escalation (Table 1) of romidepsin and lenalidomide. The first cohort will enter at dose level 1.

Dose Level	Romidepsin	Lenalidomide
-1	8 mg/m^2	10 mg
1	8 mg/m^2	15 mg
2	8 mg/m^2	25 mg
3	10 mg/m^2	25 mg
4	14 mg/m^2	25 mg

Table 1: Description of dose level

DLT is defined in cycle 1 (in phase Ib).
Definitons:

- Grade ≥ 3 non-hematologic (attributed to study drugs)
- Grade 4 hematologic toxicities (attributed to study drugs) defined as:
  - Grade 4 thrombocytopenia (platelets < 25 K/μL)
  - Grade 4 neutropenia (absolute neutrophil count (ANC) < 0.5)
- Grade 3 thrombocytopenia or neutropenia that results in a > 3 day delay in any romidepsin dose in cycle 1.
- One week or greater delay in initiating cycle 2 day 1 due to continued drug-related toxicity.

Any patient with an adverse event that meets the DLT definition is considered evaluable for MTD determination. Patients who do not have a DLT, but received <3 doses of romidepsin or <80% (17/21) of the doses of lenalidomide during cycle 1 will not be evaluable for MTD and will be replaced.

Three patients will be initially treated in each cohort until the MTD is determined. If dose level 4 (full dose of each drug) 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 (see Section14.0).

DLT is defined in cycles 1-4 (in phase IIa)
Definitons:

- Grade ≥ 3 non-hematologic (attributed to study drugs)
- Grade 4 hematologic toxicities (attributed to study drugs) defined as:
  - Grade 4 thrombocytopenia (platelets < 25 K/μL)
  - Grade 4 neutropenia (absolute neutrophil count (ANC) < 0.5)
- Grade 3 thrombocytopenia or neutropenia that results in a > 4 day delay in any romidepsin dose in cycle 1.
- One week or greater delay in initiating cycle 2 day 1 due to continued drug-related toxicity.

At the time of enrollment the patients will be identified as representing three cohorts based upon disease subtype: 1) B-cell lymphoma 2) multiple myeloma 3) PTCL. Each disease specific cohort will enroll 15 patients. We plan to accrue 38 patients into the phase IIa portion 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, CBr (for myeloma), TTR, DOR, and EFS. ORR is defined as the percentage of patients achieving a best response of CR/CRu, very good partial response (VGPR--myeloma only), or PR at any disease assessment time point. CBr is defined as CR, VGPR, PR or MR (minimal response) in myeloma patients. TTR is defined as the time or number of cycles between study registration and documentation of first response (CR/Cru, VGPR, 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.

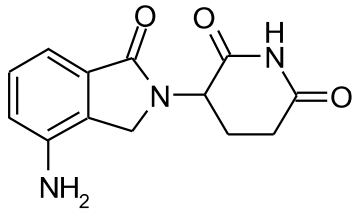
4.2 Intervention

All patients will be treated with romidepsin intravenously on days 1, 8, and 15 and lenalidomide orally on days 1-21 of a 28-day cycle. The dose will be determined by the cohort they are registered into. Once a MTD is determined this dosing level will be used for the phase IIa portion. Cycles will be continued as above until the patients wishes to be removed from the study, unacceptable toxicity develops, disease progression, treating physician recommends removal, or termination of study occurs.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 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) (formerly known as RevAssist® Program).

Dosage form

Lenalidomide will be supplied as capsules for oral administration.

Packaging

Lenalidomide will be shipped directly to patients. 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

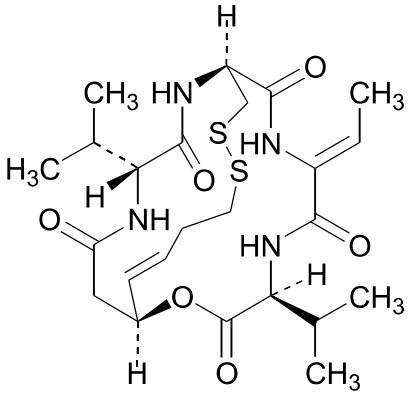
Celgene will instruct the Investigator on the return or destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the source documents. Study drug supplies will be retained at the clinical site pending instructions for disposition by Celgene. Patients 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 Celgene Corporation's Revlimid REMS® program. Per standard Revlimid REMS® program requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in, and must comply with, all requirements of the Revlimid REMS® program. 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 contains 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).

6.0 CRITERIA FOR SUBJECT ELIGIBILITY.

6.1 Subject Inclusion Criteria

1. Pathology confirmed lymphoma or multiple myeloma.
    - Hodgkin lymphoma is eligible for either phase and will be considered a B-cell lymphoma in the phase IIa study.
    - Phase IIa portion, subjects must have B-cell lymphoma, T-cell lymphoma, or multiple myeloma.
2. Relapse or progression after at least 1 systemic therapy.
3. Measurable disease for phase IIa portion only.

- Lymphoma (includes CTCL patients who are NED in skin): CT or PET/CT by modified Cheson criteria with incorporation of PET.
- Multiple myeloma: Patient must have measurable disease and therefore must have at least one of the following:
    i. Serum M-protein ≥0.5gm/dL (≥5gm/L)
    ii. Urine M-protein ≥200mg/24hr
    iii. Serum FLC assay: involved FLC ≥10mg/dL (≥100mg/L) provided serum FLC ratio is abnormal.
- CTCL: mSWAT >0, or absolute Sezary count ≥ 1000 cells/μL.

4. Age ≥18 years at the time of signing the informed consent form.
5. Able to adhere to the study visit schedule and other protocol requirements.
6. Previous systemic anti-cancer therapy must have been discontinued at least 3 weeks prior to treatment in this study. If there is progression of disease on that therapy and all adverse effects have resolved to Grade 1 or baseline, in which case 2 weeks is acceptable.
7. Previous radiation, hormonal therapy, and 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 biopsy within 2 weeks is not considered exclusionary.
8. Short course systemic corticosteroids for disease control, improvement of performance status or non-cancer indication (< 7 days) must have been discontinued at least 7 days prior to study treatment. Stable ongoing corticosteroid use (≥ 30 days) up to an equivalent dose of 15 mg of prednisone is permissible.
9. ECOG performance status of ≤ 2 at study entry (see Appendix A).
10. Laboratory test results within these ranges:
    - Absolute neutrophil count ≥ 1.0/mm³.
    - Platelet count ≥ 70 K/μL, if thrombocytopenia is due to bone marrow involvement platelet count must be ≥ 50 K/μL.
    - Renal function assessed by calculated creatinine clearance as follows (see Appendix B):
        - Phase Ib subjects must have calculated creatinine clearance ≥ 50ml/min by Cockcroft-Gault formula.

- Phase IIa subjects must have calculated creatinine clearance ≥ 30ml/min by Cockcroft-Gault formula. See section below, "Dosing Regimen", regarding lenalidomide dose adjustment for calculated creatinine clearance < 60ml/min and ≥ 30ml/min.

- Total bilirubin ≤ 1.5 x upper limit of normal (ULN); 3 x ULN if due to hepatic involvement.
- AST (SGOT) and ALT (SGPT) ≤ 3 x ULN; 5 x ULN if due to hepatic involvement.

11. 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.

12. Females 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 C: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

[†] A female of childbearing potential 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).

6.2 Subject Exclusion Criteria

1. 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.
2. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.
3. Pregnant females. (Lactating females must agree not to breast feed while taking lenalidomide or romidepsin).
4. Known hypersensitivity to thalidomide.
5. The development of erythema nodosum if characterized by a desquamating rash while taking thalidomide or similar drugs.
6. Prior use of lenalidomide if discontinued due to toxicity.
7. Prior therapy with romidepsin if discontinued due to toxicity.
8. Concurrent use of other anti-cancer agents or treatments.
9. Known seropositive and requiring anti-viral therapy for human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV).

10. Active concurrent malignancy requiring active therapy.

11. Known central nervous system or meningeal involvement (in the absence of symptoms investigation into central nervous system involvement is not required). Patients with HTLV1 ATLL and controlled CNS or meningeal involvement may be enrolled after discussion with the MSK principal investigator.

12. The following known cardiac abnormalities:

- Congenital long QT syndrome.
- QTc interval ≥ 480 milliseconds.
    - A QTc interval between 480-499 msec in the presence of a bundle branch block (BBB) or pacemaker is eligible in phase IIa after discussion with the MSK principal investigator.
- 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.
- Other significant ECG abnormalities including 2nd degree atrio-ventricular (AV) block type II, 3rd degree AV block.
- Symptomatic coronary artery disease (CAD), *e.g.,* angina Canadian Class II-IV (see Appendix D). 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.
- 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.
- Congestive heart failure (CHF) that meets New York Heart Association (NYHA) Class II to IV definitions (see Appendix E) and/or ejection fraction <45% by MUGA, echocardiogram, or cardiac MRI.
- 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).
- Hypertrophic cardiomegaly or restrictive cardiomyopathy from prior treatment or other causes.
- 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.
- Any cardiac arrhythmia requiring an anti-arrhythmic medication (excluding stable doses of beta-blockers)

13. Patients taking drugs leading to significant QTc prolongation unless able to be switched to non-QTc prolonging medication without risk of worsening underlying condition and meet all other inclusion criteria (listed in Appendix F: Medications That May Cause QTc Prolongation).

14. Concomitant use of significant CYP3A4 inhibitors unless able to be switched to a non-CYP3A4 inhibiting medication without risk of worsening underlying condition and able to meet all other inclusion criteria (listed in Appendix G).

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, New York Weill-Cornell Presbyterian, Saint Francis/Mount Sinai Regional Cancer Center, and University of Nebraska Medica Center .

8.0 PRETREATMENT EVALUATION

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

- Record prior medications and treatments
- Record prior anti-cancer therapy
- Physical examination
- ECOG performance status
- 12 lead electrocardiogram (ECG)
- Complete metabolic panel, including magnesium and phosphorus
- Lactate dehydrogenase (LDH)
- Serum/urine protein electrophoresis (SPEP/UPEP), serum/urine immunofixation, and serum free light chain (**multiple myeloma patients only**)
- Bone marrow biopsy and aspiration (**multiple myeloma patients only**)
- PET/CT or CT Chest, Abdomen, and Pelvis (B-cell lymphoma, PTCL, CTCL with extracutaneous disease)
- Register patient with REMS® program.

- mSWAT for patient with cutaneous lymphoma.
- Sezary panel in patients with Sezary syndrome only.
    - Peripheral blood flow cytometry with immunoconjugates for CD2, CD3, CD4, CD8, CD26 and or CD7, and CD52.
- Pregnancy testing for females of childbearing potential within 10-14 days and again 24 hours prior to prescribing lenalidomide per the Revlimid REMS® program.

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

- Complete blood count (CBC)

9.0 TREATMENT/INTERVENTION PLAN

9.1 Pretreatment electrolyte assessment and drug management

Prior to initiation of each dose of romidepsin the patients level of potassium (K+) and magnesium (Mg) must be confirmed to be within normal range or if low, supplement as per outlined in sections 10.1 and 10.2. In cycle 2 and beyond, magnesium and potassium levels may be checked up to 2 days before romidepsin. If within treatment range, they do not need to be repeated prior to romidepsin administration unless clinically indicated. Intravenous (IV) supplementation with potassium chloride (KCL) and/or magnesium sulfate can 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.

9.2 Treatment plan romidepsin/lenalidomide Phase Ib

Subjects enrolled into the phase 1b portion will enroll at dosing level 1 with three patients per dosing level (3X3 design) as described in Table 2 below.

Dose Level	Romidepsin	Lenalidomide
-1	8 mg/m^2	10 mg
1	8 mg/m^2	15 mg
2	8 mg/m^2	25 mg
3	10 mg/m^2	25 mg
4	14 mg/m^2	25 mg

Table 2: Description of dose level.

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 section 4.1. 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 initial starting doses for both romidepsin and lenalidomide. The treatment plan is described below for the phase Ib portion:

Romidepsin/Lenalidomide Cycle 1 Day 1

Romidepsin IVPB over 4 hours

Lenalidomide PO q days 1-21

Romidepsin/Lenalidomide Cycle 1 Day 8

Romidepsin IVPB over 4 hours

Romidepsin/Lenalidomide Cycle 1 Day 15

Romidepsin IVPB over 4 hours

***1 cycle equals 28 days**

9.3 Treatment Plan romidepsin/lenalidomide Phase IIa

The entire accrual is planned to have up to 51 patients in the phase IIa portion; each disease cohort will have 15 patients (B-cell lymphoma, multiple myeloma or PTCL). There will be an expansion of the T-cell cohort to include an additional 6 patients with acute T-cell leukemia/lymphoma. After a sufficient number of patients have been enrolled for determination of the primary and secondary objectives, cohorts may be closed to accrual by the MSK principal investigator. The MTD for lymphoma has been determined to be 14mg/m^2 romidepsin on Days 1, 8, 15 and 25mg lenalidomide from Days 1-21. The patients treated at MTD in the phase Ib cohort (if measurable disease at enrollment) and phase IIa cohort will be evaluated both collectively and by disease subtype. Patients with more than one histology are eligible and will be assigned by the principal investigator to a specific disease subtype.

- In patients with MM, due to the presence of toxicities, patients will be dosed at romidepsin 10mg/m^2 and lenalidomide 25mg (see table 2a). If two of six (or fewer) patients treated at this dose level develop dose-limiting toxicities, the initial dosing for subsequent patients will be decreased to romidepsin

10mg/m^2 and lenalidomide 15mg. For example, if two of four patients treated at this initial dose develop dose-limiting toxicities, the starting dose for subsequent patients will be reduced as above.

- At a starting dose of romidepsin 10mg/m^2 and lenalidomide 15mg, should 2 of 6 (or less) patient will be reduced to romidepsin 8mg/m^2 and lenalidomide 15mg.
- At a starting dose of romidepsin 8mg/m^2 and lenalidomide 15mg, should 2 of 6 (or less) patients have dose-limiting toxicities, the initial dose for subsequent patients will be reduced to romidepsin 8mg/m^2 and lenalidomide 10mg.

Table 2a: Multiple Myeloma Dosing for Phase IIa Portion		
Dose level	Romidepsin	Lenalidomide
1	10	25
-1	10	15
-2	8	15
-3	8	10

The treatment plan for the phase IIa portion is described below:

<u>Romidepsin/Lenalidomide Cycle 1 Day 1 + subsequent Cycle X</u>

Romidepsin MTD IVPB over 4 hours

Lenalidomide MTD PO q days 1-21

<u>Romidepsin/Lenalidomide Cycle 1 Day 8</u>

Romidepsin MTD IVPB over 4 hours

<u>Romidepsin/Lenalidomide Cycle 1 Day 15</u>

Romidepsin MTD IVPB over 4 hours

***1 cycle equals 28 days**

9.4 Lenalidomide administration

In either phase of the study patients will be asked to take the lenalidomide at approximately the same time each day. Prescriptions for lenalidomide must be signed and filled within 7-14 days prior to next cycle of therapy. 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 . 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.

9.5 Prophylactic Measures

- Subjects should receive prophylactic anti-emetics prior to romidepsin administration (ondansetron preferred).
- Phase Ib: After cycle 1, G-CSF (filgrastim) may be given at the discretion of the treating physician (phase Ib).
- Phase IIa: G-CSF (filgrastim) may be given at the discretion of the treating physician.

9.6 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 patient's clinical research database (CRDB) 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 lead investigator. Concomitant medications for other medical conditions are permitted as clinically indicated subject to specific protocol requirements outlined below.

9.6.1 Prohibited/monitored concurrent therapy

- Any investigational agent other than lenalidomide or romidepsin.
- Any medications at high risk of causing QTc prolongation or inducing torsades de pointes (as listed in Appendix F).
- 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 G 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 prolongation and ventricular arrhythmias.

9.7 Dose Continuation, Modification and Interruption

Subjects will be evaluated for AEs at each visit with the NCI CTCAE v4.0 (Appendix H): NCI CTCAE v4.0) used as a guide for the grading of severity. DLTs as defined will be tabulated in cycle 1 of the phase Ia 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. Inability to meet treatment criteria will result in holding the dose.

9.7.1 Instructions for Dose Modifications or Interruption During a Cycle

Dose delay and dose reduction rules for lenadlidomide and romidepsin are as follows and summarized in the tables 3, 4, & 5:

- In the event of dose reduction due to hematologic toxicity attributed to study drugs, lenalidomide and romidepsin will be reduced as per Tables 3 & 4.
- In the event of dose reduction due to non-hematologic toxicity attributed to study drugs, lenalidomide and romidepsin will be reduced one level per Tables 3 & 4.
- Missed doses of lenalidomide and/or romidepsin are not made up.
- Interruptions of therapy, including delays in starting a new cycle, of greater than 28 days will result in removal from study.
- Patients remaining on treatment after cycle 6, at the discretion of their physician, may elect to receive romidepsin on a day 1 and 15 schedule each cycle.
    - Patients remaining on treatment after cycle 9, at the discretion of their physician may elect to receive romidepsin on day 1 of each cycle (q4 week dosing) after discussion with the MSK Principal Investigator.
- 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 MSKprincipal investigator.

TABLE 3: Lenalidomide Dose Modification Steps	
Current Lenalidomide Dose	**One Level Dose Reduction**
25 mg daily on Days 1-21 every 28 days	20 mg daily on Days 1-21 every 28 days
20 mg daily on Days 1-21 every 28 days	15 mg daily on Days 1-21 every 28 days
15 mg daily on Days 1-21 every 28 days	10 mg daily on Days 1-21 every 28 days
10 mg daily on Days 1-21 every 28 days	5 mg daily on Days 1-21 every 28 days*
5 mg daily on Days 1-21 every 28 days*	See above

TABLE 4: Romidepsin Dose Modification Steps	
Current Romidepsin Dose	**One Level Dose Reduction**
14 mg/m^2 daily on Days 1,8,15	10 mg/m^2 daily on Days 1,8,15
10 mg/m^2 daily on Days 1,8,15	8 mg/m^2 daily on Days 1,8,15
8 mg/m^2 daily on Days 1,8,15	8 mg/m^2 daily on Days 1,15

TABLE 5: Dose Modifications for Lenalidomide and Romidepsin	
NCI CTC Toxicity Grade	**Dose Modification Instructions (also see Instructions for Initiation of a New Cycle above)**
Grade 3 neutropenia not associated with fever	• Hold lenalidomide and romidepsin dose. • Follow CBC at least weekly. • Upon recovery to grade ≤ 2 resume romidepsin and lenalidomide at one dose reduction. • Omitted doses are not made up (Romidepsin doses may be given up to 3 days late).
Grade 3 neutropenia associated with fever (temperature ≥ 38.5º C) or Grade 4 neutropenia	• Hold lenalidomide and romidepsin dose. • Follow CBC at least weekly. • Upon recovery to ≤ grade 2 resume lenalidomide and romidepsin at next lower dose level. • Omitted doses are not made up. (Romidepsin doses may be given up to 3 days late)
Thrombocytopenia ≥Grade 3 (platelet count < 50,000/mm³)	• Hold lenalidomide and romidepsin dose. • Follow CBC at least weekly. • Upon recovery to ≤ grade 2 resume lenalidomide and romidepsin at next lower dose level. • Omitted doses are not made up. (Romidepsin doses may be given up to 3 days late)
Non-blistering rash **Grade 3** **Grade 4**	• If Grade 3, hold lenalidomide dose. Follow at least weekly. • If the toxicity resolves to grade 1, resume lenalidomide at next lower dose level. • Omitted doses are not made up. • If Grade 4, discontinue lenalidomide. Remove patient from study.
Desquamating (blistering) rash- any Grade	• Discontinue lenalidomide. Remove patient from study.
Neuropathy **Grade 3** **Grade 4**	• If Grade 3, hold lenalidomide dose. Follow at least weekly. • If the toxicity resolves to grade 1 resume lenalidomide at next lower dose level. Omitted doses are not made up. • If Grade 4, discontinue lenalidomide. Remove patient from study.
Venous thrombosis/embolism ≥ Grade 3	• Hold lenalidomide and romidepsin. Start therapeutic anticoagulation, if appropriate. • Restart lenalidomide and romidepsin at investigator's discretion after discussion with PI (reduce 1 dose level of each drug). • See Anticoagulation Consideration

TABLE 5: Dose Modifications for Lenalidomide and Romidepsin	
NCI CTC Toxicity Grade	**Dose Modification Instructions (also see Instructions for Initiation of a New Cycle above)**
Hyperthyroidism or hypothyroidism	• Omit lenalidomide 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 non-hematologic toxicity ≥ Grade 3	• Hold lenalidomide and romidepsin dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 2 resume lenalidomide and romidepsin at one dose reduction. • Omitted doses are not made up.(Romidepsin doses may be given up to 3 days late) • If no further dose reduction levels patient will be removed from study.

9.7.2 Romidepsin Dose Modification in Case of Cardiac Toxicity

The guidelines for cardiac monitoring and timing of ECG assessments are presented in Table 6. Prolongation of QTc ≥500 msec is considered to be an alert associated with romidepsin administration.

Table 6: 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, the principal investigator or a local cardiologist may be consulted.	If resolved, restart romidepsin at reduced dose as per table 4. If not resolved, take off study.
Atrial dysrhythmia (SVT, atrial fibrillation, or atrial flutter)	New occurrence		
Prolongation of QTc compared to post anti-emetic ECG	To ≥ 500 msec unless BBB or pacemaker present; see section10.4		
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 medical monitor should be notified immediately and local cardiologist should be consulted.	Hold further dosing until medical monitor 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, the medical monitor or a local cardiologist may be consulted.	If resolved, restart romidepsin at reduced dose.Insome 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.

9.7.3 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.

- Dose reductions should not be performed for alopecia or for non-infectious diarrhea, nausea, or vomiting that has not been treated with aggressive anti-diarrheal or anti-emetic support.

9.8 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. Research personnel 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 REMS® program.

9.9 Concomitant Therapy

9.9.1 Recommended Concomitant Therapy

Subjects will receive full supportive care, including transfusions of blood and blood products, electrolyte supplementation, antibiotics, analgesics, and antiemetics when appropriate.

9.9.2 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 C: 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.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

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

- ANC is ≥ 1.0 K/μL
- Platelet count is ≥ 70 K/μL or within 10 K/μL of baseline.
- Serum creatinine concentration ≤ 2.0 × ULN or ≤ baseline
- AST (SGOT) and ALT (SGPT) ≤2.0 × ULN or ≤3.0 × ULN in presence of demonstrable liver metastases.
- Serum potassium and magnesium are within normal range.
    - In cycle 2 and beyond in Phase Ib and any cycle in Phase IIa, magnesium and potassium levels may be checked up to 3 days prior to administration of romidepsin. If levels are within range at that time point romidepsin may be administered without recheck 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 normal range.
        - Magnesium supplementation: If levels are below normal range, but ≥1.2mg/dL, 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 ≥3.2mEq/L, patients can receive at least 20mEq potassium IV and proceed to treatment without re-checking labs.
- Any drug-related maculo-papular rash or neuropathy that may have occurred has resolved to ≤ grade 1 severity
- Any other clnically significant adverse events that may have occurred have resolved to ≤ grade 2 severity.

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

10.2 Required Blood Parameters and Other Investigations Prior to Each Treatment

Before each dose of romidepsin, excluding cycle X, day 1 patients should be reassessed and the following criteria must be fulfilled:

- ANC is ≥1.0 K/μL.
- Platelet count is ≥ 50 K/μL.
- Serum potassium and magnesium are within normal range
    - In cycle 2 and beyond in Phase Ib and any cycle in Phase IIa, magnesium and potassium levels may be checked up to 3 days prior to administration of romidepsin. If levels are within range romidepsin may be administered without repeat testing 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 normal range.
        - Magnesium supplementation: If levels are below normal range, but ≥1.2mg/dL, 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 ≥3.2mEq/L, patients can receive at least 20mEq potassium IV and proceed to treatment without re-checking labs.
- Any clinically significant non-hematological toxicity to ≤ Grade 2 .
- 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.

10.3 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.

10.4 Cardiac Alert Findings (post anti-emetic)

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 patient's 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 (Bezett's—by machine read) is ≥500 msec

- QTc (Friderica's) will be used for manual reads by either the physician or cardiologist.
- If the patient has a known bundle branch block (BBB) and a baseline QTc of >470 msec a change in QTc of > 30 msec from the post antiemetic ECG will be used as criteria for and adverse event (as opposed to absolute QTc) and would be graded as a grade 3 adverse event. If no change >30 msec has been documented after completion of cycle 4 no further ECG will be required.
- If the patient has a pacemaker and a baseline QTc of >470 msec a change in QTc of >30 msec from the post antiemetic ECG in either the native rhythm or a paced rhythm will be used as criteria for an adverse event and would be graded as a grade 3 adverse event. A change can only be be assessed if the rhytm is conserved (i.e. native to native rhythm). If a conversion of rhytm is seen (i.e. native to paced), and if the patient is asymptomatic no adverse event will be noted. If symptomatic it would be graded as a grade 3 adverse event. If no change >30 msec has been documented after completion of cycle 4 no further ECG will be required.

- Ventricular arrhythmia: VT (≥3 beats in a row) or VF.
- Sinus tachycardia (pulse >140/min after recumbency).
- Heart rate is $\underline{\geq}$ 120 bpm with $\underline{\geq}$ 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 6 in Section 9 for recommended dose reductions, etc., in the above situations.

10.5 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 value greater than 480 msec is demonstrated by machine-read or manual read then further ECGs may be omitted for the duration of study.

If ECG monitoring continues past cycle 2, ECGs may be omitted for the duration of the study if no QTc value greater than 480 msec is demonstrated by machine-read or manual read for two consecutive cycles and no greater than or equal to Grade 3 QT prolongation.

If a QTc of ≥500 msec is encountered, ECGs should be repeated twice more. 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.

10.6 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 C: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).

10.7 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.

Table 7: Study Evaluation Schedule

Procedure	Screening	Cycle 1				Cycle 2 and beyond**				End of study
		Day 1	Day 8	Day 15	Day 22	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	X[12]	X				X
ECOG performance status[1]	X	X				X				X
12 Lead ECG[2]	X	X	X	X		X	X[10]	X		
Hematology	X	X	X	X		X	X[10]	X		X
LDH[3]	X					X				
Electolytes[3]	X	X	X	X	X[12]	X	X[10]	X		X
Liver function analysis[3]	X	X				X				X
Pregnancy testing[4]	X	X	X	X	X[12]	X				X
REMS® program (patient enrollment)	X									
Start lenalidomide[5]		X				X		X		
Romidepsin*		X	X	X		X	X[10]	X		
Disease/Response assessment [6,7,8]	X								X[11]	
Record adverse events[9]		X				X		X		X
Record concomitant medications		X				X		X		X

Table 7 Legend

* Romidepsin dosing may be delayed up to 3 days of the scheduled visit. Romidepsin doses must be given at least 7 days apart and all doses completed by day 21 of each cycle. In cycle 1, labs may be performed up to 1 day prior to treament. After completion of cycle 1, labs may be performed up to 3 days prior to treatment.

** For cycle 2 and beyond, study procedures should be performed per the study evaluation schedule (±3 days) while maintaining the minimum dosing spacing for romidepsin as above.

[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 6. 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, 8 and 15 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 (within windows for labs provided depending on the cycle of treatment).** The LDH may be omitted in patients with multiple myeloma.

[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] Lymphoma: CT including at least the chest, abdomen and pelvis or PET/CT is required for response (systemic B and T-cell lymphoma patients only) assessment. A bone marrow will only be repeated to confirm a complete response if previously known to be involved. Cutaneous T-cell lymphoma patients will have imaging at baseline and (CTCL) will have an mSWAT (Appendix I) performed monthly for the first three cycles and then at each response assessment timepoints (end of cycle 4, 6 and thereafter at the end of every third cycle). In CTCL patients, 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. After cycle 12, patients on continuous therapy may be imaged as clinically indicated, at the discretion of the treating physician. At discontinuation of therapy, end of study response assessments – including imaging – should be performed.

[8]Serum/urine protein electrophoresis, serum/urine immunofixation, quantitative immunoglobulins, and serum free light chains are required if appropriate for (multiple myeloma patients only) response assessment. A bone marrow will only be repeated if to confirm a complete response. Patients with non-secretory myeloma will have the bone marrow assessment repeated if they have been otherwise clinically stable (i.e. without new lytic lesions, soft-tissue plasmacytomas or hypercalcemia). A skeletal survey is allowed to rule out bone lesions for evaluation of disease progression and to confirm a complete response in nonsecretory multiple myeloma. PET/CT shuld be performed at screening and to confirm responses in patients with soft tissue plasmacytomas.

[9] An additional safety assessment will be done 28 days (+/- 2 days) following the last dose of protocol therapy.

[10] If romidepsin is omitted on day 8 per dose reduction algorithm (Table 4) then hematologic and electrolyte assessments are not required.

[11]Response assessment will be performed at the end of cycles 2, 4, and 6. Thereafter, response assessment will occur at the end of every third cycle (9,12,15, etc.) until disease progression or removal from study. Myeloma patients will have their disease assessed after each cycle.

[12] +/- 3 days

11.0 TOXICITIES/SIDE EFFECTS

11.1 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
- Decreased white blood cells
- Increased levels of glucose
- Decreased calcium
- Decreased magnesium
- Decreased albumin

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
- Lack of energy
- Insomnia
- Neuropathy

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

- Decreased potassium
- Decreased lymphocytes
- Increased creatinine

- Decreased sodium
- Increased magnesium
- Decreased phosphate
- Increased liver and bone enzyme tests

Rare but serious

- Anxiety
- Infections which can be serious
- Bleeding
- Increased heart rate

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

- Increased potassium
- Increased uric acid
- Deep vein thrombosis

As of September 2010, with 891 patients having received romidepsin as a single agent, 39 of 447 (9%) of patients with hematologic malignancies and 36 of 444 (8%) of patients with solid tumors have died from an adverse event during treatment with romidepsin. Not unexpectedly, the most common cause was related to the patients' underlying disease. Death as a result of disease progression has been reported in 9 (2%) of the patients with hematologic malignancies and in 24 (5%) of the patients with solid tumors. The cause of death was not otherwise specified in 2 (0.4%) of the patients with hematologic malignancies and in 4 (0.9%) of the patients with solid tumors. All other causes of death have been reported in less than <1% in either indication.

11.2 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 sydrome

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 (rhabdomyoiysis)
- Swelling of the lungs
- Severe skin rash (Stevens-Johnson syndrome)

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

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

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

11.3 Second new cancers

According to researchers, patients with cancer have a higher risk of developing a second new cancer when compared to people without cancer. In clinical studies of newly diagnosed multiple myeloma, a higher number of second cancers were reported in patients treated with induction therapy and/or bone marrow transplant then lenalidomide for a long period of time compared to patients treated with induction therapy and/or bone marrow transplant then no lenalidomide.

11.4 Other Risks

Patients should be instructed that if any physician other than the study doctor prescribes medication for another condition, or patients start to take any over-the-

counter medications or vitamins, they must inform the study staff. This is important because the interaction of some medications may cause serious side effects.

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

11.5 Risks Associated with Pregnancy

Pregnancy Risk:

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

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

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

11.5.1 Reproductive risks:

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

Women should not breastfeed a baby while on this study. It is important that the patient understand that they will need to use birth control while on this study. A list of acceptable forms of birth control methods to use and how long to use them is listed below. Pregnancy testing will be required as per Table 7.

11.5.2 Pregnancy Risk – Females:

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

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

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

Highly Effective Method	Additional Effective Methods
Intrauterine device (IUD)	Latex condom
Hormonal (birth control pills, injections, implants)	Diaphragm
Tubal ligation	Cervical Cap
Partner's vasectomy	

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

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

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

11.5.3 All Patients:

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

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

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

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

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

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

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

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 Multiple Myeloma:

Responses will be determined according to the IMWG Response Criteria (that have supplanted the older European Group for Blood and Marrow Transplantation (EBMT) criteria) using standard electrophoretic and immunofixation tests of serum and urine for a monoclonal protein (M protein), the serum free light chain assay, and the bone marrow aspirate and biopsy with immunohistochemical staining. [Rajkumar SV, 2011]

For all patients responses will be assessed at the end of each cyle. Patients will have response of the myeloma assessed with serum and urine protein electrophoresis (SPEP/UPEP), serum and urine immunofixation (IF),quantitative immunoglobulins, and serum free light chain assay. A Patients will have a repeat bone marrow biopsy to confirm a biochemical complete response .

12.1.1 Response Criteria

Responses are as follows for patients with measurable M protein:

- Stringent Complete Response (sCR) = Undetectability of the M protein by immunofixation of serum and urine, normalization of the serum free light chain ratio, and normalization of the bone marrow biopsy, including ≤5% total plasma cells and lack of clonal excess by kappa/lambda staining.
- Complete Response (CR) = Undetectability of the M protein by immunofixation of serum and urine or normalization of the serum free light chain ratio in patients without a detectable serum or urine M-spike at baseline and normalization of the bone marrow biopsy, including <5% total plasma cells and lack of clonal excess by kappa/lambda staining.
- Very Good Partial Response (VGPR) = Serum and urine M component detectable by immunofixation only but not by electrophoresis or a reduction of ≥ 90% in the M-protein concentration component plus a urine M-component <100mg/24hours..
- Partial Response (PR) = 50% or greater reduction of serum M-protein and reduction in 24-hour urinary M-portein by >90% or to >200mg/24 hours. If the serum and urine M-protein are not measurable, a decrease of 50% in the difference between involved and uninvolved FLC levels is required in place of M-protein criteria. In addition to the above criteria, if present at baseline, >50% reduction in the size of soft tissue plasmacytomas is also required.
- Minimal Response (MR) = A reduction of >25% but <50% in the M-protein concentration.
- Stable disease (SD) = An increase in the M protein by < 25% from baseline or a decrease in the M protein by < 25% from baseline.
- Progressive Disease (PD) = Incrase of 25% from lowest response value in any of the following: serum M-component (minimal absolute increase of 0.5g/dl), urine M-component (absolute increase must be 200mg/24h), and/or only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be 10mg/dl) and/or the occurrence of new hypercalcemia, new lytic lesions by skeletal survey, or new soft tissue plasmacytomas.

12.1.2 Special Considerations in Assessing Response

Low-level urinary M proteins may vary from measurement to measurement. For an increase in urinary M protein to be considered progression of disease it must be an absolute increase of at least 200 mg/day.

In quantitative immunoglobulin serum studies, the levels of heavy and light chain are often discrepant for technical reasons. If the discrepancy leads to equivocal response values, the heavy-chain value will be used since the heavy-chain value is usually a more reliable indicator because of its longer half-life and non-renal metabolism.

12.2 Lymphoma

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]

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.

12.2.1 Extracutaneous Response Criteria

Response criteria will be based on assessment following every 2 cycles for 6 months and then every 3 cycles thereafter. 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, Cru, 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

12.2.2 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 I. 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.

<u>1. Total Body Surface Area (TBSA) Involvement by Skin Disease</u>
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 case report form (Example of table from CRF 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

13.0 CRITERIA FOR REMOVAL FROM STUDY

13.1 Discontinuation of Study Treatment

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

- Disease progression
- 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 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 in section 4.1. 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). The maximum number of patients needed for this dose escalation design is 30. Patients with measurable disease treated at MTD in the phase Ib will be analyzed in phase IIa to further characterize the toxicity of romidepsin and lenalidomide in combination at the MTD determined by phase Ib. In phase IIa, we plan to enroll about 39 patients so that the total number of patients to be treated at MTD will be approximately 44(we plan to enroll 15 patients with B-cell lymphomas, 8 patients with multiple myeloma, 15 patients with T-cell lymphomasand additional 6 patients with acute T-cell leukemia/lymphoma. To subsequently monitor the safety primary endpoint in the phase IIa portion, we will employ a dose-reduction plan for the predefined DLT in the phase Ib portion during cycles 1-4. This dose-reduction plan specifies that the dose will be reduced from the phase Ib MTD to the MTD-1 (10mg/m2 romidepsin; 25mg lenalidomide) if DLT occur in cycle 1-4 in: ≥8/first 15; ≥16/first 30; or if more than 24 patients when the last (45^{th}) evaluable patient has completed the trial have any DLT. If at MTD-1 a DLT occurs in ≥8/first 15; ≥16/first 30, then MTD-2 (8mg/m2 romidepsin; 25mg lenalidomide) will be employed for the remainder of phase IIa. The probability of dose-reducing from the MTD is the following:

True toxicity rate	5%	10%	15%	20%	25%	30%	35%	40%	50%
Dose reduction prob.	0.000	0.000	0.001	0.004	0.016	0.056	0.118	0.243	0.632

18 months after the final patient is enrolled and after 80% of patients, MSKCC will analyze disease status, serious adverse events and survival for all patients.

Secondary objectives of this study aim at examining many clinical endpoints (see Sections 4 and 12 for detailed definitions). Overall response rate (ORR) and clinical benefit rate (CBr) for MM patients, complete response rate, very good partial response/partial response rate will be summarized using proportions and confidence intervals will be provided. 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, all three disease subtypes (B-cell lymphoma, multiple myeloma, PTCL) will be grouped together including those from the phase Ib that were treated at MTD. Note that the response criteria are different among the disease subtypes (see Section 12.0). To preliminarily collect the data, subset analyses will also be conducted to evaluate the ORR, TTR, DOR, and EFS for each disease subtype.

To further investigate activity of this regimen in patients with acute T-cell leukemia/lymphoma, an additional cohort of 6 patients will be added to the phase IIa portion of the study. When the true response rate is 30% or above, the probability that none of the 6 patients will respond is less than 0.12. Subset analyses will be conducted to evaluate the ORR, TRR, DOR, and EFS for each disease subtype.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

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

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

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

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.1.1 For Participating Sites:

Central registration for this study will take place at Memorial Sloan Kettering Cancer Center (MSK).

To complete registration and enroll a participant from another institution, the participating 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 (laboratory results, pathology report, radiology reports, MD notes, physical exam sheets, medical history, prior treatment records, and EKG report).

Upon receipt, the research staff at MSK will conduct an interim review of all documents. If the eligibility checklist is not complete or source documentation is missing , the participant will be registered PENDING and the site is responsible for sending a completed form within 30 days of the consent.

If the external registration submission is complete, the participating site IRB has granted approval for the protocol, and the site is in good standing, the MSK study coordinator will send the completed registration documents to the MSK Protocol Participant Registration Office for participant enrollment as stated in the protocol.

Once the participant is registered, the participant will be assigned a number in the MSK Clinical Research Database (CRDB). This number will be relayed back to study staff at the registering participating site via e-mail and will serve as the enrollment confirmation. The number is unique to the participant and must be written on all data and correspondence for the participant.

15.2 Randomization

There is no randomization in this study.

16.0 DATA MANAGEMENT ISSUES

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

The data collected for this study will be entered into CRFs by participating sites; MSK staff will enter data electronically into CRDB. Given our prior experience and

large patient population in the relapse and refractory setting we expect to enroll approximately 2 patients per month. NYPH, St. Francis Care and University of Nebraska Medical Center are expected to accrue approximately 1 patient every other month. We plan to complete accrual in two years with closure of the study in 3 years.

16.0.1 Data and Source Documentation for Participating Sites

Data
The participating site(s) will enter data onto standardized Case Report Forms (CRFs). Data entry guidelines have been generated for this study and blank case report forms will be sent to the study staff at each participating site for use. The participating site PI is responsible for ensuring these forms are completed accurately, legibly and in a timely manner. A schedule of required forms is shown in **Table 1** below. .

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 CRFs. 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 that meet study reporting requirements not previously submitted with SAE Reports
- 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-identifable information it may encounter

Participating sites should email CRFs and source documentation to MSK to the contact provided below.

E-mail: medmctcore@mskcc.org to the attention of the Multicenter OfficeCoordinator

Table 1 : Data and Source Documentation Timeline

Time point	Data	Source Documentation
Baseline	Within **24 hours** of consent (see section 15.1.1)	Within **24 hours** of consent (see section 15.1.1)

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 17.3

16.0.4 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.

16.1 Quality Assurance

Weekly 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, accuracy of evaluations, and follow-up will be monitored periodically throughout the study period. Potential problems will be brought to the attention of the study team.

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

16.1.1 Quality Assurance for Participating Sites

Quality Assurance will be conducted according to MSK guidelines and Multicenter SOPs.

Research staff at MSK will conduct periodic reviews of regulatory documentation, protocol compliance and data, and issue queries as appropriate. The level and frequency of monitoring or auditing may be adjusted based on ongoing site performance.

16.1.2 Response Review

Since therapeutic efficacy is a stated primary objective, all sites participants' 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 (MSK) were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: *http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1*. 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 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

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 IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical licenses for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators, consenting professionals and key study personnel at the participating site
- Documentation of Good Clinical Practice training for the participating site PI and co-PI
- 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.

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 90 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.

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 according to sections 7.0 and 9.0 of this addendum.

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 patient eligibility, 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.

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 all 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.

Document aintenance

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 3 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.

17.0 PROTECTION OF HUMAN SUBJECTS

17.1 Privacy

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 representatives of Celgene Corporation and, when necessary, representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws.

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

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 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 sae@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.

17.2.1 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.

Adverse Event Reporting

Toxicity will be scored using CTCAE Version 4.0 for toxicity and adverse event reporting (See Appendix H). A copy of the CTCAE Version 4.0 can be downloaded from the CTEP homepage (http://ctep.cancer.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.

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.

Pregnancies

Pregnancies 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, or within 28 days of the subject's last dose of lenalidomide, are considered immediately reportable events. Lenalidomide is 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 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 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 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 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 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 should be advised as soon as the information is available.

Overdose

Overdose, as defined for this protocol, refers to REVLIMID® (lenalidomide) combination products and comparator] dosing only.

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of Lenalidomide assigned to a given patient, regardless of any associated adverse events or sequelae.

PO any amount over the protocol-specified dose

IV 10% over the protocol-specified dose

SC 10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate. Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

Expedited Reporting by Investigator to Celgene

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events of being related to lenalidomide based on the Investigator Brochure. In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

Serious adverse events (SAE) are defined in Section 17.2.1. The 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

Investigator Reporting to the FDA

Serious adverse events (SAEs) that are **unlisted/unexpected, and at least possibly associated to the drug,** and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the MSK IND office in order to contact the Food and Drug Administration (FDA) by telephone or by fax. Fatal or life threatening SAEs that meet the criteria for reporting to the FDA will be reported to the FDA within 7 calendar days after awareness of the event. All other SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 15 calendar days after awareness of the event by the IND office at MSK. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

Adverse Event Updates/IND Safety Reports

Celgene shall notify the Investigator via an IND Safety Report of the following information:

- Any AE associated with the use of drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all AE information, including correspondence with Celgene and the IRB/EC, on file (see records retention information).

17.3 SAE Reporting for Participating Sites

Responsibility of Participating Sites

- Participating sites are responsible for reporting all SAEs to their site 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 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.

Responsibilities of MSK

- MSK is responsible for submitting all SAEs to the MSK IRB/PB and funding entities (if applicable) as described in the protocol.
- 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 report from the MSK IRB/PB.
- MSK is responsible for informing all participating sites within 24 hours or on the next business day about a death that is unforeseen and indicates participants or others are at increased risk of harm.

SAE contact information for the Coordinating Center is listed below:
Multicenter Trials Core Staff
MSK Clinical Trials Office
Email: medmctcore@mskcc.org to the attention of **[12-170]** Research Staff

AND

Steven Horwitz, MD
Memorial Sloan Kettering
Email: [horwitzs@mskcc.org]
(O) 212-639-3045

17.4 Communication of DLTs

For the purposes of this clinical trial, A DLT is defined as non-hematologic toxicity of grade ≥3 (attributed to study drug) and hematologic grade 4 (attributed to study drug) toxicity defined as grade 4 thrombocytopenia of any duration, failure of recovery of absolute neutrophil count ≥ 1.0 K/μL or platelets to ≥ 50 K/μL within 14 days of last treatment; or inability to receive day 1 of cycle 2 due to continued drug-related toxicity from the cycle. During the course of the Phase Ib portion of this study, all DLTs that occur will be immediately communicated via email to each participating site/investigator. Additionally, routine conference calls will be conducted with all participating sites to communicate all safety issues including DLTs. The frequency of these conference calls will be determined by enrollment rate of the trial. Lastly, all events that qualify as SAEs should be reported according to the protocol guidelines.

17.5 Safety Reports

MSK must submit outside safety reports to the MSK IRB/PB according to institutional guidelines. All outside 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 site IRB per their local guidelines. All site IRB approvals/acknowledgments of safety reports must be sent to MSK upon receipt.

17.5.1 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 7.0 of this addendum. 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.

18.0 INFORMED CONSENT PROCEDURES

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

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.

3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

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

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

18.1 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 partcipant's 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: ECOG Performance Status Scale
Appendix B: Cockcroft-Gault estimation of CrCl
Appendix C: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods
Appendix D: Canadian Cardiovascular Society Angina Classification
Appendix E: New York Heart Association Classification of Cardiac Disease
Appendix F: Medications That May Cause QTc Prolongation
Appendix G: Medications That May Inhibit CYP3A4
Appendix H: NCI CTC Version 4.0
Appendix I: (mSWAT): Grading Scales for Composite Assessment of Index Lesion Disease Severity

Appendix A – ECOG Performance Status Scale

SCORE	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix B – Cockcroft-Gault estimation of CrCl:

Cockcroft-Gault estimation of creatinine clearance (CrCl):

(Cockcroft, 1976; Luke 1990)

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

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

Appendix C – 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 effective 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 D – 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 E – 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 resulting limitations of physical activity. Ordinary physical activity 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 activity. 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 activity. 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 activity 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 F – 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.

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			
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			
Venlaflaxine (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			
Moexipril/Hydrochlorothiazide (Uniretic)	2-9 hr(include active metabolite) for moexipril; 5.6-14.8 hr for HCTZ	48	

Compound (Brand Name)	Compound Half-Life	Possible Washout Period (Hours)	Possible Washout Period (Days)
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
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	
Nicardipine (Cardene)	~2 hr post IV infusion	12	
Cholinergic enhancers			
Cisapride (Propulsid)	6-12 hr, up to 20 hr	60	
Diuretics			

Compound (Brand Name)	Compound Half-Life	Possible Washout Period (Hours)	Possible Washout Period (Days)
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 G – 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
Oral Contraceptives			

Compound (Brand Names)	Compound Half-Life	Possible Washout Period - Hours	Possible Washout Period - Days
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 H – NCI CTC Version 4.0

Toxicity will be scored using NCI CTC Version 4.0 for toxicity and adverse event reporting. A copy of the NCI CTC Version 4.0 can be downloaded from the CTEP homepage: (**http://ctep.info.nih.gov**). All appropriate treatment areas have access to a copy of the CTC Version.

Appendix I – Grading Scales for Composite Assessment of Index Lesion Disease Severity

SCALING	0 - No evidence of scaling on the lesion 1* 2 - Mild: Mainly fine scales; lesion partially covered 3* 4 - Moderate: Somewhat coarser scales; lesion partially covered 5* 6 - Severe: Coarse, thick scales; virtually all of the lesion covered; rough surface 7* 8 - Very severe: Coarse, very thick scales; all of the lesion covered; very rough surface
ERYTHEMA hyperpigmentation	0 - No evidence of erythema, possible brown 1* 2 - Mild: Light red lesion 3* 4 - Moderate: Red lesion 5* 6 - Severe: Very red lesion 7* 8 - Very severe: Extremely red lesion
PLAQUE/TUMOR ELEVATION above normal	0 - 0 mm: No evidence of plaque above normal skin level 1 - ≥0 to <0.5 mm: Minimal but definite plaque elevation above normal skin level 2 - ≥0.5 to <1 mm: Slight but definite plaque elevation 3 - ≥1 to <1.5 mm: Mild elevation 4 - ≥1.5 to <2 mm: Moderate elevation 5 - ≥2 to <2.5 mm: Moderate to marked elevation 6 - ≥2.5 to <3 mm: Marked elevation 7 - ≥3 to <3.5 mm: Very marked elevation 8 - ≥3.5 mm: Extreme elevation

* For scaling and erythema, intermediate intervals 1, 3, 5 and 7 were to serve as mid-points between the defined grades 0, 2, 4, 6, and 8.

HYPO-/HYPERPIGMENTATION	To have been used only when hypopigmentation or hyperpigmentation was the clinical manifestation of CTCL. 0 - No evidence of pigmentation change. 1*

2 - Mild: 25% lighter pigmentation or noticeably darker pigmentation
compared to the patient's normal skin pigmentation.
3*
4 - Moderate: 50% lighter pigmentation or twice as dark pigmentation compared to the patient's normal skin pigmentation.
5*
6 - Severe: 75% lighter pigmentation or three times as dark pigmentation compared to the patient's normal skin pigmentation.
7*
8 - Very severe: Nearly complete absence of pigmentation or nearly
as dark a pigmentation as could be observed
compared to the patient's normal skin pigmentation.

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* Intermediate intervals 1,3,5 and 7 are to serve as mid-points between the defined grades 0, 2, 4, 6 and 8.

INDEX LESION AREA	0 - 0 cm2 (no measurable area)
	1 - > 0 and ≤4 cm2
	2 - > 4 and ≤10 cm2
	3 - >10 and≤16 cm2
	4 - >16 and ≤25 cm2
	5 - >25 and ≤35 cm2
	6 - >35 and ≤45 cm2
	7 - >45 and ≤55 cm2
	8 - >55 and ≤70 cm2
	9 - >70 and ≤90 cm2
	10 - >90 and ≤110 cm2
	11 - >110 and ≤130 cm2
	12 - >130 and ≤155 cm2
	13 - >155 and ≤180 cm2
	14 - >180 and ≤210 cm2
	15 - >210 and ≤240 cm2
	16 - >240 and≤270 cm2
	17 - >270 and ≤300 cm2
	18 - >300 cm2
