Abbreviated Title: RAdR for R/R TCM

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Title: A Phase 1 Study of Romidepsin, CC-486 (5-azacitidine), dexamethasone, and lenalidomide (RAdR) for relapsed/refractory T-cell malignancies

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Drug Name:	Romidepsin (ISTODAX®; Investigational Supply)	CC-486 (5-azacitidine; Investigational Supply)	Lenalidomide (Revlimid®; Investigational Supply)	Dexamethasone
IND Number:	147481			
Sponsor:	CCR			
Manufacturer:	Bristol Myers Squibb	Bristol Myers Squibb	Bristol Myers Squibb	Generic
Supplier	Bristol Myers Squibb	Bristol Myers Squibb	Bristol Myers Squibb	CC Pharmacy

PRÉCIS

Background:

- Mature T-cell malignancies (TCM) are rare and heterogeneous group of leukemias and lymphomas accounting for 5 to 10% of all lymphomas in the US
- Patients with systemic TCM are most commonly treated with a CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone)-like regimens, that produce long-term progression-free survival in about 30% of these cases
- Patients with relapsed/refractory (R/R) TCM have very poor prognosis with median overall survival of less than 1 year. Treatment options for R/R TCM are very few and of limited efficacy, thus novel treatment strategies are urgently needed.
- Mutations in epigenetic regulators are common in aggressive TCMs and standard treatment with histone deacetylase inhibitors (HDACi) such as romidepsin show modest clinical activity with single agent the overall response (ORR) around 25%
- Combination of romidepsin and 5-azacitidine (hypomethylating agents) was synergistic in preclinical models, and has demonstrated high clinical activity with an ORR of 79%
- Many TCMs rely on The Ikaros-dependent NF-kB/IRF4 signaling pathway to maintain proliferation, which is why lenalidomide, which induces degradation of Ikaros and downregulates IRF4, has single agent activity in R/R TCM with ORR of 26% to 42%, depending on the subtype.
- Lenalidomide synergizes with romidepsin and enhances tumor cell death in TCM cell lines, predicting that the addition of lenalidomide to the established romidepsin/ CC-486 (5-azacitidine) combination will further improve efficacy.

Objectives:

- To determine the safety and toxicity profile and the maximum tolerated dose (MTD) of the four-drug combination of CC-486 (5-azacitidine), romidepsin, lenalidomide and dexamethasone in patients with TCM

Eligibility:

- Refractory/relapsed TCM (excluding in Cutaneous T-Cell Lymphoma) defined as follows:
    - Patients with systemic disease
    - Have received at least one line of prior therapy
    - Must have received brentuximab vedotin if the disease is anaplastic large cell lymphoma or CD30-positive cutaneous T-cell lymphoma
- Age $\geq$ 18 years of age
- ECOG performance status of $\leq$ 2 (or $\leq$ 3 if decrease is due to the disease)
- Histologically or cytologically confirmed relapsed and/or refractory mature TCM
- Adequate organ and marrow function

Design:

- Open-label, single-center, uncontrolled Phase 1 study

- "3 + 3" design will be used to determine the MTD of dose-escalated lenalidomide with fixed dose of romidepsin and CC-486 (5-azacitidine)
- An expansion cohort of 9 patients will be evaluated at the MTD
- Maximum 6 cycles (28-day cycle) of combination therapy
- To explore all dose levels, including further evaluation in a dose expansion cohort, the accrual ceiling will be set at 30 patients

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

TABLE OF CONTENTS

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

- Determine the safety and toxicity profile and the maximum tolerated dose (MTD) of lenalidomide given as part of a four-drug combination treatment with romidepsin, CC-486 (5-azacitidine) and dexamethasone to patients with mature T-cell malignancies (TCM).

1.1.2 Secondary Objectives

- Evaluate the potential antitumor activity of the romidepsin, CC-486 (5-azacitidine) and lenalidomide combination by assessing the overall response rate (ORR), complete response (CR) rate, duration of response (DOR), progression-free survival (PFS), event-free survival (EFS), and overall survival (OS).

1.1.3 Exploratory Objectives

- Evaluate changes in peripheral blood immune cell subsets and cytokine profiles, and correlation of these changes with clinical outcome.
- Evaluate changes in circulating tumor DNA to identify potential prognostic or predictive markers in patients with T-cell malignancies.
- Collect and store peripheral blood and other tissue samples for future correlative studies.

1.2 BACKGROUND

1.2.1 Peripheral T-cell lymphoma

Peripheral T-cell lymphoma (PTCL) is a rare heterogeneous group of neoplasms in mature T-cell malignancies (TCM) which account for 5-10% of all lymphomas. Currently, the World Health Organization (WHO) classification combines mature T- and NK-cell neoplasms under the umbrella term PTCL and the category is composed of 24 different entities, based on the different morphologic, phenotypic, molecular, and clinical features, including disease site [1]. Compared with B-cell lymphomas, many types of PTCL develop not in lymph nodes, but in specific extranodal sites such as extranodal NK/T cell lymphoma, nasal type (ENKL) in the nasal cavity, enteropathy-associated T-cell lymphoma (EATL) in the small intestine and hepatosplenic T-cell lymphoma (HSTL) in the liver and spleen. The most common histologic subtype is peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), followed by angioimmunoblastic T-cell lymphoma (AITL) or anaplastic large cell lymphoma (ALCL), either ALK positive (ALK+) or ALK negative (ALK-) and these three types account for about 60% of all cases of PTCLs [2], however, it is still rare that the age-adjusted incidence in the U.S. for PTCL-NOS, AITL and ALCL is 0.30, 0.05 and 0.25 per 100,000 person-years, respectively [3-5].

The presentation of patients with PTCL largely depends on the subtype. PTCL-NOS, AITL, and ALCL often present with generalized lymphadenopathy, and there is also frequent involvement of the skin, gastrointestinal tract, liver, spleen, and bone marrow. In contrast, a number of rare specific subtypes, such as ENKL, HSTL, and EATL, present with primarily with extranodal disease, and other subtypes, such as adult T-cell leukemia (ATL) and T prolymphocytic leukemia (T-PLL), may have a leukemic presentation. Advanced stage disease (stages III and IV) is common for most of these diseases, constituting 69% of PTCL-NOS 69%, 89% of AITL, 65% of ALK+ALCL, 58% of ALK-ALCL, 69% of EATL, and 90% of HSTL.

1.2.2 Cutaneous T-cell lymphoma

Cutaneous T-Cell Lymphomas (CTCLs) are a clinically heterogeneous subgroup of PTCL/TCM, accounting for most lymphomas arising in skin. Mycosis fungoides (MF) and Sézary syndrome (SS) are defined by their cutaneous lesions that result from the accumulation of a T-helper memory/effector subset with a CD4+, CD8-, CD45RO+CLA+ phenotype in skin and blood [1]. Most commonly, MF starts as an indolent and chronic dermatitis in the sun shielded areas. The incidence of CTCL was initially increased and now it is plateaued with currently 1.0 per 100,000 person/year, based on Surveillance, Epidemiology, and End Results (SEER) registry data, with the highest incidence rates being reported among males and African-Americans [6].

1.2.3 Treatment of relapsed/refractory PTCL and CTCL

Excluding a small proportion of indolent subtypes, PTCL is often treatment-resistant and is associated with poor prognosis [7]. Patients with systemic TCM are most commonly treated with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone)-like therapy, which is associated with long-term progression-free survival of about 30% [8-10]. Previous reports showed that the median PFS and OS after the first recurrence or disease progression were generally less than one year particularly without stem cell transplant [11-13]. British Columbia Cancer Agency reported that there was only a small difference in the OS between patients who received chemotherapy and those who did not (6.5 vs 3.7 months, respectively), indicating the need for new treatment strategies [13].

Early stage MF is characterized by eczematous or psoriasiform dermatitis covering < 80% body surface area without evidence of blood or visceral involvement. As the majority of CTCL patients present with patch/plaque stage MF and have an excellent prognosis, the initial goal of therapy is to improve symptoms and quality of life while avoiding treatment-related toxicity. Early MF is usually indolent and treated with combination skin-directed therapy. However, once they stopped responding to topical treatment or transformed to SS when needing systemic treatment, the prognosis remains poor with median PFS of less than a year [14].

Over the last decade, the U.S. Food and Drug Administration (FDA) approved several drugs with novel mechanisms of action for the treatment of patients with recurrent PTCL including cutaneous T-cell lymphoma (CTCL); these included vorinostat in 2006, pralatrexate in 2009, brentuximab vedotin (BV) for ALCL in 2011, romidepsin in 2011, belinostat in 2014 and mogamulizumab in 2018.

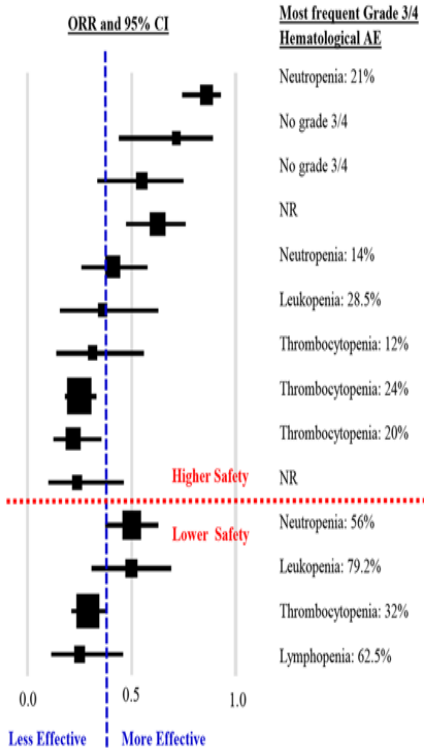
While these drugs are additions to the therapeutic options, they are approved by the response rate not by survival benefit, although response rates were generally less than 30% with the exception of BV for patients with ALCL, and an actual impact on long-term outcome is not proven. MD Anderson Cancer Center retrospectively analyzed 321 patients with PTCL-NOS and AITL and found that the median PFS after pralatrexate and romidepsin as single agents were 3.0 and 2.5 months, respectively which was not significantly different from chemotherapy approach [11]. Also, meta-analysis of available treatments for relapsed/refractory PTCL showed that even though approved, belinostat and pralatrexate have lower safety than several other regimens (**Figure 1**) [15].

These studies indicate that even with the recent new drug approvals, single agent efficacy is limited for all these drugs, that there has been no significant improvement in survival even with multiple successive salvage treatments, and that new therapies with higher efficacy and improved safety

profile are needed.

Figure 1: **Safety and efficacy of treatments for relapsed/refractory PTCL**

Study	Drug regimens	Study Design	N	Median age	Major PTCL subtype	Median no. of prior therapy	ORR	Most frequent Grade 3/4 Hematological AE
Pro et al. (2012)	Brentuximab vedotin	Phase II trial	58	52	ALCL	2	86%	Neutropenia: 21%
Zinzani et al. (2000)	Gemcitabine	Prospective study	14	58	PTCL-NOS	3	72%	No grade 3/4
Zinzani et al. (2010)	Gemcitabine	Prospective study	20	54	PTCL-NOS	3	55%	No grade 3/4
Zelenetz et al. (2003)	ICE	Prospective study	43	46	PTCL-NOS	NR	63%	NR
Horwitz et al. (2014)	Brentuximab vedotin	Phase II trial	35	64	PTCL-NOS	2	41%	Neutropenia: 14%
Enblad et al. (2004)	Alemtuzumab	Phase II trial	14	61	PTCL-NOS	2	36%	Leukopenia: 28.5%
Huang et al. (2002)	13-cRA+interferon-α	Phase II trial	17	47	PTCL-NOS	1	31%	Thrombocytopenia: 12%
Coiffier et al. (2012)	Romidepsin	Phase II trial	130	61	PTCL-NOS	2	25%	Thrombocytopenia: 24%
Morschhauser et al. (2013)	Lenalidomide	Phase II trial	51	65	AITL	3	22%	Thrombocytopenia: 20%
d'Amore et al. (2010)	Zanolimumab	Phase II trial	21	69	AITL	2	24%	NR
Damaj et al. (2013)	Bendamustine	Phase II trial	58	66	AITL	1	50%	Neutropenia: 56%
Seok et al. (2012)	A-DHAP	Phase II trial	24	49	PTCL-NOS	NR	50%	Leukopenia: 79.2%
O'Connor et al. (2011)	Pralatrexate	Phase II trial	109	58	PTCL-NOS	3	29%	Thrombocytopenia: 32%
Foss et al. (2015)	Belinostat	Phase II trial	24	64	PTCL-NOS	NR	25%	Lymphopenia: 62.5%



1.2.3.1 Brentuximab Vedotin

Brentuximab vedotin (BV) is an antibody-drug conjugate that consists of the CD30-specific monoclonal antibody conjugated with monomethyl auristatin E (MMAE) by linker peptide. Binding of the antibody-drug conjugate to CD30 on the cell surface causes internalization of the conjugate by endocytosis, and the drug subsequently travels to the lysosome, where proteases cleave the linker releasing the MMAE to cytosol [16].

In a pivotal phase II study of patients with relapsed or refractory systemic ALCL, the ORR and CR rate were 86% and 57%, respectively [17]. The median PFS duration was 13.3 months, which was significantly longer than the PFS of the most recent prior therapy (hazard ratio: 0.48, p=0.001). Long-term follow-up data from this study showed that the median duration of response for patients who achieved CR extended to 26.3 months, and 4-year OS was 64% [18, 19]. On the basis of results from this trial, the FDA approved BV for the treatment of patients with ALCL in whom at least one prior multidrug chemotherapy regimen had failed.

BV also showed activity in CTCL. Phase 3 study comparing BV to methotrexate or bexarotene in patients with CTCL showed significantly higher response rate (56.3% versus 12.5%) with BV [20] and approved by FDA.

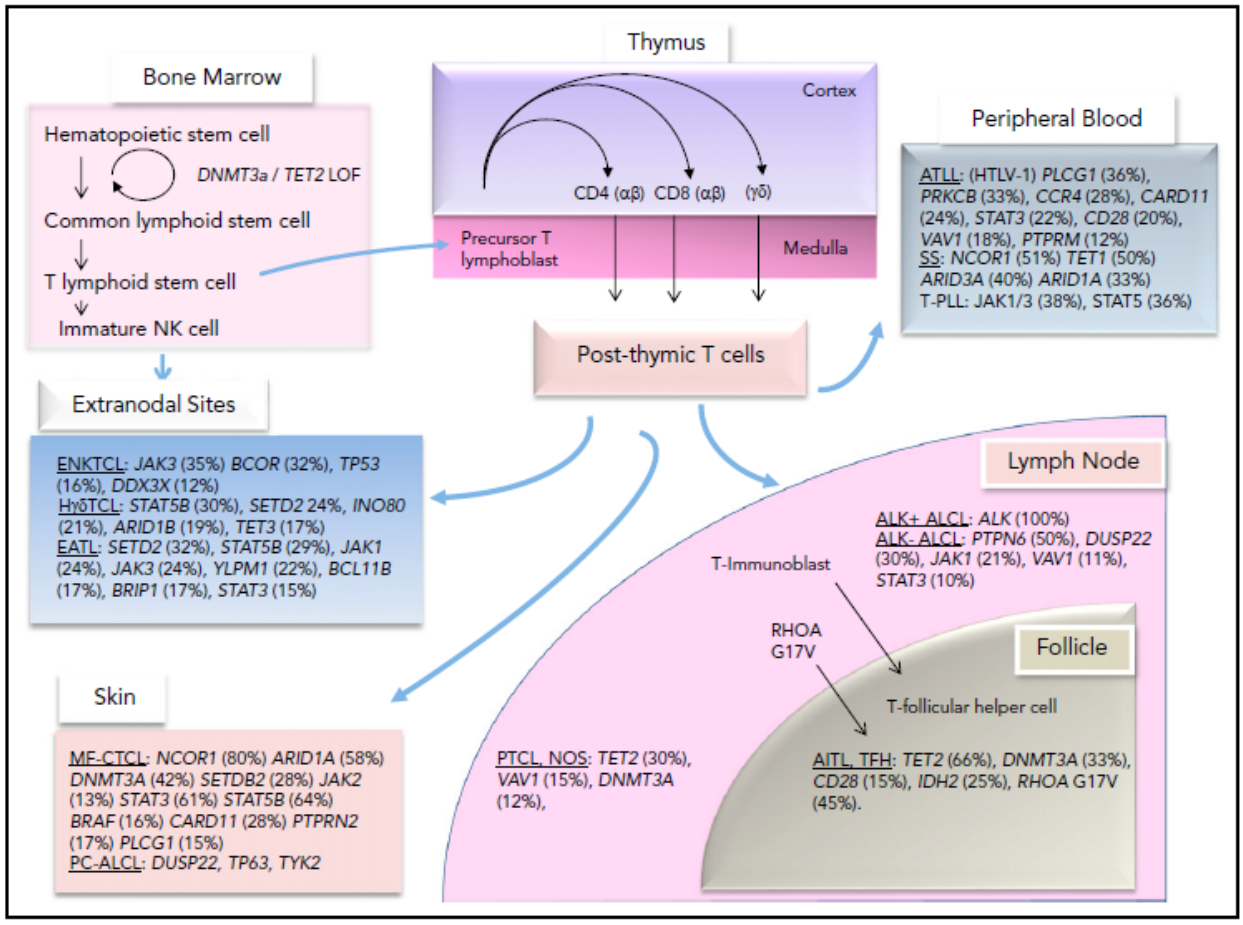
Due to these findings BV is considered a standard therapeutic option for patients with relapsed/refractory ALCL and CTCL. Therefore, patients with ALCL and CD30 positive CTCL must have had prior BV or be intolerant to it to be enrolled in the study. Although BV is a very

effective treatment, 2-year OS after BV failure is only 27.1% [21] and new investigational treatment is warranted.

1.3 EPIGENETIC REGULATORY GENES IN TCM

Many aggressive TCM, particularly AITL, have mutations of epigenetic modifiers that directly or indirectly involved in the regulation of DNA methylation/hydroxymethylation such as TET2, DNMT3A, IDH2, CREBBP and EP300 [22-26]. Mutations in IDH2 and TET2 reduce 5hmC levels due to global hypermethylation of promoters and CpG islands, likely contributing to TCM lymphomagenesis [27]. **TET2** mutations are seen in up to 70% of PTCL patients, specifically 42-83% of patients with AITL, 28-48.5% in PTCL NOS, and 10% in ATLL [28]. **DNMT3A** functions as a DNA methyltransferase catalyzing cytosine methylation of CpG islands in promoters leading to transcriptional silencing. Mutations in DNMT3A have been identified in about 11-33% of patients with PTCL and the mutations frequently co-exist with TET2 mutation [23], which may ultimately lead to transcriptional repression [29]. DNMT3A and TET1 mutations are also seen in CTCL and SS [30, 31]. Various TCM have different frequency of mutations in epigenetic regulators (**Figure 2**).

Figure 2: T-cell development and common mutations in TCM

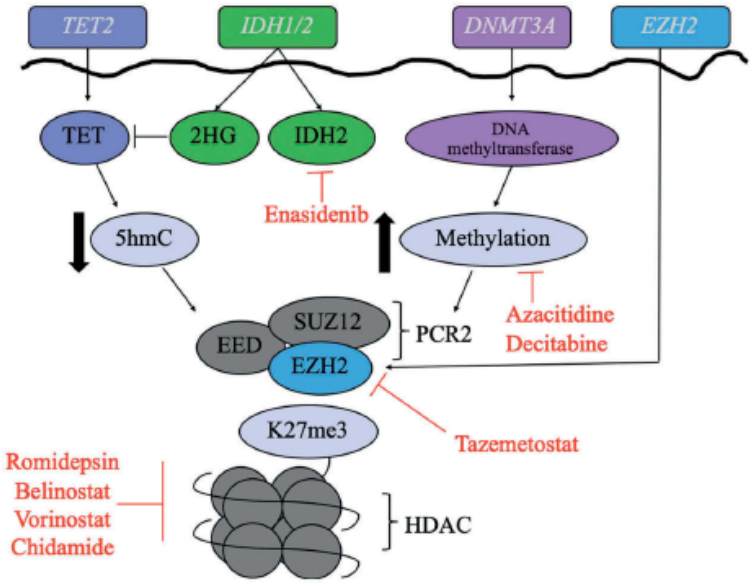


Mutation is epigenetic regulatory gene is common in ATLL. Shah et al. showed that 17 of 30 patients (57%) with ATLL had mutations in some of genes in epigenetic and histone modifying genes (TET2, EZH2, MED12, PBRM1, DNMT3A, KMT2A, HIST1H1E, SPEN, IDH1,

SMARCB1, and ASXL1), the most common being **EP300** (6/30, 20%).[32] The patients with mutation in epigenetic regulation showed shorter survival outcome showing the clinical impact of these mutations and potential benefit from treatment focusing on epigenetic regulation such as the histone deacetylase (HDAC) inhibitor romidepsin. In fact, in the phase I study of romidepsin and pralatrexate, three of five patients with multiple relapsed ATLL responded to the treatment.

Empiric findings of clinical efficacy of histone deacetylase inhibitors (HDAC inhibitors) in PTCL first drove research and later findings strongly supported to further explore epigenetic modifiers such as HDAC inhibitors and hypomethylating agents (HMA) in TCM (**Figure 3**) [28].

Figure 3: Epigenetic regulators and target agents



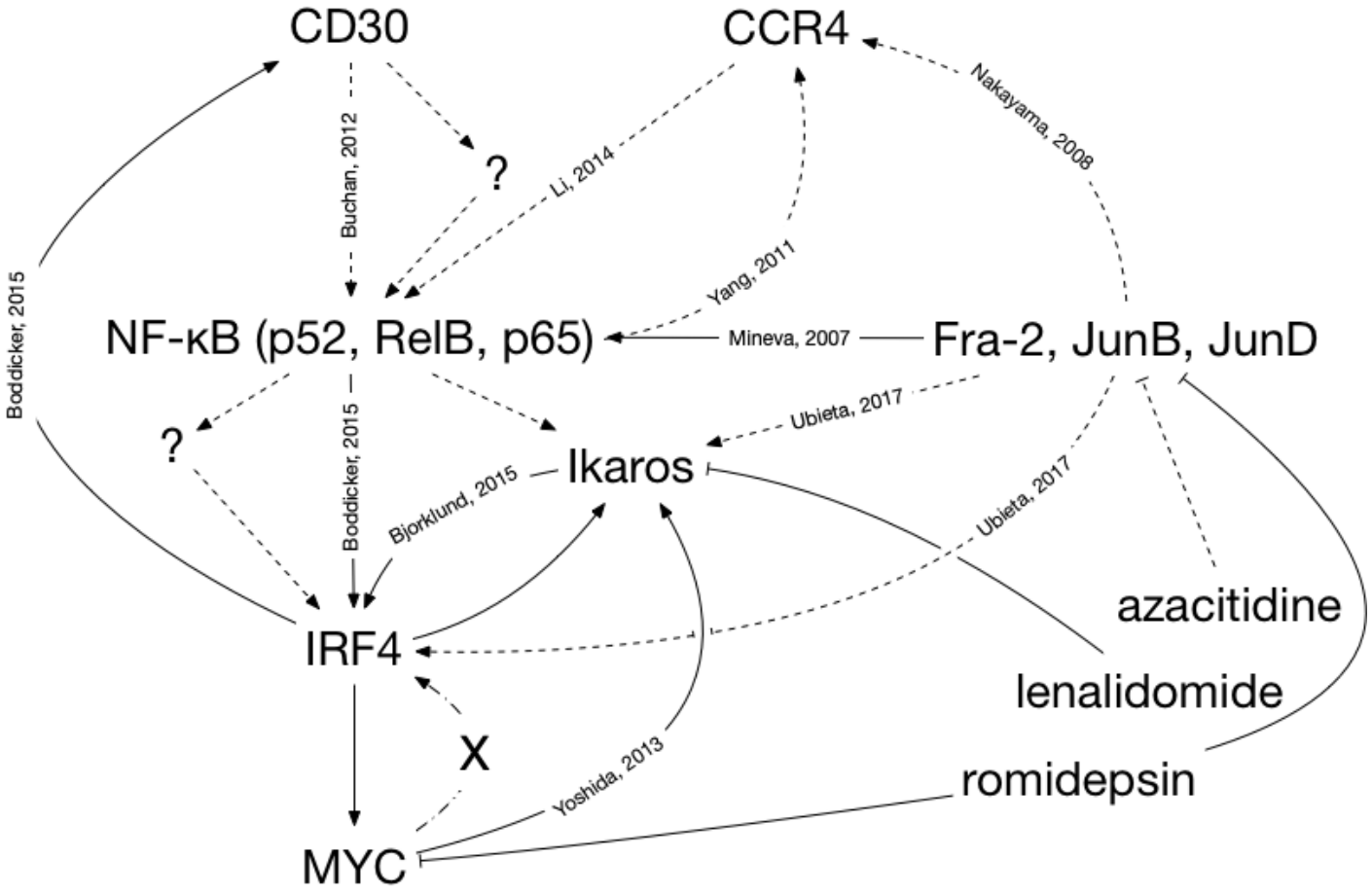
1.4 ROLE OF IRF4 IN TCM

One-third of PTCLs have over-expression of interferon regulatory factor-4 (IRF4) which regulates transcription factors involved in lymphocyte growth and differentiation [33]. The mechanism of IRF4 overexpression is not entirely clear; however, copy number abnormalities were seen in some cases. There is a positive feedback loop involving CD30, NF-kB, and IRF4 that drives PTCL cell proliferation [33]. Silencing of IRF4 by siRNA in PTCL cell line inhibited proliferation, downregulated MYC gene expression, and attenuated Myc protein expression (**Figure 4**). It therefore seems that IRF4 overexpression drives tumor growth in TCM, and would be a candidate therapeutic target.

Lenalidomide is an immunomodulatory drug approved for the treatment of multiple myeloma (MM) and MDS. In the study using MM cell line, lenalidomide induces degradation of Ikaros and downregulates IRF4 [34]. The treatment with lenalidomide was associated with a decrease in MYC levels, decreased cell proliferation and cell death. In eight MM cell lines, high IRF4 levels correlated with increased lenalidomide sensitivity. This finding was confirmed with patients. IRF4 expression was evaluated using real time PCR in bone marrow sample from 154 patients with MM

and patients who had high IRF4 expression showed significantly longer OS by lenalidomide treatment.

Figure 4**: Signaling pathway for survival and proliferation of TCM**



1.5 INVESTIGATIONAL AGENTS

Romidepsin, 5-azacitidine, and lenalidomide have all shown clinical activity in many different T-cell malignancies.

1.5.1 Romidepsin

Romidepsin is a unique bicyclic depsipeptide originally isolated from Chromobacterium violaceum strain 968. Romidepsin is one of the HDAC inhibitors which are considered as epigenetic modulating agents that induce accumulation of acetylated nucleosomal histones and induce differentiation and/or apoptosis. Results of early nonclinical studies showed that romidepsin inhibited the growth of the Ha-ras-transformed NIH3T3 clonal cell line, Ras-1, and induced reversion of the transformed morphology to normal within 1 day at a concentration of 2.5 ng/mL. While mRNA expression of the c myc oncogene in Ras-l cells was decreased in the presence of romidepsin, Ha-ras mRNA expression was unaffected by 24-hour exposure to 2.5

ng/mL of romidepsin. Romidepsin blocked cell cycle transition from G0/G1 to S phase and induced nuclear quiescence. The course of c-myc suppression paralleled that of G0/G1 arrest and correlated with the morphologic reversion of the transformed cells. These results led to the proposal that the growth inhibition and G0/G1 arrest resulted from romidepsin blocking the ras-mediated signal transduction pathway. Other investigations of the effect of romidepsin on the G1 to S transition of the cell cycle showed that romidepsin inhibits signal transduction through MAP kinase and causes p53- independent G1 arrest. Romidepsin has also been identified as a histone deacetylase (HDAC) inhibitor similar to trichostatin A based on its ability to cause arrest of the cell cycle at both G1 and G2/M phases to induce internucleosomal breakdown of chromatin, and to inhibit intracellular HDAC activity resulting in an accumulation of marked amounts of acetylated histone species within M 8 cells.

1.5.1.1 Indication and usage

ISTODAX® is a histone deacetylase (HDAC) inhibitor indicated for:

- Treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy.
- Treatment for patients with peripheral T-cell lymphoma (PTCL) who have received at least one prior therapy

1.5.1.2 Non-clinical studies

Potent antitumor effects of romidepsin have been demonstrated both in vitro and in vivo. In vitro, romidepsin exerted antiproliferative activity against 12 human solid tumor cell lines (IC50 ranged from 0.5 to 5.9 nM), but was less potent against cultured normal cells. It was found that the longer the duration of romidepsin exposure, the lower the concentration of drug necessary to induce the antiproliferative activity. Similar IC50 values were found in a study of 13 lymphoid cell lines. In a severe combined immunodeficiency disease (SCID) mouse lymphoma model, male mice inoculated intraperitoneally (IP) with U-937 cells and treated with romidepsin (0.1 to 1 mg/kg, IP) once or twice a week survived longer {median survival times of 30.5 days (0.56 mg/kg) and 33 days (0.32 mg/kg)}, than saline-treated mice (20 days). Two of 12 mice treated with 0.56 mg/kg romidepsin survived past the observation period of 60 days.

1.5.1.3 Summary of adverse events

The most common AEs reported among subjects who received romidepsin monotherapy include GI disturbances (nausea, vomiting, constipation, diarrhea), hematologic toxicities (anemia, thrombocytopenia, neutropenia), and asthenic conditions (fatigue, asthenia, lethargy). Other types of events commonly seen with romidepsin include anorexia, clinical chemistry abnormalities (hypocalcemia, hypoalbuminemia, hyperglycemia, hypomagnesemia), pyrexia, and taste disturbances.

Overall, the incidence of AEs was higher among those with hematologic malignancies, including T-cell lymphomas (343 of 353 subjects; 97%) than among those with solid tumors (337 of 428 subjects; 79%). Review of AEs by system complex showed that particular types of AEs generally occurred at a higher incidence among subjects with hematologic malignancies than those with solid tumors, including gastrointestinal disorders (77% versus 61%, respectively), general disorders and administration site conditions (74% versus 57%, respectively), blood and lymphatic system disorders (43% versus 24%, respectively), infections and infestations (39% versus 13%, respectively), and skin and subcutaneous tissue disorders (29% versus 13%, respectively).

Although the incidence of AEs was higher among subjects with hematologic malignancies than in subjects with solid tumors, the particular types of AEs reported were generally similar by indication. Tumor lysis syndrome (TLS) has been reported to occur in 1% of patients with tumor stage CTCL and 2% of patients with Stage III/IV PTCL in clinical trials. Patients with advanced stage disease and/or high tumor burden should be closely monitored, appropriate precautions should be taken, and treatment should be instituted as appropriate.

Overall, the incidence of Grade 3 or greater AEs among subjects who received romidepsin monotherapy was higher among these with hematologic malignancies (227 of 353 subjects; 64%) than among those with solid tumors (235 of 428 subjects; 55%). As was the case for AEs overall, the particular types of Grade 3 or higher AEs reported were generally similar by indication.

1.5.1.4 Summary of SAEs

The incidence of SAEs, regardless of relationship to romidepsin, among subjects receiving romidepsin monotherapy was similar among those with hematologic malignancies and solid tumors (37% versus 34%, respectively). Furthermore, the SAE profile was generally similar between subjects with hematologic malignancies and solid tumors. Among the 353 subjects receiving romidepsin monotherapy with hematologic malignancies, the most commonly reported SAEs included pyrexia (21 subjects; 6%), neutropenia (including the MedDRA preferred terms (PT) neutrophil count decreased and neutrophil count) (16 subjects; 5%), thrombocytopenia (including the MedDRA PT (s) platelet count decreased and platelet count) (16 subjects; 5%), hypotension NOS (12 subjects; 3%), and dehydration and febrile neutropenia (11 subjects each; 3%). Among the 428 subjects receiving romidepsin monotherapy with solid tumors, the most commonly reported SAEs were vomiting NOS (26 subjects; 6%), nausea (24 subjects; 6%), dyspnea (17 subjects; 4%), anemia (including the MedDRA PT(s) hemoglobin decreased and hemoglobin) (15 subjects; 4%), and dehydration and fatigue (12 subjects each; 3%).

1.5.1.5 Cardiovascular effects

There have been reports of cardiovascular effects of HDAC inhibitors including an effect on QTc prolongation. Data on File with Celgene Corporation 2006. Several treatment-emergent morphological changes in ECGs (including T wave and ST-segment changes) have been reported in clinical studies with romidepsin. Many of these ECG morphologic abnormalities were determined by automated machine readings and were also observed at baseline. These ECG changes were transient and were not associated with functional cardiovascular changes or with symptoms. No cardiac events of torsade de pointes have been reported. A comprehensive evaluation of the cardiac effects of romidepsin, including rigorous statistical analyses that followed the guidelines specified in International Conference on Harmonisation (ICH) E14, was performed under the direction of an expert cardiologist. Analyses performed were primarily based on data from 3 clinical studies of romidepsin: Study GPI-04-0001 in subjects with CTCL; NCI Study 1312 in subjects with CTCL, PTCL, or other T-cell lymphomas; and Study GPI-06-0005 in subjects with advanced solid tumors or hematologic malignancies.

A series of analyses were performed on the pool of studies as well as on individual study data to assess the impact of romidepsin on QTc prolongation, and, for Studies GPI-04-0001 and GPI-06-0005, to determine the potential confounding impact on this parameter of antiemetics given prior to romidepsin. In an analysis of the romidepsin concentration-QTc relationship based on data from 110 subjects in 3 clinical studies, a mean 2.7 msec increase (90% confidence interval (CI) upper bound 5.3 msec) in QTcF interval was measured following infusion of romidepsin when compared

to baseline post-antiemetic administration. The reported increase in QTcF interval was a mean 5 msec (90% CI upper bound 7.7 msec) in a subanalysis from Studies GPI-04-0001 and GPI-06-0005 (n=74), comparing QTc interval pre-antiemetic administration to post-infusion. Data from NCI Study 1312 shows that this QTcF change persists to 24 hours, with a return to baseline by 48 hours, while in the smaller GPI-06-0005 study, QTcF peaked 2 hours post-infusion and there was no QTcF effect seen at 24 hours. Based on these analyses, it was concluded that a significant portion of the change in QTcF was associated with anti-emetic administration.

In all studies, mean HR was shown to increase by approximately 10 bpm after study drug administration, with a return to baseline by 24 hours. This rise in HR and the resulting deficiencies in standard QT heart rate correction formulae likely contribute to an artifactual calculation in the change in the QTc interval when compared to baseline. Pharmacodynamic models, where the predominant effect seen was related to HR, with no evidence of a concentration – QTc relationship, support this hypothesis.

Shift tables showed that, in this disease population, evidence of morphologic ECG abnormalities existed at baseline. In addition, the frequency of treatment emergent abnormalities was similar to the frequency of abnormal to normal transitions, particularly between dosing days. ECG changes were not associated with functional impairment.

Per current ICH E14 guidelines, the findings from these studies show that the QTc changes are below the regulatory threshold of concern, particularly considering that these studies were conducted in a target population of generally older subjects with advanced malignancies, often with significant comorbidities and concomitant medication usage. Notably, there were no absolute QTc values greater than 480 msec, no increases of ≥ 60 msec and no cardiac events of torsade de pointes. One subject had a ventricular arrhythmic event, but also had evidence of intracardiac lymphoma. Therefore, based upon these data, romidepsin does not have a significant effect on the QT interval. There is a mild effect on HR that is no longer apparent 20 hours after study drug administration. Due to this effect on HR, there may be an artifactual change in the QTc interval due to the inherent inadequacy of correction formulae as the HR moves away from 60 bpm. In addition, there does appear to be a transient change in the T-wave / ST-segment in some subjects that may affect the precise determination of the T-wave in a clinical setting.

After the data cutoff date for this protocol introduction, a single report of QTc prolongation to a maximum value of 534 msec, from a minimum baseline value of 437 msec, has been reported from a subject in a clinical study of romidepsin and bortezomib for multiple myeloma. The event was reported as possibly related to romidepsin and unlikely related to bortezomib. The subject had also received ondansetron, which has been reported to prolong QTc.

1.5.2 CC-486 (5-azacitidine)

CC-486 (5-azacitidine), an analog of the pyrimidine nucleoside cytidine, has effects on cell differentiation, gene expression, and deoxyribonucleic acid (DNA) synthesis and metabolism, and causes cytotoxicity. Since the early 1970s, 5-azacitidine has been investigated in the United States (US) for the treatment of acute leukemia. Clinical trials have focused primarily on patients with disease refractory to conventional chemotherapy. These investigations indicated 5-azacitidine has activity in the treatment of acute myeloid leukemia (AML). Clinical trials from the 1980's through recent years have been conducted to evaluate the effects of 5-azacitidine in a variety of other malignant and hematologic disorders, including solid tumors, hemoglobinopathies (thalassemia

and sickle cell anemia), and myelodysplastic syndromes (MDS) as well as the use of 5-azacitidine in the treatment of AML in elderly patients.

1.5.2.1 Indication and usage

Vidaza®, CC-486, (5-azacitidine for injection) is approved by the US Food and Drug Administration (FDA) for all 5 subtypes of the French-American-British (FAB) classification system of MDS: refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS) (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMMoL). Vidaza is also approved by the European Commission (EU) for the treatment of adult patients who are not eligible for hematopoietic stem cell transplantation (HSCT) with the following: intermediate-2 (INT-2) and high-risk MDS according to the International Prognostic Scoring System (IPSS), CMMoL with 10% to 29% marrow blasts without myeloproliferative disorder, and AML with 20% to 30% blasts and multilineage dysplasia, according to World Health Organization (WHO) classification. Vidaza can be administered by the intravenous (IV) or subcutaneous (SC) routes as designated by country approval. As of 18 May 2017, Vidaza (5-azacitidine injectable) has received marketing authorization in 84 countries worldwide, including the US and EU.

An oral formulation of CC-486 (5-azacitidine) has been developed and is currently being evaluated in clinical trials, either as a single agent or in combination with other drugs, for the treatment of hematological and solid malignancies. As of September 2020, oral CC-486 is approved by the US FDA under the name Onureg® as a maintenance treatment for adult patients with AML who achieved a first CR or CR with incomplete blood count recovery (CRi) after intensive induction chemotherapy and who are unable to complete intensive curative therapy, such as HSCT.

1.5.2.2 Summary of adverse events

As of 18 May 2017, approximately 20,408 subjects have been treated with 5-azacitidine in clinical studies, with 2,312 in the Celgene development program worldwide (1,242 with 5-azacitidine injectable, 876 with CC-486 (5-azacitidine oral), and 198 with 5-azacitidine injectable and oral), 8,656 through National Cancer Institute (NCI)-sponsored clinical studies in the US, and an estimated 18,096 in non-Celgene sponsored studies globally. In addition, it is estimated that cumulative exposure to 5-azacitidine during marketing experience is 317,690 patients. Therefore, overall estimated cumulative exposure to 5-azacitidine during clinical trials and commercial experience is 338,098.

In general, the most common AEs reported during the 5-azacitidine clinical trials reflect the underlying nature of the disease and the cytotoxic properties of 5-azacitidine. The most commonly reported adverse reactions with 5-azacitidine treatment were hematological reactions including anemia, thrombocytopenia, neutropenia, febrile neutropenia, and leukopenia, gastrointestinal events including nausea, vomiting, abdominal pain, constipation, and diarrhea, fungal pneumonia and injection site reactions (with SC administration). Adverse reactions associated with IV administered 5-azacitidine were similar in frequency and severity compared with SC-administered 5-azacitidine; adverse reaction that appeared to be specifically associated with the IV route of administration included infusion site reactions (e.g., erythema or pain) and catheter site reactions (e.g., infection, erythema, or hemorrhage) as well as decreased weight, decreased appetite, differentiation syndrome and renal failure. Additional toxicities may also occur, including serious bleeding and fever without infection.

For the most frequently reported Treatment Emergent Adverse Events (TEAEs) (≥ 10% of subjects), the highest incidence of first occurrence was observed within Cycles 1-2. In general, no clinically relevant differences were seen when the safety data were analyzed for age, sex, or MDS subtypes. The most common adverse reactions can be managed through delays or dose decrease of 5-azacitidine and/or supportive measures. The overall safety profile of 5-azacitidine from the ongoing clinical studies is consistent with that described in the IB; however, diarrhea may be more frequent and/or more severe in patients receiving orally-administered CC-486 (5-azacitidine).

1.5.3 Lenalidomide

1.5.3.1 Mechanism of action

Lenalidomide is a proprietary IMiD® compound of Celgene Corporation. IMiD® compounds have both immunomodulatory and anti-angiogenic properties which could confer antitumor and anti-angiogenic effects.

Lenalidomide demonstrates pleiotropic activities in distinct cell types that result in direct antitumor effects on cancer cells, inhibition of stromal growth factor support, and enhancement of host anticancer immunity. The clinical activity of lenalidomide has been most notable in B-cell malignancies including MM, MCL, DLBCL, FL, and B-cell CLL.

The activity of lenalidomide may be further subdivided into the following categories: direct antiproliferative activity against hematopoietic tumor cells; immunomodulatory activity including upregulation of T cell and NK cell responses; and inhibition of monocyte responses, antiangiogenic activity, and pro erythropoietic activity.

Lenalidomide's pleiotropic activities in a range of cell types including MM cells and immune effector cells suggest modulation of multiple molecular pathways. Studies conducted to identify the molecular target(s) of lenalidomide have shown that it physically associates with the protein cereblon (encoded by the CRBN gene), a protein required for the teratogenic effects of thalidomide in zebrafish and chicken embryos. Cereblon is a substrate receptor for an ubiquitin E3-ligase complex containing deoxyribonucleic acid (DNA) damage-binding protein 1 (DDB1), cullin 4 (CUL4), and regulator of cullins 1 (Roc1) proteins (CRL4cereblon). Upon binding to Cereblon, lenalidomide induces the ubiquitination of substrate proteins, including Ikaros (encoded by the gene IKZF1) and Aiolos (encoded by the gene IKZF3), thus targeting them for proteasomal-dependent degradation. It was also demonstrated that the expression of Cereblon in MM cells is linked to the anti-proliferative effects of lenalidomide and to the acquired resistance in vitro. The downstream anti-proliferative and pro-apoptotic effects of Ikaros and Aiolos are linked to the subsequent downregulation of the MM growth-promoting factors c-Myc and IRF4.

Ikaros and Aiolos are zinc finger transcription factors initially discovered as regulators of the T cell receptor and are required for proper hematopoiesis, particularly lymphocyte development and plasma cell maturation. Cereblon expression also mediates the T-cell response to lenalidomide through the targeted degradation of Ikaros and Aiolos. In activated T cells in which cereblon was transiently decreased, interleukin-2 (IL-2) and TNF-α induction by lenalidomide was markedly reduced. Since IL-2 and TNF-α are important for tumor surveillance by activated T cells, these results indicate that some of the immunomodulatory effects of lenalidomide are mediated via initial binding to cereblon. Specifically, upon engagement with the CRL4cereblon, lenalidomide induced ubiquitination and proteasomal degradation of Ikaros and Aiolos in T cells in a time- and

concentration-dependent manner. Because Ikaros and Aiolos are known repressors of the IL-2 promoter, their degradation in response to lenalidomide and other IMiDs® compounds, explains the enhanced T cell IL-2 production.

In summary, lenalidomide exhibits potent anti-tumor activity in B cell malignancies, which appears to be mediated through the protein target, cereblon. While specific cereblon interaction networks are still to be defined, these results are key for further understanding of the mechanism of lenalidomide effects.

1.5.3.2 Indication and usage

Revlimid® (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. Revlimid® is also approved in combination with dexamethasone for the treatment of patients with multiple myeloma and Revlimid® has recently been approved in the treatment of patients with mantle cell lymphoma whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.

1.5.3.3 Summary of adverse events

Most frequently reported adverse events reported during clinical studies with lenalidomide in oncologic and non-oncologic indications, regardless of presumed relationship to study medication include: Leukopenia, Neutropenia, Febrile neutropenia, Granulocytopenia, Lymphopenia; Anemia; Thrombocytopenia; Vision Blurred; Diarrhea; Upper abdominal pain, Abdominal pain, Toothache, Constipation; Dyspepsia; Nausea; Vomiting; Asthenia; Fatigue; Edema, Peripheral edema; Pyrexia; Chills; Pneumonia, Bronchitis, Upper respiratory tract infection, Urinary tract infection, Erysipelas, Gastroenteritis, Herpes simplex, Herpes zoster, Influenza, Lower respiratory tract infection, Sinusitis, Sepsis, Bacteremia; Nasopharyngitis, Pharyngitis; Rhinitis; Weight loss; Decreased appetite; Hyperglycemia; Hypokalemia, Hypocalcemia, Hypophosphatemia, Hypomagnesemia, Hyponatremia; Pain in extremity, Pain in limb, Arthralgia, Back pain, Bone pain, Muscle spasms, Musculoskeletal pain, Muscle cramp, Chest pain and Myalgia; Dizziness; Dysgeusia, Headache; Cataract; Hypoaesthesia; Neuropathy, Peripheral neuropathy, Peripheral sensory neuropathy; Tremor; Cough; Dyspnea; Epistaxis; Pulmonary embolism, Deep vein thrombosis; Dry skin; Pruritus; Rash, Hypersensitivity (in uncommon category); Depression; Insomnia and recently Vertigo.

1.5.3.4 Additional Toxicity Information

- Venous Thromboembolism: Venous thromboembolism including deep vein thrombosis (DVT) and pulmonary embolism (PE) has been reported in patients during treatment for NHL generally, occurring at incidences from ~7% up to 20%.[35] [36] [37] In lenalidomide clinical trials, DVT and PE were reported in 7 (2.6%) and 6 (2.2%) of 266 subjects with relapsed or refractory NHL receiving lenalidomide in clinical studies NHL-002 and NHL-003[38, 39]. Anti-thrombotic prophylaxis was not suggested in NHL-002 but was required for subjects considered to be at high risk of developing DVT in NHL-003. In a study evaluating lenalidomide plus rituximab versus lenalidomide alone in relapsed follicular lymphoma subjects, thrombosis was reported in 2 (4%) of the combination arm versus 7 (16%) in the single agent arm.[40] In an additional study evaluating lenalidomide plus rituximab in MCL patients 2 (5%) Grade 3 and 1 (5%) Grade 4 thromboembolic events were reported. [41]

- Second New Cancers: According to researchers, patients with cancer have a higher risk of developing a second new cancer when compared to people without cancer. In clinical studies of newly diagnosed multiple myeloma, a higher number of second cancers were reported in patients treated with induction therapy and/or bone marrow transplant then lenalidomide for a long period of time compared to patients treated with induction therapy and/or bone marrow transplant then placebo.

1.6 CLINICAL ACTIVITIES OF INVESTIGATIONAL AGENTS IN T-CELL MALIGNANCIES

1.6.1 Romidepsin

CTCL. The activity of romidepsin was evaluated in a total of 135 evaluable subjects (EP) with CTCL in Study GPI-04-0001 and NCI Study 1312. Across all 135 evaluable subjects with CTCL, the overall response rate (ORR) was 41% (55/135) and the complete response (CR) rate was 7% (10/135). Subjects with advanced disease had a similar ORR as subjects with earlier stage disease: 42% for ≥Stage IIB and 38% for Stage I or IIA disease. Romidepsin was active in all sites of disease, had an ORR of 34%, including CR rate of 6%, including skin, lymph nodes, viscera, and blood. The median duration of response was 454 days (14.9 months) [42]. Although the median time to response was 57 days (1.9 months), in some cases an objective response to romidepsin was achieved after ≥6 months. Across all 135 subjects included in the pooled EP Analysis Set, median time to disease progression was 252 days (8.3 months). In Study GPI-04-0001, treatment alleviated pruritus in most subjects (48 of 52, 92%) who entered the study with this symptom. Patients in the pivotal study for CTCL had an ORR of 34%, including CR rate of 6%, and a median duration of response (DOR) of 15 months [42].

PTCL and other T-cell Lymphomas. Romidepsin inhibited cell proliferation and induced apoptosis through inhibiting PI3K/AKT/mTOR pathway in PTCL [43]. A phase II study (N=130) in relapsed/refractory PTCL showed ORR of 25% with CR rate of 15% [44]. Romidepsin was given at 14 mg/ m^2 as a 4-hour intravenous infusion on days 1, 8, and 15 every 28 days. The median PFS was 4 months overall. It should be noted; however, that responses were frequently durable with the median duration of response was 28 months. The most common grade 3-4 adverse events were thrombocytopenia (24%), neutropenia (20%), and infections (all types, 19%). The activity of romidepsin was evaluated in a Phase 2, NCI-sponsored study in 48 subjects with PTCL or other T-cell lymphomas. Of these 48 subjects, 28 had PTCL and 20 had other T-cell lymphomas, including angioimmunoblastic, primary cutaneous large T-cell, gamma-delta T-cell, and anaplastic large T-cell lymphomas.

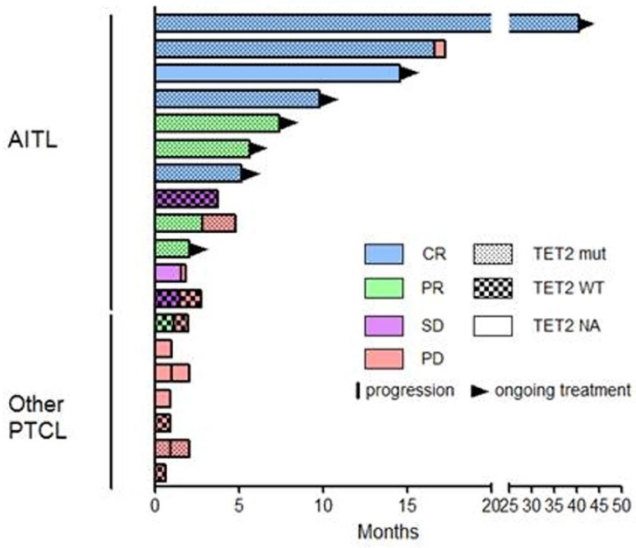
Among all 48 subjects, the ORR (CR+PR) was 31% (15/48). The CR and PR rates were 8% (4/48) and 23% (11/48), respectively. Fifteen percent (15%; 7/48) of subjects experienced stable disease. When response was evaluated among the 34 subjects who received ≥2 cycles of therapy, the ORR was 44% (15/34) and the CR and PR rates were 12% (4/34) and 32% (7/34), respectively. Twenty-one percent (7/34) of subjects who received ≥2 cycles of therapy experienced stable disease.

1.6.2 5-azacitidine

Although 5-azacitidine has not been formally evaluated in prospective trial as single agent for TCM, anecdotal cases of successful treatment with 5-azacitidine are reported in patients who have both AITL and MDS [45, 46]. Recurrent mutations of in genes involved in DNA methylation regulation similar to MDS have been described in PTCL, especially in AITL, suggests that PTCL can be sensitive to HMA. In a case series of 19 patients who received 5-azacitidine for the

treatment of PTCL (and MDS) showed ORR of 53%, and it was significantly higher in patients with AITL patients than in patients with other PTCL entities (**Figure 5**: 75% versus 15%, p=0.02) [47]. In the trial of 5-azacitidine for MDS, the common side effects from the treatment were hematological (rates are above 50% in all three lineage due to nature of original MDS).

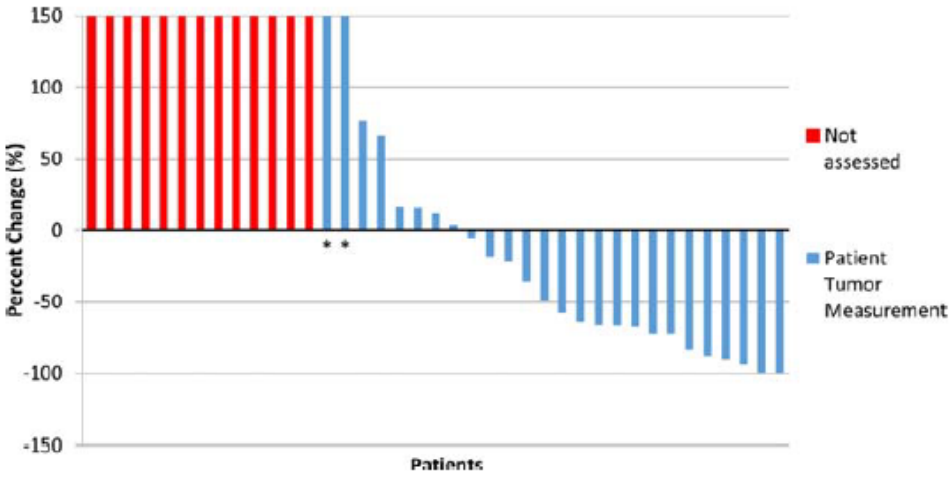
Figure 5: Response duration of 5-azacitidine in PTCL



1.6.3 Lenalidomide

Lenalidomide showed activity to PTCL [48-50]. Lenalidomide, at the dose of 25 mg, was given on days 1 to 21 of each 28-days cycle. A phase II study with 39 patients evaluating lenalidomide monotherapy to untreated who are not candidate for combination chemotherapy and relapsed/refractory PTCL showed ORR of 26% with CR rate of 8%, and the median DOR was 13 months (**Figure 6**) [48]. In subgroup analysis, untreated PTCL patients demonstrated an ORR of 50% with a median DOR of 21 months suggesting better efficacy of lenalidomide in earlier course of treatment. Another small phase II study focusing on patients with PTCL-NOS showed an ORR of 30% [50]. In a multicentre phase II trial with 54 patients conducted in France, the ORR was 22% with CR rate of 11% [49]. Non-significant slightly higher response was seen in patients with AITL with the ORR of 31% compared to 20% in PTCL-NOS. The median PFS and the median duration of response in all patients were 2.5 and 3.6 months, respectively. Lenalidomide also showed activity in patients with refractory MF/SS with ORR of 28% [51]. A phase 2 trial of lenalidomide in patients with relapsed/refractory ATLL showed ORR of 42%, including 4 confirmed and 1 unconfirmed CR [52]. Based on this study, lenalidomide was approved in Japan for use in patients with R/R ATLL. The common side effects from lenalidomide are fatigue, rash and hematological toxicities with grade 3-4 thrombocytopenia and neutropenia observed in 10-20% and 10-15% of patients, respectively.

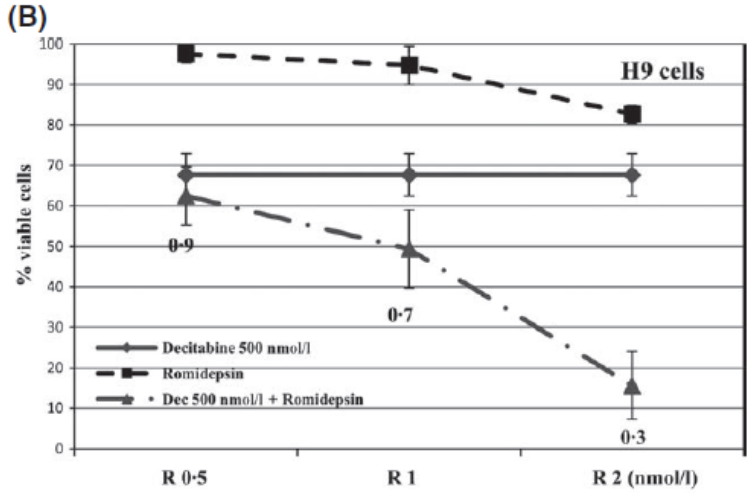
Figure 6: Response of lenalidomide in PTCL



1.7 SYNERGISTIC EFFECT OF ROMIDEPSIN AND 5-AZACITIDINE

Romidepsin and 5-azacitidine showed synergistic anti-proliferative effect in vitro for PTCL and CTCL by activating caspase cascade and inducing apoptosis (**Figure 7**) [53, 54]. As a single agent, romidepsin and decitabine (same class of medication to 5-azacitidine) modulated 76 and 54 genes, respectively, in various PTCL and CTCL cell lines by treatment; however, the combination modulated 390 more genes that are mainly involved in regulation of apoptosis [54].

Figure 7: Synergistic effect of romidepsin and HMA



Also, in our preclinical studies of drug combinations for ATLL, 5-azacitidine acted synergistically with most of the drugs tested (unpublished data).

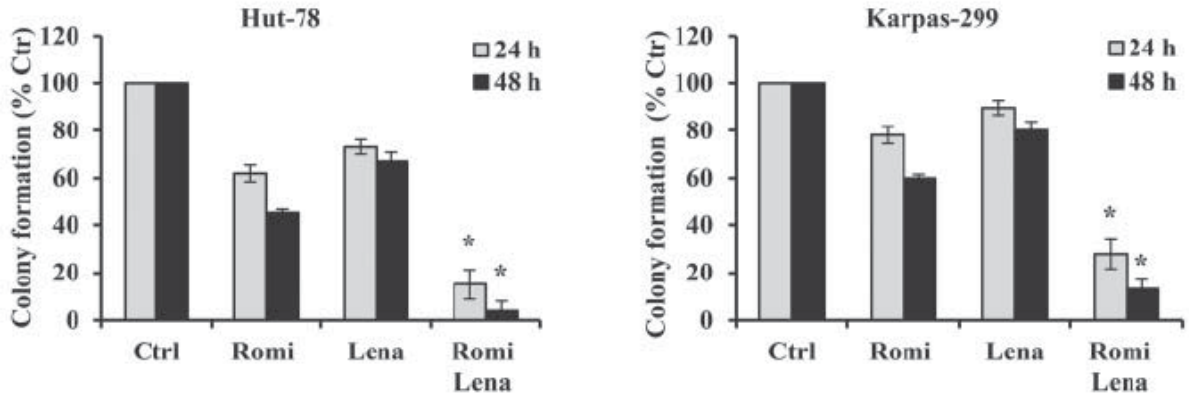
This combination, romidepsin and 5-azacitidine has proven its marked activity in clinical setting in a phase I/II trial [55, 56]. ORR in patients with T-cell lymphoma was 79% (11 of 14 patients), including 6 patients with CR (43%). Interestingly, all 6 patients with AITL have responded. Although with short follow up, response seems to be durable and some patients showing DOR over a year. The most frequent grade 3-4 hematologic adverse effects were neutropenia (39%),

lymphopenia (39%), and thrombocytopenia (28%). The most common non-hematologic grade 3-4 adverse events were febrile neutropenia (8%). The recommended phase 2 dose of the combination was CC-486 (5-azacitidine) 300 mg orally days 1-14 and romidepsin 14 mg/m^2 days 8, 15, and 22 on a 35-day cycle.

1.8 SYNERGISTIC EFFECT OF ROMIDEPSIN AND LENALIDOMIDE

The combination of lenalidomide and romidepsin showed synergistic effect and enhanced cell death in PTCL cell lines by inducing apoptosis (**Figure 8**) [57]. This apoptosis is mediated by caspase activation and the combination inactivated the AKT, MAPK, and STAT3 pathways.

Figure 8: Synergistic effect of romidepsin and lenalidomide



An early phase I/II study has been conducted to evaluate the combination of romidepsin and lenalidomide [58]. In 21 patients reported (11 PTCL, 10 CTCL), ORR was 53%, with a median event-free survival of 3.8 months. The MTD was romidepsin 14 mg/m^2 IV on days 1, 8, and 15 and lenalidomide 25 mg oral on days 1-21 of a 28-day cycle. Given the longer median DOR of lenalidomide used as single agent in untreated PTCL patients, a phase II study is currently investigating the role of the combination of lenalidomide and romidepsin in untreated PTCL patients (NCT02232516).

1.9 5-AZACITIDINE IN COMBINATION WITH LENALIDOMIDE

There have been no trials of combination 5-azacitidine and lenalidomide in TCM. In phase I study of MDS, MTD was 5-azacitidine 75 mg/m^2 on days 1 to 5 and lenalidomide 10 mg on days 1 to 21 in 28-day cycle [59]. Due to the nature of leukemic disease, hematological toxicity of this combination were difficult to assess, however, grade 3-4 non-hematological toxicities were not common and was manageable [60]. Within 36 patients enrolled, 8 patients had a dose reduction of lenalidomide: 6 were reduced from 10 to 5 mg and completed the study at 5 mg, whereas 2 were reduced to 5 mg and later were increased back to 10 mg.

1.10 RATIONALE OF COMBINATION OF LENALIDOMIDE, ROMIDEPSIN AND CC-486 (ORAL 5-AZACITIDINE)

Due to clinical activity of all three agents and synergies seen in 2 drug combinations among three drugs, we hypothesize that three drug combination in addition to dexamethasone can potentially block multiple critical pathway TCM requires for proliferation and survival (**Figure 4**).

With the safety profiles and MTDs of all lenalidomide/romidepsin, 5-azacitidine/romidepsin and 5-azacitidine/lenalidomide combinations established, and with the hypothesis that the addition of

dexamethasone may decrease tumor flares associated with lenalidomide and therefore improve its tolerability, the combination of all four agents is ready to be tested in a phase I trial.

Based on PK/PD data and phase I study of CC-486 (oral 5-azacitadine) in MDS as well as safety data from prior study of romidepsin in combination with 5-azacitidine [55, 56], CC-486 (oral 5-azacitidine) dose will be 300mg orally. CC-486 (oral 5-azacitidine) was initially tested in phase I study in patients with MDS, chronic myelomonocytic leukemia or acute myeloid leukemia and the MRD was 480mg daily (day 1-7, 28-day cycle) [61]. Later in phase II study, lower dose with longer duration of CC-486 was tested due to short half-life of CC-486 (5-azacitidine) and showed that 300mg orally (day 1-14, 28-day cycle) was safe and efficacy was comparable to subcutaneous 5-azacitidine 75 mg/m^2 administered for 7 days (28-days cycle) [62].

1.10.1 Doses of lenalidomide, romidepsin, and CC-486 (oral 5-azacitidine)

Phase I/II trial of romidepsin and CC-486 (5-azacitidine) determined romidepsin of 14 mg/m^2 days 8, 15, and 22, and CC-486 (5-azacitidine) of 300 mg orally days 1-14 on a 35-day cycle recommended dose; however, to make cycle shorter and to add lenalidomide, we will reduce the dose of both drugs to CC-486 (5-azacitidine) of 300 mg orally days 1-10 and romidepsin of 12 mg/m^2 days 1 and 10. If this dosing schedule of CC-486 (5-azacitidine) and romidepsin allows for lenalidomide to be given at the maximum dose planned (25 mg orally days 1-10), the protocol will be amended to allow for a higher dose of romidepsin (14 mg/m^2 days 1 and 10).

1.10.2 Number and duration of cycles

As noted above, allogeneic stem cell transplantation is the only curative treatment for R/R TCMs. The proposed regimen was therefore primarily developed as 1) an induction regimen for patient who are not in at least a partial remission, and are therefore not eligible for a transplant, and 2) a bridge to an allogeneic hematopoietic stem cell transplant (alloSCT) for patients who have residual disease after one or more systemic treatment and therefore have refractory lymphoma, although they may be considered a transplant candidate. Patients with lymphoid malignancies who respond to most treatment, including the drugs used in this regimen, do so within the first 4 cycles of treatment. Total number of cycles is therefore limited to 6 in this trial.

With our clinical experience in aggressive TCM at NIH particularly with ATLL showing progression within 4 weeks, treatment cycle is set as every 3 weeks (every 21 days). A shorter treatment cycle will also allow for more frequent response evaluations and more timely referrals for an alloSCT. If the proposed treatment schedule is consistently associated with prolonged neutropenia requiring treatment delays in the majority of patients, the protocol will be amended to administer treatment every 4 weeks (every 28 days).

1.10.3 Changes in Study Design

The original dosing schema included a window for lenalidomide alone for seven days before adding in the combination of romidepsin, CC-486 (5-azacitidine), dexamethasone, and lenalidomide and a cycle length of 21 days. After completing the dose escalation phase, we decided to remove the lead-in window due to the risk for toxicities related to cytokine release observed in CTCL participants treated with single agent lenalidomide. Additionally, as almost all participants have had their cycles delayed to 28 days, we are extending the cycle to 28 days and removing the lenalidomide window for the remaining participants. Extending the cycles to 28 days would be safer and more tolerable for the participants without affecting the efficacy of the treatment regimen. The remaining patients will be enrolled onto our newly added, Arm 3.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Patients must have relapsed after or progressed during at least one line of prior systemic therapy (which may include allogeneic stem cell transplantation) for mature T or NK/T neoplasm, i.e. have relapsed and/or refractory mature T and NK neoplasm per 2016 WHO classification excluding chronic lymphoproliferative disorder of NK cells, aggressive NK-cell leukemia, and Cutaneous T-Cell Lymphoma.

2.1.1.2 T or NK/T neoplasm from initial diagnosis **or** recurrence must be histologically or cytologically proven and diagnosis be confirmed by the Laboratory of Pathology, NCI,

2.1.1.3 Patients with ALCL or CD30 positive MF/SS must have relapsed after or become intolerant to prior anti-CD30 targeting therapy treatment with brentuximab vedotin

2.1.1.4 For patients without circulating leukemia/lymphoma cells detectable by flow cytometry, a formalin fixed tissue block or 15 slides of tumor sample (archival or fresh) must be available at enrollment for performance of correlative studies. **NOTE:** Patients without circulating malignant cells must be willing to have a tumor biopsy if prior tissue or adequate archival tissue is not available (i.e., post-enrollment and prior to treatment).

2.1.1.5 Disease must be measurable with at least one measurable lesion by RECIL 2017 or mSWAT criteria (see Section **6.3**), or have an abnormal clonal T-cell population detectable by peripheral blood flow cytometry

2.1.1.6 Age ≥18 years

2.1.1.7 ECOG performance status ≤2, or ≤ 3 if the decreased performance status is deemed to be due to disease and not residual toxicity from prior therapy or other causes (see **Appendix A**).

2.1.1.8 Adequate organ and marrow function as defined below:

Absolute neutrophil count	≥ 1,000/mcL
Platelets	≥ 75,000/mcL
Total bilirubin	≤ 1.5 X institutional upper limit of normal (ULN)
AST(SGOT)/ALT(SGPT)	≤ 2.5 X institutional ULN
Serum Creatinine OR Creatinine Clearance	≤ 1.5 mg/dL OR ≥ 60 mL/min/1.73 m^2 as calculated by direct measurement of 24-hour urine for creatinine clearance

2.1.1.9 Negative serum or urine pregnancy test at screening for individuals of childbearing potential (IOCBP)

NOTE: IOCBP is defined as any individual of childbearing potential who has

experienced menarche and who has not undergone successful surgical sterilization or who is not postmenopausal. IOCBP must have a negative pregnancy test (HCG blood or urine) during screening.

2.1.1.10 All study participants must be registered into the mandatory Revlimid REMS® program and be willing and able to comply with the requirements of the REMS® program (see **Appendix D**).

2.1.1.11 Individuals of child-bearing potential and individuals who can father children must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for at least 6 months after completion of treatment for individuals, and for at least 3 months after completion of treatment for individuals who can father children. Individuals of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program (see **Appendix D**).

2.1.1.12 Ability of subject to understand and the willingness to sign a written informed consent document.

2.1.2 Exclusion Criteria

2.1.2.1 Patients who are receiving any other investigational agents.

2.1.2.2 Anti-cancer treatment within 2 weeks prior to enrollment. (4 weeks for monoclonal antibodies and 6 weeks for nitrosoureas or mitomycin C).

2.1.2.3 Patients who have received two of the following drugs at any point: lenalidomide, romidepsin, and 5-azacitidine. Patients who have received only one of the three drugs remain eligible.

2.1.2.4 Patients with a diagnosis of CTCL are excluded from participation in the expansion cohort.

2.1.2.5 Other malignancy that requires ongoing systemic hormonal therapy, chemotherapy, or immunotherapy.

2.1.2.6 History of allergic reactions or known or suspected hypersensitivity attributed to compounds of similar chemical or biologic composition to lenalidomide, romidepsin and 5-azacitidine

2.1.2.7 Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring systemic therapy, or psychiatric illness/social situations that would limit compliance with study requirements.

- Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.
- For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.
- Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

2.1.2.8 History of inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis), celiac disease (i.e., sprue), prior gastrectomy or upper bowel removal, or any other gastrointestinal disorder or defect that would interfere with the absorption, distribution, metabolism or excretion of the study drug and/or predispose the subject to an increased risk of gastrointestinal toxicity.

2.1.2.9 Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), congenital long QT syndrome, or other serious cardiac arrhythmia including 2nd degree atrio-ventricular (AV) block type II, 3rd degree AV block, or bradycardia (ventricular rate less than 50 beats/min).

2.1.2.10 Hypertrophic cardiomegaly or restrictive cardiomyopathy from prior treatment or other causes.

2.1.2.11 Uncontrolled hypertension, i.e., blood pressure (BP) of ≥160/95; patients who have a history of hypertension controlled by medication must be on a stable dose (for at least one month) and meet all other inclusion criteria.

2.1.2.12 Triplicate average baseline QTcF interval ≥ 480 ms

2.1.2.13 Patients taking drugs leading to significant QT prolongation (see **Appendix E**) **Note**: A 5 half-life washout period must have elapsed following the use of these drugs prior to administration of romidepsin.

2.1.2.14 Concomitant use of rifampin and other strong CYP3A4 inhibitors and inducers (see **Appendix C**) within 2 weeks prior to starting protocol therapy.

2.1.2.15 Other severe acute or chronic medical conditions including psychiatric conditions such as recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

2.1.2.16 Pregnant or lactating individuals. Pregnant individuals are excluded from this study because lenalidomide is a Class X agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the participant of childbearing potential with lenalidomide, breastfeeding should be discontinued if the participant of childbearing potential is treated with lenalidomide. These potential risks may also apply to other agents used in this study.

2.2 RECRUITMENT STRATEGIES

Study participants will be recruited from the population of patients screened in the lymphoid malignancies clinic of the National Institutes of Health. These will include both referrals from outside physicians as well as patient self-referrals. This protocol may be abstracted into a plain language announcement posted on NIH websites: https://ccr.cancer.gov/ Lymphoid-Malignancies-Branch and https://ClinicalTrials.gov, on NIH social media platforms, and on the official Lymphoid Malignancy Branch social media accounts.

2.3 SCREENING EVALUATION

2.3.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images
- Review of existing photographs or videos
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes

2.3.2 Screening activities performed after a consent for screening has been signed

The following activities will be performed only after the subject has signed the consent for study 01C0129. Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a patient has signed the consent.

Assessments and procedures to confirm study eligibility should be completed within 28 days prior to registration (unless otherwise noted). See also the Study Calendar provided in Section **3.9**.

2.3.2.1 Clinical Evaluations

- Disease history, including: diagnosis, treatment (e.g., systemic treatments, radiation and surgeries), disease status, and significant prior/ongoing side effects and symptoms
- Complete medical and social history, including: all active conditions considered to be clinically significant by the treating investigator, as well as smoking history
- Physical examination, including: height (screening only), weight, vital signs (i.e., temperature, pulse, respiratory rate, and blood pressure); review of medications and symptoms/side effects; and, assessment of performance status

2.3.2.2 Laboratory Evaluations

NOTE: Results from outside NIH are accepted.

- CBC with differential, platelets and reticulocyte count
- Chemistry panels (as noted) or specific analyte required for eligibility, including: Creatinine (i.e., Acute Care Panel); serum calcium, phosphate, magnesium and albumin (i.e., Mineral Panel); ALT, AST, total bilirubin (i.e., Hepatic Panel, direct bilirubin if indicated); LDH
- Serum Lipase and Amylase
- Coagulation panel, including: PT/INR and a PTT
- Thyroid function tests, including: thyroid stimulating hormone (TSH) with reflex free thyroxine (T4)
- Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody, Hepatitis C antibody (HCVAb) (qualitative), HIV 1/2 antibody (qualitative) and HTLV-1/2 serologies (within 3 months). **NOTE:** For individuals with a positive hepatitis B core antibody, HBV DNA PCR will be performed to screen for subclinical infection; for patients with

positive hepatitis C antibody, HCV PCR will be performed; for patients with positive HIV antibodies, HIV1/2 viral load will be checked.

- Urinalysis (with microscopic examination if abnormal)
- Serum or urine pregnancy test (B-HCG) for individuals of childbearing potential
- Clonal T-cell receptor rearrangement by PCR (peripheral blood and/or tissue), within 3 months prior to enrollment.

2.3.2.3 Imaging Studies

NOTE: Results from outside NIH are accepted. Other body areas may be imaged if clinically indicated.

- CT neck, chest, abdomen and pelvis (CT should be performed with IV contrast, unless patient is allergic or has renal insufficiency; other imaging may be substituted at the discretion of the investigator (such as MRI))
- PET/CT torso (extremities to be included if there is confirmed or suspected disease involvement)
- MRI of brain (only in patients with suspected involvement of CNS)

2.3.2.4 Cardiac Evaluation (within 3 months)

- Electrocardiogram (EKG)
- Transthoracic echocardiogram

2.3.2.5 Pulmonary Evaluation (if indicated)

- Diffusing capacity/alveolar volume (DLCO/VA) forced expiratory volume in 1 second (FEV1) for patients with significant pulmonary or smoking history.

2.3.2.6 Other Procedures

- Pathologic review/confirmation of diagnosis by Laboratory of Pathology, NCI (no time limit). If archival sample is not available or not adequate, a fresh tumor biopsy and/or peripheral blood sample will be obtained.

2.4 Participant Registration and Status Update Procedures

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found at: https://nih.sharepoint.com/sites/NCI-CCR-OCD-Communications/SitePages/OEC-Administrative---Clinical-Research-(ADCR).aspx?Mode=Edit.

2.5 Treatment Assignment Procedures

NOTE: For NCI CCR registration and enrollment system purposes only

2.5.1 Cohorts

Number	Name	Description
1	Mature T-cell malignancies: Dose Escalation (Closed: prior to amendment 12/07/2022)	Relapsed/refractory mature T-cell malignancies: (up to 24 evaluable patients; 5 dose levels)

Number	Name	Description
2	Mature T-cell malignancies: Dose Expansion	Relapsed/refractory mature T-cell malignancies (not including CTCL): (up to 6 additional evaluable patients; 9 total evaluable at the MTD)

2.5.2 Arms

Number	Name	Description
1	Experimental Treatment: Dose Escalation (Closed: prior amendment 12/07/2022)	Lenalidomide by oral intake at escalating doses of 5, 10, 15, or 20 mg/day on days -7 to 10 of each 21-day cycle (max 6 cycles) with CC-486 (5-azacitidine) at 300mg/day by oral intake on days 1-10, romidepsin at 12mg/m^2 by IV infusion on Day 1 and 10 and dexamethasone at 40mg by oral intake on days 1 and 10 of each cycle, to determine MTD
2	Experimental Treatment: Dose Expansion(Closed: with amendment 12/07/2022)	Lenalidomide by oral intake at 20mg on days 1 to 10 of each 28-day cycle (max 6 cycles) with CC-486 (5-azacitidine) at 300mg/day by oral intake on days 1-10, romidepsin at 12mg/m^2 by IV infusion on Day 1 and 10 and dexamethasone at 40mg by oral intake on days 1 and 10 of each cycle
3	Experimental Treatment: Dose Expansion	Lenalidomide by oral intake at 20mg (MTD) on days 1 to 10 of each 28-day cycle (max 6 cycles) with CC-486 (5-azacitidine) at 300mg/day by oral intake on days 1-10, romidepsin at 12mg/m^2 by IV infusion on Day 1 and 10 and dexamethasone at 40mg by oral intake on days 1 and 10 of each cycle

2.5.3 Arm Assignment

Subjects in Cohort 1 will be directly assigned to Arm 1. Subjects in Cohort 2 will be directly assigned to Arm 2.

Once Amendment version 12/07/2022 is approved, new participants enrolled to Cohort 2 will be assigned to Arm 3 (without the lenalidomide window).

2.6 BASELINE EVALUATION

The following should be performed within 28 days prior to the first dose of lenalidomide unless otherwise noted; tests performed as part of screening do not need to be repeated if they were performed within the specified window prior to initiating treatment.

2.6.1 Clinical Evaluations

- Medical history (interim)
- Physical examination including weight, vital signs (i.e., temperature, pulse, respiratory rate, and blood pressure); review of concomitant medications and symptoms/side

effects; and assessment of performance status (ECOG performance score, see **Appendix A**).

2.6.2 Laboratory Evaluations

NOTE: Results from outside NIH are accepted

- Required within 24 hours prior to prescribing lenalidomide:
  - Serum or urine pregnancy test (B-HCG) for individuals of childbearing potential
- Required within 14 days:
  - Serum or urine pregnancy test (B-HCG) for individuals of childbearing potential (required within 10-14 days of prescribing lenalidomide). Prescriptions must be filled within 7 days as required by Revlimid REMS™.
  - CBC with differential, platelets and reticulocyte count
  - Chemistry panels including: Acute Care (sodium, potassium, chloride, CO_2, glucose, BUN, creatinine), Mineral Panel (serum calcium, phosphate, magnesium and albumin) and Hepatic Panel (alkaline phosphatase, ALT, AST, total and direct bilirubin)
  - Others: LDH, Uric acid, Total protein
  - Coagulation panel, including: PT/INR and aPTT
  - Iron panel (includes: ferritin, transferrin, iron), folate, vitamin B12
  - C-reactive protein (CRP)
  - Serum Lipase and Amylase
  - Urinalysis (with microscopic examination if abnormal)
  - HLA typing (A, B, C, DR, DQ)
- Required within 28 days:
  - Lymphocyte Phenotype: T, B and NK cell subsets
  - Peripheral blood flow cytometry

2.6.3 Imaging Studies

Every participant should have an evaluation of known sites of disease as part of baseline evaluation. **NOTE:** Only results from NIH are accepted

- One or more of the following studies: CT, MRI, FDG-PET and/or clinical photography
- Patients with neurological symptoms or signs should undergo MRI scan* of the brain and lumbar puncture

*__NOTE:__ The MRIs to be done in this study may involve the use of the contrast agent gadolinium, if clinically indicated. The risks associated with MRIs and contrast are discussed in the consent form.

2.6.3.1 Other Procedures

- Bone marrow biopsy and aspiration to assess lymphoma involvement (within 3 months)

- Selected patients with cutaneous disease (as determined by physician PI or AI) will have clinical photography and dermatology assessment performed to assess their skin disease

2.6.4 Research Correlates

NOTE: See Section **5** for additional information. The following sample types will be collected for correlative research studies:

- Required:
  - Blood samples for lymphocyte subset testing and circulating tumor DNA
  - Blood, buccal swab, or saliva for germline DNA
  - Tumor Tissue (archival or fresh)
- Optional:
  - Blood samples for tissue immune cell subset comparison (as outlined in Section **5.1**)
  - Bone marrow biopsy
  - Tumor biopsy is required if archival tissue is not available or adequate; otherwise, this is optional.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

To determine the maximum tolerated dose (MTD), and the safety and toxicity profile of the combination of lenalidomide, CC-486 (5-azacitidine) and romidepsin in patients with refractory/relapsed TCM, a phase 1 open-label, non-randomized, single-center study will be conducted at the NCI. A standard "3 + 3" design will be used to determine the MTD of dose-escalated lenalidomide in combination with fixed doses of CC-486 (5-azacitidine), romidepsin (R) and dexamethasone (D) with an expansion cohort at the MTD.

In patients with relapsed or refractory TCM, lenalidomide will be administered by oral intake in a dose-escalation with a starting dose of 5mg daily, a second dose level of 10mg daily, a third dose level at 15mg daily, and a fourth dose level at 20mg daily on days -7 to day 10 of first cycle (see **Table 1** for additional dose levels and schedules, cycles are 21 days each). After the second cycle, lenalidomide will be given from day 1 to day 10 in each cycle for up to six cycles. CC-486 (5-azacitidine) with a dose of 300mg oral intake daily will be given on day 1 to day 10, romidepsin will be administered at a dose of 12 mg/ m^2 on days 1 and 10 (±2 days) and dexamethasone will be given on day 1 and 10 (±2 days) of the cycle.

After approval of Amendment 12/07/2022: Participants will receive six cycles (each 28 days in length) of: lenalidomide at the MTD from day 1 to day 10, CC-486 (5-azacitidine) at a dose of 300mg oral intake daily given on day 1 to day 10, romidepsin administered at a dose of 12 mg/ m^2 on days 1 and 10 (±2 days) and dexamethasone on day 1 and 10 (±2 days) of the cycle.

Treatment will continue for a maximum of 6 cycles or until toxicity (i.e., dose limiting toxicity) as found in Section **3.9** or toxicity requiring discontinuation as defined in Section **3.5**) or progressive disease.

The treatment will be repeated for up to 6 cycles. The patients are allowed to proceed to stem cell transplantation (SCT) if eligible during and after the protocol treatment. Patients who undergo SCT before all 6 cycles of protocol treatment are administered will be taken off therapy. All patients who undergo SCT will continue to be followed for survival, but not for toxicity (see Section **3.8**)

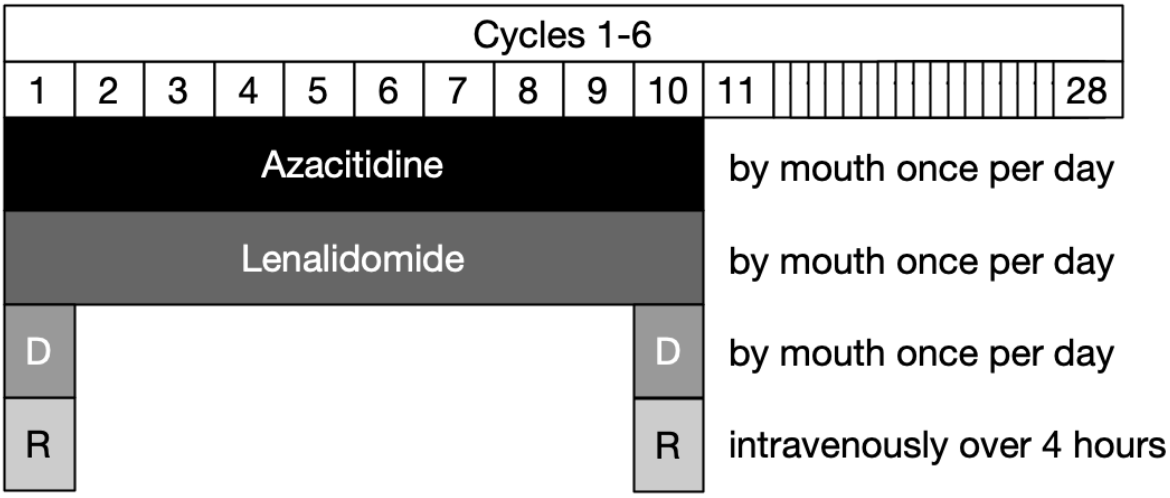


Table 1: Dose level and schedule for lenalidomide, CC-486 (5-azacitidine), romidepsin and dexamethasone

DL	Lenalidomide Day 1 -10 (7 days lead in for 1st cycle)	CC-486 (5-azacitidine) Day 1 to 10	Romidepsin Day 1 and day 10	Dexamethasone Day 1 and day 10
-2	0 mg	200 mg PO	10 mg/m^2 IV	40 mg PO
-1	2.5 mg	200 mg PO	12 mg/m^2 IV	40 mg PO
1*	5 mg	300 mg PO	12 mg/m^2 IV	40 mg PO
2	10 mg	300 mg PO	12 mg/ m^2 IV	40 mg PO
3	15 mg	300 mg PO	12 mg/ m^2 IV	40 mg PO
4	20 mg	300 mg PO	12 mg/ m^2 IV	40 mg PO
* starting dose level				
As of Amendment 12/07/2022:	Lenalidomide Day 1 to 10	CC-486 (5-azacitidine) Day 1 to 10	Romidepsin Day 1 and day 10	Dexamethasone Day 1 and day 10

DL	Lenalidomide Day 1 -10 (7 days lead in for 1st cycle)	CC-486 (5-azacitidine) Day 1 to 10	Romidepsin Day 1 and day 10	Dexamethasone Day 1 and day 10
DL				
4 (MTD)	20 mg	300 mg PO	12 mg/ m^2 IV	40 mg PO

3.2 DOSE LIMITING TOXICITY

A dose-limiting toxicity (DLT) is defined as: any treatment-emergent and related severe (grade ≥ 3) toxicity, i.e., toxicity deemed related to lenalidomide, romidepsin and/or CC-486 (5-azacitidine) by the PI or designee and occurring during the MTD observation time, defined as day -7 until end of cycle 1 (normally day 22). Each patient must receive all doses of the investigational medications during cycle 1 to be considered as successfully completing the DLT evaluation period.

The following toxicities and conditions will be recorded, however they will not be considered to be DLTs:

3.2.1 Hematologic exceptions

- Grade 3 or 4 lymphocytopenia without clinical signs of infection grade 2 or above.
    - Lenalidomide, romidepsin and CC-486 (5-azacitidine) will be continued in the event of asymptomatic grade 3 or 4 lymphocytopenia, unless there are clinical signs of significant infection (persistent fevers, labile blood pressure, localized complaints or findings on physical examination, hypoxia or organ dysfunction).
- Grade 3 neutropenia without clinical signs of infection grade 2 or above.
    - Lenalidomide, romidepsin and CC-486 (5-azacitidine) will be continued in the event of grade 3 neutropenia unless there are clinical signs of significant infection, as listed above.
- Grade 3 thrombocytopenia without signs of bleeding that resolved within 7 days of holding the study drug(s) (See Section **3.5.1** for study drug holding parameters).
- Grade 3 anemia that improves to Grade ≤2 after transfusion of up to two units of pRBCs and does not recur within 7 days.
- Grade 3 febrile neutropenia (grade 3 febrile neutropenia at any time during therapy will be considered an SAE but not DLT)

3.2.2 Non-Hematologic exceptions

- Transient (< 72 hours) grade 3 hypoalbuminemia, hypokalemia, hypomagnesemia, hyponatremia or hypophosphatemia which responds to medical intervention. Lenalidomide, romidepsin and CC-486 (5-azacitidine) will be continued while the metabolic abnormalities are corrected by intravenous or oral supplementation
- Patients who require short term hospitalization (3 days or less) only for fluid and electrolyte disturbances secondary to anorexia, nausea/vomiting/diarrhea which are common AEs for 5-azacitidine, lenalidomide and romidepsin individually and more so for the combination. This exception does not apply to secondary organ dysfunction resulting from this biochemical derangements or patients that require vasopressor BP support.

- Grade 3 rash that resolves to grade ≤2 within 7 days of holding the study drug(s) (See Section **3.5.1** for study drug holding parameters).

Management and dose modifications associated with the above adverse events are outlined in Section **3.5**. Occurrence of any DLT-defining toxicity after the first 28 days of treatment will lead to dose modification as specified below; however, it will not be deemed a DLT for purposes of dose escalation.

3.3 DOSE ESCALATION

Dose escalation will proceed according to the following schedule (**Table 2**). Dose escalation will follow the following guidelines (**Table 3**). Each patient will continue treatment at the dose level they were enrolled – there will be no intra-patient dose escalation. In case of severe toxicity, the lenalidomide dose should be reduced by one dose level, dose adaption of the other drugs as per investigators discretion.

The MTD is the dose level at which no more than 1 of up to 6 patients experience DLT during the DLT evaluation window(s), or the dose below that at which at least 2 (of ≤6) patients have DLT. The protocol will be amended to note the MTD once determined.

NOTE: If enrollment to the current or next higher dose level cannot proceed because a patient at the current dose level is still within the DLT window, screened patients who are in need of urgent treatment may be enrolled at the next lower dose level as long as the ≤6 patient limit per dose level is maintained. In the event that these additionally enrolled patients experience DLT(s) after formal evaluation of dose level determinations has taken place, the Principal Investigator will review and assess if any changes to the ongoing protocol/dose escalation or safety parameters need to be considered.

NOTE: After the dose escalation portion was completed, the MTD of lenalidomide was determined to be 20mg.

Table 2: Lenalidomide Dose Escalation Schedule

Dose Level	Lenalidomide
Level -2	0 mg
Level -1	2.5 mg
Level 1	5mg – Starting dose
Level 2	10mg
Level 3	15mg
Level 4	20mg

Table 3: Dose Escalation Guidelines

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

3.4 DRUG ADMINISTRATION

3.4.1 Summary of Original Study Design

Prior to approval of Amendment dated 12/07/2022, the original study design included a 7 day lead-in window of lenalidomide monotherapy to assess early clinical activity of this agent prior to combination therapy.

The standard treatment cycle was 21 days (3 weeks), except for the first cycle where we had 7 days lead in phase for lenalidomide (lead in was allowed to be shorter for patients requiring urgent treatment with the four-drug combination due to rapid disease progression, at PI discretion). The maximum allowable delay for completion of cycle 1 treatment was 1 week (7 days) in order to best assess the tolerability of this treatment. The maximum allowable delay for completion of treatment in all subsequent cycles was 3 weeks (21 days). The minimum window between initiation of new cycles was 19 days. For the dose escalation Cohort 1, treatment was administered on an inpatient basis during the first 2 days (after lead-in period) of the first cycle, and as outpatient during subsequent weeks and cycles unless decided otherwise by the principal investigator based on clinical judgment.

After 20 patients were enrolled and the dose escalation Cohort 1 Arm 1 was fully accrued, the study design was modified to remove the 7 day lenalidomide window (Amendment 12/07/2022).

3.4.2 Summary of Current Study Design (as of Amendment 12/07/2022)

For the Dose Expansion Cohort 2 Arm 3, treatment will be administered as outpatient for all cycles unless decided otherwise by the principal investigator based on clinical judgment. The standard treatment cycle will be 28 days (4 weeks). Reported adverse events and potential risks are described in Section **14**. Appropriate dose modifications are described in Section **3.5**. No investigational or commercial agents or therapies other than those described below may be administered during the study therapy period with the intent to treat the patient's malignancy. See **Table 4** below for description of drug regimen.

A cycle may be delayed for the following reasons:

- Scheduling or other administrative reasons (no more than 14 days)
- Administration of COVID-19 vaccination (if the delay would not result in more than 6 weeks treatment-free period)
- Toxicity/dose management as defined below

Table 4: Drug Regimen

Agent	Premedications; Precautions	Dose	Route	Schedule
Lenalidomide	Aspirin for thrombosis prophylaxis	As per dose level***	Oral	Days 1 to10
Romidepsin	Premedicate with ondansetron or granisetron *	12mg/ m^2 in 500 mL NS	IV over 4 hours	Days 1 and 10 (± 2 days)
CC-486 (5-azacitidine)	Premedicate with ondansetron or granisetron **	300mg	Oral	Days 1 to 10
Dexamethasone	No premedication	40mg	Oral	Days 1 and 10 (± 2 days)
* Mandatory for the first cycle; subsequently based on clinical judgement ** Not mandatory, administer based on clinical judgement *** Doses as appropriate for assigned dose level				

For a full detailed product description and administration guidelines, see Section **14**. Infusions may be done peripherally or via central venous access device (if present; not required to be placed by the study).

NOTE: Cycles beyond Cycle 1 may not commence until the laboratory criteria in Section **2.1.1.8** are met and non-laboratory treatment-emergent AEs have resolved to grade ≤2 (grade ≤1 if at related to treatment).

3.4.3 Agent-specific Information and Instructions

3.4.3.1 Lenalidomide

Patients will receive lenalidomide for 10 days through Cycles 1-6 of treatment (see schema Section **3.1**).

Lenalidomide is administered orally once daily and should be taken around the same time each day with at least 8 ounces of water. The capsules must be swallowed whole and may be taken with or without food.

3.4.3.2 Romidepsin

Romidepsin will be administered on day 1 and 10 of each cycle through a peripheral or central intravenous catheter over 4 hour period. If patients are also taking antiemetics to relieve the side effects associated with romidepsin these should be administered at least 60 minutes before the romidepsin. Patients concurrently receiving romidepsin and warfarin should have PT and INR

levels checked more frequently. The use of rifampin and CYP3A inducers should be avoided for the duration of the study (see Section **4** and **Appendix C**).

3.4.3.3 CC-486 (5-azacitidine)

CC-486 (5-azacitidine) will be administered on days 1 through 10 of each cycle in the clinic. CC-486 (5-azacitidine) will be taken orally, with or without food. The tablets/ capsules must be swallowed whole and may be taken with or without food.

3.4.3.4 Dexamethasone

Dexamethasone will be administered orally on Days 1 and 10.

3.4.3.5 Study Drug Diaries

Patients will be required to complete and return a drug diary as a memory aid to help document the date and time of all self-administered study drugs (**Appendix F**). This drug diary as well as study drug containers and any unused study drug should be returned to the research team at the end of each cycle of therapy.

3.4.4 Supportive Medications

3.4.4.1 Prophylactic and supportive care for lenalidomide

Patients who are not already on prophylactic or therapeutic doses of anticoagulants will be given aspirin 81mg by oral intake for prophylaxis of venous thromboembolism.

3.4.4.2 Prophylactic and supportive care for romidepsin and CC-486 (5-azacitidine)

Patients will be given ondansetron 16 mg orally or 8 mg IV (or equivalent dose of granisetron orally or transdermal in case of allergy or intolerance to ondansetron) to prevent chemotherapy-associated nausea. Anti-emetics may be omitted during the second and subsequent cycles at investigators' discretion.

3.4.4.3 Other modalities or procedures

- Patients deemed by the PI or treating investigator to be at high risk for CNS relapse who have not received CNS prophylaxis as part of their prior treatment may receive prophylaxis in the form of cytarabine 40 mg, methotrexate 15 mg, and hydrocortisone 50 mg administered intrathecally (IT) no earlier than Day 2 of Cycle 1 and every 3-6 weeks thereafter for up to six doses. Cytarabine or methotrexate may be omitted in case of prior intolerance or toxicity attributed to either drug. Platelet counts of ≥70,000 /uL need to be confirmed prior to each administration.
- If CNS disease is detected at screening or during prophylactic IT drug administration, IT treatment listed above will be administered twice weekly until abnormal lymphoid cells are no longer detectable by cytology or flow cytometry, then weekly for four additional doses.
- Patients with bulky disease (one or more lymph nodes ≥10cm), high leukemic cell count (≥50,000 cells/mm^3) or who are for other reasons deemed by the PI or designate to be at an increased risk for tumor lysis syndrome will have the laboratory evaluations as listed in Study Calendar (Section **3.9**).
- Patients will be observed in the day hospital or the inpatient unit for at least 30 minutes after administration of romidepsin for potential infusion-related reactions.

3.4.5 Missed doses

All missed doses of the protocol medications administered orally (CC-486 (5-azacitidine), lenalidomide, and dexamethasone) will be recorded in the primary source documentation at the time of the next patient visit. If a dose is not taken at the scheduled time and it has been less than 12 hours since the regularly scheduled time, it can be taken as soon as possible on the same day. If it has been more than 12 hours, the missed dose may be skipped, but the next dose should be taken at the normal time on the following day. The patient should not take extra doses to make up the missed dose.

If the patient has an episode of emesis and vomits a dose of one or more drugs, these will be recorded as missed and will not be re-administered. If there is only suspicion that the doses were vomited because emesis occurred, but there is no clear evidence for it, these doses will not be recorded as missed.

3.5 DOSE MODIFICATION

Previous clinical trial experience treating patients with relapsed refractory TCMs indicates significant efficacy for the 2 drug combinations of romidepsin and oral 5-azacitidine [63] or romidepsin and Lenalidomide **[**58**]**, but the AE listings shown below in **Table 5** also illustrate the potential for overlapping toxicity that may make it difficult to attribute specific AEs to only one of the investigational agents as well as highlight the potential for more significant AEs with the addition of the 3rd active agent. While patient safety is always of foremost concern, there will be interest in maintaining dose intensity and continuing treatment to accurately assess the clinical activity of this regimen. The single agent safety experience will provide important insight into each drugs contribution to the hematologic and GI toxicities, but individual AEs may require interrupting treatment, dose reduction or discontinuation of more than 1 drug.

Table 5: Adverse Event listings for Romidepsin/5-azacitidine Treatment emergent AEs occurring in 10% or more of the patients (n = 25)

AE	Total	Grade 1-2	Grade 3-4
Decreased platelet count	18 (72)	6 (24)	12 (48)
Decreased neutrophil count	17 (68)	7 (28)	10 (40)
Nausea	17 (68)	15 (60)	2 (8)
Hyperglycemia	15 (60)	14 (56)	1 (4)
Anemia	14 (56)	10 (40)	4 (16)
Fatigue	14 (56)	13 (52)	1 (4)
Decreased lymphocyte count	13 (52)	5 (20)	8 (32)
Diarrhea	12 (48)	12 (48)	—
Constipation	12 (48)	12 (48)	—
Vomiting	12 (48)	10 (40)	2 (8)

AE	Total	Grade 1-2	Grade 3-4
Hypoalbuminemia	11 (44)	11 (44)	—
Anorexia	10 (40)	10 (40)	—
Increased creatinine	10 (40)	10 (40)	—
Fever	8 (32)	7 (28)	1 (4)
Abdominal pain	7 (28)	6 (24)	1 (4)
Upper respiratory infection	7 (28)	6 (24)	1 (4)
Hypocalcemia	7 (28)	7 (28)	—
Headache	6 (24)	6 (24)	—
Weight loss	6 (24)	6 (24)	—
Hypophosphatemia	6 (24)	4 (16)	2 (8)
Hyponatremia	5 (20)	5 (20)	—
Dysgeusia	5 (20)	5 (20)	—
Increased aspartate aminotransferase	5 (20)	5 (20)	1 (4)
Hypokalemia	5 (20)	5 (20)	—
Rash maculopapular	4 (16)	4 (16)	—
Increased blood bilirubin	4 (16)	2 (8)	2 (8)
Urinary tract infection	4 (16)	3 (12)	1 (4)
Cough	4 (16)	4 (16)	—
Chronic kidney disease	4 (16)	4 (16)	—
Malaise	3 (12)	3 (12)	—
Nasal congestion	3 (12)	3 (12)	—
Hypoglycemia	3 (12)	3 (12)	—
Hypercalcemia	3 (12)	3 (12)	—
Increased alanine aminotransferase	3 (12)	2 (8)	1 (4)
Hypernatremia	3 (12)	3 (12)	—
Myalgia	3 (12)	3 (12)	—
Peripheral sensory neuropathy	3 (12)	3 (12)	—
Edema in the limbs	3 (12)	3 (12)	—

AE	Total	Grade 1-2	Grade 3-4
Dizziness	3 (12)	3 (12)	—
Arthralgia	3 (12)	3 (12)	—
Febrile neutropenia	3 (12)	—	3 (12)
Dyspepsia	3 (12)	3 (12)	—
Back pain	3 (12)	3 (12)	—

Table 5.1 Toxicities occurring in ≥10% of participants and all grade three and grade four toxicities for Regimen A (romidepsin and lenalidomide)

	Regimen A					
	Any grade occurring in ≥10% n (%)		**Grade 3**		**Grade 4**	
Hematological toxicities	43	88%	24	49%	18	37%
Anemia	16	33%	13	27%	–	–
Febrile neutropenia	–	–	3	6%	–	–
Neutropenia	28	57%	15	31%	9	18%
Thrombocytopenia	30	61%	18	37%	8	16%
Lymphocyte count decreased	28	57%	16	33%	9	18%
White blood cell decreased	22	45%	18	37%	4	8%
Liver function toxicities	9	18%	2	4%	–	–
Alanine aminotransferase increased	–	–	–	–	–	–
Aspartate aminotransferase increased	–	–	–	–	–	–
Alkaline phosphatase increased	–	–	1	2%	–	–
Blood bilirubin increased	5	10%	1	2%	–	–
Hypoalbuminemia	–	–	–	–	–	–
Electrolyte toxicities	27	55%	24	49%	–	–
Hyperglycemia	8	16%	7	14%	–	–
Hypermagnesemia	10	20%	10	20%	–	–

	Regimen A					
	Any grade occurring in ≥10% n (%)		**Grade 3**		**Grade 4**	
Hypocalcemia	5	10%	5	10%	–	–
Hypoglycemia	–	–	–	–	–	–
Hypokalemia	6	12%	6	12%		
Hypomagnesemia	–	–	–	–	–	–
Hyponatremia	–	–	1	2%	–	–
Hypophosphatemia	8	16%	8	16%	–	–
Creatinine increased	–	–	–	–	–	–
Other toxicities	48	98%	20	41%	–	–
Abdominal pain	6	12%	–	–	–	–
Anorexia	18	35%	1	2%	–	–
Arthralgia	–	–	1	2%	–	–
Chills	–	–	–	–	–	–
Constipation	19	39%	–	–	–	–
Dehydration			3	6%	–	–
Diarrhea	19	39%	–	–	–	–
Dysgeusia	30	61%	–	–	–	–
Dyspnea	5	10%	1	2%	–	–
Electrocardiogram QT corrected interval prolonged	–	–	1	2%	–	–
Fatigue	31	63%	11	22%	–	–
Fever	5	10%	–	–	–	–
Generalized muscle weakness	–	–	1	2%		
Headache	–	–	–	–	–	–
Hypotension	–	–	–	–	–	–
Lung infection			3	6%		

	Regimen A					
	Any grade occurring in ≥10% n (%)		**Grade 3**		**Grade 4**	
Malaise	–	–	–	–	–	–
Myalgias	7	14%	–	–	–	–
Nausea	30	63%	–	–	–	–
Phlebitis	–	–	–	–	–	–
Rash Maculo-Papular	–	–	1	2%	–	–
Syncope	–	–	1	2%	–	–
Tumor lysis syndrome	–	–	1	2%	–	–
Upper respiratory infection	–	–	1	2%	–	–
Vomiting	15	27%	–	–	–	–
Weight loss	12	22%	–	–	–	–

3.5.1 Treatment modifications for adverse reactions

All treatment modifications should be discussed with the senior clinical investigators on the study. Treatment modifications will follow the guidelines outlined in **Table 6**. Any given dose modification after Cycle 1 can be repeated twice in a patient as long as the patient is benefiting from therapy and does not meet off-treatment criteria.

If a toxicity which requires modification of therapy per **Table 6** occurs during the window period (day -7 to day -1) and does not meet the definition of a DLT, cycle 1 day 1 may start after resolution to grade ≤1 (grade ≤2 for anemia).

All grading scales in the following tables are according to the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Table 6: Dose Modification of Lenalidomide, romidepsin and CC-486 (5-azacitidine) for treatment related AEs

Event	Initial management	Follow-up Management
Cycle 1 DLT Evaluation Period		
Grade 1 AEs		
Any AE	Continue treatment	Continue monitoring and laboratories at least once weekly
Grade 2 AEs		
ANC: <1.5 - 1.0 x 10^9/L	Continue treatment	Monitor cell counts at least twice weekly **Pegfilgrastim***

Event	Initial management	Follow-up Management
Platelet: < 75,000 - 50,000/mcL	**Consider holding treatment for up to 7 days**	Monitor cell counts at least twice weekly Restart treatment when platelet count >75,000/mcL
Hgb: < 10.0 - 8.0g/dL	Continue treatment	Monitor cell counts at least twice weekly **Consider transfusion before cycle 2**
Any other AE	Continue treatment	Continue monitoring and laboratories once weekly
Grade 3 AEs		
ANC: <1.0 -0.5 x 10^9/L	**Hold treatment for up to 7 days** Restart treatment at full doses	Monitor cell counts at least twice weekly G-CSF# and Pegfilgrastim*;
Platelet: <50,000 - 25,000/mcL	**Hold treatment for up to 7 days** Restart treatment at when platelets > 75, 000/mcL	Monitor cell counts at least twice weekly **If platelets are not > 75,000/mcL the patient is off treatment DLT**
Hgb < 8.0g/dL	**Hold treatment for up to 7 days** Restart treatment after transfusion	Monitor cell counts at least twice weekly Transfusion until Hgb > 9 g/L
Any other AE	**Hold treatment for up to 7 days** Restart treatment when AE has resolved to ≤ grade 1	Continue monitoring and laboratories at least twice weekly **If the AE has not improved to ≤ grade 1, the patient is off treatment DLT**
Grade 4 AEs at any time during cycle 1		
Any AE	**Discontinue treatment**	**Off treatment DLT**
Cycles 2 through 6		
Event	**Initial management**	**Follow-up Management**
Grade 1 AEs		
Any AE	Continue treatment	Continue monitoring and laboratories at least once weekly
Grade 2 AEs		
ANC: <1.5 – 1.0 x 10^9/L	Continue treatment	Monitor cell counts at least twice weekly
Platelets <75,000 to 50,000/mcL	Continue treatment	Monitor cell counts at least twice weekly
Hgb: < 10.0 – 8.0g/dL	Continue treatment	Consider transfusion before the start of next cycle
Any other AE	Continue treatment	Continue monitoring and laboratories at least twice weekly

Event	Initial management	Follow-up Management
Grade 3 AEs		
ANC: < 1.0 - 0.5 x 10^9/L **Or**	**1st event: continue treatment**	Monitor cell counts at least twice weekly and use G-CSF support for the remainder of current cycle and all future cycles
	2nd event: hold lenalidomide and 5-azacytidine for remainder of cycle; next cycle may resume once ANC is >1.0	Monitor cell counts at least twice weekly and use G-CSF support **Dose reduce both 5-azacytidine and lenalidomide for the next cycle**
	3rd event: hold lenalidomide and 5-azacytidine for remainder of cycle; next cycle may resume once ANC is >1.0	Monitor cell counts at least twice weekly and use G-CSF support **2nd dose reduction of 5-azacytidine and lenalidomide** and consider dose reduction of romidepsin with the next cycle
	4th event: hold lenalidomide and 5-azacytidine for remainder of cycle	Off study treatment
Platelet: <50,000 - 25,000/mcL	**1st event: hold lenalidomide and 5-azacytidine for remainder of cycle; next cycle may resume once platelets are >75,000/mcL** **2nd event: hold lenalidomide and 5-azacytidine for remainder of cycle; next cycle may resume once platelets are >75,000/mcL** **3rd event: hold lenalidomide and 5-azacytidine for remainder of cycle**	**Dose reduce both 5-azacytidine and lenalidomide for the next cycle** **2nd dose reduction of both 5-azacytidine and lenalidomide for the next cycle; consider dose reduction of romidepsin** Off study treatment
Hgb < 8.0g/dL	Continue treatment and consider blood transfusion	Monitor cell counts at least twice weekly
Any other grade 3 AE at least possibly related to study treatment	**1st event: hold study treatment for the remainder of the cycle**	Continue monitoring and laboratories at least twice weekly **1st Dose reduction of 5-azacytidine and lenalidomide** for the next cycle
	2nd event: hold treatment for the remainder of the cycle **3rd event: hold study treatment for the remainder of the cycle**	**2nd dose reduction of 5-azacytidine and lenalidomide and consider 1st dose reduction of romidepsin** Off study treatment
Grade 4 AEs		
ANC < 0.5 x 10^9/L or Platelets <25,000/mcL	**1st event: hold study treatment for the remainder of the cycle; next cycle may resume once ANC is >1.0 and platelets are >75,000/mcL**	Monitor cell counts at least twice weekly **Dose reduce 5-azacytidine and lenalidomide next cycle** **Consider dose reduction of romidepsin**

Event	Initial management	Follow-up Management
	2nd event: hold study treatment for the remainder of the cycle	Monitor cell counts at least twice weekly **2nd dose reduction of 5-azacytidine, lenalidomide** with next cycle, **1st dose reduction of romidepsin**
Hgb Life threatening	**Discontinue treatment**	**Off treatment unacceptable toxicity**
Any other AE	**1st event: hold treatment 7 to 14 days**	Continue monitoring and laboratories at least twice weekly **1 to 2 dose level reduction of 5-azacytidine or lenalidomide or romidepsin** for most likely causative agent or all 3 drugs **Consider discontinuation of treatment**
	2nd event: discontinue treatment	**Off treatment unacceptable toxicity**

3.5.2 Lenalidomide dose modifications for decreased creatinine clearance

For each cycle to commence, creatinine clearance must be > 60 mL/min/1.73 m^2 calculated by eGFR in the clinical lab per Section **2.1.1.8**. For a decrease of creatinine clearance, which occurs during the cycle, the dose of lenalidomide will be modified per **Table 7**. Decreases of creatinine clearance deemed treatment-related, may result in discontinuation of protocol therapy as per **Table 6**.

Table 7: Lenalidomide renal dose adjustments

Creatinine clearance calculated by eGFR in the clinical lab	**Lenalidomide dose**	**Lenalidomide schedule** Days 1 to 10 (Day -7 to 10 for first cycle)
31-60 mL/min/1.73 m^2	Reduce by 50%	Daily
≤30 mL/min/1.73 m^2	Reduce by 50%	Every other day

3.6 PROTOCOL STOPPING RULE

In the event of patient death (grade 5) determined to be related to the investigational treatment, further enrollment will be halted, consideration will be given to discontinuing treatment for all active patients and suspension of the protocol until the exact cause of the death is fully understood and whether the protocol should be terminated.

3.7 ON STUDY EVALUATIONS

Prior to romidepsin administration (Day 1 and 10), pre-dose assessments must be performed (up to 3 days prior). After Cycle 1, pre-dose assessments may be performed up to 3 days prior to a cycle except where otherwise noted. The results from all procedures/tests must be reviewed prior to initiation of each cycle of treatment for consideration of dose modifications and delay of therapy.

Treatment with lenalidomide, romidepsin and CC-486 (5-azacitidine) will continue for six cycles or until disease progression, unacceptable treatment-related toxicity or other reasons outlined in Section **3.11.1**.

Refer to the Study Calendar (Section **3.9**) for a complete list of procedures to be performed at each scheduled study visit. See also Section **5** for all samples to be collected for correlative research. During treatment, it is expected that all laboratory and clinical assessments be conducted at the NIH (including post-treatment imaging evaluations); results from outside NIH will only be accepted at the discretion of the investigator.

NOTE: Recently a patient treated in this study had symptoms of an unusual very uncommon serious toxicity called rhabdomyolysis related to one of the study drugs which is damage to skeletal muscles that produces significant elevations in the serum of muscle enzymes like creatinine kinase or aldolase. If a patient experiences suspicious symptoms, or has physical exam findings suggestive of this toxicity, the patient will be evaluated clinically (e.g., blood and urine tests will be performed) at the direction of the Principal Investigator/treating investigator to determine if the patient is having this toxicity.

3.8 POST-TREATMENT EVALUATIONS

Patients who discontinue investigational therapy before completing protocol treatment due to disease progression will be followed clinically until completion of the Safety Follow-up Visit or until death, whichever occurs first. These patients will continue to be followed for overall survival as outlined Section **3.8.2**. Patients removed from study treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

3.8.1 Safety Follow-Up Visit

The safety follow-up visit should occur 30 days (+7 days) after the last dose of trial treatment, or before the initiation of a new anti-cancer treatment, whichever comes first. Required testing is as noted in the Study Calendars (Section **3.9**). All AEs that occur prior to the Safety Follow-Up Visit should be recorded. See section **6.1.1**for documentation of AEs after study treatment has ended.

3.8.2 Follow-Up Visits - Prior to Disease Progression

Patients who complete trial treatment without evidence of disease progression will move into the Follow-up Phase and may be assessed every 60 days (± 7 days) for 6 months; then every 90 days (± 14 days) for 2 years; then every six months (± 28 days) for 2 years, then annually (±6 weeks) after finishing treatment by radiologic imaging or other clinical assessments to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, or end of the study If the patient cannot return to the Clinical Center for any of these visits, a request will be made to have a local physician or laboratory collect a CBC with differential and send the results. If this is not possible, patients may be assessed by telephone or email for symptoms.

3.8.3 Follow-Up Visits - Survival/Post-Disease Progression

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted (e.g., phone, email, etc.; in-person visit not required) at least every 3 to 6 months to collect information on new anti-cancer treatments received and to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first (see Study Calendar, Section **3.9**). Any adverse events which

are present at the time of discontinuation should be followed in accordance with the safety requirements.

3.9 STUDY CALENDAR

Procedure	**Screening**	**Baseline**	**Study Cycles**					**Disease Evaluations**	**End of Treatment and Disease Progression**	**Post-Treatment Follow-Up**		
			C1			C2-6				Safety[1]	Follow-Up (Prior to PD)	Survival (Post-PD)
Scheduling Window (Days):	-35 to -8[2]		1 (±3)	10 (±3)	15 (±3)	1 (±3)	10 (±3)	Every 2 cycles[3]	Treatment discontinuation/PD [4]	Day 30 (+7)	Every 60 or 90 days[5]	Every 3 months[6]
Confirmation of Diagnosis [7]	X											
Clonal T-cell receptor rearrangement by PCR	X											
Medical, social and disease history[8]	X	X										
Physical Exam and ECOG PS [9]	X	X	X			X			X	X	X	
Symptoms/Adverse Events Assessment, Concomitant Medication Review	X	X	X			X			X	X	X	
CBC with Differential	X	X	X	X		X	X		X	X	X	
Reticulocyte Count	X	X				X			X	X	X	
Chemistry Panels [10]	X	X	X	X		X	X		X	X	X	
LDH, Serum Lipase and Amylase	X	X	X	X		X	X		X	X	X	
PT/INR and aPTT[22]	X	X				X			X	X	X	
TSH and free T4	X											
Urinalysis	X	X							X			
Pregnancy Test[11]	X	X	X (weekly during cycle 1)			X			X			
EKG, TTE	X											
Pulmonary function tests [12]	X											

Procedure	**Screening**	**Baseline**	**Study Cycles**					**Disease Evaluations**	**End of Treatment and Disease Progression**	**Post-Treatment Follow-Up**		
			C1			C2-6				Safety[1]	Follow-Up (Prior to PD)	Survival (Post-PD)
Scheduling Window (Days):	-35 to -8[2]		1 (±3)	10 (±3)	15 (±3)	1 (±3)	10 (±3)	Every 2 cycles[3]	Treatment discontinuation/PD [4]	Day 30 (+7)	Every 60 or 90 days[5]	Every 3 months[6]
HBsAg, HBcAb, HCVAb, HIV Antibody, HTLV-1/2[13]	X											
Imaging studies [14]	X	X						X	X		X	
MRI, Lumbar Puncture [15]		X						X	X		X	
Bone Marrow Aspiration/Biopsy [16]		X							X	X		
Flow Cytometry[17]		X						X	X	X	X	
Clinical photography and dermatology assessment/ global score [18]		X						X	X		X	
Radiologic Evaluation/ tumor measurement[19]		X						X	X		X	
Uric Acid, Total Protein		X	X	X		X	X					
HLA typing (A, B, C, DR, DQ)		X										
T, B, NK cell subsets		X	X			X			X	X	X	
Iron panels, Folate, and B12, C-reactive Protein		X	X					X[20]				
Research Blood, Buccal and/or Saliva Samples[21]		X	Refer to Table Section **5.1.1**									
Tissue Samples		X										
Survival Status												X

NOTE: Any other tests should be performed as clinically indicated. See Section **3.4** for drug administration information. See Section **5** for information on research blood samples/correlative studies to be collected.

[1] 30 days (±7) following last dose of any study drug (via clinic or phone). If initiating new anti-cancer therapy within 30 days after last dose of any study drug, 30-day safety follow-up visit must occur before first dose of new therapy.

[2] Screening and Baseline evaluations should be performed within 28 days prior to enrollment and dosing, respectively, unless otherwise noted and with the following exceptions: Confirmation of diagnosis (no time limit); HIV antibody, HTLV-1/2 serologies, Hepatitis B surface antigen and Hepatitis C antibody, EKG, TTE, bone marrow aspiration/biopsy and Clonal T-cell receptor rearrangement by PCR (all within 3 months), baseline pregnancy testing (within 10 – 14 days and within 24 hours prior to prescribing lenalidomide) **NOTE:** Any screening tests performed within the specified time frame for baseline do not need to be repeated.

[3] To be performed on Day 21 (±2 days) of Cycles 2, 4, and 6. Confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

[4] To be done at end of treatment (30 days after last dose of study treatment; may be combined with 30 day safety follow-up, if timing coincides). If subject to initiate new anti-cancer therapy assessments should occur before the first dose of the new therapy.

[5] Follow-up to occur about every 60 days (±7 days) for first 6 months, every 90 days (±14 days) for 2 years, then every 6 months (± 28 days) for another 2 years and then annually (± 6 weeks) until disease progression or initiation of new anti-cancer therapy.

[6] After disease progression or initiation of new anti-cancer therapy, contact for survival about every 3 to 6 months (±4 weeks).

[7] Pathologic review/confirmation of diagnosis by Laboratory of Pathology, NCI (no time limit). If archival sample is not available or not adequate, a fresh tumor biopsy and/or peripheral blood sample will be obtained.

[8] Complete medical history at screening/baseline. Interim on study and in follow-up. Disease and social history required only at screening.

[9] Physical exams to include vitals, weight, and height (screening only).

[10] Chemistry panels include: Acute care, Hepatic, and Mineral. For screening, Chemistry panels (as noted) or specific analyte required for eligibility, including: Creatinine (i.e., Acute Care Panel); serum calcium, phosphate, magnesium and albumin (i.e., Mineral Panel); ALT, AST, total bilirubin (i.e., Hepatic Panel, direct bili if indicated). If a patient has physical exam evidence or complains of symptoms suggestive of rhabdomyolysis, clinical work-up will be performed (e.g., creatinine kinase, aldolase, possibly serum myoglobin and additional urine studies) to determine if the patient is experiencing rhabdomyolysis and the tests will be repeated to monitor for resolution of this event; dose modification or interruption or discontinuation of treatment will occur, as needed.

[11] Individuals of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of lenalidomide treatment, including dose interruptions and then every 28 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 28 following lenalidomide discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days of lenalidomide treatment, including dose interruptions, and then every 14 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 14 and Day 28 following lenalidomide discontinuation.

[12] Diffusing capacity/alveolar volume (DLCO/VA) forced expiratory volume in 1 second (FEV1) for patients with significant pulmonary or smoking history.

[13] HBV DNA PCR, HCV PCR, and/or HIV 1/2 viral load will be tested for patients with positive serologies.

[14]At screening CT scans of neck, chest, abdomen, and pelvis should be performed (with IV and PO contrast, unless patient is allergic or has renal insufficiency; other imaging may be substituted at the discretion of the investigator). Other body areas may be imaged if clinically indicated. MRI of the brain is only required

in patients with suspected involvement of CNS. Also, at screening, a FDG-PET/CT torso (extremities to be included if there is confirmed or suspected disease involvement). At baseline one or more of the following studies: CT, MRI, FDG-PET/ CT and or clinical photography; MRI of the brain is only required in patients with suspected involvement of CNS. A FDG-PET/ CT will be done after Cycle 2 and at the End of Treatment.

[15] Patients with neurological symptoms or signs should undergo MRI scan of the brain and lumbar puncture.

[16] Baseline bone marrow aspiration/ biopsy with flow cytometry must be done within 3 months prior to starting treatment. During post-treatment follow-up, repeat bone marrow aspiration/ biopsy needed only to confirm a CR.

[17] Clinical peripheral blood flow cytometry (Laboratory of Pathology, NCI) may be done for disease evaluation of patients who had circulating leukemic cells detected at baseline, and for patients with CTCL regardless of their baseline results.

[18] To be performed in selected patients with cutaneous disease (as determined by PI or AI).

[19] Dermatology assessment & Global/mSWAT scoring be used instead of/ in addition to radiologic evaluation for patients with predominantly cutaneous disease.

[20] Patients with elevated CRP and soluble IL2Rα will have them repeated every 6 weeks as part of disease evaluation.

[21] Samples for correlative research are to be collected as indicated in Section **5**. If archival tissue is not available or adequate, baseline punch biopsy of the skin or core needle biopsy of a lymph node/visceral lesion is required, otherwise this is optional.

[22] PT/ INR and aPTT are required at screening, baseline and before procedures (as clinically indicated). Other timepoints are optional as tubes are available.

3.10 COST AND COMPENSATION

3.10.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures are performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by insurance their company.

3.10.2 Compensation

No direct compensation will be provided on the study.

3.10.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the subject as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.11 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all patients complete a safety visit approximately 30 days following the last dose of study therapy. Additional safety visits and follow-up will continue as per Section **3.8**.

3.11.1 Criteria for removal from protocol therapy

Patients who meet the following criteria should be discontinued from protocol therapy:

- Completion of protocol therapy (i.e., up to 6 cycles)
- Confirmed disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable toxicities as listed in Section **3.9** or those toxicities listed in Section **3.5** that requires treatment to be stopped.
- Subject's request to withdraw from protocol therapy
- Investigator's decision to withdraw the patient
- Subject's non-compliance with trial treatment or procedure requirements that requires removal in the opinion of the PI
- Pregnancy
- The drug manufacturer can no longer provide the study agent
- Study is cancelled for any reason

3.11.2 Off-Study Criteria

- Subject requests to be withdrawn from study
- Subject is lost to follow-up
- Death
- Study is cancelled for any reason

3.11.3 Lost to Follow-up

A participant will be considered lost to follow-up if they fail to return for two (2) scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 3 business days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, an IRB approved certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4 CONCOMITANT MEDICATIONS/MEASURES

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required.

For premedication and supportive care measures, see Section **3.4.3.1**, **3.4.3.2** and **3.4.3.3**.

4.1 ACCEPTABLE MEDICATIONS

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded.

4.2 CONCOMITANT MEDICATIONS TO BE USED WITH CAUTION

Concomitant medications that fall into the categories below could potentially lead to adverse reactions and should be considered cautionary (except where noted). If a potential study patient is taking any of the medications in the categories described below, the investigator must assess and document the use of medications known or suspected to fall in the following medication categories:

- Growth factors: initiation of G-CSF support (e.g. filgrastim or pegfilgrastim) will be administered at the discretion of the investigator for instances of G2 or higher neutropenia or as prophylaxis to prevent neutropenia. If short-acting G-CSF is initiated (e.g., filgrastim), dosing should continue daily until the patient completes their day 14 study therapy AND the neutrophil count > 5000 cells/μL. Alternatively, patients may receive

long-acting G-CSF (e.g., pegfilgrastim) at the discretion of the investigator. Once G-CSF (filgrastim or pegfilgrastim) has been initiated during a previous cycle, the patient should receive prophylactic G-CSF support during all subsequent cycles of therapy. Short-acting G-CSF (e.g., filgrastim) should be given daily starting on day 3 (+/-1 day) and should continue until the patient completes their day 14 study therapy AND the neutrophil count > 5000 cells/μL. Alternatively, patients may receive prophylaxis with long-acting G-CSF (e.g., pegfilgrastim) administered on day 3 (+/-1 day) of each cycle at the discretion of the investigator.

- Romidepsin concomitantly with warfarin: Monitor PT and INR more frequently in patients concurrently receiving romidepsin and warfarin. It is not known if there is an interaction with co-administration of lenalidomide and warfarin. Close monitoring of PT and INR is recommended.
- Digoxin: For subjects taking digoxin, periodic monitoring of digoxin plasma levels is recommended due to increased C_{max} and AUC with concomitant lenalidomide therapy (please see prescribing information).
- Erythropoietin stimulating agents or estrogen containing therapies: Subjects taking concomitant therapies such as erythropoietin stimulating agents or estrogen containing therapies, may have an increased risk of venous thromboembolism (please see prescribing information).
- CYP3A4 inhibitors: After the DLT evaluation window, subjects who need to start treatment with strong CYP3A4 inhibitors (**Appendix C**), should be monitored closely for toxicities. These are prohibited during the DLT window.

4.3 PROHIBITED MEDICATIONS

Patients are prohibited from receiving the following therapies during treatment on this trial:

- Other therapy for the disease under study not specified in this protocol, unless specifically noted as permitted
- Investigational agents other than lenalidomide, romidepsin and CC-486 (5-azacitidine)
- Rifampin and other strong CYP3A4 inducers (**Appendix C**)
- Agents that may cause QTc prolongation (**Appendix E**)
- Radiation therapy

  NOTE: Radiation therapy to a symptomatic solitary lesion may be allowed at the investigator's discretion.

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, typhoid vaccine and FluMist.

A list of common CYP3A inhibitors or inducers is provided in **Appendix C**; a comprehensive list of inhibitors, inducers, and substrates may be found at:

http://medicine.iupui.edu/clinpharm/ddis/table.aspx.

This website is continually revised and should be checked frequently for updates.

Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study treatment. Patients may receive other medications that the investigator deems to be medically necessary.

5 CORRELATIVE STUDIES FOR RESEARCH

5.1 BIOSPECIMEN COLLECTION

5.1.1 Summary

This study will test the feasibility of concomitant NFκ-B inhibition with lenalidomide and epigenetic modification with CC-486 (5-azacitidine) and romidepsin in patients with T-cell malignancies. Although increased efficacy with the combination has been demonstrated *in vitro*, effects of the combined treatment on the tumor microenvironment, circulating immune cell subsets, cytokine production, and exosome composition are not known. The correlative studies performed in this trial will focus on how lenalidomide alone and in combination affects tumor cells, immune cell subsets, and cytokines in tumor tissue and peripheral blood, and whether these may represent a predictive or prognostic biomarker in patients with TCMs.

Composition of the tumor microenvironment will be analyzed via immunohistochemistry, flow cytometry, and single-cell RNAseq before treatment, after 7 days of single-agent lenalidomide, and after 15 days of combined treatment with lenalidomide, romidepsin, and CC-486 (5-azacitidine). Differences in circulating immune cell subsets associated with administration will be followed throughout treatment to both study the effects of combined therapy on the immune system, and to identify potential biomarkers that would be predictive of response. Circulating tumor DNA and exosome composition will be followed and analyzed with the same goal in mind. Germline DNA will be sequenced to distinguish circulating tumor DNA from other cell-free DNA.

Sample	**Collection Details***	**Time Points†**							**Supervising Laboratory/ Investigator ^**
		Baseline [4] (C1 D-7)	C1 D1	C1 D10	C1 D15	C2-6 D1	C2-6 D10	Follow-up[#]	
Blood Samples									
Lymphocyte subset testing	• 2 x 10mL K_2EDTA (lavender-top) tubes	X	X	X	(X)		(X)	(X)[1]	DLM
PBMC banking	• 3 x 10mL Na-heparin (green-top) tube	X	X	X	(X)	X	(X)	X	Leidos CSL
Circulating tumor DNA, plasma banking**	• 1 x 10mL K_2EDTA tube • 1 x 10mL Streck/BCT tube	X	X			X		X[2]	Leidos CSL
Tissue Samples									
Tissue immune cell subsets	• Two core biopsy samples in RPMI 1640 with 10% human serum and antibiotics • One core biopsy sample in formalin NOTE: Samples may be tumor tissue or bone marrow aspirate/biopsy	X***	(X)		(X)			(X) At disease progression	(RPMI 1640) and DLM/ NCI LP (formalin)

Sample	Collection Details*	Time Points†							Supervising Laboratory/ Investigator ^
		Baseline [4] (C1 D-7)	C1 D1	C1 D10	C1 D15	C2-6 D1	C2-6 D10	Follow-up#	
Other Samples									
Germline DNA	• Blood, Buccal Swab, or Saliva (preferred) – see **5.4**	X							Leidos CSL

(X) = Optional; samples will be collected if adequate time/staff available for processing, and if research blood drawn is less than the allowed limit noted in Section **5.1.3**. If an optional sample is not collected at baseline, it would also not be collected in follow-up unless specifically requested by the PI.

^ The location of specimen processing or analysis may be adjusted with the permission of the PI or laboratory investigator.

*Tubes/media may be adjusted at the time of collection based upon materials available or to ensure the best samples are collected for planned analyses.

** May be omitted if research blood drawn would be over the allowed limit noted in Section **5.1.3**.

***Tumor biopsy (bone marrow, skin, or ultrasound-guided LN biopsies) is required if archival tissue is not available or adequate; otherwise, this is optional

† All time points during treatment are ±3 days. All follow-up time points are ±7 days.

#Subjects who discontinue treatment for a reason other than disease progression and who do not start new treatment should continue to have study bloods collected at the scheduled time points.

[1] At the end of treatment only.

[2] At each follow-up visit prior to disease progression, as specified in Section **3.8.2**.

[4] With the exception of tissue immune cell subset (if applicable) and Germline DNA which are to be collected during Baseline, samples correlating to the lead-in window will no longer be collected as the lead-in window has been retired.

5.1.2 Sample Collection and Processing

5.1.3 Summary

The planned sample collection will be done as specified below and analyses described below may be done on leftover and/or shared sample portions from the respective laboratories, as needed. In addition to the prospectively collected samples below, leftover portions of samples sent for routine laboratory testing (e.g., plasma from CBC/hematologies) may also be retrieved for research tests prior to being discarded. The planned prospective analyses are identified below; laboratories may share resources or collaborate on analyses, if appropriate.

Portions of all samples may be banked for future research analyses; prospective consent will be obtained during the informed consent process.

Tissue samples will also be sent to the Hematopathology Section of the National Cancer Institute Laboratory of Pathology, by courier service.

5.2 BLOOD SAMPLES

All blood samples will be drawn by NIH Clinical Center phlebotomy, inpatient unit, outpatient clinic, or day hospital staff.

5.2.1 Lymphocyte subset testing by flow cytometry (FACS)

- Collect blood in EDTA tubes; gently invert tubes 8-10 times immediately after collection

- Labels listing the patient's name, date of birth, date and time of the blood draw will be affixed to all the tubes by the staff person who obtained the samples.
- Lymphoid Malignancies Branch Clinical Research personnel will arrange for these samples to be delivered to: Immunology Lab, NIH Clinical Center Bldg. 10/ Room 2C410. If the Immunology Section Laboratory is unable to perform these analyses (Lymphocyte Subset Testing-CTCL for patients with cutaneous T-cell lymphoma and Lymphocyte Subset Testing-antiTAC for all other patients) on the specified days, this assessment maybe omitted or replaced with standard TBNK panel

5.2.2 Cell-free DNA (cfDNA), circulating tumor DNA (ctDNA) and plasma banking

- Collect 10 mL of blood in one cell-free DNA (e.g., Streck BCT/collection tubes) and 10 mL of blood in one K2EDTA tube; gently invert the tubes 8-10 times immediately after collection.
- Labels listing the patient's name, date of birth, date and time of the blood draw will be affixed to all the tubes by the staff person who obtained the samples. Plasma will be isolated and frozen at -80ºC until analysis (e.g., centrifuged at 1800 x g for 10 minutes at room temperature; plasma transferred/frozen in aliquots of 1.5-2 mL each).
- Lymphoid Malignancies Branch Clinical Research personnel will arrange for these samples to be delivered to Clinical Support Laboratory, Leidos Biomedical Research, Inc.in Frederick, MD for sample processing per established techniques maintained within standard operating procedures in the laboratory.

5.2.3 Peripheral blood mononuclear cell (PBMC) banking

- Collect blood in 10 mL Na-heparin (green-top) tubes; gently invert tubes 8-10 times immediately after collection.
- Labels listing the patient's name, date of birth, date and time of the blood draw will be affixed to all the tubes by the staff person who obtained the samples. Peripheral blood mononuclear cells (PBMCs) will be isolated by Ficoll-High-Paque Density Gradient Centrifugation and frozen at -20°C or lower until analysis.
- Lymphoid Malignancies Branch Clinical Research personnel will arrange for these samples to be delivered to Clinical Support Laboratory, Leidos Biomedical Research, Inc.in Frederick, MD for sample processing per established techniques maintained within standard operating procedures in the laboratory.

5.3 TISSUE SAMPLES

5.3.1 Immunohistochemistry (IHC)

- Archival block(s) or slides (i.e., at least 15 unstained slides, 5-microns) are required at baseline for participants if there are no circulating lymphoma cells or if the amount of circulating leukemia/lymphoma cells is insufficient to perform the correlative studies. Patients with prior skin, lymph node, or visceral biopsies performed at NIH or outside institutions must make specimen blocks available to the NCI Pathology Department for analysis. If no prior biopsies are available at the time of screening, patients with Cutaneous T-cell lymphoma and other lymphoma with skin involvement will undergo a punch biopsy of a skin lesion, performed by an NIH Clinical Center dermatologist. Patients with lymph node and/or visceral involvement will undergo an 18g core biopsy performed by the

Department of Radiology and Imaging Sciences' Interventional Radiologists (IR). An optional biopsy will be performed in the same manner at timepoints listed in **5.1.1**.

- Prior specimen blocks will be sent to NCI Pathology Department via FedEx. For patients with no prior samples who undergo biopsy as part of screening (if needed for diagnosis) or baseline, core tumor tissue (or bone marrow aspirate/biopsy) samples will be collected and placed in appropriate media (e.g., RPMI 1640 with 10% human serum and antibiotics, and formalin) and processed per established techniques. As indicated (Sections **5.1** and **5.2**), samples will be sent to the Department of Laboratory Medicine (DLM)/ NCI Laboratory of Pathology (LP) for concurrent routine histologic analysis and reporting and IHC testing and tumor-associated immune cells in addition to research testing (i.e., storage for subsequent single-cell analyses).

5.4 OTHER SAMPLES

5.4.1 Germline DNA

- Germline DNA will be collected by blood, buccal swab, and/or saliva samples (preferred). These will ideally be collected at baseline; however, may be collected at any point on study based on supplies. Standardized, commercial collection kits or tubes will be used (e.g., 1, 5-10 mL K_2EDTA tube for blood; Isohelix SK-1 for buccal swabs; Salviette/Oragene® for saliva). In the case of buccal swabs, two (2) samples may be collected in order to ensure adequate DNA collection.
- Lymphoid Malignancies Branch Clinical Research personnel will arrange for these samples to be delivered to Clinical Support Laboratory, Leidos Biomedical Research, Inc. in Frederick, MD for sample processing per established techniques maintained within standard operating procedures in the laboratory.

5.5 BIOMARKER AND RESEARCH METHODS

The technology platforms that are able to interrogate genomic structure and function are constantly in flux; therefore, the exact nature of the methodologies that will be employed will be assessed at the time that the samples are collected and ready for analysis. The protocol will be amended at that time, if needed, to describe the intended techniques prior to initiating the analyses.

Note: Platforms and procedures for analysis may be adjusted based upon current technology and/or collaborations in place at the time of actual analyses.

The following are technologies that are currently in use for each planned analysis:

5.5.1 Molecular Profiling

Immunohistochemical (IHC) analyses, including FISH and/or PCR testing, will take part in tumor tissue samples, including but not necessarily limited to CD2, CD3, CD4, CD5, CD7, CD8, CD14, CD16, CD20, CD25, CD38, CD45RA, CD45RO, CD56, CD62L, CD69, CD79a/CD79b, CD122, Foxp3, perforin, gamma/delta, CXCR3, CCR4, and NKG2D.

5.5.2 Immune Subset Analysis

Peripheral blood mononuclear cells (PBMC) will be assessed using multiparameter flow cytometry for immune subsets including but not necessarily limited to CD8+ T-cells, CD4+Foxp3- T-cells, Tregs, T_{ex}, Th1, Th2 and Th17+ CD4+ T-cells, NK cells and subsets, monocyte subsets, MDSC

subsets. Assessment may include functional markers, i.e. PD-1, Tim-3, CTLA-4, PD-L1, HLA-DR, Ki67 and/or CD40.

5.5.3 cfDNA/ctDNA

Since the methods of molecular monitoring in the peripheral blood is an emerging field with numerous technologies under development, the storage of peripheral blood mononuclear cells (PBMC), serum, and plasma will all be performed allowing for future comparison of the different compartments for analytes that include cell-free circulating tumor DNA (ctDNA), and RNA sequencing of circulating tumor cells. Studies to be performed on these samples include: cfDNA/ctDNA for liquid genotyping as a non-invasive dynamic monitoring of disease as well as monitoring for individual molecular aberrations that herald progression or disease transformation; specifically, amplification and sequencing of the VDJ segment of the immunoglobulin receptor is planned. Germline DNA obtained from saliva, blood, or buccal mucosa will be used to discriminate somatic from germline mutations during cfDNA and ctDNA analyses.

5.5.4 DNA/RNA Sequencing

Genomic DNA and total RNA will be extracted from tumor samples using a Qiagen All-prep kit. For individual target genes that are recurrently mutated in T-cell malignancies, classical Sanger sequencing will be performed on PCR amplicons, using primers surrounding the known sites of mutation. To broadly assess mutations, next generation sequencing (e.g., on an Illumina HiSeq 2000 platform) will be employed, using a paired end sequencing strategy of libraries constructed from tumor DNA. DNA will either be sequenced in its entirety from a whole genome library or will be first enriched for exonic sequences using the Agilent Sure Select system, aiming for 30X or 100X average coverage per base, respectively. The sequence fragments will be mapped back to the genome using the BWA algorithm. Of sequences overlapping a particular base pair in the genome, the percent mutant calls greater that 20% with a minimum of 25X coverage will be considered as an arbitrary threshold for single nucleotide variants (SNVs). SNVs that are not present in the matched normal sample will be considered candidate somatic mutations.

A related technology, RNA-Seq, utilizes RNA from the tumor specimen to create a cDNA library for high-throughput sequencing. RNA-seq will be performed using Illumina kits followed by high-throughput sequencing on an Illumina HighSeq 2000 machine. The cutoffs for coverage and percent mutant calls mentioned above will also be used to identify putative SNVs. RNA sequencing will also be used to read out digital gene expression across the genome as described.

Recent advances in genomic technologies enable GEP at the single cell level, a distinct advantage over conventional GEP which cannot always distinguish tumor vs non-tumor gene expression. Single-cell approaches allow identification of the evolution of rare populations of resistant tumor cells, as well as identification of TME cells critical for the survival of the tumor. The Center for Cancer Research (CCR) has recently opened a single cell analysis core facility with expert staff headed by Dr. Michael Kelly within the CCR Genomics Core. This facility has the ability to take purified viably frozen cells banked from patient biopsies and prepare them, using well-validated 10X Genomics technology, for single-cell RNA sequencing. This core is directly integrated with the NCI Sequencing core facility to provide high-quality, deep-sequencing of the single cell RNA-SEQ samples, as well as ‘first-pass’ data processing and analysis. Data will then be transferred to lymphoma researchers and bio-informaticians for further analysis of gene expression patterns and cellular population dynamics.

5.5.5 Future Use

Any blood, tissue, or other products or portions leftover from other analyses will be stored for future research.

5.6 SAMPLE STORAGE, TRACKING, AND DISPOSITION

5.6.1 General

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required.

5.7 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.7.1 Description of the scope of genetic/genomic analysis

The research correlates for this study are expected to include DNA/RNA sequencing of tumors, including circulating tumor (ct) DNA. In addition, whole exome sequencing may include evaluation for known lymphoma mutations. For any genetic studies performed, the results will be deposited in a database such as dbGaP per NIH requirements. Although there is controlled access to such a database, such a submission carries theoretical risks of revealing the identity of the subject. This is discussed in the consent.

5.7.2 Description of how privacy and confidentiality of medical information/biological specimens will be maximized

Confidentiality for genetic samples will be maintained as described (Section **5.6**). In addition, a Certificate of Confidentiality has been obtained for this study.

5.7.3 Management of Results

Subjects will be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis.

5.7.4 Genetic Counseling

Subjects will be contacted at this time with a request to provide a sample to be sent to a CLIA certified laboratory. If the research findings are verified in the CLIA certified lab, the subject will be offered the opportunity to come to NIH to have genetic education and counseling to explain this result; at the time of any such event(s), these activities will be funded by the NCI/CCR in consideration of the specific circumstances. If the subject does not want to come to NIH, a referral to a local genetic healthcare provider will be provided (at their expense).

This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

6.1.1 Summary

The PI will be responsible for overseeing entry of data into a 21 CFR Part 11-compliant data capture system provided by the NCI CCR and ensuring data accuracy, consistency and timeliness.

The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events (AEs), including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document AEs from the first study intervention, Study Day 1 through 30 days after the last intervention. Beyond 30 days after the last intervention, only adverse events which are serious and related to the study intervention need to be recorded.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in Section **7.2.1**.

6.1.2 Data Collection/Recording Exceptions

6.1.2.1 Abnormal Laboratory Values

An abnormal laboratory value will be recorded as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows:

_X_ Coded, linked data in an NIH-funded or approved public repository.

_X_ Coded, linked data in another public repository

_X_ Coded, linked data in BTRIS (automatic for activities in the Clinical Center)

_X_ Identified or coded, linked data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through:

_X_ An NIH-funded or approved public repository. Insert name or names: ClinicalTrials.gov,

dbGaP.

_X_ BTRIS (automatic for activities in the Clinical Center)

_X_ Approved outside collaborators under appropriate individual agreements.

_X_ Publication and/or public presentations.

When will the data be shared?

_X_ Before publication.

_X_ At the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.3 RESPONSE CRITERIA

6.3.1 Response Assessments

Tumor response will be assessed by the investigator using the RECIL 2017 criteria [66] for all patients with T-cell lymphoma other than CTCL. Global Response Score [67], and modified severity weighted assessment tool (mSWAT) [68] will be used for patients with CTCL. For leukemic disease, leukemic cells (ATL, Sezary or T-PLL) as percentage of PBMCs will also be assessed and reported separately and response will be assessed using consensus guideline [69]. Patient will be re-evaluated for response as outlined in the Study Calendar, Section **3.9**.

6.3.1.1 Response Criteria for PTCL

RECIL 2017 criteria [66] use the Deauville five-point scale for assessment of response via FDG-PET. The five-point scale (5-PS) has been validated for use at interim staging and at the end of treatment and was adopted as the preferred reporting method at the First International Workshop on PET in Lymphoma in Deauville, France (i.e., Deauville criteria), and in several international trials.

The 5-PS PS scores the most intense uptake in a site of initial disease:

1. if present, as follows: no uptake or no residual uptake (when used at interim)
2. slight uptake, but below blood pool (mediastinum)
3. uptake above mediastinal, but below or equal to uptake in the liver
4. uptake slightly to moderately higher than liver
5. markedly increased uptake or any new lesion (on response evaluation)

The sum of longest diameter (SLD) is used for assessment of tumor burden. In patients with disseminated disease, a maximum of three target lesions should be selected and used to estimate tumor response. Target lesions should be selected from those with the largest size that can be reproducibly measured and preferably representing multiple sites and/organs. In most cases, lymph nodes can be considered target lesions if the lymph node longest diameter measures ≥15 mm. A lymph node measuring between 10 and 14 mm is considered abnormal but should not be selected as a target lesion. Lymph nodes measuring <10 mm in diameter are considered normal. In certain anatomical sites (inguinal, axillary, and portocaval), normal lymph nodes may exist in a narrow, elongated form, and such nodes should not be selected as target lesions if alternatives are available. Extranodal lesions are selected as target lesions if they have soft tissue component, based on their

size, and the ease of reproducibility of repeated measurements, with a minimum measurement of the longest diameter of ≥ 15 mm. All other lesions should be identified as nontarget lesions and should be recorded at baseline, without the need to measure them. Nontarget lesions should be followed and reported as present, absent, or clear progression.

Table 86: Response categories based on assessment of target lesions

	% Change in sum of diameters of target lesions from nadir				
	CR	PR	MR	SD	PD
% change from baseline	• Complete disappearance of all target lesions and all nodes with long axis <10mm • ≥30% decrease in the sum of longest diameters of target lesions (PR) with normalization of FDG-PET	≥30% decrease in the sum of longest diameters of target lesions but not a CR	≥10% decrease in the sum of longest diameters of target lesions but not a PR (<30%)	<10% decrease or ≤ 20% increase in the sum of longest diameters of target lesions	• >20% increase in the sum of longest diameters of target lesions • For small lymph nodes measuring <15 mm post therapy, a minimum absolute increase of 5 mm and the long diameter should exceed 15 mm • Appearance of a new lesion
FDG-PET	Normalization of FDG-PET (Deauville score 1-3)	Positive (Deauville score 4-5)	Any	Any	Any
Bone marrow involvement	Not involved	Any	Any	Any	Any
New lesions	No	No	No	No	Yes or No

CR, complete response; CT, computerized tomography; FDG-PET, [18F]2-fluoro-2-deoxy-D-glucose; MR, minor response; PD, progression of disease; PR, partial response; SD, stable disease.

6.3.1.2 Response Criteria for CTCL

Global Response (GR) score **(Appendix B)** will be used for assessing response in patients with CTCL [67]. GR score incorporates separate responses in each component of the TNBM staging (i.e., skin, nodes, viscera and blood; (**Appendix B**). No patient with a global OR should have less than a PR in the skin.

The mSWAT [68] is an instrument utilized to track the skin tumor burden in MF/SS. It measures the percentage total body-surface area (TBSA, %) involvement separately for patches, plaques, and tumors within 12 body regions using the patient's palm and fingers representing 1% of TBSA. Patients with erythroderma are assessed for percentage of TBSA involved with patches and/or plaques. The percentage of TBSA for each lesion type is multiplied by a number (patch = 1, plaque = 2; tumor = 4) and summed to derive the mSWAT score. The mSWAT for each patient will be determined by the same individual at all study visits.

A complete response (CR) requires 100% clearing of skin disease and a partial response (PR) requires ≥ 50% reduction in the mSWAT score compared with baseline. CR/PR requires confirmation by repeat assessment after ≥ 4 weeks. Stable disease is defined as less than 50% reduction to less than 25% increase in the mSWAT score compared with baseline. PD is defined as ≥ 25% increase in the mSWAT score from baseline or ≥ 50% increase in the sum of the products of the greatest diameters of pathologically positive lymph nodes compared with baseline.

Time to response is the time from the first treatment dose until the patient first meets the criteria for a 50% decrease in the GR score. The duration of response (DOR) is the time from first CR/PR until the GR score is increased from nadir to more than 50% of the difference between the baseline and nadir scores. Time to progression (TTP) is the time from start of treatment until PD. If patients go off treatment for any purpose, this date is used for determination of TTP and/or DOR.

Table 9: Calculating mSWAT Score

Body Region	% BSA in Body Region	Assessment of Involvement in Patient's Skin		
		Patch[1]	Plaque[2]	Tumor[3]
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of lesion BSA				
Weighing factor		x1	x2	x4
Subtotal lesion BSA x weighing factor				

NOTE: mSWAT score equals summation of each column line.

Abbreviations: BSA, body surface area; mSWAT, modified Severity Weighted Assessment Tool.

[1] Any size lesion without induration or significant elevation above the surrounding uninvolved skin; poikiloderma may be present

[2] Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present.

[3] Any solid or nodular lesion ≥ 1cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

6.3.2 Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

6.3.3 Duration of Response

The duration of response (DOR) is measured from the time measurement criteria are met for CR or PR (whichever is recorded first) 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), death, or, in the absence of PD, date of last assessment.

6.3.4 Event-Free Survival

Event-free survival (EFS) is defined as the duration of time from the date of study enrollment until time of disease relapse, disease progression, alternative anti-lymphoma therapy, or death, whichever occurs first.

6.3.5 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from the date of study enrollment until time of disease relapse, disease progression, or death, whichever occurs first.

6.3.6 Overall Survival

Overall survival (OS) is defined as the time from the date of study enrollment until time of death from any cause.

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

7 NIH REPORTING REQUIREMENTS/ DATA SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/hrpp-policy-guidelines/.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found at:

https://irbo.nih.gov/hrpp-policy-guidelines/.

Note: Only IND Safety Reports that meet the definition of an unanticipated problem or present new information that might affect the willingness of participants to enroll or remain on the study will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/hrpp-policy-guidelines/.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reviewed by the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore, a separate submission for these reports is not necessary.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 NIH Required Data And Safety Monitoring Plan

7.4.1 Principal Investigator/Research Team

The clinical research team will meet at least once weekly when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation will be made during the meeting based on the toxicity data from prior patients and documented in the meeting minutes.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in Section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7.4.2 Safety Monitoring Committee (SMC)

NOTE: CCR SMC was added in an amendment; protocol version 11/12/2021.

This protocol will be periodically reviewed by an intramural Safety Monitoring Committee. comprising physicians, biostatisticians and a lay member selected based on experience, area of expertise, reputation for objectivity, absence of conflicts of interest and knowledge of or experience with clinical trial research. Initial review will occur as soon as possible after the annual NIH Intramural IRB continuing review date. Subsequently, each protocol will be reviewed as close to annually as the quarterly meeting schedule permits or more frequently as may be required by the SMC based on the risks presented in the study. For initial and subsequent reviews, protocols will not be reviewed if there is no accrual within the review period.

The SMC will operate under the rules of an approved charter that will be written and reviewed at the organization meeting of the SMC. Each review will focus on unexpected protocol-specific safety issues that are identified during the conduct of the clinical trial.

Written outcome letters will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

8 SPONSOR PROTOCOL/ SAFETY REPORTING

8.1 Definitions

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2)).

8.1.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse event (see section **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
  - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
  - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient or subject convenience) is not considered a serious adverse event.
  - Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32).

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 5.0.

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.2 ASSESSMENT OF SAFETY EVENTS

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution (return to baseline or stabilization) of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution (return to baseline or stabilization).

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to section **6.1**. All serious adverse events recorded from the time of first investigational product administration must be reported to the sponsor with the exception of any listed in section **8.4**.

8.3 REPORTING OF SERIOUS ADVERSE EVENTS

Any AE that meets protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety. Any exceptions to the expedited reporting requirements are found in section **8.4.**

All SAE reporting must include the elements described in section **8.2**.

SAE reports will be submitted via an electronic SAE reporting system (e.g. HiLIT). In the event of system downtime or issues , SAE reports will be submitted using the CCR SAE Report form to the sponsor at: OSROSafety@mail.nih.gov. CCR SAE report form and instructions can be found at:

https://nih.sharepoint.com/:u:/r/sites/NCI-CCR-OCD-Communications/SitePages/Forms-and-Instructions.aspx?csf=1&web=1&e=uWBX

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 WAIVER OF EXPEDITED REPORTING TO CCR

As progression free survival, which includes death due to disease progression is part of the study objectives, and captured as an endpoint in this study, death due to disease progression will not be reported in expedited manner to the sponsor. However, if there is evidence suggesting a causal relationship between the study drug and the event, report the event in an expedited manner according to section **8.3**.

8.5 SAFETY REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATORS

Reporting will be per the collaborative agreement.

8.6 REPORTING PREGNANCY

All required pregnancy reports/follow-up to OSRO will be submitted to: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. Forms and instructions can be found here: https://nih.sharepoint.com/:u:/r/sites/NCI-CCR-OCD-Communications/SitePages/Forms-and-Instructions.aspx?csf=1&web=1&e=uWBXtI

8.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the pregnancy becomes known.

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (section **8.1.2**) should be reported as SAEs.

The outcome of all pregnancies should be followed up and documented.

8.6.2 Paternal exposure

Individuals who can father children should refrain from fathering a child or donating sperm during the study and for 28 days after the last dose of lenalidomide and for 3 months after the last dose of CC-486 (5-azacitidine).

Pregnancy of the patient's partner is not considered to be an AE. The outcome of all pregnancies occurring from the date of the first dose until 6 months after the last dose should, if possible, be followed up and documented. Pregnant partners may be offered the opportunity to participate in an institutional pregnancy registry protocol (e.g., the NIH IRP pregnancy registry study) to provide data about the outcome of the pregnancy for safety reporting purposes.

8.7 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

8.8 SPONSOR PROTOCOL DEVIATION REPORTING

A Protocol Deviation is defined as any non-compliance with the clinical trial Protocol, Manual of Operational Procedures (MOP) and other Sponsor approved study related, GCP, or protocol-specific procedural requirements on the part of the participant, the Investigator, or the study site staff inclusive of site personnel performing procedures or providing services in support of the clinical trial.

It is the responsibility of the study Staff to document any protocol deviation identified by the Staff or the site Monitor in the CCR Protocol Deviation Tracking System (PDTS) online application. The entries into the PDTS online application should be timely, complete, and maintained per CCR PDTS user requirements.

In addition, any deviation to the protocol should be documented in the participant's source records and reported to the reviewing IRB per their guidelines. OSRO required protocol deviation reporting is consistent with E6(R2) GCP: Integrated Addendum to ICH E6(R1): 4.5 Compliance with Protocol; 5.18.3 (a), and 5.20 Noncompliance; and ICH E3 16.2.2 Protocol deviations.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure:

- That the rights of the participants are protected;
- that the study is implemented per the approved protocol, Good Clinical Practice and standard operating procedures, and,
- the quality and integrity of study data and data collection methods are maintained.

Monitoring for this study will be performed by NCI CCR Office of Sponsor and Regulatory Oversight (OSRO) Sponsor and Regulatory Oversight Support (SROS) Services contractor. Clinical site monitoring activities will be based on OSRO standards, FDA Guidance E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) March 2018, and applicable regulatory requirements.

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by OSRO. CMPs will be protocol-specific, risk-based and tailored to address human subject protections and integrity of the study data. OSRO will determine the intensity and frequency of monitoring based on several factors, including study type, phase, risk, complexity, expected enrollment rate, and any unique attributes of the study and the site. The Sponsor will conduct a periodic review of the CMP to confirm the plan's continued appropriateness. A change to the protocol, significant or pervasive non-compliance with GCP, or the protocol may trigger CMP updates.

OSRO SROS Monitoring visits and related activities will be conducted throughout the life cycle of each protocol. The first activity is before the study start to conduct a Site Assessment Visit (SAV) (as warranted), followed by a Site Initiation Visit (SIV), Interim Monitoring Visit(s) (IMVs), and a study Close-Out Visit (COV).

Some monitoring activities may be performed remotely, while others will take place at the study site(s). Monitoring visit reports will describe visit activities, observations, findings of protocol non-adherence and associated action items or follow-up required for resolution of findings. Monitoring reports will be distributed to the study PI, NCI CCR QA, coordinating center (if applicable) and the Sponsor regulatory file.

The site Monitor will inform the study team of any deviations observed during monitoring visits. If unresolved, the Monitor will request that the site Staff enter the deviations in the CCR Protocol Deviation Tracking System (PDTS) for deviation reporting to the Sponsor and as applicable per institutional and IRB guidance.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL HYPOTHESIS

- Primary Endpoint(s):
  - Maximum tolerated dose (MTD) of lenalidomide administered orally in combination with romidepsin and CC-486 (5-azacitidine) for up to 6 cycles
  - Frequency (number and percentage) of treatment-emergent AEs
- Secondary Endpoint(s):
  - Overall response rate (including complete response rate and partial response rate), after treatment
  - Duration of response, after treatment
  - Progression-free survival after treatment
  - Event-free survival after treatment
  - Overall survival

10.2 SAMPLE SIZE DETERMINATION

The MTD will be based on the assessment of DLT during the first cycle of treatment and will be defined as the dose level at which less than one-third of patients (0 of 3 or 0-1 of 6 patients) treated experience a DLT, with the next higher dose level demonstrating one-third or a greater number of patients (≥ 2 of 3 or ≥ 2 of 6 patients) having a DLT. If a subject did not experience a DLT and did not finish one cycle of treatment (21 days) they will not be evaluable for determination of the MTD and would be replaced in the dose level. An additional 3 to 6 patients will be enrolled at the MTD, so that a total of 9 patients will be treated at this dose.

Using this dose-escalation scheme the probability of escalating to the next dose level will be based on the true rate of DLT at the current doses given by the following table (each group will be considered independently of the other); Thus, if the true underlying proportion of DLTs is 50% at the current dose there is a 17% probability of escalating to the next dose.

True toxicity at a given dose	10%	20%	30%	40%	50%	60%
Probability of escalating	0.91	0.71	0.49	0.31	0.17	0.08

If all four dose levels are evaluated with 6 patients per dose level and 9 total patients at the MTD, a maximum of 27 evaluable patients will be enrolled. Similarly, if all dose levels are evaluated with 3 patients per dose level and 9 total patients at the MTD, the minimum number of evaluable patients required will be 18. To account of unevaluable patients, accrual ceiling will be set at 36. It is expected that the accrual can be completed in 29 months.

A maximum of 30 patients will be enrolled over 29 months, at a rate of 1-2 patients per month.

After execution of amendment 12/07/2022, we will no longer enroll into the original Arm 2 expansion cohort and will test a new modified dose-expansion arm removing the lenalidomide lead-in window and expanding the cycle length to 28 days to enroll the remaining participants.

10.3 POPULATION FOR ANALYSIS

10.3.1 Evaluable for toxicity:

All patients will be evaluable for toxicity from the time of their first treatment with lenalidomide, romidepsin and CC-486 (5-azacitidine).

10.3.2 Evaluable for objective response:

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated above, Section **6.3**. (**NOTE:** Patients who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.)

10.3.3 Evaluable Non-Target Disease Response:

Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

10.3.4 Evaluable for DLT:

All participants who either completed cycle 1 treatment or experienced a DLT during cycle 1 will be evaluable for DLT. If a participant did not experience DLT and did not finish cycle 1 treatment, they will not be evaluable for toxicity and will be replaced in the dose level.

10.4 STATISTICAL ANALYSES

10.4.1 General Approach

The response rate will be determined and reported along with a 95% Agresti-Coull confidence interval [70]. Other time-to-event outcomes will be reported using Kaplan-Meier curves.

10.4.2 Analysis of the Primary Endpoints

Safety summaries will include summaries in the form of tables and listings. Reports will include the frequency (number and percentage) of treatment emergent AEs grouped by severity of the AE (per CTCAE, v5.0) and by relationship to study drug (e.g., lenalidomide, romidepsin, CC-486 (5-azacitidine) in any combinations).

Laboratory shift tables containing counts and percentages will be prepared by treatment assignment, laboratory parameter, and time. Summary tables will be prepared for each laboratory parameter. Figures of changes in laboratory parameters over time will be generated.

Results of vital sign assessments, ECGs, and physical exams will be tabulated and summarized.

10.4.3 Analysis of the Secondary Endpoints

Overall response rate (ORR), complete response (CR) rate will be estimated. Every report of response rates and time to progression should contain all patients included in the study. For the response calculation, the report should contain at least a section with all eligible patients. Another section of the report may detail the response rate for evaluable patients only. However, a response rate analysis based on a subset of patients must explain which patients were excluded and for which reasons. 95% confidence limits will be given.

The duration of response (DOR), overall survival (OS), event-free survival (EFS), and progression free survival (PFS) will be estimated using Kaplan-Meier curves with appropriate confidence intervals reported. For EFS, PFS, and OS, censoring time is defined as time from baseline to date of last follow-up. DOR for responders also calculated using the Kaplan-Meier approach is defined in section **6.3.3**. Censoring time for duration of response is defined as time from the initial response to date of last follow-up.

10.4.4 Safety Analyses

The type, grade and frequency of toxicities will be reported.

10.4.5 Baseline Descriptive Statistics

Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions and CIs for discrete variables) will be used to summarize data as appropriate.

10.4.6 Planned Interim Analyses

No interim analyses are planned because of the single stage design of the trial.

10.4.7 Tabulation of Individual Participant Data

None.

10.4.8 Exploratory Analyses

The exploratory objectives such as seeking to identify potential biomarkers or T-cell clones in peripheral blood which are associated with response, will be assessed using descriptive statistics as well as non-parametric methods such as exact Wilcoxon rank sum tests. The analyses will be done without formal adjustment for multiple comparisons, but in the context of the number of tests performed.

11 COLLABORATIVE AGREEMENTS

11.1 CLINICAL TRIALS AGREEMENT (CTA)- CELGENE

A CTA (#01166) between the National Cancer Institute and Celgene, the manufacturer of lenalidomide, romidepsin and CC-486 (5-azacitidine) was executed on 11/24/2020.

12 HUMAN SUBJECTS PROTECTIONS

12.1 RATIONALE FOR SUBJECT SELECTION

All subjects from both sexes and all racial/ethnic groups are eligible for this study if they meet the eligibility criteria outlined in the protocol and provide informed consent to protocol participation. Pregnant or nursing individuals are excluded because of the potential teratogenic effects of therapy.

We expect individuals who can father children and individuals of childbearing potential to be equally represented among the enrolled patients.

12.2 PARTICIPATION OF CHILDREN

Subjects under the age of 18 are excluded because recurrent T-cell lymphomas are rare in young patients, and the inclusion of an occasional younger patient will not provide generalizable information that would justify their inclusion on this study. Additionally, because no dosing or adverse event data are currently available on the use of lenalidomide, romidepsin and CC-486 (5-

azacitidine) in patients <18 years of age, children are excluded from this study, but may be eligible for future pediatric trials.

12.3 Participation of Subjects Unable to Give Consent

Adults who are unable to consent are excluded from enrolling in this study. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation during treatment (Section **12.5**), and because overall survival is one of the secondary outcomes, all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study.

Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation to assess ongoing capacity of the subjects and to identify an LAR, as needed.

Please see Section **12.6.1** for consent procedure.

12.4 Evaluation of Benefits and Risks/Discomforts

The potential benefit of adding lenalidomide to romidepsin and CC-486 (5-azacitidine) combination in treatment of mature T-cell malignancies is unknown, but romidepsin and CC-486 (5-azacitidine) combination have shown activity as outlined in Section **1.7**. There is a risk of additive toxicity of the two drugs, in particular for hematologic toxicities (including neutropenia, thrombocytopenia), fatigue, rash, Liver Function Test (LFT) and abnormalities.

12.5 Risks/Benefits Analysis

12.5.1 Known Potential Risks

The potential risks of adding romidepsin, CC-486 (5-azacitidine), dexamethasone, and lenalidomide include, in particular, GI disturbances (nausea, vomiting, constipation, diarrhea, abdominal pain), hematologic toxicities (anemia, thrombocytopenia, neutropenia, leukopenia, febrile neutropenia), and asthenic conditions (fatigue, asthenia, lethargy), edema, anorexia, clinical chemistry abnormalities (hypocalcemia, hypoalbuminemia, hyperglycemia, hypomagnesemia), pyrexia and insomnia.

As noted in **Table 4**: Drug Regimen, premedication will be given prior to each cycle to reduce the risk of these AEs occurring. Subjects will be monitored closely, and manufacturer recommendations for delaying and discontinuing study medications and initiating supportive therapy will be followed.

12.5.1.1 Risks related to Imaging

CT, PET, and/ or MRI scans may be used to monitor a patient's disease on this study. CT and PET scans expose a patient to radiation; the amount depends on the number of body areas scanned. In addition, CT, PET and MRI scans involve use of contrast (oral and/or IV). An IV line may need to be inserted for administration of the contrast agent and can cause pain at the site where the IV is placed. There is also a small risk of bruising or infection. If a contrast agent is given with the scan there is a small risk of having a reaction to the contrast. In the small group of patients who have a reaction, the most common symptoms are nausea, pain in the vein where the contrast was

given, headache, a metallic or bitter taste in the mouth, and a warm or flushing feeling that lasts from 1-3 minutes. Rarely, these symptoms may require treatment. In very rare cases, people have had more severe allergic reactions that result in skin rashes, shortness of breath, wheezing, or lowering of the blood pressure.

12.5.1.2 Risks from Radiation Exposure

The procedures for performing the chest CT and ^{18}F-FDG PET/CT scans will follow clinical policies, no special procedures apply to these additional assessments for research purposes. In summary, subjects may receive additional radiation exposure from up to eight (8) additional CT scans of the neck, chest, abdomen, and pelvis, and three (3) additional ^{18}F-FDG PET/CT scans.

The total additional radiation dose for research purposes will be approximately 14 rem. Such radiation exposure is associated with an increased risk of cancer.

12.5.1.3 Risks from Blood Draws

The possible side effects of drawing blood include pain, bleeding, bruising, dizziness, light-headedness, fainting and, on rare occasions, local blood clot formation or infection with redness and irritation of the vein. Up to about 8.6 tablespoons of blood may be collected at any day, up to about 25.9 tablespoons may be collected within 8 weeks.

12.5.1.4 Risks from Bone Marrow Biopsy and Aspirate

A numbing agent that can cause a stinging or burning sensation may be injected at the site of your bone marrow biopsy. The biopsy needle will go through the skin into the bone and may produce a brief, sharp pain. As the bone marrow liquid is taken from the bone, there may be a brief, sharp pain. Since the inside of the bone cannot be numbed, this procedure may cause some discomfort, however not all people experience discomfort. The possible side effects associated with a bone marrow biopsy include pain, bleeding, bruising, and infection, as well as a reaction to the numbing agent.

12.5.1.5 Risks from Tumor Biopsy

The likely side effects include discomfort or pain, redness, swelling, and/or bruising at the site of the needle insertion. Bleeding from the site of the needle insertion is a less likely risk. Rarely, significant infection or bleeding from this procedure, allergic reaction to the anesthetic, or formation of a scar at the site of needle entry occurs. The procedure may be performed under conscious sedation.

12.5.1.4 Risks from Conscious Sedation

The common side effects of conscious sedation include drowsiness, delayed reflexes, hypotension, headache, and nausea. These are generally mild and last no more than a few hours.

12.5.1.5 Catheter insertion

Insertion of catheters can cause site pain, inflammation of the vein, bruising, infection, blood clots, leak of the infused liquid, and if this is a central line, puncture of the lung that can result in lung collapse.

12.5.1.6 Risks from Saliva Capture and/or Buccal Swab collection

There are no risks associated with the saliva capture and buccal swab collection. The buccal swab collection may cause momentary discomfort.

12.5.2 Known Potential Benefits

The benefit of taking romidepsin, CC-486 (5-azacitidine), dexamethasone, and lenalidomide are unknown. All four drugs have shown clinical activity in T-cell malignancies as noted in section **1.10**.

12.5.3 Assessment of Potential Risks and Benefits

Since relapsed/ refractory PTCL and CTCL are associated with a poor prognosis and a median overall survival of less than 2 years, new treatment strategies are needed. Single agent therapy has proven unable to provide durable responses, and combination therapy is necessary, as is the case with B-cell malignancies. We hypothesize that the four-drug combination can potentially block multiple critical pathways TCMs require for proliferation and survival. The safety profiles and MTDs of lenalidomide/romidepsin, CC-486 (5-azacitidine)/romidepsin and CC-486 (5-azacitidine)/lenalidomide combinations are established. Dexamethasone is added to the combination to further improve tolerability, as lenalidomide-associated skin flares were a major toxicity in the lenalidomide combination trials. Pulse instead of continuous therapy is also used to minimize toxicity and improve tolerability. Finally, the 3+3 design ensures that patients will not be unduly exposed to higher than tolerated doses of the study drugs.

12.6 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided as a physical or electronic document to the participant or consent designee(s) as applicable for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with local policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Note: When required, witness signature will be obtained similarly as described below for the investigator and participant.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or on the electronic document.

Manual (non-electronic) signature on electronic document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location, but is not required.

Both the investigator and the subject will sign the document using a finger, stylus or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found at: https://nih.sharepoint.com/sites/NCI-CCR-OCD-Communications/SitePages/OEC-Administrative---Clinical-Research-(ADCR).aspx?Mode=Edit.

12.6.1 Consent Process for Adults Who Lack Capacity to Consent to Research Participation

For participants addressed in section **12.3**, an LAR will be identified consistent with Policy 403 and informed consent obtained from the LAR, as described in Section **12.6.**

13 REGULATORY AND OPERATIONAL CONSIDERATIONS

13.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigators, funding agencies, the Investigational New Drug (IND) sponsor and regulatory authorities, as applicable. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and as applicable, Food and Drug Administration (FDA).

13.2 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented

(recorded), and reported in compliance with the protocol, International Council for Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13.3 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIH has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.4 CONFIDENTIALLY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil,

criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14 PHARMACEUTICAL INFORMATION

This study will be conducted under a CCR-held IND: IND #147481.

14.1 ROMIDEPSIN (DEPSIPEPTIDE, FK228, ISTODAX®)

14.1.1 Source Acquisition and Accountability

Romidepsin (ISTODAX®) is a commercially available agent. An investigational supply will be provided by Bristol Myers Squibb to the NCI for dispensing to study participants as per an arranged research agreement.

14.1.2 Toxicity

See Section **1.5.1.3** , **1.5.1.4** and **1.5.1.5** for a summary of AEs and SAEs.

14.1.3 Formulation and preparation

The lyophilized, sterile finished product contains romidepsin, 10 mg/vial, and Povidone, compendial grade (Ph. Eur./USP), 20 mg/vial. ISTODAX (romidepsin) for injection is supplied in a dual-pack configuration with a single-use diluent for romidepsin vial that contains 2 mL of 80% propylene glycol, compendial grade (Ph. Eur./USP), and 20% dehydrated alcohol (ethanol), compendial grade (Ph. Eur./USP); sterile for use in reconstitution of the lyophilized powder. After reconstitution with 2 mL of the supplied diluent, the reconstituted solution will contain romidepsin 5 mg/mL.

A volume of the resultant 5 mg/mL stock solution containing the appropriate dose for the patient is diluted in 0.9% sodium chloride injection, compendial grade (Ph. Eur./USP), to a final drug concentration, as recommended in the labeling or as directed in the protocol.

The romidepsin infusion solution is compatible with polyvinyl chloride (PVC), ethyl vinyl acetate (EVA), and polyethylene (PE) IV infusion bags, as well as glass bottles. Individual study protocols may stipulate different doses and dosing schedules.

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 (Ph.Eur./USP) before IV 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 solution is chemically stable for at least 8 hours at room temperature

14.1.4 Stability and Storage

Unopened vials must be stored as directed.

The reconstituted drug product should be stored as directed on the label or in the protocol.

The reconstituted stock solution at 5 mg/mL is chemically stable for at least 8 hours at room temperature, and the romidepsin infusion solution is chemically stable for at least 24 hours at room temperature. However, whenever possible, drug should be prepared within 4 hours of dose administration. The drug should be administered as soon after dilution as possible.

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

14.1.5 Administration procedures

Extract the appropriate amount of romidepsin from the vials to deliver the desired dose, using proper aseptic technique. Before IV infusion, further dilute romidepsin in 500 mL 0.9% Sodium Chloride Injection (Ph.Eur./USP). Infuse over 4 hours. Romidepsin is a cytotoxic drug. Use appropriate handling procedures. See section **3.4.3.2** for administration details.

14.1.6 Incompatibilities

The romidepsin infusion solution is compatible with polyvinyl chloride (PVC), ethyl vinyl acetate (EVA), and polyethylene (PE) IV infusion bags, as well as glass bottles. Refer to section **3.4.3.2** and section **4.3**. Please see the prescribing information for romidepsin.

14.2 CC-486 (5-AZACITIDINE)

14.2.1 Source Acquisition and Accountability

CC-486 (5-azacitidine) is an investigational agent that will be provided by Bristol Myers Squibb. Bristol Myers Squibb will provide the investigational supply to the NCI for dispensing to the study participants as per an arranged research agreement.

14.2.2 Toxicity

See Section **1.5.2.2** for a summary of AEs.

14.2.3 Formulation and preparation

Different formulations of oral CC-486 (5-azacitidine) have been developed and are being used in clinical studies. CC-486 (5-azacitidine) has been developed for clinical investigation in strengths of 20, 60, 100, 150, 200, and 300 mg tablets. The CC-486 (oral 5-azacitidine formulations) may use any of the following excipients: mannitol USP, silicified microcrystalline cellulose NF, crospovidone NF, magnesium stearate NF, croscarmellose sodium, vitamin E TPGS NF, methacrylic acid copolymer (enteric coating) NF, Opadry coating, triethyl citrate NF, talc USP, hydroxypropyl cellulose NF, and hard gelatin capsule. CC-486 (5-azacitidine) capsules contain 100 mg of the active ingredient only. Only tablets will be provided for this study.

14.2.4 Stability and Storage

Store as directed on the label. CC-486 (5-azacitidine) is a cytotoxic drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing CC-486 (5-azacitidine). If reconstituted 5-azacitidine comes into contact with the skin, immediately and thoroughly wash with soap and water. If it comes into contact with mucous membranes, flush thoroughly with water. Procedures for proper handling and disposal of CC-486 (5-azacitidine) (vials or reconstituted CC-486 (5-azacitidine), tablets, or capsules) should be applied according to

standards established at each facility for cytotoxic drugs. If a vial, capsule, or tablet is broken or damaged, dispose of the drug product and do not use.

14.2.5 Administration procedures

CC-486 (5-azacitidine) is taken by mouth with or without food. See section **3.4.3.3** for additional details.

14.2.6 Incompatibilities

No formal clinical drug interaction studies with CC-486 (5-azacitidine) have been conducted.

Based on in-vitro data, CC-486 (5-azacitidine) metabolism does not appear to be mediated by cytochrome P450 isoenzymes (CYPs); therefore, CYP inhibitors and inducers are unlikely to have any impact on the metabolism of CC-486 (5-azacitidine). Clinically relevant inhibitory or inductive effects of azacitidine on the metabolism of CYP450 substrates are unlikely.

14.3 LENALIDOMIDE (REVLIMID)

14.3.1 Source Acquisition and Accountability

Lenalidomide (Revlimid®) is a commercially available agent. Bristol Myers Squibb will provide the investigational supply to the NCI for dispensing to the study participants as per an arranged research agreement.

14.3.2 Toxicity

See **1.5.3.3** for a summary of AEs and see the prescribing information for lenalidomide/ REVLIMID®.

There are boxed warnings for lenalidomide, embryo-fetal toxicity (please see **Appendix D**), hematologic toxicity and venous thromboembolism. Lenalidomide can cause significant neutropenia and thrombocytopenia; for venous thromboembolism please see background section (Section **1.5.3.3**).

In addition, there are warnings regarding allergic reactions, tumor lysis syndrome, tumor flare reaction and second primary malignancies.

Allergic reactions: Hypersensitivity, anaphylaxis, angioedema, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

Tumor lysis syndrome: Fatal instances of tumor lysis syndrome have been reported during treatment with lenalidomide. The subjects at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. These subjects should be monitored closely and appropriate precautions taken.

Tumor flare reactions: Serious tumor flare reactions have occurred during investigational use of lenalidomide for chronic lymphocytic leukemia and lymphoma.

Adverse Events: Most frequently reported adverse events reported during clinical studies with lenalidomide in oncologic and non-oncologic indications, regardless of presumed relationship to study medication include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting and diarrhea, dehydration, rash, itching, infections, sepsis, pneumonia, UTI, Upper respiratory infection, atrial fibrillation, congestive heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural

effusion, pulmonary embolism, deep vein thrombosis, CVA, convulsions, dizziness, spinal cord compression, syncope, disease progression, death not specified and fractures. Other rare or uncommon adverse events are gastrointestinal hemorrhage (Uncommon), small intestinal obstruction (Rare), chest pain (Rare), hepatocellular injury (Rare), decreased appetite (Uncommon), peripheral neuropathy (Uncommon), hypoxia (Rare), and pleuritic pain (Rare).

Second new cancers: Please see background (Section **1.5.3.4**).

14.3.3 Formulation and preparation

Lenalidomide will be supplied as capsules for oral administration. Each capsule contains the following inactive ingredients: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. Lenalidomide will be shipped to the pharmacy at the study site in individual bottles or blister packs. Bottles or blister packs will contain a sufficient number of capsules to last for 1 cycle of dosing. Lenalidomide must be dispensed in the original packaging with the label clearly visible. Only enough lenalidomide for 1 cycle of therapy may be provided to the subject each cycle.

14.3.4 Stability and Storage

Store as directed on package label. Please see local prescribing information for Revlimid® for detailed instructions on storage conditions and stability. Store at 20°C - 25°C (68°F - 77°F); excursions permitted to 15°C - 30°C (59°F - 86°F). Care should be exercised in the handling of REVLIMID. REVLIMID capsules should not be opened or broken. If powder from REVLIMID contacts the skin, wash the skin immediately and thoroughly with soap and water. If REVLIMID contacts the mucous membranes, flush thoroughly with water.

Procedures for the proper handling and disposal of anticancer drugs should be considered.

14.3.5 Administration procedures

Lenalidomide is taken by mouth with or without food. See section **3.4.3.1** for administration details.

Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with Celgene/BMS 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 (see **Appendix D**).

Further information about the Revlimid REMS® program is available at:

https://www.celgeneriskmanagement.com

14.3.6 Incompatibilities

In vitro studies demonstrate that lenalidomide is not a substrate of CYP enzymes. In addition, lenalidomide shows little inhibitory or induction potential towards the CYP enzymes in vitro. Hence, coadministration of CYP substrates, inhibitors, or inducers with lenalidomide is not likely to result in clinically relevant drug-drug interactions in humans.

In vitro, lenalidomide is not a substrate of BCRP, MRP1, MRP2, MRP3, OAT1, OAT3, OATP1B1, OCT1, OCT2, MATE1, OCTN1, or OCTN2. Thus, it is unlikely that substrates or inhibitors of these transporters would affect lenalidomide disposition in humans.

Lenalidomide is not an inhibitor of BSEP, BCRP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, or OCT2. Thus, lenalidomide is not anticipated to cause any significant drug-drug interactions due to inhibition of these transporters.

Lenalidomide is not an inhibitor of UGT1A1 and is not anticipated to cause any significant drug-drug interactions due to UGT1A1 inhibition.

Please refer to Sections **3.4.3.1**, **4** for full drug interactions and toxicities.

14.4 DEXAMETHASONE

14.4.1 Source Acquisition and Accountability

Dexamethasone is commercially available and will be purchased by the CCR and supplied to the patients enrolled on the study by the NIH Clinical Center Pharmacy Department.

14.4.2 Toxicity

The most commonly reported toxicities have included: insomnia, mood changes, increased appetite, gastrointestinal problems, muscle weakness, increased blood sugar levels, impaired wound healing and fluid retention. Please refer to package insert for a complete listing of all toxicities.

14.4.3 Formulation and Preparation

Dexamethasone is commercially available in oral pill and liquid formulations; it is intended that we will exclusively use the pill formulation in this study. All formulation excipients are compendial and are commonly used in oral formulations.

14.4.4 Stability and Storage

Dexamethasone will be packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All supplied drug will be dispensed in child-resistant packaging.

Please refer to the package insert for additional guidance on drug preparation, handling and storage

14.4.5 Administration Procedures

Dexamethasone will be administered orally per the drug administration schedule in Section **3.4.3.4**.

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16 APPENDIX

16.1 APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

16.2 APPENDIX B: GLOBAL RESPONSE SCORE AND DEFINITIONS OF RESPONSE IN SKIN, LYMPH NODES, VISCERA, AND BLOOD

Global Response Score					
Global Score	Definition	Skin	Nodes	Blood	Viscera
CR	Complete disappearance of all clinical evidence of disease	CR	All categories have CR/NI		
PR	Regression of measurable disease	CR	All categories do not have a CR/NI and no category has a PD		
		PR	No category has a PD and if any category involved at baseline at least one has a CR or PR		
SD	Failure to attain CR, PR, or PD representative of all disease	PR	No category has a PD and if any category involved at baseline, no CR or PR in any		
		SD	CR/NI, PR, SD in any category and no category has a PD		
PD	Progressive disease	PD in any category			
Relapse	Recurrence of disease in prior CR	Relapse in any category			
Abbreviations: CR, complete response; NI, noninvolved; PR, partial response; PD, progressive disease; SD, stable disease.					

Response in Skin	
Response	Definition
Complete response	100% clearance of skin lesions
Partial response	50%-99% clearance of skin disease from baseline without new tumors (T3) in patients with T1, T2 or T4 only skin disease
Stable disease	<25% increase to <50% clearance in skin disease from baseline without new tumors (T3) in patients with T1, T2, or T4 only skin disease
Progressive disease	≥25% increase in skin disease from baseline or New tumors (T3) in patients with T1, T2, or T4 only skin disease or Loss of response: in those with complete or partial response, increase of skin score of greater than the sum of nadir plus 50% baseline score
Relapse	Any disease recurrence in those with complete response
Notes: Percentages refer to mSWAT score. A biopsy of normal appearing skin is unnecessary to assign a complete response. However, a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease (persistent erythema or pigmentary change) where otherwise a complete response would exist. If histologic features are suspicious or suggestive of mycosis fungoides/Sézary syndrome, the response should be considered a partial response only.	

Response in Lymph Nodes	
Response	Definition
CR	All lymph nodes are now ≤1.5 cm in greatest transverse (long axis) diameter by method used to assess lymph nodes at baseline or biopsy negative for lymphoma; in addition, lymph nodes that were N3 classification and ≤1.5 cm in their long axis and >1 cm in their short axis at baseline, must now be ≤1 cm in their short axis or biopsy negative for lymphoma
PR	Cumulative reduction ≥50% of the SPD of each abnormal lymph node at baseline and no new lymph node >1.5 cm in the diameter of the long axis or >1.0 cm in the diameter of the short axis if the long axis is 1-1.5 cm diameter
SD	Fails to attain the criteria for CR, PR, and PD
PD	≥50% increase in SPD from baseline of lymph nodes OR Any new node >1.5cm in the long axis or >1cm in the short axis if 1-1.5 cm in the long axis that is proven to be N3 histologically OR Loss of response: >50% increase from nadir in SPD of lymph nodes in those with PR (whichever occurs first)
Relapse	Any new lymph node >1.5 cm in the long axis in those with CR proven to be N3 histologically
Abbreviations: CR, complete response; PR, partial response; SPD, sum of the maximum linear dimension (major axis) × longest perpendicular dimension (minor axis); SD, stable disease; PD, progressive disease.	

Response in Viscera	
Response	Definition
CR	Liver or spleen or any organ considered involved at baseline should not be enlarged on physical exam and should be considered normal by imaging; no nodules should be present on imaging of liver or spleen; any post treatment mass must be determined by biopsy to be negative for lymphoma
PR	≥50% regression in any splenic or liver nodules, or in measurable disease (SPD) in any organs abnormal at baseline; no increase in size of liver or spleen and no new sites of involvement
SD	Fails to attain the criteria for CR, PR, and PD
PD	>50% increase in size (SPD) of any organs involved at baseline OR New organ involvement OR Loss of response: >50% increase from nadir in the size (SPD) of any previous organ involvement in those with PR (whichever occurs first)
Relapse	New organ involvement in those with CR
Abbreviations: CR, complete response; PR, partial response; SPD, sum of the maximum linear dimension (major axis) × longest perpendicular dimension (minor axis); SD, stable disease; PD, progressive disease.	

16.3 APPENDIX C: CYP3A4 INDUCERS AND INHIBITORS

Inhibitors of CYP3A are defined as follows. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx. The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below. Refer to Section **4.2** and **4.3** on instructions for concomitant use of CYP3A inhibitors and inducers with study medications.

Inhibitors of CYP3A		**Inducers of CYP3A**
Strong inhibitors: INDINAVIR NELFINAVIR RITONAVIR CLARITHROMYCIN ITRACONAZOLE KETOCONAZOLE POSACONAZOLE NEFAZODONE SAQUINAVIR TELITHROMYCIN SUBOXONE **Moderate inhibitors:** aprepitant erythromycin diltiazem fluconazole grapefruit juice Seville orange juice verapamil	**Weak inhibitors:** cimetidine **All other inhibitors:** amiodarone NOT azithromycin chloramphenicol boceprevir ciprofloxacin delaviridine diethyl-dithiocarbamate fluvoxamine gestodene imatinib mibefradil mifepristone norfloxacin norfluoxetine star fruit telaprevir troleandomycin voriconazole gestodene norfluoxetine	Carbamazepine Efavirenz Nevirapine Barbiturates Glucocorticoids Modafinil Oxcarbarzepine Phenobarbital Phenytoin Pioglitazone Rifabutin Rifampin St. John's Wort Troglitazone

Source: **http://medicine.iupui.edu/clinpharm/ddis/table.aspx**

16.4 APPENDIX D: RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS FOR LENALIDOMIDE

Risks Associated with Pregnancy

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

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

Criteria for individuals of childbearing potential (ICBP)

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

The investigator must ensure that:

- Individuals of childbearing potential comply with the conditions for pregnancy risk minimization, including confirmation that they have an adequate level of understanding.
- Individuals NOT of childbearing potential acknowledge that they understand the hazards and necessary precautions associated with the use of lenalidomide.
- Individuals who can father children taking lenalidomide acknowledge that they understand that traces of lenalidomide have been found in semen, that they understand the potential teratogenic risk if engaged in sexual activity with an individual of childbearing potential or an individual of childbearing potential, and that they understand the need for the use of a condom even if they undergo a vasectomy, if engaged in sexual activity with an individual of childbearing potential or pregnant female.

Contraception

Individuals of childbearing potential (ICBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) throughout the entire duration of lenalidomide treatment; 3) during dose interruptions; and 4) for at least 28 days after lenalidomide discontinuation.

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

- Highly effective methods:
    - Intrauterine device (IUD)

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

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

Pregnancy Testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for individuals of childbearing potential, including individuals of childbearing potential who commit to complete abstinence, as outlined below.

Before starting lenalidomide

Individuals of Childbearing Potential*:*

ICBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to prescribing lenalidomide. The first pregnancy test must be performed within 10–14 days prior to prescribing lenalidomide and the second pregnancy test must be performed within 24 hours prior to prescribing lenalidomide. The patient may not receive lenalidomide until the Investigator has verified that the results of these pregnancy tests are negative.

Individuals Who Can Father Children*:*

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

During study participation and for 28 days following lenalidomide discontinuation

Individuals of Childbearing Potential*:*

- ICBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of lenalidomide treatment, including dose interruptions and then every 28 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 28 following lenalidomide discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days of lenalidomide treatment, including dose interruptions, and then every 14 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 14 and Day 28 following lenalidomide discontinuation.

- At each visit, the Investigator must confirm with the ICBP that they are continuing to use two reliable methods of birth control at each visit during the time that birth control is required.
- If pregnancy or a positive pregnancy test does occur in a study patient, lenalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a patient misses their period or if their pregnancy test or their menstrual bleeding is abnormal. Lenalidomide treatment must be temporarily discontinued during this evaluation.
- Individuals of childbearing potential must agree to abstain from breastfeeding during study participation and for at least 28 days after lenalidomide discontinuation.

Individuals Who Can Father Children*:*

- Must practice complete abstinence or use a condom during sexual contact with pregnant individuals or individuals of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.
- If pregnancy or a positive pregnancy test does occur in the partner of an individual who can father children during study participation, the investigator must be notified immediately.
- Individuals who can father children should not donate semen or sperm during therapy or for at least 28 days following discontinuation of lenalidomide.

Additional Precautions:

- Patients should be instructed never to give lenalidomide to another person.
- Patients should not donate blood during therapy and for at least 28 days following discontinuation of lenalidomide.
- Only enough lenalidomide for one cycle of therapy may be prescribed with each cycle of therapy.
- Any unused lenalidomide must be returned as instructed through the Revlimid REMS™ program.

16.5 APPENDIX E: MEDICATIONS THAT MAY CAUSE QTC PROLONGATION

The following table presents a list of drugs that may prolong the QTc. These drugs are prohibited during the study. Romidepsin may be administered after a 5 half-life washout period elapses following the use of these drugs. Washout period is based on roughly 5 half-lives and rounded to a convenient interval.

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

Compound (Brand Name)	Compound Half-Life	Possible Washout Period (Hours)	Possible Washout Period (Days)
Antiemetics			
Dolasetron (Anzemet)	8.1 hr		
Droperidol (Inapsin)	2.2 hr	10	
Domperidone (Motilium)	7-8 hr	48	
Palonosetron (Aloxi)	40 hr		10
Antihypertensives			
Moexipril/Hydrochlorothiazide (Uniretic)	2-9 hr(include active metabolite) for moexipril; 5.6-14.8 hr for HCTZ	48	
Antimalarials			
Halofantrine (Halfan)	6-10 days (variable among individuals)		45
Quinidine (Quinaglute, Cardioquin, Quinidex)	6-8 hr in adult; 3-4 hr in children	36	
Antimanics			
Lithium (Eskalith, Lithobid, Lithonate)	24 hr (10-50)		7
Antineoplastics			
Arsenic trioxide (Trisenox)	Not characterized		
Tamoxifen (Nolvadex)	5-7 days (biphasic)		30
Antiprotozoals			
Pentamidine (NebuPent, Pentam)	6.4 ± 1.3 hr	36	
Antipsychotic agents			
Chlorpromazine (Thorazine)	30 ± 7 hr		7
Haloperidol (Haldol)	18 ± 5 hr		5
Mesoridazine (Serentil)	24-48 hr (animal study)		10
Pimozide (Orap)	55 hr		14

(Continued from previous page)

Antipsychotic agents *(cont'd)*			
Quetiapine (Seroquel)	6 hr	36	
Risperidone (Risperdal, Risperdal Consta)	3-20 hr (extensive to poor metabolizer) 9-hydroxyrisperidone (active metabolite) T ½ = 21-30 hr (extensive to poor metabolizer)		4
Thioridazine (Mellaril)	20-40 hr (Phenothiazines)		7
Ziprasidone (Geodon, Zeldox)	7 hr	36	
Antispastics			

Compound (Brand Name)	Compound Half-Life	Possible Washout Period (Hours)	Possible Washout Period (Days)
Tizanidine (Zanaflex)	2.5 hr	12	
Antivirals			
Amantadine (Symadine, Symmetrel)	17 ± hr (10-25)		4
Foscarnet (Foscavir)	87.5 ± 41.8 hr (distribution and release from bone)		20
Analgesics			
Levomethadyl (Orlaam)	Multiple compartment PK with active metabolite 2.6 day for LAAM, 2 day for nor-LAAM, 4 day for dinor-LAAM		20
Asthma medications			
Salmeterol (Advair Diskus, Serevent, Serevent Diskus)	5.5 hr (only one datum)	36	
Calcium channel blockers			
Bepridil (Vascor)	42 hr (26-64)		10
Isradipine (DynaCirc)	8 hr (multiple metabolites)	48	
Nicardipine (Cardene)	~2 hr post IV infusion	12	
Cholinergic enhancers			
Cisapride (Propulsid)	6-12 hr, up to 20 hr	60	
Diuretics			
Indapamide (Lozol)	14 hr (biphasic elimination)		3
Immunosuppressants			
Tacrolimus (Prograf, Protopic)	~34 hr in healthy patients ; ~19 hr in kidney transplant		7
Migraine medications			
Naratriptan (Amerge)	6 hr	36	
Sumatriptan (Imitrex)	2.5 hr	12	
Zolmitriptan (Zomig)	2.8-3.7 hr (higher in female)	18	
Narcotic pain relievers			
Methadone (Dolophine, Methadose)	15-30 hr		7
Sedatives			
Chloral hydrate	Readily converted to Trichloroethanol (active metabolite T½= 7-10 hour)	48	

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

16.6 APPENDIX F: STUDY DRUG DIARY

Study Drug Diary

Patient Initials:		Principal Investigator: Gordon
Patient Study ID #:		Research Nurse:
Drug Doses:	Lenalidomide (days 1-10): _____ CC-486 (5-azacitidine): _____	Cycle #: _____

Instructions:

- Use this diary to record all doses of oral study medication taken.
- You should bring this study drug diary and each of your study medications (including leftover pills and empty bottles) with you to each clinic visit.
- On clinic days, oral medications must be brought with you and taken in clinic.
- Contact us if you have any side effects or before starting any new medications or over-the-counter drugs.
- If you have questions at any time, please contact your doctor or nurse.

Study Drugs:

The study medications should be taken as follows, the dose of each will be assigned to you by your doctor:

Lenalidomide capsules should be taken with a glass of water with or without food
Dexamethasone tablets will be given in clinic and taken by mouth (PO)
CC-486 (5-azacitdine) capsules should be taken with a glass of water with or without food
Romidepsin is given by IV, in the clinic

Additional Information:

- Each of the study drugs should be taken at about the same time each day, with or without food as described above
- If you do not remember to take all or any of the medications on any day, please tell us. Do not make-up the dose or take extra the following day to make-up for the missed dose.
- If you vomit after taking a dose, you should not take another dose that day.
- Lenalidomide and CC-486 (5-azacitidine) are to be administered orally once daily. The capsules are to be taken around the same each day with (8 ounces of water). The capsules must be swallowed whole and may be taken with or without food. If a dose is not taken at the scheduled time and it has been less than 12 hours since the regularly scheduled time, it can be taken as soon as possible on the same day. If it has been more than 12 hours, skip the missed dose but take the next dose at the normal time on the following day Do not take extra doses to make up the missed dose. Do not take 2 doses at the same time.
- Patients who are not already on prophylactic or therapeutic doses of anticoagulants will be given aspirin 81mg to be taken by mouth daily
- Patients will be given ondansetron 8mg by oral or by IV to prevent chemotherapy-associated nausea on Days 1 and 10 (may be omitted during cycles 2-6 per doctor's instructions)

Study Drug Diary:

Please record the dose/number of pills of each study drug taken in the table below:

Cycle Day	Date	Lenalidomide/ Revlimid®		CC-486 (5-Azacitidine)		Dexamethasone	Romidepsin	Comments (Please note reason if dose is missed)
		#/ Dose Taken	Time	#/ Dose Taken	Time			
1						PO in clinic	IV in Clinic	
2								
3								
4								
5								
6								
7								
8								
9								
10						PO in clinic	IV in Clinic	
11-28								

STAFF USE ONLY

Date returned/reviewed: _____ Staff member: _____

Notes/Comment