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Phase II Study of Romidepsin Plus Lenalidomide for Patients with Previously Untreated PTCL

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Study Drugs: Romidepsin
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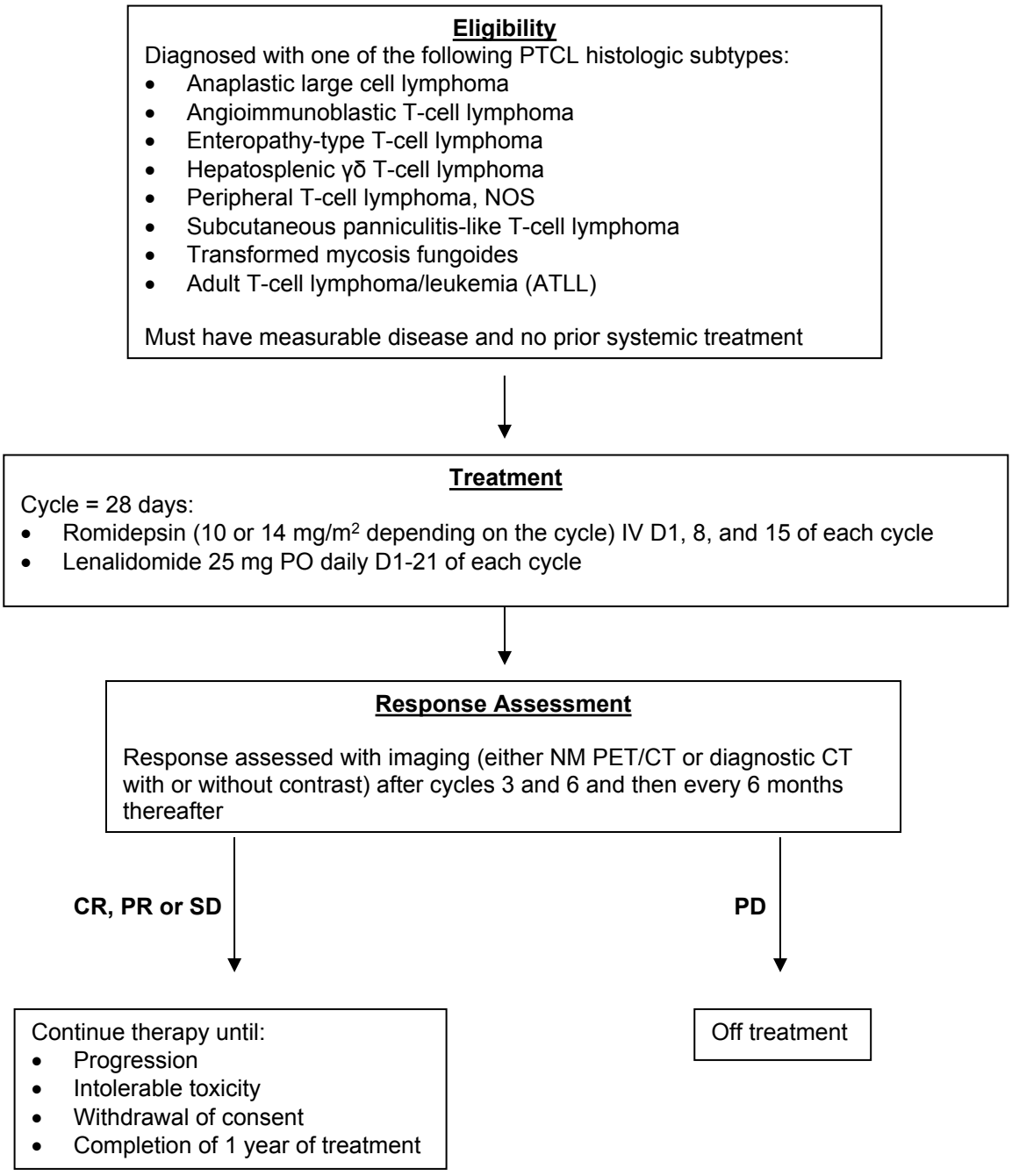
List of Abbreviations

AE	Adverse Event
AITL	Angioimmunoblastic T-Cell Lymphoma
ALCL	Anaplastic Large Cell Lymphoma
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ATLL	Adult T-cell Lymphoma/Leukemia
BUN	Blood Urea Nitrogen
BSA	Body Surface Area
CBC	Complete Blood Count
CHOP	Cyclophosphamide, Doxorubicin, Vincristine and Prednisone
CIRS	Cumulative Illness Rating Scale
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CRR	Complete Response Rate
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T-Cell Lymphoma
CTO	Clinical Trials Office
DLBCL	Diffuse Large B-Cell Lymphoma
DOR	Duration of Response
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
EFS	Event-Free Survival
FL	Follicular Lymphoma
H&P	History & Physical Exam
HDAC	Histone Deacetylase
HIV	Human Immunodeficiency Virus
HL	Hodgkin Lymphoma
IV (or iv)	Intravenously
LDH	Lactate Dehydrogenase
MCL	Mantle Cell Lymphoma
MM	Multiple Myeloma
NCI	National Cancer Institute
NHL	Non-Hodgkin Lymphoma
ORR	Overall Response Rate
OS	Overall Survival
PTCL	Peripheral T-Cell Lymphoma
PD	Progressive Disease
PFS	Progression Free Survival
p.o.	per os/by mouth/orally
PR	Partial Response
PRR	Partial Response Rate
REMS	Risk Evaluation and Mitigation Strategy
RP2D	Recommended phase II dose
SAE	Serious Adverse Event
SCT	Stem Cell Transplant
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
TMA	Tissue MicroArray
TTFCC	Time to First Cytotoxic Chemotherapy
WBC	White Blood Cells

Study Schema



Study Summary

Title	Phase II Study of Romidepsin Plus Lenalidomide for Patients with Previously Untreated PTCL
Version	November 17, 2021 (Amendment 11)
Methodology	Phase II, open-label, single-arm, Simon two-stage, multicenter
Study Duration	Approximately 24 months
Study Centers	**Lead site:** Northwestern University Robert H. Lurie Comprehensive Cancer Center **Participating Sites**: City of Hope, Cornell Medical College
Objectives	**Primary** Evaluate the efficacy of romidepsin plus lenalidomide in patients with PTCL; this will be done by evaluating the objective response rate by Cheson criteria. **Secondary objectives:** 1. Evaluate safety (as defined by frequency and severity of toxicity events). 2. Further evaluate efficacy as measured by PFS and OS measured at 1 and 3 years after beginning treatment. 3. Further evaluate efficacy as measured by duration of response and time to first cytotoxic chemotherapy. **Exploratory objectives:** 1. Further evaluate the use of NM PET/CT vs CT imaging in PTCL. 2. Validate a new prognostic model for newly diagnosed PTCL. 3. Investigate the tumor immunohistochemical profile to identify potential biomarkers associated with prognosis and treatment response.
Study Population	Up to 35 adult patients with previously untreated PTCL (see specific histologic subtypes in Schema and Section 3.0) may be enrolled to obtain 20 evaluable patients.
Treatment Plan	Patients will receive treatment in cycles defined as 28 days each: • Romidepsin 10 mg/m^2 IV on days 1, 8, and 15 of each cycle (dose escalated to 14 mg/m^2 if tolerated first 6 doses) • Lenalidomide 25 mg PO daily days 1- 21 of each cycle Patients may receive treatment for up to 1 year (unless discontinued prior to that for progression of disease, intolerable toxicity, or withdrawal of consent)
Statistical Methodology	The study will analyze n=20 evaluable patients. This will allow us to estimate the underlying true response rate with a half width of an approximate 95% confidence interval equal to 1.96x0.5/sqrt(20) = 1.96x0.11 = 0.22.

1.0 Introduction – Background and Rationale

1.1 Disease Background

Peripheral T-cell lymphoma (PTCL) is an uncommon subset of non-Hodgkin lymphoma (NHL) that carries a poor prognosis with frequent early relapses despite intensive therapy. PTCL represents approximately 10-15% of all NHL in Western populations. PTCLs originate from mature post-thymic T-cells.[1] The current World Health Organization (WHO) classification for lymphoid malignancies incorporates immunophenotyping, molecular, clinical, and pathologic features for diagnosis of the differing subtypes.[2] Understanding the biologic nature of this disease has been difficult given the rarity and the heterogeneity of the histologic subtypes.

In North America, the most common subtype of PTCL is PTCL, unspecified (PTCLu), which comprises a heterogeneous group of predominantly nodal T-cell lymphomas. PTCLu do not have consistent immunophenotypic, genetic, or clinical features. Less common PTCL subtypes include the predominantly nodal systemic anaplastic large cell lymphoma (ALCL) and angioimmunoblastic T-cell lymphoma (AITL). Rare subtypes of PTCL include NK/T-cell lymphoma nasal type, enteropathy type T-cell lymphoma, hepatosplenic γδ T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, and the adult T-cell lymphoma/leukemia (ATLL) which is associated with HTLV-1 infection. All these rare subtypes of PTCL are predominantly extranodal with the exception of ATLL.[3]

Primary treatment for most subtypes of PTCL remains anthracycline-based regimens, predominantly the combination of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). The primary response rate for all PTCL subtypes remains at less than 60% and most patients will relapse after initial treatment with cytotoxic agents.[4] The median survival of all PTCL patients (excluding the ALK-positive ALCL subtype) is approximately 3-4 years, with a 5-year survival of less than 30%. The 5-year survival rate for ALK-positive ALCL is 60-90%. Further intensification of therapy, with either the addition of etoposide (e.g., CHOEP), or with consolidative autologous stem cell transplant (autoSCT), has not been shown to improve outcomes. The value of anthracyclines as part of upfront therapy is also unclear. At present, there remain no therapies approved specifically for PTCL.

Such data, along with the recent regulatory approval of several novel, reasonably well-tolerated agents (particularly in comparison to CHOP-like regimens) for relapsed/refractory NHL, has led to the hypothesis that these agents might form a novel and highly active upfront therapy for patients with PTCL.

1.2 Histone Deacetylases (HDAC) and HDAC Inhibitors

Histone deacetylases (HDAC) are enzymes that catalyze the removal of acetyl groups from the lysine residues of various proteins, including histones and transcription factors. The transcription of genes is partially regulated by acetylation of nucleosomal histones. The core nucleosomal histones are the most widely studied of the proteins that become acetylated following inhibition of HDAC activity.[5] In some cancer cells, there is an overexpression of HDACs, or an aberrant recruitment of HDACs to oncogenic transcription factors causing hypoacetylation of core nucleosomal histones. Hypoacetylation of histones is associated with a condensed chromatin structure and repression of gene transcription.

Inhibition of HDAC activity allows for the accumulation of acetyl groups on the histone lysine residues resulting in an open chromatin structure and transcriptional activation. HDAC inhibitors can induce tumor cell growth arrest, differentiation, or apoptosis in vitro and inhibit tumor growth in animals.[6, 7] HDAC inhibitors as a class appear to have significant activity in T-cell lymphomas for reasons that are not clearly understood. HDAC inhibitors work through several different mechanisms including alteration in the

expression of genes that regulate cell cycle, acetylation of non-histone proteins that may impair their function to influence cell growth and survival, and by direct activation of apoptotic pathways.[8] Attempts at understanding the mechanisms of HDAC inhibitors have involved gene expression profiling on paired tissue samples both pre- and post-treatment that have shown only 5-10 % of the genome can be affected. As many genes are unregulated as are down regulated following treatment with most HDAC inhibitors. The genes that were consistently affected included genes that alter cell cycle (CCNDI, IGFI), apoptosis (septin10, TEF, SORBBS2), angiogenesis (GUCY1A1, ANGPT1), and immune modulation (LAIR1).[9] QT-PCR was used to confirm that the findings on gene array analysis were indeed biologically accurate, with a strong correlation between gene array and the PCR data. Tumor tissue specimens treated with various HDAC inhibitors have shown an increase in histone acetylation, decreased vascularity, and translocation of nuclear proteins like STAT-s which is associated with inactivation.[10]

1.2.1 Romidepsin

Romidepsin (Istodax®, FK228) is a HDAC inhibitor commercially available from Celgene. It is a unique HDAC inhibitor as it is a prodrug. Upon entering cells romidepsin is reduced to an active compound, capable of preferentially interacting with the zinc in the active site of the HDAC1, HDAC2 and HDAC3 (Class I).[11] Romidepsin currently has FDA approval for patients with cutaneous T-cell lymphomas (CTCL) that have received at least one prior therapy (as well as for relapsed/refractory PTCL – see 1.2.4 below). It is currently being assessed for the treatment of a variety of malignant and inflammatory diseases.

1.2.2 Toxicity and Safety of Romidepsin

The clinical experience with romidepsin from multiple clinical trials has shown a well tolerated toxicity profile. Phase 1 trials have provided the safety profile and dosing schedule.[12, 13] Romidepsin doses ranging from 1.0 to 24.9 mg/m2 administered intravenously over 4 hours have been investigated in treatment of advanced cancers.[14] A more standardized regimen has been defined as 14 mg/m2 intravenously over a 4 hour period on days 1, 8 and 15 of a 28-day cycle.[15] The major hematologic toxicity includes anemia, leukopenia, lymphopenia, and thrombocytopenia. Other common adverse events include gastrointestinal symptoms, constitutional symptoms, and dysgeusia. In addition, it was found that romidepsin may cause QTc prolongation/ECG changes however this may be the result of a drug:drug interaction with select antiemetics. Based on non-clinical findings, male and female fertility may be compromised by treatment with Romidepsin.

1.2.3 Efficacy of Romidepsin

The use of romidepsin is best established in CTCL. A phase II trial with romidepsin in relapsed CTCL showed single agent activity in patients that previously had been heavy pretreated with a median of 4 prior therapies.[16] A total of 71 patients were treated with an overall response rate (ORR) of 34% including 4 patients with a complete response. The median duration of response (DOR) was 13.7 months. This trial and a registration directed trial by Gloucester Pharmaceuticals, previous owners of romidepsin, led to full regulatory approval by the FDA for the treatment of relapsed CTCL. A phase II trial of romidepsin in patients with heavily treated relapsed/refractory PTCL demonstrated an ORR of 25% with median DOR lasting a somewhat remarkable 17 months.[15] The treatment regimen was romidepsin administered as a 4-hour infusion on days 1, 8, and 15 of a 28-day cycle with a dose of 14 mg/m^2. Based on this trial, romidepsin gained FDA approval in 2011 for use in relapsed/refractory PTCL.

1.3 Immunomodulatory and Antineoplastic Agents

Thalidomide gained notoriety in the 1960s due to profound limb deformities observed in infants of pregnant women who used the medication for morning sickness. Laboratory based re-evaluation of the agent in the 1990s later showed important antiangiogenic, anti-inflammatory, and antineoplastic effects. By the early 2000s, thalidomide had emerged as a new treatment for multiple myeloma (MM). Subsequently, other more potent derivatives of thalidomide have been developed including pomalidomide and lenalidomide.[17]

1.3.1 Lenalidomide

Lenalidomide (Revlimid®, CC-5013) and its predecessor, thalidomide, are proprietary IMiD™ compounds of Celgene Corporation. Lenalidomide is an orally available and more potent thalidomide derivative that has a more favorable side effect profile. The exact mechanism of action is unclear, however lenalidomide has been shown to have immunomodulatory and anti-angiogenic effects. In general, its effects include inhibition of regulatory T-cells, co-stimulation of other T-cell subsets, inhibition of cell cycle regulatory proteins, and downregulation of a variety of cytokines including IL-6 and TNFα.[18] Preclinical studies have shown that lenalidomide inhibits neovascularization via VEGF inhibition of the P13K-Akt pathway signaling. It also has an inhibitory effect on protein interactions critical for endothelial cell cord formation including HIF-1α expression, the main mediator of hypoxia-mediated effects and a key driver of angiogenesis and metastasis.[19, 20] The dual mechanism of action with both direct tumorical activity and immunomodulation has shown promising responses in hematologic malignancies. Lenalidomide is indicated for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities; it is also approved in combination with dexamethasone for the treatment of patients with multiple myeloma that have received at least one prior therapy.

1.3.2 Toxicity and Safety of Lenalidomide

The clinical experience with lenalidomide from multiple clinical trials has shown a well tolerated toxicity profile. Phase 1 trials have provided the initial safety profile and dosing schedules.[21-23] Doses up to 50 mg daily have been evaluated in both hematologic and solid tumor populations. Lenalidomide has less myelosuppression when a 7-day break is introduced, and the most common schedule selected for further development is 25 mg daily on Days 1-21, followed by a 7-day drug “holiday”. A majority of side effects are mild and include rash, pruritus, diarrhea, and fatigue. Grade 3 and 4 toxicities observed in these trials include neutropenia and thrombocytopenia in approximately 10% of patients. Importantly, severe constipation, neuropathy and somnolence that characterize thalidomide were not seen.

Based on the history of limb defects associated with thalidomide, prescribers must enroll patients through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS), called the REVLIMID REMS™ program. The program provides a structured process for monitoring prescriptions of this teratogenic agent.

1.3.3 Efficacy of Lenalidomide

The use of lenalidomide is best established in multiple myeloma (MM) however there are several clinical trials investigating the use of lenalidomide monotherapy in patients with relapsed lymphomas. Lenalidomide monotherapy was reported in aggressive lymphomas composed on diffuse large B-cell lymphoma (DLBCL), grade 3 follicular lymphoma (FL), mantle cell lymphoma (MCL), and transformed

FL.[24] The ORR was 35% with a median duration of response to 6.2 months and median progression free survival (PFS) of 4 months. The trial included a population of heavily pre-treated patients with a median of 4 prior regimens and 30% had previously relapsed following an autologous stem cell transplant (autoSCT). The same regimen was studied in indolent non-Hodgkin lymphomas (NHL) with a similar heavily pretreated population including 50% with refractory disease. Here the ORR was 23% in all patients and 27% in relapsed FL.[25] Interestingly, the median PFS was only 4.4 months however the median DOR for responding patients is greater than 16.5 months. Lenalidomide monotherapy appears particularly active in mantle cell lymphoma, with an ORR of 53% and a median DOR of 13.7 months.[26] In 2013, lenalidomide was approved for relapsed/refractory MCL in patients with prior exposure to bortezimib containing regimens based on the phase II "EMERGE" trial.[27] A completed international phase II trial (NHL-003) published follow up results for the MCL subset of patients. They report ORR was 35% with 12% complete responses with a median DOR of 16.3 months. Median PFS was 8.8 months and OS has yet to be reached.[28] These single agent studies as well as preclinical studies of potential synergy have prompted an intense development agenda for lenalidomide in NHL, with many trials currently underway.

1.4 Study Rationale

The toxicity associated with anthracycline-containing regimens (eg, CHOP) prevent its safe deployment in a substantial portion of patients with newly diagnosed PTCL. In addition, intensification does not clearly yield improved clinical outcomes. The emerging regimen for relapsed/refractory NHLs with combination romidepsin and lenalidomide supports promising responses. In patients with PTCL, particularly those with AITL, the use of either romidepsin or lenalidomide may provide therapeutic options. The safety of combination therapy with these two agents has already been evaluated in other malignancies.

Romidepsin was approved in 2011 for the treatment of patients with relapsed/refractory PTCL based upon results of a phase II trial that demonstrated an overall response rate (ORR) of 25%, with median DOR lasting a somewhat remarkable 17 months.[15] The drug was well-tolerated with fatigue, infections, and cytopenias observed as the main toxicities. Lenalidomide was approved in 2013 for the treatment of relapsed/refractory mantle cell lymphoma (MCL) based upon phase II data demonstrating an ORR of 25% in heavily pre-treated patients.[27] Two separate phase II trials of lenalidomide in relapsed/refractory PTCL, involving a total of 44 patients, each demonstrated ORR of 30%.[29, 30] The main adverse events in both trials consisted of cytopenias and fatigue. A third, ongoing trial is evaluating the role of lenalidomide in Japanese patients with PTCL with particular focus on those with adult T-cell leukemia/lymphoma (ATLL).[31] Romidepsin and lenalidomide each appear to have particularly notable activity in patients with angioimmunoblastic T-cell lymphoma (AITL), which is the second most frequent type of PTCL in North America. Specifically, median DOR has not been reached and is at least 48 months among patients with relapsed/refractory AITL treated with romidepsin as part of the phase II registration trial.[32] Durable responses of over two years have likewise been reported for patients with relapsed/refractory AITL receiving lenalidomide.[33]

Currently, a Phase I/II trial evaluating the combination of romidepsin and lenalidomide in patients with relapsed hematologic malignancies is open to enrollment (NCT01755975). The trial included a 3+3 design with five dosing cohorts to determine the maximal tolerated dose with a total of 20 patients treated on the study. Results presented at ASCO annual meeting in 2014 revealed that the combination was well-tolerated[34]. A dose limiting toxicity was demonstrated in one patient of seven receiving romidepsin 14 mg/m2 with lenalidomide 25 mg. The most common grade 3-4 toxicities included

electrolyte abnormalities, myelosuppression, and transaminitis. The trial enrolled patients with a range of lymphoma subtypes including eight patients with T-cell NHL. An ORR of 66% was seen in six evaluable patients including two patients with PTCL-NOS and one patient with AITL. The trial is proceeding to the phase II portion with romidepsin 10 mg/m2 and lenalidomide 25 mg as a recommended dose schedule. A second phase I/IIa trial evaluating combination romidepsin and lenalidomide is currently open for patients with relapsed/refractory Hodgkin lymphoma (HL), mature T-cell lymphoma (including CTCL and PTCL), and MM (NCT01742793). Results from this clinical trial are not available.

We propose proceeding with a phase II trial evaluating the safety and efficacy of the combination of romidepsin and lenalidomide in patients with previously untreated PTCL. The treatment population will include patients ≥ 60 years of age who often have comorbidities that prevent the use of cytotoxic chemotherapy. In addition, the trial will enroll patients age ≥ 18 years to < 60 years with a cumulative illness rating scale (CIRS) score ≥ 6 or deemed ineligible for cytotoxic chemotherapy by the treating investigator. A CIRS score ≥ 6 is a previously established cutoff to define increased treatment risk. The proposed dosing and schedule for romidepsin and lenalidomide are both FDA approved. The protocol will allow an increased dose of romidepsin from 10 mg/m^2 to 14 mg/m^2 pending tolerance assessment. The initial romidepsin dose of 10 mg/m^2 is chosen to avoid potential cytopenias with combination therapy. Up to 35 patients may be treated on the protocol in order to achieve a total of 20 evaluable. The trial will include a two-side design with an early assessment of futility following treatment of the first 12 patients with an early stopping point if 6 or fewer patients have a complete or partial response. Response will be determined by interval imaging; the 3 month response assessment time point will be used for the purposes of the interim efficacy analysis. Patients may be treated for up to 1 year or until progression of disease, intolerable toxicity, or withdrawal by patient.

1.5 Exploratory Studies

Prior translational research has looked to incorporate marker expression into a clinical prognostic tool.[35] While no clear marker has been identified for PTCL, several may help predict a poor outcome including EBER, CD15, and Ki-67. A protein, nm23-H1, that is over expressed in lymphoma cells is an emerging marker that may predict a poorer prognosis.[36] Two cytotoxic molecules, TIA-1 and granzyme B, have been correlated with a more aggressive clinical course.[37] Another study showed high expression of IL-6 and TNF-α expression in PTCL which is particularly interesting given the down regulation of these proteins with administration of one of our study drugs, lenalidomide.[38] Correlative studies will be analyzed on collected blood and tissue samples. In addition to the study objectives, we plan to assess tumor samples for the immunohistochemical biomarkers that may correlate with prognosis and more importantly with treatment response. A tissue microarray (TMA) of paraffin-embedded lymphoid tissue biopsies of all patients will be created in order to determine how marker expression correlates with clinical outcome.

A new prognostic model was recently defined for PTCL. An analysis of the SEER registry was conducted to evaluate the impact of variables including age, race, histology, and stage.[38] In this model, overall survival can be predicted however further validation is required. Enrolled patients will provide a prospective look at this proposed predictive model.

The current standard modality for staging and response assessment in PTCL remains CT imaging. The role of NM PET/CT in management of PTCL is poorly understood though often utilized in clinical practice. Prior analysis has shown that NM PET/CT can identify additional sites of disease however there is no influence on treatment decisions[39]. Conversely, the role of NM PET/CT in the management of other lymphomas is well

established. The use of NM PET/CT in Hodgkin lymphoma is now standard of care. Use of NM PET/CT in non-Hodgkin lymphomas including DLBCL and FL has proven useful in staging and guiding treatment decisions[40]. We will investigate the role of NM PET/CT in the treatment of PTCL.

2.0 Study Objectives and Endpoints

2.1 Primary Objective & Endpoint

The primary objective of this phase II trial will be to evaluate the efficacy of the combination of romidepsin plus lenalidomide in patients with previously untreated PTCL.

The endpoint for this objective will be objective response rate (ORR), defined per Cheson criteria. Response will be assessed by imaging after cycles 3 and 6, and then every 6 months thereafter. Response at 3 months (after cycle 3) will be used for purposes of the interim efficacy analysis.

2.2 Secondary Objectives & Endpoints

2.2.1 Evaluate the safety of the combination of romidepsin and lenalidomide.

The endpoint will be the frequency and severity of toxicity events using the NCI CTCAE v 4.03.

2.2.2 Further evaluate efficacy of the combination of romidepsin and lenalidomide.

The endpoints will be progression-free survival (PFS) and overall survival (OS) at 1 and 3 years after start of treatment as well as the duration of response from start of therapy, defined per Cheson criteria.

2.2.3 Evaluate the delay to cytotoxic chemotherapy

The endpoint will be time (in months) to first cytotoxic chemotherapy (TTFCC) from start of treatment.

2.3 Exploratory Objectives & Endpoints

2.3.1 Evaluate the use of NM PET/CT vs CT imaging in PTCL.

The endpoint will be a review of the utilized imaging modalities during treatment as a tool of response assessment. When both imaging modalities are chosen for a patient, response assessment will be compared.

2.3.2 Validate a new prognostic model for newly diagnosed PTCL.[41]

The endpoint will be clinical biomarkers including age, race, histology, and stage as an assessment of prognosis.

2.3.3 Investigate the tumor immunohistochemical profile to identify potential biomarkers associated with prognosis and treatment response.

The endpoint we be comparison of immunohistochemical profiles with treatment outcomes on archived tissue samples.

3.0 Patient Eligibility

The target population for this phase II study is patients with histologically confirmed (previously untreated) peripheral T-cell lymphoma (PTCL). Northwestern University will serve as the lead site and coordinating center for this study. Participating sites will include Weill Cornell Medical College, and City of Hope.

A total of 20 evaluable subjects will be needed for this trial; up to 35 may be accrued to obtain 20 who are evaluable. Approximately 3 potentially eligible patients are seen per month, and it is anticipated that at least 1 per month will be accrued (once all sites are up and running). Potential patients may be referred to the Principal Investigator (PI) at Northwestern University, , or to the local PI at each participating site.

Eligibility will be evaluated by the study team according to the following criteria. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered. After registration, treatment should begin with 14 days. Please refer to Section 11.4 for complete instructions regarding registration procedures.

3.1 Inclusion Criteria

3.1.1 Histologically confirmed diagnosis of PTCL (using the most recent edition of the WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues as guidance) including:

- Anaplastic large cell lymphoma, ALK-negative
- Angioimmunoblastic T-cell lymphoma
- Enteropathy-type T-cell lymphoma
- Hepatosplenic γδ T-cell lymphoma
- Peripheral T-cell lymphoma, unspecified (NOS)
- Transformed mycosis fungoides
- Subcutaneous panniculitis-like T-cell lymphoma
- Adult T-cell lymphoma/leukemia (ATLL) in need of systemic therapy.

NOTE: Patients with adequate archived (well-preserved, formalin-fixed) biopsy tissue remaining will be required to submit a portion for exploratory studies. This is not optional if tissue is available; however, lack of adequate tissue for exploratory studies will not preclude patients from participating.

3.1.2 Patients must have bi-dimensionally measurable disease (≥1 cm) by CT imaging. *NOTE: Patients with marrow-only disease <u>are eligible</u>; response for these patients will be assessed by repeat bone marrow biopsy.*

3.1.3 Patients must fit into one of the following categories:

- Age ≥ 18 years to < 60 years with a cumulative illness rating scale (CIRS) score ≥ 6 OR deemed ineligible for cytotoxic chemotherapy by the treating investigator (see Appendix A for CIRS scoring[42])
- ≥ 60 years

3.1.4 Patients must have adequate organ and marrow function (documented within 14 days prior to registration) as outlined below:

System	Laboratory Values
Hematologic	
ANC	≥ 750/mcl
Hemoglobin	≥ 8 g/dl
Platelets	≥ 50,000/mcl
Hepatic	
Total Bilirubin	≤ 2x upper limit normal (ULN)
AST (SGOT) and ALT (SPGT)	≤ 3x ULN
Renal	
Creatinine Clearance	≥ 30 mL/min
See Appendix D to reference the Cockgroft-Gault equation for calculating creatinine clearance.	

3.1.5 Patients must have an ECOG performance status ≤ 2 (see Appendix B).

3.1.6 All patients must agree to use effective contraception while on study, and all patients must agree to undergo counseling sessions every 28 days about pregnancy precautions and risks of fetal exposure.

Females of childbearing potential (FCBP) must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control: one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before starting lenalidomide, during lenalidomide therapy, during dose interruptions, and for at least 28 days following discontinuation of lenalidomide therapy (refer to the patient resources materials or http://www.revlimidrems.com for more information).

Males receiving lenalidomide must agree to use a latex condom during any sexual contact with FCBPs even if they have undergone a successful vasectomy.

NOTE: A FCBP is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- *Has not undergone a hysterectomy or bilateral oophorectomy*
- *Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).*

FCBP should be referred to a qualified provider of contraceptive methods, if needed.

3.1.7 FCPB must have a negative urine or serum pregnancy test within 7 days prior to registration, and be willing to adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.
NOTE: Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.8 Patients must be free of any prior malignancies for ≥1 year at the investigator's discretion.
NOTE: The exception to this would be currently treated squamous cell and basal cell carcinoma of the skin, carcinoma in situ of the cervix, breast, or bladder, or surgically removed melanoma in situ of the skin (stage 0) with histologically confirmed free margins of excision.

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

3.1.10 Patients must have the ability to understand and the willingness to sign a written informed consent prior to registration.

3.2 Exclusion Criteria

3.2.1 Patients with a diagnosis of any of the following are not eligible:
- Anaplastic large cell lymphoma, ALK-positive
- Anaplastic large-cell lymphoma, primary cutaneous type
- Precursor T-lymphoblastic lymphoma/leukemia
- Mycosis fungoides/Sezary syndrome (except transformed MF)
- NK-cell leukemia
- T-cell granular lymphocytic leukemia
- T-cell prolymphocytic leukemia.

3.2.2 Patients must not have received prior systemic therapy for PTCL (except for corticosteroids, which are permitted to treat lymphoma for 10 or fewer days at any dose; no washout period required in this case as long as they discontinue prior to starting study therapy).
NOTE: Corticosteroids are permitted on study for treatment of any condition other than PTCL.
NOTE: Topical treatment may have been given for prior existence of cutaneous lymphoma that has since become systemic PTCL. However, these topical therapies should be stopped at time of registration.

3.2.3 Patients who received chemotherapy (including monoclonal antibodies) or radiotherapy, administered for any condition, ≤28 days prior to registration are not eligible.

3.2.4 Patients who have received any other HDAC inhibitors or IMID agents for any reason are not eligible.

3.2.5 Patients receiving ongoing treatment with any other investigational agents are not eligible.

3.2.6 Patients receiving concurrent immunosuppressive medications post-transplant (at the time of registration) are not eligible.

3.2.7 Patients with known CNS (central nervous system) involvement of lymphoma are not eligible.

3.2.8 Patients who have an uncontrolled intercurrent illness including, but not limited to any of the following are not eligible:
- ongoing or active infection
- symptomatic congestive heart failure
- unstable angina pectoris
- cardiac arrhythmia
- psychiatric illness/social situations that would limit compliance with study requirements.

3.2.9 Patients with a known HIV infection are not eligible.

3.2.10 Patients who are pregnant or actively nursing an infant are not eligible.

3.2.11 Patients with a QT interval > 480 msec (using the Bazett's formula) ≤28 days prior to registration are not eligible.

4.0 Treatment Plan

Patients will be treated in cycles of 28 days (±3 days). Patients will receive romidepsin (at a dose of either 10 or 14 mg/m^2 – see 4.1.1 for details) IV on days 1, 8, and 15 as well as lenalidomide 25 mg PO daily on days 1- 21 of each cycle. Treatment may continue for one year or until disease progression or unacceptable toxicity. Patients who do not achieve a response of PR or better should continue to be treated only if they have SD (i.e., not PD), and if they do not have other options available that would present a more favorable risk/benefit ratio. Clinical suspicion of progressive disease (PD) or loss of response should be investigated radiographically (or by repeat bone marrow biopsy for marrow-only disease), and if confirmed, will result in removal from active therapy; such patients will remain in study follow up. In this case, it is strongly recommended that investigators consider early initiation CHOP or similar chemoimmunotherapy (off trial).

Treatment will be based on weight at baseline. Dosing should only be modified if the patient's weight has changed by more than 10% from baseline or the BSA has changed more than 5%.

It is intended that all treatments will be administered on an outpatient basis. However, treatment can be initiated during hospitalization (i.e., for newly-diagnosed patients), and can continue during unforeseen hospitalizations, but only at the discretion of the local primary investigator (PI).

4.1 Treatment Dosage & Administration

4.1.1 Romidepsin

Romidepsin will be administered IV on days 1, 8, and 15 of each 28-day cycle. Initially, romidepsin will be given at a dose of 10 mg/m^2; patients who tolerate 2 or more cycles (or 6 total doses) at 10mg/m^2 *may be escalated* to 14 mg/m^2 for later cycles if the following criteria are met: a) patient *has not* achieved a CR, and b) patient *has not* experienced a drug-related grade 3-4 AE. If the treating-investigator wishes to escalate a patient that has experienced > grade 3 treatment-related AEs, the QAM must be notified and DSMC approval granted prior to escalation. Patients who are escalated to 14 mg/m^2 may be de-escalated back to 10 mg/m^2 at the discretion of the treating investigator, but must remain at that dose for the duration of study treatment (i.e. may not be re-escalated to 14 mg/m^2). All changes in dosing should be clearly documented in the patients' medical records.

On days where romidepsin is given, it does not matter whether administration occurs before or after oral lenalidomide. Infusion should occur over a span of approximately 4 hours.

Approximately 30 minutes prior to each infusion of romidepsin, it is recommended that patient be given premedication with Zofran 16 mg IVPB and dexamethasone 10 mg IVPB (or equivalent per treating investigator's discretion).

4.1.2 Lenalidomide

Lenalidomide will be given orally (PO) at a dose of 25 mg daily on days 1-21 of each 28 day cycle. NOTE: The dose and schedule should be adjusted in patients with moderate or severe renal impairment who are enrolled on the study (creatinine clearance < 60 mL/min). Please refer to Table 1b below for details. Lenalidomide should be taken at approximately the same time each day (preferably in the morning) with water. Lenalidomide capsules may be taken with or without food. Patients will be instructed to not crush, chew or open capsules. Only enough pills for 1 cycle may be dispensed at one time (prior to the start of each cycle). On days where patients will have romidepsin infusion, it does not matter whether lenalidomide is taken before or after the IV infusion.

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 (i.e. patients should not take 2 doses the following day). Patients will be given a mediation diary on which to record all doses taken, missed, or skipped. This diary will be reviewed with study staff during visits prior to the start of each new cycle (before medication for upcoming cycle is dispensed).

4.1.3 Treatment regimen & supportive therapies

Table 1 below summarizes the treatment regimen and recommended supportive therapies for patients on this trial.

Table 1a: Treatment Regimen

Agent	Recommended Premedications[1]	Dose	Route	Schedule[3]	Duration
Romidepsin[2]	30 min prior: 5-HT3 receptor antagonist[4] Dexamethasone 10 mg IVPB	10 mg/m^2	IV	Days 1, 8, 15	1 year or until POD
		14 mg/m^2	IV	Days 1, 8, 15	1 year or until POD
Lenalidomide	None	25 mg[5]	po	Daily Days 1-21[5]	1 year or until POD

[1]Premedication protocol is for romidepsin infusions and includes recommended agents and doses; similar alternate medications may be given at the discretion of the treating investigator.
[2]The parameters specified in the shaded boxes represent optional dose increase if patient tolerates 2 or more cycles (6 total doses) at 10 mg/m^2
[3]Each cycle will be 28 days; romidepsin infusions should occur within ±3 days of day 1, and within +3 days of days 8 and 15.
[4]The recommended agent/dose is Zofran 16 mg IVPB or equivalent.
[5]The dose and schedule of lenalidomide should be adjusted for patients with moderate or severe renal impairment, as detailed in Table 1b below.

Table 1b: Lenalidomide Dose Adjustments for Patients with Renal Impairment

Category	Renal Function	Dose and Schedule
Moderate	Creatinine clearance 30-60 ml/min[1]	10 mg daily (Days 1-21)
Severe	Creatinine clearance < 30 ml/min (not requiring dialysis)[1]	15 mg every other day (Days 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, and 21)

[1] Creatinine clearance (CrCl) will be measured and calculated prior to initiating each cycle as described in the Study Procedures Table in Section 5.0. (Refer to Appendix D for instructions on calculating CrCl). The dose of lenalidomide will be adjusted per Table 1b. Any questions regarding dose calculations/adjustments should be directed to the **Lead PI**.

4.2 Toxicities, Dosing Delays, and Dose Modifications

All patients receiving at least one treatment on this protocol will be evaluable for toxicity endpoints. Each patient will be assessed for the development of toxicity according to the Time and Events Table (See Section 5). Toxicity will be assessed according to the NCI-CTCAE v 4.03. Dose adjustments should be made according to the system showing the greatest degree of toxicity. Toxicity should be attributed to one study drug whenever possible. Modifications/delays may apply to only the drug which caused toxicity, or both if appropriate. If lenalidomide and/or romidepsin are dose-reduced, they may not be re-escalated (unless clinically indicated and after discussion with the PI). If study drug is delayed more than 21 days (1 treatment cycle), treatment may be discontinued after discussion with the PI.

Refer to Table 2 below for dose modification instructions. Additionally, **with PI approval**, dose modifications (interruptions and reductions) may be permitted for any grade AE deemed intolerable by the patient, or per treating investigator discretion (with PI approval), if thought to be in the best interest of the patient.

Please also refer to sections of this protocol that contain more detailed information on the potential adverse events and risks associated with each agent (Sections 1.2.2 and 1.3.2). Doses reduced per protocol due to occurrence of adverse events are not counted as missed doses.

4.2.1 Pregnancy

Female patients who become pregnant, are suspected to be pregnant, or have a positive pregnancy test while on lenalidomide must discontinue study treatment immediately. If the female partner of a male patient becomes pregnant, the male patient taking lenalidomide should notify the investigator, and the pregnant partner should be advised to call their healthcare provider immediately. See section 7.2.6 for pregnancy reporting requirements.

Table 2: Non-Hematologic Drug-Related Toxicity Dose Delays/Reductions

CTCAE v 4.03 Grade	Romidepsin[1,3]	Lenalidomide[1,3]
0-2	No change from original starting dose	No change from original starting dose *Exception: Any grade of blistering rash requires lenalidomide discontinuation.*
3-4	Hold until resolved to ≤ Grade 1, then dose reduce 1 level[2]	Hold until resolved to ≤ Grade 1, then resume at same dose, with the following exceptions: • *Grade 3 non-blistering rash or neuropathy*: Hold lenalidomide and follow weekly. If the toxicity resolves to ≤ Grade 1 (Grade 2 for rash) prior to Day 21 of the current cycle, reduce dose by 5 mg and restart through Day 21 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose by 5 mg at the start of the next cycle. Omitted doses are not made up. • *Grade 4 non-blistering rash or neuropathy, any grade blistering rash*: Discontinue lenalidomide. • *Grade 3 or 4 tumor lysis syndrome*: Hold until resolved to ≤ Grade 1, then reduce dose by 5 mg and resume. • *Grade 3 or 4 tumor flare*: Hold dose and start corticosteroids, NSAIDs, and/or narcotics. Once toxicity resolves to ≤ Grade 1, reduce dose by 5 mg and resume.
2nd or 3rd episode of 3	Hold until resolved to ≤Grade 1, then dose reduce 1 level[2]	Hold until resolved to ≤ Grade 1, then reduce dose by 5 mg
Any recurrence of 4	Remove from trial therapy	Remove from trial therapy

[1] Toxicity should be attributed to one study drug whenever possible. Modifications/delays may apply to only the drug which caused toxicity, or both if appropriate.
[2] Romidepsin dose reductions: 1 level dose reduction of 14 mg/m^2 to 10 mg/m^2 or dose reduction of 10 mg/m^2 to 8 mg/m^2.
[3] Additionally, **with PI approval**, dose modifications (interruptions and reductions) may be permitted for any grade AE deemed intolerable by the patient, or per treating investigator discretion (with PI approval), if thought to be in the best interest of the patient.

Table 3: Hematologic Drug-Related Toxicity Dose Delays/Reductions

CTCAE v 4.03 Grade	Romidepsin[1,3]	Lenalidomide[1,3]
0-2	No change from original starting dose	No change from original starting dose
3-4 (neutropenia, thrombocytopenia, and/or anemia)	Hold until ANC ≥ $1.5x10^9$/L and/or platelet count ≥$75x10^9$/L or baseline, restart at prior dose	Hold until resolved to ≤ Grade 1, then resume at same dose
4 (febrile (≥38.5°C) neutropenia, anemia, and/or thrombocytopenia requiring transfusion)	Hold until cytopenia returns to ≤ Grade 1 or baseline, dose reduce by 1 level[2]	Hold until resolved to ≤ Grade 1, then resume at same dose
2nd episode of grade 3-4	Hold until ANC ≥ $1.5x10^9$/L and/or platelet count ≥$75x10^9$/L or baseline, dose reduce by 1 level[2]	Hold until resolved to ≤ Grade 1, then reduce dose by 5 mg
3rd episode of grade 3-4	Remove from trial	Remove from trial

[1] Toxicity should be attributed to one study drug whenever possible. Modifications/delays may apply to only the drug which caused toxicity, or both if appropriate.
[2] Romidepsin dose reductions: 1 level dose reduction of 14 mg/m^2 to 10 mg/m^2 or dose reduction of 10 mg/m^2 to 8 mg/m^2.
[3] Additionally, **with PI approval,** dose modifications (interruptions and reductions) are permitted for any grade AE deemed intolerable by the patient, or per treating investigator discretion (with PI approval), if thought to be in the best interest of the patient.

4.3 Concomitant Medications/Treatments

NOTE: No other treatment modalities or procedures are required as part of the study treatment. Any patient receiving radiation therapy and/or surgery related to progression of malignancy will be removed from protocol therapy. In addition, any patient that subsequently undergoes stem cell transplant will be removed from protocol therapy.

4.3.1 Recommended concomitant medications include:

- 5-HT3 receptor antagonist (such as Zofran 16 mg IVPB or equivalent dose) prior to romidepsin infusions
- Dexamethasone 10 mg IVPB (or similar) prior to romidepsin infusions

4.3.2 Permitted concomitant medications:

- Symptomatic treatment as needed for nausea, vomiting, and/or diarrhea, including 5-HT3 antagonists, corticosteroids, benzodiazepines, and anti-motility agents
- Topical and systemic treatment for rash, including corticosteroids.
- Hormonal birth control medications.
- Concurrent antiviral therapy for HBV surface antigen positivity.
- Corticosteroids are permitted for any indication other than to treat lymphoma
- Transfusions and growth factor are permitted at physician discretion and per institutional guidelines.

4.3.3 Prohibited concomitant medications and treatments:

- Concurrent chemotherapy, radiotherapy, or other investigational agents.

NOTE: Radiotherapy is permitted to treat a single non-target lesion for symptom control.

- Corticosteroids intended to treat lymphoma *(NOTE: There is no washout for prior corticosteroid treatment of lymphoma, however patients may not have received such corticosteroids for >10 days)*
- CYP3A4 inducers (see appendix C)
  Note: As this list is constantly evolving, if a medication is incorrectly documented as prohibited in this protocol, documentation from the site pharmacist to the contrary will be acceptable for the purposes of registration.
- High risk QTc prolonging agents in the case of patients who have developed QTc prolongation on study (see appendix C)

4.4 Duration of Therapy & Early Withdrawal

Treatment may continue for up to one (1) year or until any of the following occur, resulting in early withdrawal from study treatment (or in some cases withdrawal from the study as a whole):

- disease progression
- inter-current illness that prevents further administration of treatment
- unacceptable toxicity
- patient decides to withdraw from study treatment (or study as a whole)
- general or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the treating investigator

Note: Patients who have not achieved PR or CR after 4 cycles should continue to be treated on the current protocol only if they have SD (i.e., not PD), AND if they do not have other options available that would present a more favorable risk/benefit ratio.

Patients will be removed (withdrawn) from study therapy for any of the criteria listed above. The PI and the Quality Assurance Monitor (QAM) at NU is to be notified of such events; the reason(s) for removal and the date the patient was removed are to be documented in the appropriate electronic case report form (eCRF). The patient should be followed as described below in Section 4.5.

Patients who withdraw consent from the study as a whole will be noted to have withdrawn from both treatment and any further follow-up.

4.5 Duration of Follow Up

Once patients are off treatment for any reason, they will have a final off-treatment visit approximately 30 days post-last dose of study therapy. Thereafter, they will be followed with at least one clinic visit every 3 months for up to 1 year from start of treatment, then every 6 months up to 3 years from start of treatment (or until death, whichever occurs first). Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

4.6 Patient Replacement

Any patient who is registered to the study and then withdrawn without receiving any study treatment may be replaced. Any patient who completes fewer than 2 total cycles of therapy and is withdrawn for any reason except POD or toxicity will still be considered evaluable for toxicity endpoints but will not be evaluable for efficacy endpoints; for the purpose of efficacy endpoints, another patient may be added to the accrual goal with the approval of the Data and Safety Monitoring Committee (DSMC) at NU.

4.7 Suspension of Accrual

This study will be monitored in accordance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. The DSMC will review all toxicity data, and in the event of an excessive toxicity, the DSMC may require suspension of accrual.

5.0 Study Procedures

Table 4: Time and Events

Study Period	Baseline	On Treatment[10] (1 cycle = 28 days)			Off Treatment Visit	Follow-Up[14]
Procedures & Assessments	**Screening[9]**	**Day 1 of Each cycle[11] (±3 days)**	**Day 8 and 15 of Each cycle[11] (-1 to +3 days)**	**Response Assessments**	**28-Days Post Last Dose[13]**	**Survival Status**
Informed consent	X					
Medical history	X					
Physical exam[1]	X	X			X	X
ECOG status	X	X			X	X
Imaging[2, 12]	X[2]			X[12]	X	
Hematology Labs[18, 9]	X	X	X			
Chemistry Labs[3, 9]	X	X	X			
Pregnancy test[4]	X[4]		X[19]			
EKG[5]	X					
Bone marrow biopsy[17]	X			X	X	
Tissue for research[6]	X					
REMS® program[7]	X	X				
Adverse events[8]	X	X			X	
Concomitant medications	X	X				
Creatinine Clearance Check[20]		X				
Lenalidomide treatment		X[15]				
Romidepsin treatment		X[16]				

[1] Physical exam should include vitals (blood pressure, heart rate, temperature, respirations), height (baseline only), and weight.

[2] Tumor assessment with diagnostic quality CT (chest, abdomen, pelvis; neck if clinically indicated) with or without contrast imaging within 28 days prior to registration; in addition, NM PET/CT is not required but encouraged prior to starting therapy (with or without contrast).

[3] Lactate dehydrogenase (LDH), magnesium (Mg) and comprehensive metabolic panel (CMP) including albumin, alkaline phosphatase, ALT(SGPT), AST(SGOT), BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin.

[4] Either urine or serum pregnancy test required within 7 days prior to registration for WOCBP; additional pregnancy testing required throughout the treatment period as outlined in the REMS® program.

[5] EKG required within 28 days of registration (for eligibility) and then as clinically indicated thereafter.

[6] If available, archived tissue from a previous biopsy is required for exploratory studies (patients who do not have available/adequate tissue may still enroll). See Section 9 for details.
[7] All study participants must be registered into the mandatory REMS® program, and be willing and able to comply with the requirements.
[8] SAE's will be collected from the time of consent until 30 days after treatment discontinuation.
[9] All screening procedures are required within 28 days prior to registration unless otherwise indicated. Chemistry and Hematology labs are required within 14 days of registration.
[10] Cycle 1 to begin within 14 days after registration; Treatment will continue up to 1 year unless any of the criteria in Section 4.4 are met.
[11] One cycle = 28 days ±3 days for start of cycle. Day 8 and 15 each have a window of -1 to +3 days
[12] Response will be assessed with diagnostic quality CT (chest, abdomen, pelvis; neck if clinically indicated) with or without contrast imaging after cycles 3 and 6 (±7 days), and then every 6 months (±7 days). Response may be assessed more often if clinically indicated. Although not required, we encourage the use of NM PET/CT performed at baseline and repeated along the same schedule throughout (with or without contrast).
[13] All patients should have a visit approximately 28 days (+/- 7 days) post-last dose of study treatment.
[14] Once off treatment, patients will be followed clinically every 3 months (±7 days) for up to 1 year from start of study treatment, then every 6 months (±14 days) up to a total of 3 years (or until death, whichever comes first) for survival endpoints.
[15] Lenalidomide will be given at a dose of 25 mg PO daily on days 1-21 of each cycle (followed by a 7 day break prior to the start of the next cycle). Patients will be given a medication diary to complete, which will be reviewed with a member of the study team at visits.
[16] Romidepsin will be administered intravenously on days 1, 8, and 15 of each cycle. The dose for the first 2 cycles (6 doses total) will be 10 mg/m^2; in some cases, patients may be escalated to a dose of 14 mg/m^2 for remaining cycles (see Section 4.1.1 for specific criteria). A window is allowed for romidepsin infusion visits (within ±3 days of day 1, and within -1 to +3 days of days 8 and 15).
[17] Bone marrow biopsy will be done within 90 days of registration if clinically indicated, per treating physician's discretion. In patients with known bone marrow involvement at baseline, a bone marrow biopsy will be performed after the patient achieves a CR.
[18] Complete blood count with differential will be performed weekly for the first 2 cycles, every other week for cycles 3-6, and at the start of each cycle thereafter.
[19] Day 15 of each cycle only.
[20] Creatinine clearance will be measured and calculated prior to initiating each cycle (Refer to Appendix D for instructions on calculating creatinine clearance). The dose of lenalidomide will be adjusted per Table 1b. Any questions regarding dose calculations/adjustments should be directed to the **Lead PI**. Refer to Section 4.1.3 for additional information.

6.0 Assessment of Endpoints

6.1 Toxicity Endpoints

The frequency and severity of adverse events will be assessed once per cycle according the NCI-CTCAE version 4.03. All patients who receive at least one dose of either study drug will be evaluable for toxicity endpoints.

6.2 Efficacy Endpoints

Response and progression will be evaluated using the 2007 Revised Response Criteria for Malignant Lymphoma (RRCML) as defined by Cheson, et al.[43] See Table 5 for a summary of the follow definitions:

6.2.1 Complete Remission (CR)

CR requires the following:

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

1. Typically FDG-avid lymphoma: in patients with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

   Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤ 1.0cm in their short axis after treatment.

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

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

6.2.2 Partial Response (PR)

PR requires the following:

1. At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

2. No increase should be observed in the size of other nodes, liver, or spleen.

3. Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter.

4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.

5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B-cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.

6. No new sites of disease should be observed.

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

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

6.2.3 Stable Disease (SD)

SD requires the following:

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

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

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

6.2.4 Relapsed Disease (after CR) or Progressive Disease (after PR or SD)

1. Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes ≤ 1.0 x ≤ 1.0 cm will not be considered as abnormal for relapse or progressive disease.

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

3. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic

or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥ 50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.

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

5. Lesions should be PET positive if observed in a typical FDG avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be.

Table 5: Response and Progression from RRCML adopted from Cheson, et al.

Table 2. Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

6.2.5 Progression Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression. PFS will be reported at 1 and 3 years after the start of treatment.

6.2.6 Overall Survival

Overall survival (OS) is defined as the duration of time from start of treatment to time of death, up to three years from the start of study treatment. OS will be reported at 1 and 3 years after the start of treatment.

6.2.7 Duration of Response

6.2.7.1 **Duration of overall response:**

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

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

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

6.2.8 Time to first cytotoxic chemotherapy
Time to first cytotoxic chemotherapy (TTFCC) is defined as the time from start of study treatment to time of first dose of anti-neoplastic cytotoxic chemotherapy that is administered to treat lymphoma. This does not include corticosteroids, antivirals, or chemotherapeutic agents used for either non-neoplastic diseases or other malignant processes (not lymphoma).

6.3 Exploratory Endpoints

6.3.1. Evaluate the use of NM PET/CT vs. CT imaging in PTCL.

The endpoint will be a review of the utilized imaging modalities during treatment as a tool of response assessment. All patients will have CT imaging for enrollment and response assessment time points as outlined in Table 4. When both imaging modalities are chosen for a patient (per treating investigator's discretion), response assessment will be compared.

6.3.2 Validate a new prognostic model for newly diagnosed PTCL.[41]

The endpoint will be clinical biomarkers including age, race, histology, and stage as obtained at enrollment. A points based system will be used to correlate with recently developed prognostic model.

6.3.3 Investigate the tumor immunohistochemical profile to identify potential biomarkers associated with prognosis and treatment response.

The endpoint we be comparison of immunohistochemical profiles with treatment outcomes on archived tissue samples. A tumor microarray on paraffin-embedded tissue samples will be constructed for comparison. Tissue will be obtained from patients who have tissue available at baseline for these studies. If tissue is not available, it will not preclude patients from participating. However, for those with tissue available, it is a mandatory component of participation.

7.0 Adverse Events

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. All adverse events will be reported on the appropriate eCRF. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline
- any abnormal laboratory values have returned to baseline
- there is a satisfactory explanation other than the study drug for the changes observed
- death

7.2 Definitions & Descriptions

7.2.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

Recording of AEs should be done in a concise manner using standard, acceptable medical terms. In general, AEs are not procedures or measurements, but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement. Preexisting conditions that worsen in severity or frequency during the study should also be recorded (a preexisting condition that does not worsen is not an AE). Further, a procedure or surgery is not an AE; rather, the event leading to the procedure or surgery is considered an AE.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the AE whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, “hepatitis” and not “elevated liver function tests” should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an AE, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

7.2.2 Severity of Adverse Events

All AEs will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE v4.03 is available at http://ctep.cancer.gov/reporting/ctc.html.

If no CTCAE grading is available, the severity of an AE is graded as follows:

1. Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
2. Moderate (grade 2): the event causes discomfort that affects normal daily activities.
3. Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
4. Life-threatening (grade 4): the patient was at risk of death at the time of the event.
5. Fatal (grade 5): the event caused death.

7.2.3 Serious Adverse Events

All SAEs, regardless of attribution, occurring during the study (from the time of consent) or within 30 days of the last administration of study drug must be reported to the PI upon discovery or occurrence. Additional expedited or routine reporting may be required, depending on the nature of the SAE (as outlined below). A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that:

1. Results in death.
   If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
2. Is life-threatening.
   The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

3. Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
4. Results in persistent or significant disability or incapacity.
5. Is a congenital anomaly/birth defect.
6. Is an important medical event.
   Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
   For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

7.2.4 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO)

A UPIRSO includes events that are unanticipated in terms of nature, severity, or frequency, place the research subject or others at a different or greater risk of harm, and are deemed to be related or possibly related to participation in the study.

A UPIRSO is a type of SAE that includes events that meet ALL of the following criteria:

- is unexpected (in terms of nature, severity, or frequency) given the procedures described in the research protocol documents (e.g., the IRB-approved research protocol and informed consent document) and the characteristics of the human subject population being studied
- is related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places human subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized, even if no harm has actually occurred.

7.2.5 Attributions

Determine whether the adverse event is related to the protocol therapy. Adverse events should be attributed to one study drug whenever possible.
Attribution categories are as follows:

1. Definite – The AE is clearly related to the study treatment.
2. Probable – The AE is likely related to the study treatment.
3. Possible – The AE may be related to the study treatment.
4. Unrelated – The AE is clearly NOT related to the study treatment.

7.2.6 Pregnancy

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 IP, or within 30 days of the subject's last dose, are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female subject may be referred to an obstetrician-gynecologist (not necessarily one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

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, or approved equivalent 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 OTHERAPPROPRIATE METHOD, WITHIN 24 HOURS OF THE INVESTIGATOR'S KNOWLEDGE OF THE EVENT USING THE NU 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 NU SAE Report Form.

7.2.6.1 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.

7.2.7 Overdose

Overdose, as defined for this protocol, refers to romidepsion and lenalidomide dosing only.

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of lenalidomide or romidepsin 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

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.

7.3 Expedited Reporting of SAEs

7.3.1 Reporting to the QAM/DSMC:

All SAEs must be reported to the assigned Quality Assurance Monitor (QAM) within 24 hours of becoming aware of the event (croqualityassurance@northwestern.edu). Completion of the NU CTO SAE Form is required. The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:

- Protocol description and number
- Patient's Identification Number
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics

- Hospital Discharge Summary (if available)
- Country of incidence

All SAEs will be reported to, and reviewed by, the DSMC per the DSMP.

7.3.2 Reporting to the NU IRB

The following information pertains to the responsibilities of the lead site (Northwestern University). Additional participating sites should follow their local IRB guidelines for reporting to their local IRBs.

- Any death of an NU subject that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the NU IRB within 24 hours of notification.
- Any death of a non-NU subject that is unanticipated and at least possibly related and any other UPIRSOs will be reported to Northwestern University and to the NU IRB within 5 working days of notification.
- Information pertaining to an NU subject that fits into any of the categories listed on the Reportable New Information page will be reported to the NU IRB within 5 business days of knowledge or notification.

7.3.3 Reporting to the FDA:

In the event that an IND is granted for this study, the following notifications will be handled by the NU QAM (if the protocol is determined to be IND exempt, this section will not apply):

- The FDA will be notified within 7 calendar days of any SAE that is associated with study treatment, is unexpected, and is fatal or life-threatening.
- The FDA will be notified within 15 calendar days of any SAE that is associated with the study treatment, unexpected, and serious but not fatal or life-threatening. This includes any previous SAEs that were not initially deemed reportable, but are later determined to meet the criteria for reporting (i.e. by the DSMC).

All other SAEs will be reported on an annual basis as part of the annual FDA report.

7.3.4 Reporting to Celgene

Any SAE that occurs in a study subject must be reported to Celgene within 24 hours of first awareness of the event. The NU CTO SAE form will be used for reporting. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product, if available. 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-XX-PI-###), when available, 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 or email confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records. The Principal Investigator will assist in investigating any SAE and will provide any follow-up information reasonably requested by Celgene. The assigned study coordinator will facilitate all reporting to Celgene Drug Safety and email QA a copy of the report upon completion. Celgene Drug Safety can be notified at:

Celgene Corporation
Global Drug Safety and Risk Management
556 Morris Avenue
Building S12

Summit, New Jersey 07901
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

7.3.5 Routine Reporting

All other adverse events, such as those that are expected, or are unlikely or definitely not related to the study participation, are to be reported on a regular basis to the assigned QAM for the study in accordance with the Robert H. Lurie Comprehensive Cancer Center's Data Safety Monitoring Plan (DSMP). These will be reviewed by the Data and Safety Monitoring Committee on an on-going basis.

7.4 Stopping Rules

The study will be stopped early if there are 6 or fewer responses (CR or PR at the 3 month response assessment time point) in the first 12 patients, as this will be considered evidence of inadequate efficacy. Regardless of overall accrual status, individual patients (enrolled in the first stage) who demonstrate clinical benefit (SD or better) may continue to receive study treatment up to 1 year in accordance with the duration of therapy criteria (see Section 4.4). In addition, the Data Safety Monitoring Committee will monitor the study in accordance with the DSMP and may suspend or close the study to accrual at any point if required, as out lined in the DSMP.

8.0 Drug Information

8.1 Romidepsin

Refer to the romidepsin package insert for complete information.

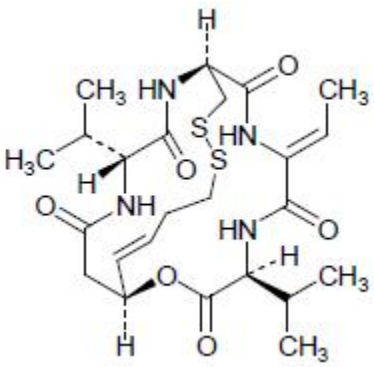
8.1.1 Other Names

Istodax; Romidepsin for Injection; FK228; depsipeptide

8.1.2 Classification

Romidepsin is a histone deacetylase (HDAC) inhibitor indicated for the treatment of CTCL in patients who have received at least 1 prior systemic therapy. At room temperature, romidepsin is a white powder and is described chemically as (1*S*,4*S*,7*Z*,10*S*,16*E*,21*R*)-7-ethylidene-4,21-bis(1methylethyl)-2-oxa-12,13-dithia-5,8,20,23-tetraazabicyclo[8.7.6]tricos-16ene-3,6,9,19,22-pentone. The empirical formula is C24H36N4O6S2.

The molecular weight is 540.71 and the structural formula is:



8.1.3 Mode of Action

Romidepsin is a unique bicyclic depsipeptide originally isolated from *Chromobacterium violaceum* strain 968. 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. *In vitro*, romidepsin causes the accumulation of acetylated histones, and induces cell cycle arrest and apoptosis of some cancer cell lines with IC50 values in the nanomolar range. The mechanism of the antineoplastic effect of romidepsin observed in nonclinical and clinical studies has not been fully characterized.

8.1.4 Supply, Storage, and Stability

Romidepsin is supplied as a kit including a sterile, lyophilized powder in a single-use vial containing 10 mg of romidepsin and 20 mg of the bulking agent, povidone, USP. In addition, each kit includes one sterile Diluent vial containing 2 mL (deliverable volume) of 80% propylene glycol, USP, and 20% dehydrated alcohol, USP.

NDC 46026-983-01: ISTODAX® KIT containing 1 vial of romidepsin, 10 mg and 1 vial of diluent for romidepsin, 2 mL per carton.

The carton must be stored at 20° to 25°C, excursions permitted between 15° to 30°C. (See USP Controlled Room Temperature.) Keep out of reach of children.

8.1.5 Preparation, Protocol Dose, and Administration

Romidepsin should be handled in a manner consistent with recommended safe procedures for handling cytotoxic drugs.

Romidepsin must be reconstituted with the supplied diluent and further diluted with 0.9% Sodium Chloride Injection, USP before intravenous infusion.

Each 10 mg single-use vial of romidepsin must be reconstituted with 2 mL of the supplied Diluent. With a suitable syringe, aseptically withdraw 2 mL from the supplied Diluent vial, and slowly inject it into the romidepsin for injection vial. Swirl the contents of the vial until there are no visible particles in the resulting solution. The reconstituted solution will contain romidepsin 5 mg/mL. The reconstituted romidepsin solution is chemically stable for at least 8 hours at room temperature. However, whenever possible, drug should be prepared within 4 hours of dose administration.

Extract the appropriate amount of romidepsin from the vials to deliver the desired dose, using proper aseptic technique. Before intravenous infusion, further dilute romidepsin in 500 mL 0.9% Sodium Chloride Injection, USP.

Infuse over 4 hours. Patients will receive romidepsin (at a dose of either 10 or 14 mg/m^2 – see 4.1.1 for details) IV on days 1, 8, and 15 of each cycle.

The diluted solution is compatible with polyvinyl chloride (PVC), ethylene vinyl acetate (EVA), polyethylene (PE) infusion bags as well as glass bottles. Romidepsin is stable for 24 hours at room temperature after reconstitution per package insert

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

8.1.6 Availability & Drug Ordering

Romidepsin will be provided to research subjects for the duration of their participation in this trial by the Celgene Corporation at no charge to them or their insurance providers. Romidepsin ordering instructions are available at the Northwestern Oncology Trial Information System (NOTIS) website -contact croqualityassurance@northwestern.edu for any issues/concerns.

8.1.7 Side Effects

The most common side effects of romidepsin include nausea, fatigue, infections, vomiting, anorexia, anemia, thrombocytopenia, ECG T-wave changes, neutropenia, and lymphopenia.

8.1.8 Nursing Implications

Implement appropriate cardiovascular precautions, such as the monitoring of electrolytes and ECGs at baseline and as clinically indicated thereafter.

8.2 Lenalidomide

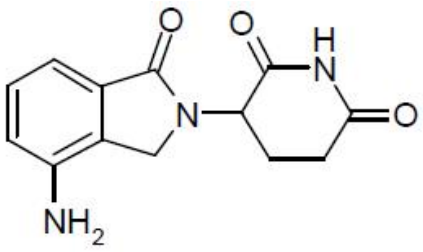
Refer to the lenalidomide package insert for complete information.

8.2.1 Other Names

Revlimid®, IMiD CC-5013

8.2.2 Classification

Immunomodulatory drug with antiangiogenic and antineoplastic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione. The empirical formula for lenalidomide is C13H13N3O3, and the gram molecular weight is 259.3. It has the following chemical structure:



8.2.3 Mode of Action

Lenalidomide is a thalidomide analogue indicated for the treatment of multiple myeloma (MM), myelodysplastic syndrome (MDS) associated with deletion 5q, and mantle cell lymphoma (MCL). Lenalidomide has been used successfully to treat both inflammatory disorders and malignancies. Lenalidomide has been shown to induce direct anti-tumor effects, alter the tumor microenvironment, and play a role in immunomodulatory activity.

Lenalidomide inhibits proliferation and induces apoptosis of certain hematopoietic tumor cells including multiple myeloma, mantle cell lymphoma, and del (5q) myelodysplastic syndromes *in vitro*. Lenalidomide causes a delay in tumor growth in some *in vivo* nonclinical hematopoietic tumor models including multiple myeloma. Immunomodulatory properties of lenalidomide include activation of T cells and natural killer (NK) cells, increased numbers of NKT cells, and inhibition of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes. In multiple myeloma cells, the combination of lenalidomide and dexamethasone synergizes the inhibition of cell proliferation and the induction of apoptosis.

8.2.4 Storage, Supply, and Stability

Lenalidomide is an off-white to pale-yellow solid powder. Lenalidomide is supplies as white opaque capsules imprinted “REV” on one half and “25 mg” on the other half in black ink: 25 mg bottles of 21 (NDC 59572-425-21) or 25 mg bottles of 100 (NDC 59572-425-00).

Lenalidomide should be stored away from moisture and direct sunlight and protected from excessive heat and cold. Capsules should be stored at 20°C - 25°C (68°F - 77°F); excursions permitted to 15°C - 30°C (59°F - 86°F) [See USP Controlled Room Temperature].

Care should be exercised in the handling of lenalidomide. Lenalidomide capsules should not be opened or crushed. If powder from lenalidomide contacts the skin, wash the skin immediately and thoroughly with soap and water. If lenalidomide contacts the mucous membranes, flush thoroughly with water. Procedures for the proper handling and disposal of anticancer drugs should be considered.

At the study sites, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access. Before lenalidomide is dispensed, patients must 1) have a negative pregnancy test (if applicable) and 2) be counseled about the risks associated with teratogenic agents.

8.2.5 Protocol Dose & Administration

Lenalidomide will be administered on an out-patient basis at a dose of 25 mg daily on days 1-21 of each 28-day cycle. Lenalidomide is taken by mouth with or without food. Patients should not crush, chew or open capsules. Only a supply sufficient for 1 cycle may be dispensed at one time. Investigators may not mail lenalidomide to patients.

8.2.6 Potential Drug Interactions

In vitro, lenalidomide did not significantly inhibit marker enzyme activities for CYP1A2, CYP2C9, CYP2C19, CYP2E1, or CYP3A4. In rats, no induction of any CYP450 enzymes was observed. These data suggest that lenalidomide is not likely to cause metabolic drug interactions in man.

8.2.7 Availability

Lenalidomide 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. Please see additional resource material on the Revlimid REMS® site at: http://www.revlimidrems.com.

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. Lenalidomide will be shipped directly to patients or to the clinic site for IND studies. Bottles will contain a sufficient number of capsules for one cycle of dosing. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

Lenalidomide must be ordered from Biologics, Inc., using the "*REVLIMID (Lenalidomide) Study Drug Shipment Request Form (IND STUDY)"* (see Northwestern Oncology Trial Information System [NOTIS] website). A patient must have signed consent and the REMS program requirements must be completed before the order will be filled. *Note: If Biologics receives the order by 2PM Eastern time, the lenalidomide will be shipped overnight that day.* Lendalidomide is shipped to the Investigational Pharmacy at each site. The Investigational Pharmacy dispenses the lenalidomide to the patient. Additional details will be provided prior to site activation, or by calling Biologics at 800.693.4906, or by emailing croqualityassurance@northwestern.edu.

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

Celgene will provide instructions 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.

8.2.8 Black Box Warning

WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS THROMBOEMBOLISM
See full prescribing information for complete boxed warning.

EMBRYO-FETAL TOXICITY
Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of contraception. REVLIMID is available only through a restricted distribution program called the REVLIMID REMS™ program (formerly known as the "RevAssist® program")

HEMATOLOGIC TOXICITY.
REVLIMID can cause significant neutropenia and thrombocytopenia. For patients with del 5q myelodysplastic syndromes, monitor complete blood counts weekly for the first 8 weeks and monthly thereafter.

VENOUS THROMBOEMBOLISM
Significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with multiple myeloma receiving REVLIMID with dexamethasone.

8.2.9 Nursing/Patient Implications and Monitoring requirements

1. Effective contraception must be used by patients for at least 4 weeks before beginning lenalidomide therapy, during lenalidomide therapy, during dose interruptions, and for 4 weeks following discontinuation of lenalidomide therapy. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or because the patient has been postmenopausal naturally for at least 24 consecutive months. Two reliable forms of contraception must be used simultaneously, by females, unless continuous abstinence from heterosexual sexual contact is the chosen method. Females of childbearing potential should be referred to a qualified provider of

contraceptive methods, if needed. Males receiving lenalidomide must always use a latex condom during any sexual contact with females of childbearing potential even if they have undergone a vasectomy.

2. Caution patient not to drive or use hazardous machinery until the potential sedative effects of the drug are known in the patient.
3. Caution patient to report leg swelling or shortness of breath, because of the risk of thrombosis/embolism
4. Counsel patient to report abnormal sensations in hands or feet, such as decreased sensation or dysesthesia. Paresthesias are often noted early before neuropathy develops.
5. Advise patient to immediately report rashes or fever.

Because of the embryo-fetal risk, lenalidomide is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS), the REVLIMID REMS™ program (formerly known as the "RevAssist®" program). Required components of the REVLIMID REMS™ program include the following:

- Prescribers must be certified with the REVLIMID REMS™ program by enrolling and complying with the REMS requirements.
- Patients must sign a Patient-Prescriber agreement form and comply with the REMS requirements. In particular, female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements.
- Pharmacies must be certified with the REVLIMID REMS™ program, must only dispense to patients who are authorized to receive REVLIMID and comply with REMS requirements.

Further information about the REVLIMID REMS™ program is available at http://www.revlimidrems.com or by telephone at 1-888-423-5436.

9.0 Exploratory Studies

9.1 Evaluate the use of NM PET/CT vs CT imaging in PTCL

The endpoint will be a review of the utilized imaging modalities during treatment as a tool of response assessment. All patients will have CT imaging for enrollment and response assessment time points as outlined in Table 4. When both imaging modalities are chosen for a patient (at treating investigator's discretion), response assessment will be compared.

9.2 Validate a new prognostic model for newly diagnosed PTCL.

Variables for prognosis assessment are part of the eligibility checklist including age, race (African-American vs other), histology, and stage. Variables will be assigned points to determine a prognostic score. Survival by prognostic score are separated into three categories with score = 0-1, 2, or 3-5. Points assigned are outline below:

Variable	Determinant	Reference	HR	Points Assigned
Age	>/=55	<54	1.51	1
Race	Black	All others	1.43	1
Histology	AITL	PTCL-NOS	1.19	1
	SCPTL		0.71	0
	ALCL		0.88	1
	HSTL		1.76	2
	EATL		2.32	2
	ATLL		1.34	1
	ENKTL		1.50	2
	T-LGL		0.43	0
	T-PLL		N/A	2
Stage	Distant	Local	1.79	1

9.3 Investigate the tumor immunohistochemical profile to identify potential biomarkers associated with prognosis and treatment response.

9.3.1 Technique

A tissue microarray (TMA) of paraffin-embedded lymphoid tissue biopsies of all patients will be created and analyzed. This TMA will quantify expression of multiple markers in order to determine how such markers correlate with clinical outcome. Proposed analysis includes immunohistochemistry for CD4, CD8, CD5, CD7, CD8, CD15, CD20, CD30, EBER, Ki-67, p53, TIA-1, granzyme B, TCR F1, TNF-α, IL-6, and nm23-H1.

9.3.2 Tissue Collection

Paraffin-embedded tumor samples will be collected from prior diagnostic biopsies prior to enrollment. Construction of the TMA will require 1.0 to 1.5 mm punch cores for proper analysis. Samples will be sent to the Northwestern PathCore facility. Samples from outside institutions may be sent in batches. The analysis will be conducted by our collaborators in hematopathology. Collection of tissues samples is mandatory however if sample is inadequate a repeat biopsy will not be required nor will patients be excluded from clinical trial enrollment.

10.0 Statistical Considerations

10.1 Primary Endpoint & Sample Size Calculations

The primary objective of this phase II trial will be to evaluate the efficacy of the combination of romidepsin plus lenalidomide in patients with previously untreated PTCL. The endpoint for this objective will be objective response rate (ORR), defined per Cheson criteria. Response will be assessed by imaging after cycles 3 and 6, and then every 6 months thereafter. Single agent romidepsin or lenalidomide have response rates of approximately 25% in patients with relapsed/refractory PTCL [3, 44, 45]. However, a recently presented study (unpublished) of the combination of romidepsin and lenalidomide demonstrated an objective response rate in relapsed/refractory PTCL of 50%[46]. The front-line setting has not been tested.

Due to recruitment issues, we will limit the study to n=20 evaluable patients. This will allow us to estimate the underlying true response rate with a half width of an approximate 95% confidence interval equal to 1.96x0.5/sqrt(20) = 1.96x0.11 = 0.22.

10.2 Secondary Endpoints

To evaluate the safety of the combination of romidepsin and lenalidomide, the endpoint will be the frequency and severity of toxicity events using the NCI CTCAE v 4.03. All

adverse events will be summarized as to type, severity, frequency, timing and attribution. Descriptive frequencies and proportions will be used for this analysis.

To further evaluate efficacy of the combination of romidepsin and lenalidomide, the endpoint will be progression-free survival (PFS) and overall survival (OS) at 1 and 3 years after start of treatment as well as the duration of response from start of therapy, defined per Cheson criteria. Kaplan-Meier curves will be determined for progression-free survival and overall survival and the one- and three-year point on this curve, along with 90% confidence limits. Duration of response will be summarized by descriptive statistics in responders (mean, median, range).

To evaluate the delay to cytotoxic chemotherapy, the endpoint will be time to first cytotoxic chemotherapy (TTFCC) from start of treatment. This will be summarized by descriptive statistics (mean, median, range).

10.3 Exploratory Endpoints

To evaluate the use of NM PET/CT vs CT imaging in PTCL, the endpoint will be a review of the utilized imaging modalities during treatment as a tool of response assessment. When both imaging modalities are chosen for a patient, response assessment will be compared using Kappa statistics.

To validate a new prognostic model for newly diagnosed PTCL.[41], the endpoint will be clinical biomarkers including age, race, histology, and stage as an assessment of prognosis. These factors will be related to response and survival using logistic regression and proportional hazards regression respectively.

To investigate the tumor immunohistochemical profile to identify potential, biomarkers associated with prognosis and treatment response, immunohistochemical profiles with related to treatment outcomes on archived tissue samples using the regression methods described above.

11.0 Study Management

11.1 Conflict of Interest

All investigators will follow the Northwestern University conflict of interest policy.

11.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.3 Required Documentation (for multi-site studies)

Before the study can be initiated at any external participating sites, the following documentation must be provided to the Clinical Trials Office (CTO) at NU.

- A copy of the official IRB approval letter for the protocol and informed consent
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation
- A copy of the IRB approved consent form
- Executed clinical research contract

11.4 Registration Procedures

Patients may not begin protocol treatment prior to registration. All patient registrations will be registered centrally through the Clinical Trials Office (CTO) at Northwestern University before enrollment to study. In order for registrations to be processed efficiently, staff are asked to inform the QAM of date and time that by which the patient will need to be registered. Please contact the assigned Quality Assurance Monitor (QAM) or email the QA Department (croqualityassurance@northwestern.edu) for questions regarding patient registration.

Prior to registration, eligibility criteria must be confirmed by the assigned QAM. The study coordinator will screen all subjects for potential registration via the web-based application NOTIS (Northwestern Oncology Trial Information System), which is available at: https://notis.nubic.northwestern.edu. Please note that a username and password is required to use this program, and will be provided during site activation prior to training on the NOTIS system.

BEFORE a patient can be treated on study, please complete and submit the following items to confirm eligibility and receive an identification number:

- Patient's signed and dated informed consent form (upload to NOTIS and keep original hard copy in a secure location/study chart)
- Eligibility checklist (signed and dated by the treating physician – upload to NOTIS)
- Eligibility eCRF (complete in NOTIS)
- Copy of the pathology report (upload to NOTIS)

Training on eCRF completion will be provided at the time of site activation. Please refer to the eCRF demonstration videos on the CTO website for additional instructions on registering a patient.

The QAM will review the registration, register the patient, assign a subject identification number, and send a confirmation of registration to study personnel. Registration will then be complete and the patient may begin study treatment.

11.5 Data Management and Monitoring/Auditing

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to the DSMP hyperlink for additional information). The level of risk attributed to this study requires High Intensity Monitoring, as outlined in the DSMP. The assigned Quality Assurance Monitor, with oversight from the Data and Safety Monitoring Committee, will monitor this study in accordance with the study phase and risk level. Please refer to NOTIS for additional data submission instructions.

11.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.6.1 Emergency Modifications

Investigators may implement a deviation from, or a change of the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within five business days of making the change, and the QAM must be notified within 24 hours of such change.

11.6.2 Other Protocol Deviations

All other deviations from the protocol must be reported to the assigned QAM using the appropriate form.

A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the Institutional Review Board (IRB). Protocol deviations must be reported according to the policies and procedures of the IRB of record.

An unplanned protocol variance is considered a violation and may be considered an instance of Reportable New Information (RNI) if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has compromised the rights and welfare of the research subject
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

11.7 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be initiated and maintained by the assigned Medical Writer. Requests for revisions may come from multiple sources, including but not limited to the Principal Investigator, study team, drug company, or FDA. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

All amendments will be subject to the review and approval of the appropriate local, institutional, and governmental regulatory bodies, as well as by Celgene. Amendments will be distributed by the lead institution (Northwestern) to all affiliate sites upon approval by the Northwestern University IRB.

11.8 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an

International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.9 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

11.10 Publication Policy

All potential publications and/or data for potential publications (e.g. manuscripts, abstracts, posters, clinicaltrials.gov releases) must be approved in accordance with the DSMC Data Release Policies and Processes. The assigned QAM will prepare a preliminary data set for DSMC approval no later than 3 months after the study reaches its primary completion date, as defined by ClinicalTrials.gov. This is the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated. If the investigator would like data release to be approved by the DSMC prior to when study design specifies, and/or prior to three months after a study's primary completion date, the PI must send a written request for data approval to the QAM which includes justification. Requests must be made a minimum of six to eight weeks in advance of the expected deadline. The request will be presented to the DSMC at their next available meeting. Any DSMC decisions regarding data release will be provided to the PI. If the request is approved, the QAM will present the data set to the DSMC for approval. A final, DSMC-approved dataset, as applicable, will then be released 6-8 weeks after the request was made. The investigators are expected to use only DSMC-approved data and statistical analyses any time they are disseminating trial data. The investigators must send a copy of the draft abstract/poster/manuscript to the study's biostatistician and assigned QAM to confirm that the DSMC-approved data and statistical analyses are used appropriately. Once the biostatistician and QAM gives final approval, the publication may be submitted to external publisher.

11.11 Criteria for Suspension in Accrual

The following is a list of criteria that will trigger suspension of accrual. In the even that such a suspension would occur, the Data and Safety Monitoring Committee (DSMC) would have to approve re-opening of accrual pending appropriate protocol revision (if needed):

- Interim/cumulative data for evidence of unacceptable rates and/or severity of study-related adverse events;

  Specifically, The Data and Safety Monitoring Committee at Northwestern University will analyze toxicity data every 2 weeks. After every 5 patients an interim analysis will be performed to determine whether there is excessive toxicity. These analyses will be done separately within each arm. Excessive toxicity will be defined as any grade ≥ 4 neutropenia, grade ≥ 4 thrombocytopenia, or grade ≥ 3 organ toxicity (neurologic,

pulmonary, cardiac, gastrointestinal, genitourinary, renal, hepatic, cutaneous) with ≥3 occurrences which is at least possibly related to the study regimen occurring in no more than 20%. Using a Bayesian approach with a non-informative (uniform) prior, it will be determined that there is excessive toxicity if the posterior probability of the toxicity rate being greater than 20% exceeds 80%. This will occur if there are 3 or more excessive toxicity events (as described above) out of 5 treated patients, 4 or more out of 10, 5 or more out of 15, 6 or more out of 20, 8 or more out of 25, or 9 or more out of 30. If, by 30 patients treated, the study has not been terminated for toxicity, it will continue to the goal accrual.

- Incidence of >20% of any single excessive toxicity event (grade ≥ 4 neutropenia or thrombocytopenia OR grade ≥ 3 organ toxicity - minimum 10 patients treated)
- Treatment-related mortality of three or more patients
- Interim/cumulative data for evidence of efficacy according to pre-established statistical guidelines, if appropriate;
- Clear lack of data quality, completeness, and timeliness;
- Clear deficits in performance issues of individual centers;
- Inadequacy of compliance with goals for recruitment and retention, including those related to the participation of women and minorities;
- Failure to adhere to the protocol;
- Presence of factors that might affect the study outcome or compromise the confidentiality of the trial data (such as protocol violations, unmasking, etc.);
- Presence of factors external to the study, such as scientific or therapeutic developments that may impact participant safety or the ethics of conduct of the study.

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Appendix A – Modified Cumulative Illness Rating Scale (CIRS)

		SCORE
1. Cardiac	Heart only	
2. Hypertension	Rating based on severity; affect systems are rated separately	
3. Vascular	Blood, blood vessels and cells, marrow, spleen, lymphatics	
4. Respiratory	Lungs, bronchi, trachea below the larynx	
5. EENT	Eye, ear, nose, throat, larynx	
6. Upper GI	Esophagus, stomach, duodenum, biliary and pancreatic tree; do not include diabetes	
7. Lower GI	Intestines, hernias	
8. Hepatic	Liver only	
9. Renal	Kidneys only	
10. Other GU	Ureters, bladder, urethra, prostate, genitals	
11. Musculo-Skeletal-Integumentary	Muscle, bones, skin	
12. Neurologic	Brain, spinal cord, nerves; do not include dementia	
13. Endocrine-Metabolic	Diabetes, diffuse infections, infections, toxicity	
14. Psychiatric/Behavioral	Dementia, depression, anxiety, agitation, psychosis	
	TOTAL	

Each system is rated as follows:

- 0 = NONE: No impairment to that organ/system
- 1 = MILD: Impairment does not interfere with normal activity; treatment may or may not be required; prognosis is excellent. (Examples could be skin lesions, hernias, or hemorrhoids)
- 2 = MODERATE: Impairment interferes with normal activity; treatment is needed; prognosis is good. (Examples could be gallstones, diabetes, or fractures)
- 3 = SEVERE: Impairment is disabling; treatment is urgently needed; prognosis is guarded. (Examples could be resectable carcinoma, pulmonary emphysema, or congestive heart failure)
- 4 = EXTREMELY SEVERE: Impairment is life threatening; treatment is urgent or of no avail; prognosis is grave. (Examples could be myocardial infarction, cerebrovascular accident, gastrointestinal bleeding, or embolus)

Appendix B – ECOG Performance Status

Grade	ECOG
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 house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Appendix C – Concomitant Medications – Prohibited or Cautionary Use

Note: As these lists are constantly evolving, if a medication is incorrectly documented as prohibited in this protocol, documentation from the site pharmacist to the contrary will be acceptable for the purposes of registration.

CYP3A4 inducers (prohibited):

Carbamezepine
Ethosuximide
Griseofulvin
Phenytoin
Primidone
Progesterone
Rifabutin
Rifampin
Nafcillin
Nelfinavir
Nevirapine
Oxcarbazepine
Phenobarbital
Phenylbutazone
Rofecoxib
St John's wort
Sulfadimidine
Sulfinpyrazone
Troglitazone

High Risk QTc Prolonging Agents (cautionary use):

Note: The following medications are only prohibited in the case that a patient develops known QTc prolongation on study.

Amiodarone	Flecainide
Anagrelide	Halofantrine
Arsenic trioxide	Haloperidol
Azithromycin	Ibutilide
Chloroquine	Methadone
Chlorpromazine	Moxifloxacin
Citalopram	Ondansetron**
Clarithromycin	Pentamidine
Disopyramide	Pimozide
Dofetilide	Quinidine
Dronedarone	Sevoflurane
Droperidol	Sotalol
Erythromycin	Thioridazine
Escitalopram	Vandetanib

**Will be given as pre-medication for romidepsin unless patient develops known QTc prolongation

Appendix D – Creatinine Clearance

The following equations should be used to calculate creatinine clearance.

For males:

$$\text{Creatinine Clearance} = \frac{(140 - \text{age [years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine [mg/dL]})}$$

OR

$$\frac{(140 - \text{age [years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine [µmol/L]})}$$

For females:

$$\text{Creatinine Clearance} = \frac{0.85\,(140 - \text{age [years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine [mg/dL]})}$$

OR

$$\frac{0.85\,(140 - \text{age [years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine [µmol/L]})}$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

Appendix E – Protocol History of Changes

Original Version Submitted to IRB & FDA – June 24, 2014			
Amendment 1 – Changes Required During IRB & FDA Review – September 3, 2014			
Section(s) Affected	***Prior Version***	***Amendment 1 Changes***	***Rationale***
Cover-page	IND# listed as pending	IND# updated to 123,818	Administrative
Throughout	n/a	Corrects minor spelling and/or grammatical errors.	Administrative
Study Summary	Summary of statistical methodology appeared to suggest the study was designed to demonstrate superior response rates compared to historical controls. Percentages and accrual goals didn't clearly align with other sections of the protocol.	Revised summary to more accurately reflect the design and numbers as described in the full statistical section.	Change requested by IRB during initial review.
1.4 (Study Rationale), 7.4 (Stopping Rules)	Accrual goal not clear (35 vs. 32) and criteria for early stopping incorrectly listed as 5 of 11 in the first stage.	Clarified that up to 35 patients may be enrolled to achieve 32 evaluable; also corrected early stopping criteria to indicate that if 6 or fewer of the first 12 patients had a response, the study would be closed to further accrual.	Change requested by both FDA and IRB during initial review.
1.4 (Study Rationale), 2.1 (Primary Objective & Endpoint), 10.1 (Primary Endpoint & Sample Size Calculations)	Not clear what response assessment time point would be used for the purposes of evaluating early stopping.	Clarifies that response at the 3 month time point (after cycle 3) will be used to determine whether or not the trial meets early stopping criteria for efficacy.	Clarification requested by FDA during initial review.
3.2 (Exclusion Criteria)	Excluded patients with a QT interval > 500 msec.	Revised to exclude patients with a QT interval > 480 msec.	Change requested by FDA during initial review.
4.0 (Treatment Plan), 4.4 (Duration of Therapy)	n/a	Adds clarification that patients who do not achieve a response of PR should only remain on treatment up to 1 year if they have SD (not PD) AND if no other options are available that would offer a more favorable risk/benefit ratio.	Clarification requested by FDA during initial review.
4.1.1 (Romidepsin Administration), 5.0 – Table 4 (Time & Events)	Stated that patients who tolerated the regimen for 2 cycles (6 doses) could be escalated to 14 mg/m^2 at the investigator's discretion.	Revises this to allow escalation to the 14 mg/m^2 dose only if the patient has not achieved a CR and has not experienced any grade 3-4 AEs.	Safety change required by FDA during initial review.
4.1.2 (Lenalidomide Administration), 4.1.3	n/a	Adds different dosing for patients with moderate or	Safety change required by FDA during initial review.

(Table 1b)		severe renal impairment (creatinine clearance < 60 ml/min) who are enrolled on the trial.	
4.2 (Toxicities, Dosing Delays, and Dose Modifications)	Grade 3-4 non-hematologic toxicities required to resolve to ≤ Grade 2 before further treatment.	Changed to require resolution to ≤ Grade 1; also notes that any recurrence of a grade 4 non-hematologic toxicity must result in removal from trial therapy.	Safety change required by FDA during initial review.
4.4 (Duration of Therapy)	n/a	Adds "& Early Withdrawal" to the section title and clarifies that the occurrence of the listed events will result in early withdrawal from study treatment or (in some cases) the study as a whole.	Clarification requested by FDA during initial review.
4.7 (Suspension of Accrual)	n/a	New section added to clarify monitoring and the authority of the Data Monitoring Committee to suspend accrual in the event of excessive toxicity.	Clarification requested by FDA during initial review.
5.0 – Table 4: Time & Events	CBC required at baseline and once per cycle.	Changed to require CBC weekly for the first 2 cycles, then every other week for cycles 3-6, then at the start of each cycle thereafter.	Safety change required by FDA during initial review.
7.4 (Stopping Rules)	n/a	Clarifies that individual patients (enrolled in the first stage) who demonstrate clinical benefit (SD or better) may continue to receive study treatment up to 1 year in accordance with the duration of therapy criteria.	Clarification requested by IRB during initial review.
Amendment 2 – Additional Changes Required During FDA Review – October 3, 2014			
Section(s) Affected	***Prior Version***	***Amendment 2 Changes***	***Rationale***
4.3.2 (Permitted Conmeds)	Stated that leukocyte growth factors may be given concurrently with protocol treatment.	Removes this statement.	Safety change required by FDA during initial review.
11.0 (Study Management)	n/a	Adds new section 11.11 to include a list of specific criteria that will trigger automatic suspension of study accrual.	Added per FDA requirement during initial review.
Amendment 3 – Additional Changes Required During FDA Review – December 17, 2014			
Section(s) Affected	***Prior Version***	***Amendment 3 Changes***	***Rationale***

11.11 (Criteria for Suspension of Accrual)	Definition of excessive toxicity included >20% of any single grade 4 toxicity after at least 10 subjects are treated, or more that 30% grade 4-5 toxicity with at least 90% probability.	Revises this to rule to define the toxicity event as any grade ≥ 4 neutropenia, grade ≥ 4 thrombocytopenia, or grade ≥ 3 organ toxicity *at least possibly related to the study regimen*, and limits the toxicity events to no more than 20% with 80% posterior probability.	Revised per FDA requirement during review of clinical hold.
Amendment 4 – Changes due to Transition of PI – November 16, 2015			
Section(s) Affected	***Prior Version***	***Amendment 4 Changes***	***Rationale***
Cover Page	Adam Petrich listed as PI and IND Holder	Removes Adam Petrich and adds Barbara Pro as PI and IND Holder	Administrative – change in faculty
Cover Page	Listed Yale Cancer Center as a participating site	Removes Yale and adds Ohio State University as a participating site	Administrative
Signature Page	Includes signature page	Removes signature page	Aligns with new NU protocol template
Schema, Study Procedures (Sec 5.0, Footnote 2, 11)	Response assessment included diagnostic CT with contrast	CT's can be performed with or without contrast	Revised per discussion with PI
Patient Eligibility (Sec 3.0)	Stated that study will be conducted in NMDTI	Removes language specifying NMDTI as location for study procedures	Allows flexibility to avoid deviations
Inclusion Criteria (Sec 3.1.1 & 3.1.6)	3.1.1 - Lists "extranodal NK/T-cell lymphoma, nasal type" as included type of PTCL	3.1.1 – removes "extranodal NK/T-cell lymphoma, nasal type" as type of PTCL	Per PI discussion
	3.1.1 - Included note specifying markers to be present for eligibility	3.1.1 – removes note for biomarkers	Per PI discussion – allows for less stringent eligibility
	3.1.6 - Referred to attached for REMS program	3.1.6 – removes reference to REMS program	Referenced elsewhere
Exclusion Criteria (Sec 3.2.2, 3.2.4, 3.2.6	3.2.2 – Note listed twice	3.2.2 – Removes Second Note	Redundant
	3.2.4 – "Patients who received prior exposure to…"	3.2.4 – "Patients who have received…"	Revised for clarity
	3.2.6 – "Patients who have known CNS…"	3.2.6 – "Patients with known CNS…"	Revised for clarity
Study Procedures (Sec 5.0)	"Each Cycle" column	"Day 1 of Each Cycle"	Revised for clarity
	n/a	Added column for Day 8 & 15 of cycles	Revised for clarity

	Pregnancy test required "each cycle"	Footnote 18 – Pregnancy test only required D15 of each cycle	Revised for clarity
	Footnote 5 – ECG required "at baseline"	Footnote 5 – ECG required "within 28 days of registration"	Revised for clarity
	Footnote 8 – required physical exam and medical history to be within 14 days	Footnote 8 – requires only Chemistry and Hematology to be within 14 days	Per PI discussion – allows appropriate flexibility for procedure
	Footnote 9 – allowed for labs to be used for C1D1 if within 7 days	Footnote 9 – removes language, requiring new labs for C1D1	Per PI discussion – labs should be checked for safety
	Footnote 16	Footnote 16 – Bone marrow biopsy "within 90 days of registration"	Per PI discussion – allows appropriate flexibility for procedure
Romidepsin Availability & Drug Ordering (Sec 8.1.6)	"Please see separately attached Appendix F for details"	"Romidepsin order form is available at the NOTIS website – contact QA for any issues/concerns"	Administrative – allows for changes in order form without amending protocol
Lenalidomide Availability (Sec 8.2.7)	n/a	Adds instructions for ordering Revlimid through Biologics, Inc.	Administrative – study coordinator request
Amendment 5 – June 16, 2016			
Section(s) Affected	***Prior Version***	***Amendment 5 Changes***	***Rationale***
Cover Page	• Listed Ohio State University • Had incorrect address for Cornell Medical College	• Removed Ohio State University • Added correct address for Cornell Medical College	Administrative – change in affiliate sites participating
Study Summary page	• N/A	• Updated Participating sites	Administrative – change in affiliate sites participating
Amendment 6 – March 10, 2017			
Section(s) Affected	***Prior Version***	***Amendment 6 Changes***	***Rationale***
Cover Page; Study Summary; 3.0 (Patient Eligibility)	Included University of Washington as an affiliate site	Removes University of Washington from affiliates	Administrative
Study Schema; 3.1.1 (Inclusion Criteria); 3.2.1 (Exclusion Criteria)	n/a	Adds adult T-cell lymphoma/ leukemia (ATLL) as eligible PTCL subtype (removes from excluded subtypes)	Expansion of eligibility to increase enrollment
Study Summary	Included short title and protocol number in summary	Removes short title and protocol number	To align with current NU protocol template
3.2.2 (Exclusion Criteria); 4.3.2 (Permitted	Corticosteroids were listed as being generally excluded in eligibility	Adds clarification that corticosteroids are permitted on study to treat any	Clarification – prior language was unclear whether corticosteroids of any type

Concomitant Medications); 4.3.3 (Prohibited Concomitant Medications)	criteria, and were not listed in concomitant medications	condition other than PTCL. Corticosteroids for PTCL are excluded during study treatment, but are permitted prior to treatment for 10 or fewer days	were excluded, rather than steroids to treat PTCL
3.2.3, 3.2.10 (Exclusion Criteria)	Excluded chemotherapy and high QT "within 4 weeks" prior to registration	Excludes chemotherapy and high QT"≤ 28 days" prior to registration	Clarification for simplicity
3.2.6 (Exclusion Criteria)	n/a	Expands CNS (central nervous system)	Clarification
4.0 (Treatment Plan); 4.1.3 (Treatment regimen & supportive therapies); 5.0 (Study Procedures #10)	Allowed a cycle window of ±1 business day	Allows cycle window of ±3 days	Allows greater flexibility for visits
4.1.1 (Romidepsin)	Patients may be escalated to 14mg/m^2 romidepsin if they don't have grade 3-4 AE's	Patients may be escalated to 14mg/m^2 romidepsin if they don't have **drug-related** grade 3-4 AE's	Clarification – only a drug-related AE would preclude patients from escalating in dose
4.1.1 (Romidepsin); 4.1.3 (Treatment regimen & supportive therapies); 4.3.1 (Recommended Concomitant Medications Include);	Recommended pre-medications are Zofran 16mg and dexamethasone 10mg (**or similar agents**)	Pre-medications are listed as Zofran 16mg and dexamethasone 10mg (**or equivalent**)	An equivalent dose is recommended (rather than saying "similar agent", which may include a higher dose) to avoid higher doses that may prolong QTc (e.g. kytril > 2mg)
4.1.3 (Treatment regimen & supportive therapies); 5.0 (Study Procedures #10,15)	"Romidepsin infusions should occur within 1 business day of days 1, 8, and 15"	"Romidepsin infusions should occur within ±3 days of day 1, and within +3 days of days 8 and 15."	Allows greater flexibility on day 1 (to align with cycle windows), but maintains appropriate window between infusions.
4.1.3 (Treatment regimen & supportive therapies);	Table 1b: "Dose Adjustments…"	Table 1b: "**Lenalidomide** Dose Adjustments"	Clarification – previously unclear which drug was to be modified
	Table 1b: severe renal impairment defined as CrCl ≤ 30	Table 1b: severe renal impairment defined as CrCl < 30	Discrepancy – CrCl = 30 previously fell into both moderate and severe categories
4.2 (Toxicities, Dosing Delays, and Dose Modifications); 6.1 (Toxicity Endpoints); 7.2.2 (Severity of AE's)	CTCAE v4.0	CTCAE v4.03	Administrative update
4.2 (Toxicities, Dosing Delays, and Dose Modifications); 7.2.5 (Attributions)	Both study drugs were to be delayed or modified in the case of a drug-related toxicity	Adds that toxicity should be attributed to one study drug whenever possible. Modifications/delays may apply to only the drug which caused toxicity, or both.	Clarification – clinically, if one study drug is not related to an AE, it should be continued as normal
4.2 (Toxicities, Dosing Delays, and Dose Modifications)	For any Grade 3-4 toxicity, lenalidomide was to be resumed at the same dose upon	Adds exceptions for Grade 3-4 AE's where the dose of lenalidomide should be reduced by 5mg (G3 rash or	Aligns more closely with lenalidomide dosing in standard practice

	resolution of the first occurrence	neuropathy, G3 or 4 tumor lysis syndrome or tumor flare) or discontinued (G4 rash or neuropathy, or any grade blistering rash)	
	Romidepsin dose could be reduced from 10mg/m^2 to 7mg/m^2	Changes dose reduction to 8mg/m^2 (from 10mg/m^2)	To align with standard dosing
4.2.1 (Pregnancy)	n/a	Patients who become or are suspected to be pregnant while on study treatment must discontinue immediately. Refers to 7.2.6 for reporting requirements	Required Celgene language for pregnancy reporting and monitoring.
4.3.3 (Prohibited Concomitant Medications); Appendix C	Referenced appendix E for list of CYP3A4 inducers	References appendix C and adds note that pharmacist list of prohibited CYP3A4 inducers will take priority over list in the protocol.	The list of CYP3A4 inducers is constantly evolving
	QTc prolonging agents were strictly prohibited	QTc prolonging agents are only prohibited in patients who develop QTc prolongation on study	QTc prolonging agents are not a risk unless a patient already has prolonged QTc; patients are required to have QTc ≤ 480 msec before the study
5.0 (Study Procedures)	n/a	Adds 1 cycle = 28 days	Clarification
	n/a	Adds cycle window (±3 days)	Clarification
	#2: n/a	#2: CT's must be of chest, abdomen, pelvis; neck if clinically indicated, and with or without contrast	Clarification
	#11: n/a	#11: Adds window of ±7 days for CT's, and clarifies they can be with or without contrast	Clarification
	#13: n/a	#13: Adds windows for follow-up visits (±7 days for q3months and ±14 days for q6months)	Clarification
	#16: Bone marrow biopsy was to be done at baseline and as response assessment for patients with marrow only disease and as clinically indicated in other patients	#16: Bone marrow biopsy will be done at baseline if clinically indicated. In patients with known bone marrow involvement at baseline, a biopsy will be performed after the patient achieves a CR	Clarification – language was previously unclear
7.2.6 (Pregnancy); 7.2.7 (Overdose)	n/a	Adds reporting requirements for patients who become pregnant or have an overdose of study treatment. Pregnancy and pregnancy outcomes must be reported on Celgene-	Additional safety language required by Celgene

		specific forms, and overdose must be reported on case report forms.	
7.3.4 (Reporting to Celgene)	n/a	Adds contact information (fax and email) for Celgene Drug Safety and additional reporting instructions	Clarification to align with Celgene protocol template
8.1.6 (Availability & Drug Ordering)	Referenced a drug shipment request form, a fax and email for ordering romidepsin	Removes contact details for ordering romidepsin, and references instructions in NOTIS.	NOTIS should be used for drug orders to avoid protocol amendments in case of changing instructions
11.5 (Data Management & Monitoring/Auditing); Appendix C; Appendix D	Referred to Appendices for the DSMP and data submission guidelines	Removes references and Appendix C & D, instead referencing the DSMP hyperlink and NOTIS	To align with current NU protocol template and policies
11.7 (Amendments to the Protocol)	Amendments must be sent to the IRB for approval.	Adds that amendments will be sent for review by "local, institutional, and governmental regulatory bodies, as well as by Celgene". Amendments will also be sent to affiliates	Broader language to cover all required reviews and approvals.
Appendix C	All medications were listed as "not permitted"	Clarifies that QTc prolonging agents are "cautionary"; also clarifies that ondansetron will be used as a pre-medication unless a patient develops QTc prolongation	Clarification to align with 4.3.3

Amendment 7 – July 25, 2018 *SRC-approved on October 30, 2018*			
Section(s) Affected	***Prior Version***	***Amendment 7 Changes***	***Rationale***
3.1.4 (Inclusion Criteria); Appendix D	Organ function listed a cutoff for Creatinine as ≤2x ULN	Changes creatinine cutoff to Creatinine Clearance, where the cutoff is ≤30 mL/min Adds Appendix D to provide the formula for calculating Creatinine Clearance	To align with dose adjustment criteria listed in 4.1.3 and standard of care criteria for lenalidomide.
3.1.8 (Inclusion Criteria)	Patients must be free of any prior malignancies for ≥1 year	Adds that "free of prior malignancies" is at the investigator's discretion.	To clarify prior confusion as to the definition of malignancy free
3.2.6 (Exclusion Criteria)	n/a	Excludes patients who are receiving concurrent immunosuppressive medications post-transplant	To address clarification brought up by an affiliate site. It is not clinically appropriate to treat patients on immunosuppressive medications with the study treatment.
4.2 (Toxicities, Dosing Delays, and Dose Modifications)	n/a	Adds: "If study drug is delayed more than 21 days (1 treatment cycle),	Clarification; there was previously no language about maximum length of

		treatment may be discontinued after discussion with the PI."	holding patients for toxicity.
4.3.2 (Permitted Concomitant Medications)	n/a	Transfusions and growth factor are clarified to be permitted at physician discretion and per institutional guidelines	Clarification requested by affiliate site; transfusion and growth factor were not previously mentioned
4.3.3 (Prohibited Concomitant Medications & Treatments)	Concurrent radiotherapy was generally prohibited	Adds a stipulation that radiotherapy is permitted to treat a single non-target lesion for symptom control	Clarification resulting from a clinical situation. Patients should be permitted to receive radiotherapy separate from the disease target lesions as it does not affect disease assessments or study endpoints
4.6 (Patient Replacement); 4.7 (Suspension of Accrual); 7.3 (Expedited Reporting of SAEs) 11.10 (Publication Policy); 11.11 (Criteria for Suspension in Accrual)	Referenced Data Monitoring Committee (DMC)	Updates to reference Data and Safety Monitoring Committee (DSMC)	Administrative update to align with internal policies
5.0 (Study Procedures, #8)	n/a	SAE's are to be collected from the time of consent until 30 days after treatment	Clarification for easier referencing to align with SAE timelines within the protocol
7.2.3 (Serious Adverse Events)	SAE's were to be collected during the study and for 30 days after treatment	Adds that SAE's will be collected from the time of consent until 30 days after treatment	Clarification requested by affiliate site
Amendment 8 – July 5, 2019 *SRC-approved on December 6, 2019*			
Section(s) Affected	***Prior Version***	***Amendment 8 Changes***	***Rationale***
Cover Page	Listed Alfred Rademaker as the Biostatistician	Updates to Borko Jovanovic as the new Biostatistician	Administrative update to account for staffing change
Cover Page and Throughout	Coordinating Center was listed as the Clinical Research Office (CRO) at Northwestern	Updates the name of the coordinating center to the Clinical Trials Office (CTO) at Northwestern	Administrative update to account for a change in the coordinating center's name; the coordinating center itself will remain the same.
Study Summary, Section 1.4 (Study Rationale), Section 3.0 (Patient Eligibility), and Section 10.0 (Statistical	Listed an accrual goal of 32 evaluable subjects	Updates to an accrual goal of 20 evaluable subjects and provides a new statistical plan in Section 10.0.	The study has been slow to accrue, and reducing the sample size will increase the feasibility of completing the trial in a timely manner.

Considerations)			Modification requested by the lead site after receiving support from Celgene to reduce sample size.
Section 4.0 (Treatment Plan)	N/A	Adds the following: With PI approval, dose modifications (interruptions and reductions) may be permitted for any grade AE deemed intolerable by the patient, or per treating investigator discretion (with PI approval) if thought to be in the best interest of the patient.	Modification requested by the DSMC to align with best interests of participating patients.
Section 4.6 (Patient Replacement)	Stated: Any patient who completes fewer than 2 total cycles of therapy and is withdrawn for any reason except POD or toxicity will still be considered evaluable for toxicity endpoints; however, for the purpose of efficacy endpoints, another patient may be added to the accrual goal with the approval of the Data and Safety Monitoring Committee (DSMC) at NU.	Updates language to include the bolded text: Any patient who completes fewer than 2 total cycles of therapy and is withdrawn for any reason except POD or toxicity will still be considered evaluable for toxicity endpoints **but will not be evaluable for efficacy endpoints**; for the purpose of efficacy endpoints, another patient may be added to the accrual goal with the approval of the Data and Safety Monitoring Committee (DSMC) at NU.	Language clarification requested by the Quality Assurance Monitor to clarify replacement of non-evaluable patients
Section 5, Table 4 (Time and Events)	N/A	Adds a -1 day window to D8 and D15 assessments	To allow flexibility in patient schedules
Section 7.2.1 (Adverse Events)	N/A	Now includes standard language describing examples of AE classification	To align with current NU protocol template
Section 11.6.2 (Protocol Deviations)	N/A	Now includes standard language describing Reportable New Information (RNI)	To align with current NU protocol template
Throughout	N/A	Corrects minor grammatical/typographical errors and formatting	Administrative change
Amendment 9 – December 9, 2019 *SRC-approved on March 3, 2020*			
Section(s) Affected	***Prior Version***	***Amendment 9 Changes***	***Rationale***
Cover Page and	Protocol version dated July	Updates version date to	Administrative update

Throughout	5, 2019 (Amendment 8)	December 9, 2019 (Amendment 9)	
Table of Contents	N/A	Updates page numbers	Administrative update
Inclusion Criterion 3.1.4	Required creatinine clearance of **≤** 30 mL/min	Requires creatinine clearance of **≥** 30 mL/min	Corrects typographical error. Replaces "≤ 30 mL/min" with "≥ 30 mL/min"
Section 7.2.4 (UPIRSO) Section 7.2 (Expedited Reporting of SAEs) Section 11.6 (Adherence to the Protocol) Section 11.7 (Amendments to the Protocol) Section 11.10 (Publication Policy)	N/A	Updates standard language to align with new Northwestern University protocol template	Administrative update
Section 9.3.2 (Tissue Collection)	Construction of the TMA will require **minimum of five unstained slides of tissue** for proper analysis.	Construction of the TMA will require **1.0 to 1.5 mm punch cores** for proper analysis.	Updates for flexibility in tissue collection procedures
Appendix E (Protocol History of Changes)	N/A	Adds SRC-approval date for protocol amendment 8 Summarizes revisions for protocol amendment 9	Administrative update
Amendment 10 – May 22, 2020			
Section(s) Affected	***Prior Version***	***Amendment 9 Changes***	***Rationale***
Cover Page and Throughout	Protocol version dated December 9, 2019 (Amendment 9)	Updates version date to May 22, 2020 (Amendment 10)	Administrative update
Table of Contents	N/A	Updates page numbers	Administrative update
Section 4.1.2 (Lenalidomide); Section 4.1.3 (Treatment Regimen & Supportive Therapies); Table 1b	The dose should be adjusted in patients with moderate or severe renal impairment… Table heading: Dose	Addition of bolded text: The dose **and schedule** should be adjusted in patients with moderate or severe renal impairment… Table heading: Dose **and Schedule**	Clarification. Clarifies language to align with the contents of Table 1b, which describes the adjusted dose and schedule for lenalidomide for patients with moderate or severe renal impairment.
Table 1b	N/A	Addition of bolded text in footnote. **[1] Creatinine clearance (CrCl) will be measured and calculated prior to**	Clarification. Adds footnote 1 to Table 1b to clarify the process to calculate creatinine

		initiating each cycle as described in the Study Procedures Table in Section 5.0. (Refer to Appendix D for instructions on calculating CrCl). The dose of lenalidomide will be adjusted per Table 1b. Any questions regarding dose calculations/ adjustments should be directed to the Lead PI.	clearance to determine lenalidomide dosing.
Section 5.0 (Study Procedures)	[16] Romidepsin will be administered intravenously on days 1, 8, and 15 of each cycle. The dose for the first 2 cycles (6 doses total) will be 10 mg/m2; in some cases, patients may be escalated to a dose of 14 mg/m2 for remaining cycles (see Section 4.1.1 for specific criteria). A window is allowed for romidepsin infusion visits (within ±3 days of day 1, and within +3 days of days 8 and 15).	Addition of bolded text to footnote: [16] Romidepsin will be administered intravenously on days 1, 8, and 15 of each cycle. The dose for the first 2 cycles (6 doses total) will be 10 mg/m2; in some cases, patients may be escalated to a dose of 14 mg/m2 for remaining cycles (see Section 4.1.1 for specific criteria). A window is allowed for romidepsin infusion visits (within ±3 days of day 1, and within **-1 to** +3 days of days 8 and 15).	Corrects discrepancy. Modifies footnote 16 to revise the window for D8 and D15 to be <u>-1 to</u> +3 days to align with footnote 11. Footnote 11 states that, "Day 8 and 15 each have a window of -1 to +3 days."
Section 5.0 (Study Procedures)	N/A	Adds "creatinine clearance check" to the Study Procedure's Table with a corresponding footnote. Addition of bolded text below:	Clarification. Clarifies the process to calculate creatinine clearance to determine

		[20] Creatinine clearance will be measured and calculated prior to initiating each cycle (Refer to Appendix D for instructions on calculating creatinine clearance). The dose of lenalidomide will be adjusted per Table 1b. Any questions regarding dose calculations/ adjustments should be directed to the Lead PI. Refer to Section 4.1.3 for additional information.	lenalidomide dosing.
Appendix C; Appendix D	Appendix C and Appendix D did not appear in the Table of Contents. Appendix D did not have a title.	Revises formatting and adds title to appendix so both appendices appear in the Table of Contents appropriately.	Administrative update
Appendix E (Protocol History of Changes)	N/A	Adds SRC-approval date for protocol amendment 9. Summarizes revisions for protocol amendment 10.	Administrative update
Throughout	N/A	Minor formatting adjustments.	Administrative update
Amendment 11 – November 17, 2021			
Section(s) Affected	Revision		Rationale
Cover page & Throughout	Updates the principal investigator from Dr. Barbara Pro to Dr. Jonathan Moreira and provides contact information		Administrative revision
Throughout	Editorial revisions: Updates the protocol version/date and Appendix E (Protocol History of Changes)		Administrative revision