SUMMARY OF CHANGES

For Protocol Amendment #16 to:

Phase I/II Investigation of Temsirolimus Plus Lenalidomide in Relapsed Non-Hodgkin Lymphomas

NCI Protocol #: **8309**
Local Protocol #: **09-443-A**

NCI Version Date: 12/20/2015 (last NCI approved version)
Protocol Date: **6/8/2016 (**current version)

#	Section	Page	Change
1.	n/a	4	Updated protocol version date to 6/8/2016 and the protocol history section.
2.	n/a	1-2	Updated PI information for Northwestern.
3.	CAEPR for Lenalidomide	36-38	Under section 7.1.2: Updated CAEPR for Lenalidomide (CC-5013, NSC 703813) with version 2.6, December 24, 2015

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TITLE: Phase I/II Investigation of Temsirolimus Plus Lenalidomide in Relapsed Non-Hodgkin Lymphomas

Coordinating Center: *University of Chicago Phase II Consortium*

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Contract #	
NCI Supplied Agents:	Temsirolimus (NSC#683864), IND#61010 Lenalidomide(NSC#703813), IND#70116
NCI Approval:	8309 / Approved

UC Protocol Approval:	09-443-A /Approved

Protocol History:

Version Date	Description of Action
07/27/09	First Submission to NCI
10/05/09	Consensus Review Response
11/12/09	Follow Up Review Response
2/16/10	Amendment # 1 Cover Page: Version Date changed to 2/16/10. Protocol History updated. Section 6.1 updated in accordance with revised CAEPR for Temsirolimus v. 2.2 January 22, 2010. Section 6.2 updated in accordance with revised CAEPR for Lenalidomide v. 2.2 January 15, 2010. Consent Form: Version Date changed to 2/16/10. "What are the Risks" Section updated in accordance with revised CAEPR for Lenalidomide v. 2.2 January 15, 2010 and for Temsirolimus v. 2.2 January 22, 2010.
03/15/2010	NCI Approved version 02/16/10 of Protocol and consent.
10/28/2010	Protocol amended to expand the phase II cohort, update correlative collection process and procedures. Add Appendices F, G and H for data collection and update to staff.
12/15/2010	Protocol amendment to address recommendations from NCI received on 11/02/10.
4/20/2011	Protocol updated to include Secondary Malignancy reporting in section 10.1.5.
5/04/2011	Amendment 4/20/11 was disapproved; 5/04/2011 is a resubmission of this version correcting section 10.1.5.
5/16/2011	This amendment is in response to Dr. Johnson's May 3, 2011 request for change in reproductive risk language and lenalidomide bottle counts.
9/20/2011	Protocol amendment submitted in response to RRA for lenalidomide received from CTEP 8/24/11. Updated CAEPR for lenalidomide to version 2.3, June 27, 2011.
02/27/2012	Protocol amendment submitted in response to RRA for temsirolimus received from CTEP 1/12/12. Updated CAEPR for temsirolimus to version 2.3, December 15, 2011. Updated participating sites on facesheet.
06/20/2012	Changes made with faculty and staff on face sheet of protocol and changes made throughout the protocol, major change includes: adding mantle cell lymphoma as a subtype in Group C and an expansion of correlative objectives and methods.
02/15/2013	Added new sites, made administrative and formatting changes throughout protocol to fit the new e-protocol requirements.
10/24/2013	Updated lenalidomide dispensing language and agent ordering information in section 8.2. Updated CAEPR for Temsirolimus in section 7.1.
11/4/2013	Updated the lenalidomide CAEPR version and cleaned up the agent ordering information section for lenalidomide per CTEP request.
04/30/14	Added a Ft Wayne PI and also updated the safety event reporting mechanism from AdEERs to CTEP-AERS.
10/9/14	Protocol amendment submitted in response to RRA for lenalidomide received from CTEP 9/17/14. Updated CAEPR for lenalidomide to version 2.5, July 16, 2014.
12/20/2015	Protocol amendment submitted to change PI for two sites and update contact information.
6/8/2016	CAEPR for Lenalidomide and update to Northwestern PI information.

SCHEMA

Eligibility Criteria

Phase II:

Previously treated, histologically confirmed mature NHL stratified by histology:

Group A: Diffuse large B-cell lymphoma
Group B: Follicular lymphoma
Group C: Lymphoma NOS (including Hodgkin lymphoma, T-NHL, marginal zone lymphoma, lymphoplasmacytic lymphoma, mantle cell lymphoma)

Phase I and Phase II:

No limit to number of prior therapies as long as other entry criteria are met. Prior autologous stem cell transplant is allowed.
Age ≥ 18 years.
ECOG Performance Status 0-2.
Measurable disease (see Section 3.1.7).
No known CNS involvement by lymphoma.
Non-pregnant and non-nursing.
No "currently active" second malignancy (see Section 3.2.6).
No history (within 3 months of study entry) of DVT/PE (see Section 3.2.7).

Required Initial Laboratory Values

ANC	≥ 1000		
platelets	≥ 75K/mL		
total bilirubin	≤ 1.5 X ULN	AST/ALT	≤ 2.5 X ULN
CrCl	≥ 60 mL/min**		
fasting serum cholesterol	≤ 350 mg/dL		
fasting serum triglyceride	≤2.5 X ULN		

**Creatinine clearance must be calculated using the Cockcroft-Gault equation.

Dose Escalation Schedule			
Dose Level	**Dose**		
	Temsirolimus (flat dose in mg)	**Lenalidomide (flat dose in mg)**	
Level -2	15 mg	10 mg	
Level -1	25 mg	10 mg	
Level 1	25 mg	15 mg	
Level 2	25 mg	20 mg	
Level 3	25 mg	25 mg	
For the phase II portion of the study: Temsirolimus will be administered at 25 mg IV weekly for at least 2 consecutive 4 week cycles. Oral lenalidomide 20mg daily will be given on Days 1-21 of each 28 day cycle Patients showing at least stable disease after 2 cycles may continue treatment up to 52 weeks of therapy. Missed doses will not be made up.			

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1. OBJECTIVES

1.1 Primary Objectives

Phase I portion:

1.1. To determine the safety, toxicity, and maximum tolerated dose of lenalidomide when combined with temsirolimus in patients with relapsed lymphomas.

Phase II Portion:

1.2. To determine complete and overall response rate of lenalidomide plus temsirolimus in patients with relapsed lymphomas as stratified by histology: follicular lymphoma, diffuse large B-cell lymphoma, and lymphoma NOS (including Hodgkin lymphoma, T-NHL, lymphoplasmacytic lymphoma, mantle cell lymphoma)

1.3. To determine duration of response, progression-free survival, and overall survival of lenalidomide plus temsirolimus in patients with relapsed lymphomas as stratified by histology: diffuse large B-cell lymphoma, follicular lymphoma, and lymphoma NOS (including Hodgkin lymphoma, T-NHL, lymphoplasmacytic lymphoma, mantle cell lymphoma).

Primary correlative objectives for both phase I and phase II portion:

1.4. To determine mTOR pathway activation in pre-treatment tumor tissue.

1.5. To determine angiogenic and microenvironmental status of pre-treatment tissue and peripheral blood samples, and to evaluate changes following treatment with temsirolimus and lenalidomide.

1.6. To determine differentially expressed genes associated with differences in clinical response and in progression-free survival (PFS) in patients with DLBCL and FL (Groups A and B, respectively)

1.7. To determine a methylation signature predictive of clinical response and PFS in patients with DLBCL and FL (Groups A and B, respectively)

2.0 BACKGROUND

2.1 Non-Hodgkin lymphoma (NHL)

Nearly 70,000 new cases of non-Hodgkin lymphomas were diagnosed in 2008, making NHL the 5th most common cause of cancer in women and the 6th most common cause of cancer in men. New treatments have improved the clinical outcome for many patients, but NHL remains among the top 10 causes of cancer mortality with nearly 20,000 annual deaths, and much work remains to be done in terms of understanding the biology and treatment of various subtypes.

A major challenge in NHL is the heterogeneity of the disease, which now includes more than several dozen subtypes. The two most common NHL subtypes are diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL), each respectively being the prototype of aggressive and indolent lymphomas. Although the biology of unique lymphoma subtypes may differ, aberrations of both the mTOR pathway and of the lymphoma microenvironment appear to be shared features and thus represent rational targets for treatment.

2.1.1 mTOR (mammalian target of rapamycin in NHL)

Mammalian target of rapamycin (mTOR): mTOR is a central transducer of growth signals in

normal and neoplastic cells via translational modulation. Under normal conditions, mTOR utilizes various companion proteins and upstream signals from PI3K/Akt to sense favorable environments for growth and cell cycle progression; conversely, unfavorable conditions lead to a halt in mTOR-mediated cellular protein production and induction of cell cycle arrest.

Other functions include mediating cellular adaptability to external stress signals, such as hypoxia, by translating a group of proteins known as hypoxia-inducible factors (HIF-α).[1] In addition, mTOR is emerging as a regulator of neoangiogenesis via translational control of vascular endothelial derived growth factor (VEGF), and mTOR inhibition may have antiangiogenic effects.[2,3] Cancer cells use mTOR's control over protein translation to their advantage, making mTOR inhibition an appropriate target for anti-cancer therapies.

PI3K/Akt/mTOR axis: The PI3K/Akt pathway connects multiple extracellular signals to the translational machinery and is summarized below (Figure 1). In the case of mTOR, Akt activation releases the negative control of two tumor suppressor proteins (tuberous sclerosis proteins 1 and 2, or TSC1 and TSC2) on mTOR, which is then free to phosphorylate its own downstream effectors, p70 S6K1 and 4EBP1, discussed in more detail below. Several excellent and more detailed reviews are also available.[4-7] The entire pathway is under constitutive negative regulation by PTEN (phosphatase and tensin homolog deleted on chromosome 10), which thus has a critical tumor suppressor function.[8] Loss of the tumor suppressor gene, PTEN, allows for uncontrolled PI3K signaling and has been observed in many tumors including lymphomas. The loss of even a single PTEN allele in mice leads to lymphomas resistant to standard cytotoxics but sensitive to rapamycin with or without chemotherapy.[9]

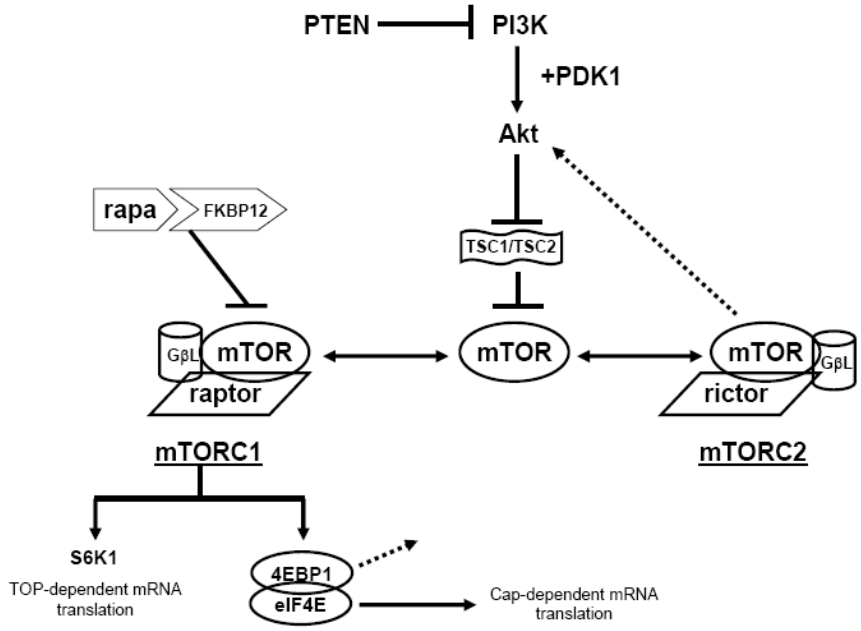

Figure 1. PI3K/Akt/mTOR pathway. (from Smith SM, Reviews on Recent

Downstream of mTOR: The key oncogenic potential of mTOR lies in its control over the initiation of translation and protein biosynthesis via two downstream targets: S6K1 (40S ribosomal protein S6) and 4EBP1 (eIF4E binding protein). Sequential S6K1 phosphorylation initiates translation of an important subset of mRNA possessing a TOP (terminal oligopyrimidine tract in the 5' untranslated region) region. Although accounting for fewer than 200 genes, TOP-

dependent mRNA's comprise up to one-third of total cellular mRNA.[10] TOP-dependent mRNA include many ribosome biogenesis factors, ribosomal proteins, and elongation factors important in ribosome synthesis, as well as proteins that upregulate synthesis of other proteins.[11] S6K1 (and its homolog S6K2) may be an important marker of PI3K/Akt/mTOR pathway activation, and is overexpressed in tumors with PTEN deletions. It is important to note, however, that there are several parallel pathways capable of phosphorylating S6K1, including direct activation from PDK1 and indirectly from Akt/PKB (phosphokinase B).[10] Despite these caveats, S6K1 phosphorylation status has become a commonly used marker to assess the pharmacodynamic effects of mTOR inhibitors.

The second major downstream effector, 4EBP1, controls translation of another group of mRNA, all of which contain a 7-methylguanosine residue capping the 5' end (cap-dependent mRNA). This group of mRNA includes essential components of the cell cycle machinery, including mRNAs encoding cyclin D1 and c-MYC, both of which are important in lymphomagenesis. Other cap-containing mRNA's include fibroblast growth factor and VEGF. 4EBP1 is normally tightly bound in an inhibitory manner to eIF4E (elongation initiation factor). 4EBP1 phosphorylation by mTOR releases eIF4E to interface with its family members, such as eIF4G and eIF3, and recruits the 40S ribosomal subunit to the 5' ends of capped mRNAs, thus allowing translation initiation.(reviewed in [12]) The initiation of translation is an important regulatory and rate-limiting checkpoint, and highlights the significance of inhibitory control over eIF4E.

mTORC1 and mTORC2: A potentially relevant aspect of the PI3K/Akt/mTOR pathway for clinical applications is that the mTOR protein can exist as part of two distinct and mutually exclusive intracellular pools: mTORC1 and mTORC2. mTORC1, which includes the scaffold protein, raptor, and GβL, was first identified as a rapamycin-sensitive complex that dissociates in the presence of rapamycin-FKBP12. Raptor is a stabilizing protein that facilitates and enhances mTOR's activation of downstream targets, and its loss leads to near-absence of mTOR's control over S6K1 and 4EBP1.[13,14] mTORC2 contains another scaffold protein, rictor (*r*apamycin *i*nsensitive *c*ompanion), which has an important role in maintaining the actin cytoskeleton and does not participate in mTORC1 tasks such as protein biosynthesis.[15] As the name implies, mTORC2 is not a substrate for rapamycin and remains intact with exposure to mTOR inhibitors.[15] However, mTORC2 has a recently identified second function, which is to paradoxically phosphorylate Akt at Ser^{473}.[16] Since mTOR exists in an equilibrium between these two complexes, rapamycin's dissolution of the mTORC1 complex allows free mTOR to associate with rictor and increases the amount of intracellular mTORC2 which is then capable of activating Akt. mTORC2 mediated Akt activation could potentially reverse the effects of mTOR inhibitors.

mTOR abnormalities in NHL: Many lymphoma subtypes possess abnormalities of the mTOR pathway, suggesting a role in lymphomagenesis. The PI3K/Akt/mTOR axis may have transforming capability. Wlodarski and colleagues found constitutive mTOR activation in multiple transformed lymphoma cell lines irrespective of EBV status; they further demonstrated that mTOR is required for cell proliferation in transformed B-cells.[17] Akt overexpression leads to an aggressive lymphoma phenotype in murine models, similar to bcl-2 overexpressing lymphomas in the same series.[18] In this study, rapamycin induced apoptosis, and the combination of chemotherapy plus mTOR inhibition led to dramatic lymphoma regression in the Akt

overexpressing but not Bcl-2 overexpressing tumors. Furthermore, eIF4E and the proto-oncogene c-myc (frequently deregulated in lymphomas) may cooperate in promoting lymphomagenesis since the introduction of both eIF4E and c-myc decreases the latency of lymphoma formation in mice from16 months to 1 month[19], suggesting a joint effect. The specific interaction between eIF4E and c-myc remains to be elucidated, but it is clear that eIF4E directly inhibits apoptosis and allows the malignant lymphomatous phenotype to be expressed.[18-20]. Finally, the mTOR inhibitor everolimus (RAD001) was shown to restore normal B-cell differentiation and prevent c-MYC induced malignant transformation in Eμ-*myc* mice as compared to placebo.[21]

Preclinical models have shown important relevance of the PI3K/Akt/mTOR pathway in mantle cell lymphoma, follicular lymphoma, diffuse large B-cell lymphoma, and alk-positive anaplastic large cell lymphoma. Mantle cell lymphoma has been a paradigm disease highlighting the central role of mTOR activation in lymphomagenesis. Although an uncommon disease accounting for approximately 5% of all lymphomas, mantle cell lymphoma is an incurable subtype with a median survival of only 3-5 years. The t(11;14)(q13;q32) translocation and consequent cyclin D1 overexpression is a pathognomonic and pathogenetic feature of mantle cell lymphoma. Cyclin D1 is a cap-dependent mRNA and is therefore potentially amenable to mTOR translational control. Several groups have demonstrated that inhibition of PI3K, Akt, or mTOR results in downregulation of cyclin D1 levels. The rapamycin analog, everolimus, downregulated mTOR and 4EBP1 in several MCL cell lines concomitant with G1 arrest.[22] Peponi and colleagues used mTOR-specific siRNA and this was associated with downregulation of both cyclin D1 and anti-apoptotic proteins.[23] Rudelius and colleagues confirmed the central role of Akt in the pathogenesis of MCL, particularly in the more aggressive blastoid variant, and conclude that the extent to which MCL relies on PI3K/Akt/mTOR for survival correlates with biologic aggressiveness.[24] Inhibition of Akt signaling in all models tested led to apoptosis, concurrent with decreased mTOR activity. Clinical trials of mTOR inhibitors in MCL are encouraging and discussed below. Evidence for pathway activation is also observed in patient samples and cell lines of the two most common NHL histologies: follicular lymphoma and diffuse large B-cell lymphoma. Lesaux and colleagues compared follicular lymphoma cells to normal tonsils and demonstrated substantially increased S6K1 phosphorylation that was rapamycin- and everolimus-sensitive.[25] Activated mTOR was critical for follicular lymphoma survival. This is consistent with proteomic data in which constitutive Akt activation was characteristic of follicular lymphoma samples.[26] Finally, both rapamycin and everolimus induce G1 cell cycle arrest in diffuse large B-cell lymphoma cell lines, with both mTOR inhibitors augmenting rituximab (anti-CD20) cytotoxicity.[27] Certainly, the optimal development of mTOR inhibitors is predicated on identifying tumors reliant on activation of mTOR and its pathway members, and the discussion above supports lymphomas as being an appropriate tumor type in which to test mTOR inhibitors.

2.1.2 Role of microenvironment in NHL

Although less well understood than solid tumor counterparts, it is increasingly clear that the lymphoma microenvironment plays an important role in sustaining the malignant phenotype. There are several entities comprising the lymphoma microenvironment, including normal and transforming features of the germinal center, pro-angiogenic proteins, the immune response to lymphoma cells, and the cytokine milieu. In follicular lymphoma, features of the non-malignant

background cells have demonstrated an effect on overall survival, and targeting these cells and/or interaction between the microenvironment and lymphoma represents a valid therapeutic strategy.[28] This is underscored by the inability to sustain ex vivo follicular lymphoma cell populations without cytokine or stromal support.[29-31] Furthermore, gene-expression profiling of patient samples surprisingly shows that the genetic signature of the non-malignant infiltrating immune cells, and not the gene-expression profile of FL cells themselves, determines survival.[28] Patients with a predominant monocytic or dendritic cell infiltrate had a 9.35-fold increased relative risk of death compared to patients with a predominant T-cell infiltrate. Similarly, increased numbers of FOXP3 positive T regulatory cells portends a good prognosis. Varying lymphocyte subpopulations, including FOXP3+ cells, CD57+ cells, and CD8+ cells all play a critical role in FL clinical outcome.[32-34]In terms of angiogenesis, we now know that increased microvessel density (MVD) is a poor prognostic marker in DLBCL, that increased MVD corresponds to the activated B-cell phenotype in DLBCL, that vascularization predicts both overall survival and transformation risk in FL, and that the intensity of VEGF-D corresponds to increased IPI.[35-38]

Immunomodulatory agents, such as thalidomide and lenalidomide, have pleiotropic effects on the lymphoma microenvironment. The two major mechanisms of action appear to involve changing the cytokine milieu (and thus interrupting lymphoma-ME crosstalk) and inhibition of angiogenesis. Proof of concept is provided by preliminary clinical studies showing single-agent activity of lenalidomide in patients (see discussion below) with both relapsed indolent and aggressive NHL, ranging from 26% to 34%.[39,40] The oral availability and acceptable toxicity profile of lenalidomide makes it an attractive agent to study in combination settings.

2.2 TEMSIROLIMUS

Temsirolimus (sirolimus 42-ester with 2,2-bis(hydroxymethyl propionic-acid) is a water soluble ester of rapamycin, currently in development by Wyeth Research (Collegeville, PA). Temsirolimus (also called cell cycle inhibitor 779, CCI-779, Torisel™) is a prodrug of rapamycin, and differs in structure by virtue of a semisynthetic substitution in the lactone ring.[5,41] After intravenous injection, temsirolimus is rapidly converted to rapamycin. Four single agent phase I trials and two randomized phase II trials have characterized temsirolimus pharmacokinetics in humans. Hidalgo and colleagues tested a unique schedule of temsirolimus administered daily for five days every other week.[42] This schedule was based on preclinical data in mice demonstrating antitumor activity without permanent T-cell dysfunction, and is the sole published temsirolimus study not utilizing a weekly schedule. The starting dose was 0.75 mg/m2/day with 20% dose escalations per cohort, and a final maximum tolerated dose of 19 mg/m2/day. A total of 63 patients with advanced solid tumors were enrolled, and pharmacokinetic analysis demonstrated a Cmax and AUC that increased with dose in a less than proportional manner. Temsirolimus was converted to sirolimus within 15 minutes, and had a terminal half-life ranging form 13 to 25 hours. Although generally well-tolerated, the most common toxicities included asthenia, mucositis, nausea, rash, thrombocytopenia, and leucopenia, with the severity of side effects somewhat related to the dose of temsirolimus as well as the intensity and number of prior therapies. Of interest, although some of the toxicity (i.e. thrombocytopenia requiring dose reductions) appeared to be dose related, hints of activity were observed at several dose levels. These findings support the use of a flat dose of temsirolimus in future studies and highlight the limitations of toxicity-based phase I trials for many newer agents.[42]

Two other phase 1 trials have also been completed and published in final form. The study by Raymond and colleagues evaluated weekly temsirolimus at doses ranging from 7.5 mg/m2 to 220 mg/m2 in 24 patients with advanced solid cancers.[43] In the weekly dosing schedule, AUC increased proportionally with doses up to 150 mg, but this disappeared with doses greater than 300 mg. Temsirolimus concentration declined polyexponentially, and sirolimus could be detected within 15 minutes with a peak at 0.5 to 2 hours following drug administration. The terminal half-life of sirolimus was 61-69 hours. The authors also evaluated BSA-based dosing and flat dosing, and found comparable pharmacokinetic profiles, again supporting the use of flat dosing for future studies.

As mentioned above, mantle cell lymphoma is emerging as a paradigm for mTOR inhibitor activity in lymphoma; the pathologic expression of cyclin D1 resulting from the t(11;14) translocation is enhanced by mTOR translational effects and provides a direct rational for testing MTI in this setting. The Mayo Clinic Consortium performed a pilot phase 2 study of temsirolimus 250 mg weekly in 35 patients with relapsed mantle cell lymphoma.[44] This was a poor prognosis group of patients with a median age of 70 and a median of 3 prior treatment regimens; 54% of patients were deemed refractory to their most recent treatment regimen prior to temsirolimus. The investigators observed an encouraging 38% overall response rate, with 1 (3%) patient achieving a complete remission. The median duration of response was 6.9 months. However, very few of the patients could tolerate the dose of 250 mg weekly, and all but 4 patients required substantial dose reductions, mainly due to reversible thrombocytopenia or other cytopenias. Other adverse effects of temsirolimus include stomatitis, hyperglycemia, hypertriglyceridemia, infection without neutropenia, and rash. Although the authors evaluated mTOR activity via S6 phosphorylation status, they could not identify a correlation with response in a limited sample set. Several conclusions can be drawn from this study. First, the response rate to single agent temsirolimus is encouraging in such a heavily pretreated and elderly population with acceptable and reversible toxicity. Second, the optimal biologic dose of temsirolimus may be much lower than 250 mg weekly. Indeed, a parallel study in patients with renal cancer suggests that activity can be observed with one-tenth this dose, and ongoing trials have incorporated lower doses.

The North Central Cancer Treatment Group used the lower 25 mg flat dose, and readdressed the issue of efficacy in relapsed MCL.[45] In a group of 27 evaluable patients, they demonstrated an impressive overall response rate of 41%, although all but one was a partial response. Similar to the higher dose, they observed a median duration of response of 6.2 months in responding patients. The incidence of grade 3 and 4 thrombocytopenia decreased dramatically (12% and 0%, respectively) although dose reductions were still required in over half of the patients for unspecified reasons. Regardless, the equivalent response rate with one-tenth the original dose is proof of principle that future studies can justifiably be based on biologic parameters and not necessarily pharmacologic or toxicity-based features. In contrast to phase II studies suggesting preserved efficacy with lower doses, results of an international phase III trial evaluating “high dose” and “low dose” temsirolimus versus investigator’s choice suggests that the temsirolimus dose may impact results. In this study, Hess and colleagues compared three treatment arms: temsirolimus 175 mg weekly x 3 weeks followed by either 75 mg weekly (“high dose”) or 25 mg weekly (“low dose”), and investigator’s choice of single agent therapy (i.e. gemcitabine, fludarabine, and others). The ORR was highest for the high dose arm (22%), and only 6% and a

surprising 2% for the low dose and investigator's choice arms, respectively. The median duration of response was also improved in the high dose arm (7.1 months) versus 3.2 months for the low dose. The high dose arm met the statistical endpoint of improved PFS (4.8 months) as compared to the control arm (1.9 months); the low dose arm had a median PFS of 3.4 months. Toxicity appeared similar across all arms, although the high dose arm had approximately 90% of patients with grade 3 or 4 adverse events, compared to approximately 80% in the low dose arm and 68% in the investigator's choice arm. It is unknown if there is a similar dose response in other lymphoma subtypes.

Although much of the clinical interest in MTI in NHL has focused on MCL based on the rationale stated above, The University of Chicago Phase II Consortium initiated a CTEP-sponsored phase II study of temsirolimus in non-mantle cell lymphoma histologies, with results presented at ASCO 2008.[46] Patients were accrued into one of three cohorts: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), or other indolent lymphomas including CLL/SLL. Data on 82 evaluable patients revealed an intent-to-treat ORR 40%, and ORR of 46% in patients completing at least 2 cycles.[47] Efficacy was strongest in follicular lymphoma, with an overall response rate over 50% and a median PFS of 9 months in heavily pretreated patients. Of interest, none of the patients with small lymphocytic lymphoma/chronic lymphocytic leukemia (1/15, 6%) met criteria for response; response rate when excluding patients with CLL/SLL was 49%, with 20% complete remission rate. Toxicities were generally mild, with metabolic changes (hyperglycemia, hypertriglyceridemia, hypercholesterolemia) and transient myelosuppression (thrombocytopenia) being most common. The significant single agent activity observed in this multicenter phase II trial prompts the current trial, which aims to combine temsirolimus with another active agent, lenalidomide, that should have complementary effects.

2.3 LENALIDOMIDE

Lenalidomide and its predecessor, thalidomide, are proprietary IMiD™ compounds of Celgene Corporation. Thalidomide gained notoriety in the 1960s due to profound limb deformities observed in offspring of pregnant women who used thalidomide as a sedative. A re-evaluation of the agent several decades later showed important antiangiogenic, anti-inflammatory, and antineoplastic effects. Lenalidomide (Revlimid®, CC-5013) is an orally available and more potent thalidomide derivative that has a more favorable side effect profile, including lower rates of sedation and neuropathy. Lenalidomide has both immunomodulatory and anti-angiogenic effects, but the precise mechanism of action remains unknown. In general, its effects include inhibition of regulatory T-cells, co-stimulation of other T-cell subsets, VEGF inhibition, Akt inhibition, inhibition of cell cycle regulatory proteins (i.e. p21), and downregulation of a variety of cytokines including IL-6 and TNFα. Preclinical studies have shown that lenalidomide inhibits neovascularization, most likely via VEGF inhibition. In addition, lenalidomide decreases blood vessel sprouting in hypoxic conditions, possibly by downregulating HIF1α induced angiogenesis.[48] The interaction between lenalidomide and the Akt axis is particularly relevant for the current clinical study, since Akt is upstream of mTOR and is often paradoxically activated with mTOR inhibitor therapy. Lenalidomide has been shown to inhibit Akt phosphorylation, allowing multiple potential "hits" to the PI3K/Akt/mTOR axis when combined with an mTOR inhibitor.[49] In addition, in vitro data shows synergy between rapamycin and lenalidomide in

multiple myeloma cell lines, forming the basis for an ongoing clinical trial in multiple myeloma.[50]

Phase I trials with lenalidomide were prompted by preclinical data suggesting anti-tumor effects.[51-54] Doses up to 50 mg daily have been evaluated in both hematologic and solid tumor populations. Lenalidomide has less myelosuppression when a 7-day break is introduced, and the most common schedule selected for further development is 25 mg daily on Days 1-21, followed by a 7-day rest period. The vast majority of side effects are mild, and include rash, pruritus, diarrhea, and fatigue. Grade 3 and 4 toxicities observed in these trials include neutropenia and thrombocytopenia in approximately 10% of patients. Importantly, severe constipation, neuropathy and somnolence that characterize thalidomide effects were not seen.

There are several trials investigating lenalidomide monotherapy in patients with relapsed lymphomas. Wiernik and colleagues recently published a final analysis of lenalidomide 25 mg daily on Days 1-21 repeated every 28 days in 49 patients with relapsed aggressive lymphomas.[55] Approximately half of patients had DLBCL, with the remaining patients comprised of grade 3 follicular lymphoma, mantle cell lymphoma, and transformed follicular lymphoma. The overall response rate was 35%, with a median duration of response 6.2 months and median PFS 4.0 months. This was a heavily pretreated population of patients, with a median of 4 prior regimens, and 30% of patients having failed a prior autologous stem cell transplant. A subsequent international trial of single agent lenalidomide (NHL-003) at the identical dose found an ORR of 29% in heavily pretreated DLBCL patients; accrual to this study is ongoing.[56] Witzig and colleagues reported on the same schedule of lenalidomide in patients with relapsed indolent lymphomas;[57] again, the patient population was very heavily pretreated with 50% being refractory to their most recent regimen and near universal prior rituximab exposure. In this study, the ORR was 23% in all patients, and 27% in relapsed FL patients. What is interesting, however, is that although the median PFS is 4.4 months, the median duration of response for responding patients has not yet been reached and is greater than 16.5 months. Lenalidomide monotherapy appears particularly active in mantle cell lymphoma, with an ORR of 53% and a median duration of response 13.7 months.[58] An ongoing international phase II trial of lenalidomide monotherapy (NHL-003) updated findings in patients with MCL.[59] The authors report an ORR of 43% in 54 elderly and heavily pretreated patients; when evaluating subsets of patients with prior bortezomib exposure and/or stem cell transplant, the response rates were 53% and 57%, respectively. This suggests a non-overlapping mechanism of action from other therapies, and is encouraging in this patient population. These single agent studies as well as preclinical studies of potential synergy have prompted an intense development agenda for lenalidomide in NHL, with many trials currently underway.

2.4 RATIONALE

The current trial proposes to combine lenalidomide with temsirolimus in patients with relapsed lymphomas due to a variety of observations suggesting potential additive and/or synergistic effects. Aberrations of both the mTOR pathway and the lymphoma microenvironment contribute to lymphomagenesis and lymphoma progression, and the current proposal aims to inhibit both of these components. Potential points of overlap between these two agents are as follows. First, a downstream mRNA target of mTOR is VEGF, and pre-clinical studies support the ability of mTOR inhibitors to downregulate VEGF through indirect and direct mechanisms.[60,61] The

mRNA for VEGF is under mTOR translational control. Second, lenalidomide has been shown to inhibit Akt phosphorylation, allowing multiple "hits" to the PI3K/Akt/mTOR axis when combined with an mTOR inhibitor.[49] Akt phosphorlyation can be paradoxically increased in patients treated with mTOR inhibitors, most likely via an undesired increase in mTORC2 formation, and Akt activation is known to mediate resistance to mTOR inhibitors. In addition, mTORC1 inhibition acting through S6 kinase phosphorylation of insulin receptor substrate 1 (IRS1) has also been shown to activate Akt.[62] In vitro data shows synergy between rapamycin and lenalidomide in multiple myeloma cell lines, forming the basis for an ongoing clinical trial in multiple myeloma.[50] Finally, as discussed above, HIF1α, which stimulates neovascularization, can be inhibited by both mTOR inhibitors (which controls mRNA translation) and lenalidomide (unknown mechanism).[48,63] Clinical trials have established single agent efficacy for both of the agents to be tested, and a combination should be at least additive and perhaps synergistic.

Building upon The University of Chicago Phase II Consortium's prior experience with single agent temsirolimus, this protocol will determine the safe combined dose of lenalidomide when added to temsirolimus in patients with relapsed lymphomas. Temsirolimus dosing will be identical to the recently completed trial (25 mg weekly with 4 week cycles), and oral lenalidomide will be added in a phase I dose escalation design. Once the dosing regimen has been determined in the phase I portion of the study, a phase II component stratified by histology will determine the efficacy of the combination in patients with follicular lymphoma and diffuse large B-cell lymphoma. A third exploratory cohort will determine the efficacy of the combination in other indolent relapsed lymphomas.

2.5 CORRELATIVE STUDIES BACKGROUND

N/A

3.0 PATIENT SELECTION

On-study guidelines

This clinical trial can fulfill its objectives only if patients appropriate for the trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy and therefore only enroll patients for whom the agents administered are appropriate. Although they will not be considered as formal eligibility (exclusion) criteria, as part of the decision-making process physicians should recognize that the following may increase the risk to the patient entering this protocol:

- Serious medical illness of psychiatric condition which would prevent compliance with treatment or informed consent.
- Medical condition such as uncontrolled infection, uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonable hazardous for the patient.
- Patients considered to be at high risk of developing DVT/PE or arterial thromboses are to receive prophylactic aspirin or low molecular weight heparin unless contraindicated. High risk will be defined as a history of

DVT/PE, significant family history, performance status > 2, smoking history, use of oral contraceptives, and concurrent use of epoetin. Patients with diabetes mellitus or coronary artery disease are considered to be at high risk for arterial thromboembolic events.

3.1 Eligibility Criteria

3.1.1 Histology: Bone marrow biopsies (with the exception of lymphoplasmacytic lymphoma) as the sole means of diagnosis are not acceptable. Fine needle aspirates are *not* acceptable.

3.1.1.1 Phase I: Previously treated, histologically confirmed Hodgkin and non-Hodgkin lymphomas. The only exception to a requirement for a lymph node biopsy is lymphoplasmacytic lymphoma, which can be diagnosed based on morphologic evidence in the bone marrow plus the appropriate paraprotein.

3.1.1.2 Phase II: Previously treated, histologically confirmed mature NHL stratified by histology:

3.1.1.2.1 Group A: Diffuse large B-cell lymphoma (**NOTE**: all patients with DLBCL must have germinal center vs. non-germinal center phenotype established via immunohistochemistry—See Appendix D)[64]

3.1.1.2.2 Group B: Follicular lymphoma

Group C: Lymphoma NOS (including Hodgkin lymphoma, T-NHL, marginal zone lymphoma, lymphoplasmacytic 3.1.2 No limit to number of prior therapies. Prior autologous transplantation is allowed.

3.1.2 Age ≥18 years.

3.1.3 ECOG performance status ≤2 (see Appendix A).

3.1.4 Patients must have normal organ and marrow function as defined below:

– absolute neutrophil count	≥1000/μl
– platelets	≥75,000/μl
– total bilirubin	≤1.5 X ULN (unless due to Gilbert's)
– AST(SGOT)/ALT(SGPT)	≤2.5 X ULN
– creatinine clearance	≥60 mL/min as determined by calculated Cockcroft-Gault equation.
– Fasting serum cholesterol	≤ 350 mg/dL
– Fasting serum triglycerides	≤ 2.5 X ULN

3.1.5 All patients are required to have measurable disease. Non-measurable disease alone is not acceptable. Any tumor mass > 1 cm is acceptable.

Lesions that are considered non-measurable include the following:

- Bone lesions (lesions if present should be noted)
- Ascites
- Pleural/pericardial effusion
- Lymphangitis cutis/pulmonis
- Bone marrow (involvement by lymphoma should be noted)
- For Waldenstrom's macroglobulinemia, Measurable disease is defined as at least one lesion with a single diameter of greater than 2 cm by computed tomography **or** bone marrow involvement with greater than 10% malignant cells and quantitative monoclonal protein (IgM, IgG, IgA) greater than 1,000 mg/dL.

3.1.6 Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days and again within 24 hours prior to starting Cycle 1 of lenalidomide. Further, they must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control: one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before starting lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP, even if they have had a successful vasectomy. A FCBP is a sexually mature woman 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). All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. (See **Appendix I**: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods, and also **Appendix J**: Education and Counseling Guidance Document).

3.1.7 Ability to understand and the willingness to sign a written informed consent document.

3.1.8 Patients who are HIV positive are allowed to participate BUT must meet the following criteria (see also Appendix D):

3.1.8.1 No AIDS-defining illness, AND
(see http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5710a2.htm)

3.1.8.2 CD4 count $\geq$ 400 cells/mm3, AND

3.1.8.3 No anti-retroviral therapy (including HAART) within 7 days of starting protocol therapy, AND

3.1.8.4 Patient may not take concurrent anti-retroviral therapy (including HAART) while on protocol (See also Section 10)

3.1.8.5 NOTE: It is not generally recommended to suspend anti-retroviral therapy (including HAART). The medical team enrolling a patient who suspends anti-retroviral therapy for the purpose of study participation must have a documented note reviewing the potential

risks/benefits with the patient in the medical chart

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

3.2.2 Patients who are receiving any other investigational agents.

3.2.3 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to temsirolimus or lenalidomide used in study.

3.2.5 Because of the high potential for drug-drug interaction, patients requiring active anti-retroviral therapy for HIV are excluded.

3.2.6 No "currently active" second malignancy, other than non-melanoma skin cancers. Patients are not considered to have a "currently active" second malignancy if they have completed anti-cancer therapy and are considered by their physicians to be at less than 30% risk of relapse.

3.2.7 No history (within 3 months of study entry) of DVT/PE. Patients with a distant history (greater than 3 months before study entry) of DVT/PE are eligible, but should receive prophylactic aspirin or low molecular weight heparin.

3.2.8 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.9 Patients with relapsed/refractory DLBCL or HL who are eligible and willing to undergo potentially curative stem cell transplant.

3.2.10 Patients with CLL/SLL are excluded.

3.2.11 No corticosteroids within 14 days prior to study, except for maintenance therapy for a non-malignant disease. Maintenance therapy dose may not exceed 10 mg/day prednisone or equivalent. Any patient on steroid therapy must receive thromboembolic prophylaxis.

3.3 Inclusion of Women and Minorities

Both men and women and members of all ethnic groups are eligible for this trial. Based on the nature of our study population at the University of Chicago and the Phase II Consortium, we expect at least 50% of our enrollment to be women and 30% to be non-white.

study.

Accrual Targets								
Ethnic Category	**Sex/Gender**							
	Females			**Males**			**Total**	
Hispanic or Latino	38		+	37		=	75	
Not Hispanic or Latino	37		+	38		=	75	
Ethnic Category: Total of all subjects	75	(A1)	+	75	(B1)	=	150	(C1)
Racial Category								
American Indian or Alaskan Native	5		+	5		=	10	
Asian	5		+	5		=	10	
Black or African American	10		+	10		=	20	
Native Hawaiian or other Pacific Islander	5		+	5		=	10	
White	50		+	50		=	100	
Racial Category: Total of all subjects	75	(A2)	+	75	(B2)	=	150	(C2)
	(A1 = A2)			(B1 = B2)			(C1 = C2)	

4.0 REGISTRATION PROCEDURES

4.1 General Guidelines

All patients must be registered on study centrally with the University of Chicago Study Coordinator/ Registrar (see face page) via email and phone: PhaseIICRA@bsd.uchicago.edu, (773) 834-5368 at least 7 days prior to the commencement of treatment to allow for sufficient time for supplies to arrive from the PMB. Confirm all the selection criteria listed in Section 3.0 are met and then call the appropriate study coordinator/registrar (contact info above or see face page) with the following information:

- Provider of information
- Study # and Institution
- Treating Physician
- Patient name and hospital ID number
- Patient's zip code of residence
- Date of signed informed consent
- Race, gender, date of birth of patient
- Diagnosis and date of initial diagnosis

The UC Registrar/Study Coordinator will issue a confirmation of registration as follows: The research nurse or data manager at the participating site will initiate contact with the UC Registrar/Study Coordinator to verify eligibility. To complete the registration process, the study coordinator/registrar will

- assign a patient study number
- register the patient on the study
- assign the patient a dose
- fax or e-mail the patient study number and dose to the participating site
- call the research nurse or data manager at the participating site and verbally confirm registration.

Following registration, patients should begin protocol treatment within 7-days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for group studies.

Each site must have two trained counselors available for counseling all patients receiving lenalidomide supplied by the Division of Cancer Treatment and Diagnosis. **Trained counselors must complete training using the online program provided free by Celgene, the Lenalidomide Counseling Program (LCP).** Registration for LCP is done by completing the form found in Appendix L and following the directions provided in the email notification. After the training is complete, the counselors must generate a training certificate and provide it to the University of coordinating office/PMB) for documentation. Sites may not order lenalidomide until documentation for two trained counselors is provided to the appropriate office.

4.2 Registration Process

Registration
Submit the ***Phase II Consortium Affiliate Clinical Trial Patient Registration Form*** and all source documentation for the protocol required eligibility criteria and pre-study procedures.

Weekly
Submit the ***Phase II Consortium Affiliate Clinical Trial Patient Weekly Treatment Summary Form*** with supporting source documentation by noon on Friday of each week, for review at the weekly Phase II Conference. All other source documentation for protocol required procedures should be submitted within a week after it is created or modified.

Evaluations
At each response evaluation as specified in the protocol, submit supporting source documentation for the response.

Off-study
Submit the ***Phase II Consortium Affiliate Clinical Trial Patient Off Treatment Form*** with appropriate source documentation**.**

Follow-up
Submit the ***Phase II Consortium Affiliate Clinical Trial Patient Follow-Up Form*** with appropriate source documentation**.**

Please contact the study coordinator for the appropriate CRF's for this study.

All required forms and source documentation should either be faxed to (773) 702-4889 or mailed to: Phase II Program Data Managers 5841 S. Maryland Avenue MC 2115 Chicago, IL 60637

Data Safety and Monitoring will occur at the weekly University of Chicago Phase II Consortium meetings, which are lead by senior level medical oncologists. At each meeting, all active Phase II Consortium studies will be reviewed for safety and progress toward completion. Toxicities and adverse events will be reviewed at each meeting and a Data Safety and Monitoring form will be filled out for each protocol and signed by either the principal investigator, the Chairman of the Phase II Consortium or by his designate if the chairman is not available.

5.0 TREATMENT PLAN

Agent Administration (Phase I portion is completed)

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks for temsirolimus and lenalidomide are described in Section 6. Appropriate dose modifications for temsirolimus and lenalidomide are described in Section 5. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Dose Escalation Schedule		
Dose Level	**Dose***	
	Temsirolimus (flat dose in mg)	**Lenalidomide (flat dose in mg)**
Level -2	15 mg	10 mg
Level -1	25 mg	10 mg
Level 1	25 mg	15 mg
Level 2	25 mg	20 mg

Level 3	25 mg	25 mg	

5.1.1 Temsirolimus

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 6. Appropriate dose modifications for CCI-779 are described in Section 5. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Patients will receive 25 mg of CCI-779 administered over 30 minutes IV weekly continuously (i.e. without interruption between cycles). For the purposes of evaluation, a cycle will be defined as 4 weeks (28 days). It is expected that CCI-779 administration will continue on the same day of the week throughout the treatment period. However, it may be given up to 2 days early or late due to holiday or scheduling reasons. Missed doses should not be made up.

Because of the idiosyncratic hypersensitivity reactions, patients receiving IV CCI-779 should be premedicated with diphenhydramine 25 – 50 mg IV (or a similar antihistamine) approximately 30 minutes before the start of the CCI-779 infusion.

CCI-779 will be administered over approximately 30 minutes as an IV infusion, via an automatic dispensing pump (e.g. IMED, Harvard, Travenol), using non-polyvinyl chloride (PVC) tubing with the appropriate filter. See section 6.0 (Incompatibilities subsection) for list of appropriate tubings and filters.

5.1.2 Lenalidomide

Lenalidomide is administered orally once daily for 21 days every 28 days. Clinical studies have shown that administering lenalidomide with food intake appears to delay absorption to some degree, although the extent of absorption is not altered. Lenalidomide can be taken with or without food. Patients will be requested to maintain a medication calendar recording the dates and times of each dose of lenalidomide. A copy of the medication diary/calendar has been included as Appendix C to the protocol.

Lenalidomide capsules should be swallowed whole, and should not be broken, chewed, or opened. If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If a dose of lenalidomide is missed for the entire day, it should **NOT** be made up. Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

5.2 Definition of Dose-Limiting Toxicity (Phase I Portion Completed)

DLT evaluation for purposes of dose escalation will occur at the end of cycle 1, although toxicity data will continue to be collected for the duration of treatment. There will be no intra-patient dose escalation. The definition of DLT will be as follows:

- any grade 3 or 4 non-hematologic toxicity with the exception of the following:
    - grade 3 or 4 hypokalemia and/or hypomagnesemia that responds to oral or IV repletion. Persistent grade 3 or 4 hypokalemia and/or hypomagnesemia that does not respond to oral or IV repletion after 2 weeks will lead to a reduction by one dose level.
    - Grade 3 or 4 hypertriglyceredemia, hypercholesterolemia, and/or hyperglycemia that responds to appropriate diet and/or medical intervention. Persistent grade 3 or 4 hypertriglyceridemia, hypercholesterolemia, and/or hyperglycemia that does not respond to appropriate diet and/or medical intervention after 2 weeks will lead to a reduction by one dose level.
    - Grade 3 or 4 nausea, vomiting, diarrhea without optimal intervention
- grade 4 thrombocytopenia lasting greater than 7 days **OR** associated with clinically significant bleeding **OR** requiring > 1 platelet transfusion in one week
- ANC ≤ 500/μL lasting greater than 7 days despite the use of growth factors
- Any thromboembolic event (irrespective of prophylaxis)

Management and dose modifications associated with the above adverse events for the phase II portion of the trial are outlined in Section 5. Management and dose modifications for the phase I portion of the trial are in Section 4.2.1.

Dose escalation for the phase I portion of the trial will proceed according to a "3+3" design (see section 11). Dose-limiting toxicity (DLT) is defined above.

5.2.1 Dose modifications for the phase I portion of the trial. For purposes of dose escalation, DLT evaluation will occur at the end of Cycle 1, but toxicity information will continue to be collected for the duration of treatment. For patients on the phase I portion of the trial, treatment modifications are as follows:

Neutropenia

- For ≥ grade 3 neutropenia on day 1 of a cycle, hold both temsirolimus and lenalidomide, and monitor CBC weekly. Resume therapy at next lower dose level when neutropenia resolves to ≤ grade 2. Hence, for neutropenia occurring on day 1 of a cycle, the cycle may be delayed.
- For ≥ grade 3 neutropenia during a cycle, hold both temsirolimus and lenalidomide. and monitor CBC weekly. Resume therapy at next lower dose level when neutropenia resolves to ≤ grade 2.
- If treatment is delayed for more than 6 weeks, discontinue all protocol therapy and remove patient from study.

Thrombocytopenia

- For ≥ grade 3 thrombocytopenia on day 1 of a cycle, hold both temsirolimus and lenalidomide and monitor CBC weekly. Resume therapy at the next lower dose level for the next cycle when thrombocytopenia resolves to ≤ grade 2.
- For ≥ grade 3 thrombocytopenia during a cycle, hold both temsirolimus and lenalidomide for remainder of the cycle. Resume therapy at the next lower dose level for the next cycle, provided thrombocytopenia has resolved to ≤ grade 2.
- If treatment is delayed for more than 6 weeks, discontinue all protocol therapy and and remove patient from study.

Anemia

- In the instance of **drug-related** anemia based on hemoglobin on day 1 that has worsened by one or more grade levels from previous cycle, reduce temsirolimus and lenalidomide by one dose level.
- In the instance of **drug-related** grade 4 hemoglobin at any time during a cycle, discontinue temsirolimus and lenalidomide.
- Epoetin may be used to treat drug-related anemia. If epoetin is used, patients should receive either prophylactic aspirin or low molecular weight heparin unless contraindicated.

Dermatologic Toxicity

In the instance of any grade desquamating rash, lenalidomide must be stopped. In the instance of grade 3 non-desquamating rash, the rash must resolve to grade 1 or less prior to restarting lenalidomide. Lenalidomide should be restarted 5mg less than prior dose.

Other Non-Hematologic Toxicity

In the instance of grade 3 other non-hematologic toxicity, hold protocol therapy, notify the Principal Investigator, and monitor toxicity at least weekly. If toxicity resolves to ≤ grade 2, then resume therapy at next lower dose level with the following exceptions:

- Grade 3 non-desquamating rash must resolve to grade 1 prior to restarting lenalidomide.
- Grade 3 neuropathy must resolve to grade 1 prior to restarting lenalidomide.
- Grade 3 or 4 hypokalemia and/or hypomagnesemia can be pre-emptively treated with oral or IV repletion. Persistent grade 3 or 4 hypokalemia and/or hypomagnesemia that does not respond to oral or IV repletion after 2 weeks will lead to a reduction by one dose level.
- Grade 3 or 4 hypertriglyceredemia, hypercholesterolemia, and/or hyperglycemia can be pre-emptively treated with appropriate diet and/or medical intervention. Persistent grade 3 or 4 hypertriglyceridemia, hypercholesterolemia, and/or hyperglycemia that does not respond to appropriate diet and/or medical intervention after 2 weeks will lead to a reduction by one dose level.

In the instance of grade 4 other non-hematologic toxicity, remove patient from protocol therapy.

If a patient's creatinine clearance (CrCl) decreases to 30-59 cc/min, the dose of lenalidomide should be decreased by one dose level.

Venous or Arterial Thrombosis

See Appendix D. Patients who develop signs or symptoms suggestive of thrombosis should be evaluated and treated as clinically indicated. Lenalidomide should be held for patients with grade 3 thrombosis or asymptomatic pulmonary embolism. Lenalidomide may resume when patient is adequately anticoagulated. Patients with recurrent thrombosis despite adequate anticoagulation should be removed from protocol therapy. For grade 4 thrombosis or symptomatic pulmonary embolism, discontinue protocol therapy. If lenalidomide is held for thrombosis, continue temsirolimus.

Abnormal Menstruation or Pregnancy Test

If a female misses a period, or for abnormal menstrual bleeding or abnormal pregnancy test, obtain a pregnancy test and counseling as appropriate. Hold all protocol therapy until pregnancy is ruled out. Discontinue protocol therapy if pregnancy test is positive.

5.3 Supportive Care Guidelines

Temsirolimus-specific guidelines
Because of the idiosyncratic hypersensitivity reactions, subjects receiving IV temsirolimus should be premedicated with diphenhydramine 25 – 50 mg IV (or a similar antihistamine) approximately 30 minutes before the start of the temsirolimus infusion. If the subject begins to develop a hypersensitivity reaction despite pretreatment with diphenhydramine, the infusion should be stopped for at least 30 – 60 minutes, depending upon the severity of the reaction. The infusion may be resumed by administering a histamine H_2-receptor antagonist approximately 30 minutes before restarting the CCI-779 infusion. Famotidine 20 mg IV or ranitidine 50 mg IV are recommended rather than cimetidine, because of the lack of likely metabolic/pharmacologic interactions with the former drugs. The rate of the CCI-779 infusion may also be slowed from 30 minutes to over an hour. All subjects should be monitored while receiving the CCI-779 infusion and emergency medical equipment and health care personnel must be readily available to respond to hypersensitivity reactions or other medical emergencies.

Although drug interaction studies have not been reported, a potential drug interaction involving CCI-779 and warfarin/Coumadin™ (with an increase in INR) was reported. Patients on warfarin should have PT/INR monitored frequently after starting and discontinuing CCI-779 to determine whether the warfarin dose needs to be adjusted.

Lenalidomide-specific guidelines

Patients considered to be at high risk of developing DVT/PE or arterial thromboses are to receive either prophylactic aspirin or low molecular weight heparin unless contraindicated (See

Appendix D). High risk will be defined as a history of DVT/PE, significant family history, performance status ≥ 2, smoking history, use of oral contraceptives, chronic steroid use, and concurrent use of epoetin. Patients with diabetes mellitus or coronary artery disease are considered to be at high risk for arterial thromboembolic events.

Other supportive care (including growth factor use)

Treatment with hormones used as chemotherapy or other chemotherapeutic agents may not be administered except for steroids given for adrenal failure; hormones administered for non-disease related conditions (e.g., insulin for diabetes; birth control pills). The use of dexamethasone and other steroidal antiemetics is prohibited. Routine supportive measures for cancer patients such as erythropoietin, analgesics, blood transfusions, antibiotics, bisphosphonates, hematopoetic colony stimulating factors for treatment of cytopenias are permitted as per ASCO guidelines but must be clearly documented. Due to the weekly schedule of administration, the use of pegfilgrastim will not be allowed.

5.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for *52* or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- The patient becomes eligible for an autologous or allogeneic stem cell transplant

5.5 Duration of Follow Up

Patients will be followed for one year after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.6 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.4 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6.0 DOSING DELAYS/DOSE MODIFICATIONS FOR PHASE II PORTION

Dose Levels for the phase I portion of the study are as per the Section 5.0. During the phase II portion of the trial, dose delays/modifications are per the table below. Once the dose of an agent has been reduced, no dose re-escalation is permitted. If a scheduled dose is delayed for more than 6 weeks due to treatment-related toxicity, remove the patient from protocol

therapy. No dose reductions below Dose Level -3 are permitted. A missed dose should not be made up, so that cycle lengths are always 28 days irrespective of the number of doses delivered in that cycle. **NOTE**: Dose delays/dose reductions for the phase II portion of the study will be re-evaluated at the conclusion of the phase I portion of the study, and the following section is subject to revision.

Temsirolimus (T)/Lenalidomide (L) Dose Levels for Phase II Portion Only

	INDUCTION THERAPY
Starting Dose	T: 25mg IV weekly, repeated every 28 days L: 20mg PO daily on Days 1-21, repeated every 28 days
Dose Level –1	T: 25mg IV weekly, repeated every 28 days L: 15mg PO daily on Days 1-21, repeated every 28 days
Dose Level –2	T: 20mg IV weekly, repeated every 28 days L: 15mg PO daily on Days 1-21, repeated every 28 days
Dose Level –3	T: 20mg IV weekly, repeated every 28 days L: 10mg PO daily on Days 1-21, repeated every 28 days

6.1 Hematologic toxicity

6.1.1 Neutropenia and thrombocytopenia

Observation	Action	Comments
Neutropenia ≥ gr 3	• Hold both agents • Resume therapy at same dose level once neutropenia resolves to ≤ grade 2 • If recurs, reduce by one dose level. • If recurs again, reduce by one additional dose level. • If recurs again, discuss with PI	Monitor CBC weekly. Consider use of growth factor support. If treatment is delayed by more than 6 weeks due to treatment-related toxicity, remove patient from study
Thrombocytopenia ≥ gr 3	• Hold both agents • Resume therapy at same dose level once neutropenia resolves to ≤ grade 2 • If recurs, reduce by one dose level.	Monitor CBC weekly. If treatment is delayed by more than 6 weeks due to treatment-

	• If recurs again, reduce by one additional dose level. • If recurs again, discuss with PI	related toxicity, remove patient from study

6.1.2 Anemia

- In the instance of **drug-related** anemia based on hemoglobin on day 1 that has worsened by one or more grade levels from previous cycle, reduce temsirolimus and lenalidomide by one dose level.
- In the instance of **drug-related** grade 4 hemoglobin at any time during a cycle, discontinue temsirolimus and lenalidomide.
- Epoetin may be used to treat drug-related anemia. If epoetin is used, patients should receive either prophylactic aspirin or low molecular weight heparin unless contraindicated.

6.1.3-DERMATOLOGIC TOXICITY

In the instance of any grade desquamating rash, lenalidomide must be stopped. In the instance of grade 3 non-desquamating rash, the rash must resolve to grade 1 or less prior to restarting lenalidomide. Lenalidomide should be restarted 5mg less than prior dose.

6.1.4-Other Non-Hematologic Toxicity

Observation	Action	Comments
AE resolves promptly with supportive care	Maintain dose level	
Grade 3 or higher non-hematologic AE (except for those listed below) related to temsirolimus or lenalidomide that does not resolve to grade 2 or below despite maximum supportive care	• Hold both agents • Resume therapy at same dose level once AE resolves to ≤ grade 2 • If recurs, reduce by one dose level. • If recurs again, reduce by one additional dose level. • If recurs again, discuss with PI	Monitor CBC and CMP weekly. If treatment is delayed by more than 6 weeks due to treatment-related toxicity, remove patient from study
Grade 3 or 4 non-desquamating rash	• Hold lenalidomide • Resume lenalidomide at 5mg less than prior dose once rash is ≤ grade 1	

	• If recurs, discuss with PI	
Grade 3 or 4 neuropathy	• Hold lenalidomide • Resume lenalidomide at 5mg less than prior dose once neuropathy is ≤ grade 1	Provide optimal supportive care If treatment is delayed by more than 6 weeks due to treatment-related toxicity, remove patient from study
Grade 3 or 4 hypokalemia, hypomagnesemia, hypertriglyceridemia, hypercholesterolemia, and/or hyperglycemia	• Provide optimal supportive care • If AE does not resolve after 2 weeks of optimal intervention, reduce by one dose level. • If AE recurs, reduce by one additional dose level • If AE recurs, discuss with PI	
Decrease in CrCl to 30-59 cc/min	• Decrease lenalidomide by one dose level • If recurs, decrease lenalidomide by one additional dose level • If recurs, discuss with PI	

6.1.5-Venous or Arterial Thrombosis

See Appendix D. Patients who develop signs or symptoms suggestive of thrombosis should be evaluated and treated as clinically indicated. Lenalidomide should be held for patients with grade 3 thrombosis or asymptomatic pulmonary embolism. Lenalidomide may resume when patient is adequately anticoagulated. Patients with recurrent thrombosis despite adequate anticoagulation should be removed from protocol therapy. For grade 4 thrombosis or symptomatic pulmonary embolism, discontinue protocol therapy. If lenalidomide is held for thrombosis, continue temsirolimus.

6.1.6- Abnormal Menstruation or Pregnancy Test

If a female misses a period, or for abnormal menstrual bleeding or abnormal pregnancy test, obtain a pregnancy test and counseling as appropriate. Hold all protocol therapy until pregnancy is ruled out. Discontinue protocol therapy if pregnancy test is positive.

7.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting (via CTEP-AERS) **in addition** to routine reporting.

7.1 COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LISTS (CAEPRS) FOR Temsirolimus (CCI-779, NSC 683864)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1927 patients.* Below is the CAEPR for temsirolimus (CCI-779, Torisel).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, July 2, 2013[1]

Adverse Events with Possible Relationship to Temsirolimus (CCI-779, Torisel) (CTCAE 4.0 Term) [n= 1927]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
ENDOCRINE DISORDERS			
	Endocrine disorders - Other (decreased testosterone)		***Endocrine disorders - Other (decreased testosterone) (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal distension		***Abdominal distension (Gr 2)***

	Abdominal pain		***Abdominal pain (Gr 3)***
	Anal mucositis[2]		***Anal mucositis[2] (Gr 2)***
	Constipation		***Constipation (Gr 3)***
Diarrhea			***Diarrhea (Gr 3)***
		Gastrointestinal fistula[3]	
		Gastrointestingal perforation[4]	***Gastrointestinal perforation[4] (Gr 2)***
Mucositis oral[2]			***Mucositis oral[2] (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Rectal mucositis[2]		***Rectal mucositis[2] (Gr 2)***
	Small intestinal mucositis[2]		***Small intestinal mucositis[2] (Gr 2)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema face		***Edema face (Gr 2)***
	Edema limbs		***Edema limbs (Gr 3)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Flu like symptoms		***Flu like symptoms (Gr 2)***
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr 2)***
	Pain		
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[5]		***Allergic reaction[5] (Gr 2)***
INFECTIONS AND INFESTATIONS[6]			
	Infection[7]		***Infection[7] (Gr 3)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Wound dehiscence[8]		***Wound dehiscence[8] (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
Cholesterol high[9]			***Cholesterol high[9] (Gr 4)***
	Creatinine increased		***Creatinine increased (Gr 3)***
	Fibrinogen decreased		***Fibrinogen decreased (Gr 2)***
	GGT increased		***GGT increased (Gr 2)***
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased[10]		***Neutrophil count decreased[10] (Gr 4)***
Platelet count decreased[10]			***Platelet count decreased[10] (Gr 4)***
	Weight loss		***Weight loss (Gr 3)***
	White blood cell decreased		***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Acidosis		***Acidosis (Gr 2)***
Anorexia			***Anorexia (Gr 3)***
	Glucose intolerance[11]		***Glucose intolerance[11] (Gr 2)***
	Hyperglycemia[11]		***Hyperglycemia[11] (Gr 3)***
	Hypertriglyceridemia[9]		***Hypertriglyceridemia[9] (Gr 4)***
	Hypocalcemia		***Hypocalcemia (Gr 3)***
	Hypokalemia		***Hypokalemia (Gr 4)***
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
	Metabolism and nutrition disorders - Other		***Metabolism and nutrition disorders - Other (hyperlipidemia)[9] (Gr 4)***

	(hyperlipidemia)[9]		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		***Back pain (Gr 2)***
	Myalgia		***Myalgia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Depressed level of consciousness		***Depressed level of consciousness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 3)***
PSYCHIATRIC DISORDERS			
	Depression		***Depression (Gr 2)***
	Insomnia		***Insomnia (Gr 2)***
	Libido decreased		***Libido decreased (Gr 2)***
RENAL AND URINARY DISORDERS			
		Acute kidney injury[12]	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
	Erectile dysfunction		***Erectile dysfunction (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Epistaxis		***Epistaxis (Gr 2)***
	Laryngeal mucositis[2]		***Laryngeal mucositis[2] (Gr 2)***
	Pharyngeal mucositis[2]		***Pharyngeal mucositis[2] (Gr 2)***
	Pleural effusion		***Pleural effusion (Gr 3)***
	Pneumonitis[13]		***Pneumonitis[13] (Gr 3)***
	Sinus disorder		***Sinus disorder (Gr 2)***
	Tracheal mucositis[2]		***Tracheal mucositis[2] (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		***Dry skin (Gr 2)***
	Pruritus		***Pruritus (Gr 2)***
	Rash acneiform		***Rash acneiform (Gr 2)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***
	Skin and subcutaneous tissue disorders – Other (nail disorder/nail changes)[15]		***Skin and subcutaneous tissue disorders – Other (nail disorder/nail changes)[15] (Gr 2)***
	Urticaria		***Urticaria (Gr 2)***
VASCULAR DISORDERS			
	Hypertension		***Hypertension (Gr 3)***
	Hypotension		***Hypotension (Gr 3)***
		Thromboembolic event	***Thromboembolic event (Gr 4)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Mucositis/stomatitis: Gingivitis, mucositis/stomatitis, ulcers in mouth and throat, pharyngitis, and dysphagia have been reported in subjects receiving temsirolimus.

[3]Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Enterovesical fistula, Gastric fistula, Gastrointestinal fistula, Ileal fistula, Jejunal fistula, Oral cavity fistula, Pancreatic fistula, Rectal fistula, and Salivary gland fistula under the GASTROINTESTINAL DISORDERS SOC.

[4]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC. GI perforation (including fatal outcome) has been observed in subjects who received temsirolimus.

[5]Hypersensitivity /infusion reactions (including some life threatening and rare fatal reactions), including and not limited to flushing, chest pain, dyspnea, hypotension, apnea, loss of consciousness, hypersensitivity, and anaphylaxis, have been associated with the administration of temsirolimus. These reactions can occur very early in the first infusion, but may also occur with subsequent infusions. Patients should be monitored early during infusion and appropriate supportive care should be available. Temsirolimus infusion should be interrupted in all patients with severe infusion reactions and appropriate medical care administered. A risk-benefit assessment should be done prior to the continuation of temsirolimus therapy in patients with severe life-threatening reactions.

[6]Infections: Bacterial and viral infections including opportunistic infections have been reported in subjects. Infections may originate in a variety of organ systems/body regions and may be associated with normal or grade 3-4 neutropenia. Bacterial and viral infections have included cellulitis, herpes zoster, herpes simplex, bronchitis, abscess, pharyngitis, urinary tract infection (including dysuria hematuria, cystitis, and urinary frequency), rhinitis folliculitis, pneumonia, and upper respiratory tract infection.

[7]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[8]Wound Dehiscence: The use of temsirolimus has been associated with abnormal wound healing. Therefore, caution should be exercised with the use of temsirolimus in the perisurgical period.

[9]Cholesterol High: The use of temsirolimus in subjects has been associated with increases in serum levels of triglycerides and cholesterol. This may require initiation of or increase in the dose of lipid-lowering agents.

[10]Thrombocytopenia and Neutropenia: Grades 3 and 4 thrombocytopenia and/or neutropenia have been observed at higher frequency in subjects with mantle cell lymphoma (MCL).

[11]Hyperglycemia/Glucose Intolerance: The use of temsirolimus in subjects was associated with increases in serum glucose level. This may result in the need for an increase in the dose of, or initiation of, insulin and/or oral hypoglycemic agent therapy.

[12]Acute Kidney Injury: Renal failure (including fatal outcome) has been observed in subjects receiving temsirolimus for advanced RCC and/or with pre-existing renal insufficiency.

[13]Interstitial Lung Disease: There have been cases of nonspecific interstitial pneumonitis, including rare fatal reports. Some subjects were asymptomatic with pneumonitis detected on computed tomography scan or chest radiograph. Others presented with symptoms such as dyspnea, cough, and fever. Some subjects required discontinuation of temsirolimus or treatment with corticosteroids and/or antibiotics, while some subjects continued treatment without additional intervention.

[14]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[15]Nail Disorder/Nail Changes includes Nail discoloration, Nail loss, and Nail ridging under the SKIN AND SUBCUTANEOUS TISSUE DISORDERS SOC.

Also reported on temsirolimus (CCI-779, Torisel) trials but with the relationship to temsirolimus (CCI-779, Torisel) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (coagulopathy); Hemolysis; Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac arrest; Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Pericardial effusion; Right ventricular dysfunction; Sinus tachycardia; Supraventricular tachycardia; Ventricular fibrillation; Ventricular tachycardia
EAR AND LABYRINTH DISORDERS - Vertigo
ENDOCRINE DISORDERS - Endocrine disorders - Other (Cushing's syndrome); Endocrine disorders - Other (diabetes mellitus)
EYE DISORDERS - Blurred vision; Cataract; Conjunctivitis; Dry eye; Eye disorders - Other (diplopia); Eye pain; Flashing lights; Photophobia; Retinopathy
GASTROINTESTINAL DISORDERS - Anal pain; Anal ulcer; Ascites; Bloating; Colitis; Colonic obstruction; Colonic ulcer; Dry mouth; Duodenal ulcer; Dyspepsia; Dysphagia; Enterocolitis; Esophageal pain; Esophageal ulcer; Esophagitis; Flatulence; Gastritis; Gastrointestinal disorders - Other (anal fissure); Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal disorders - Other (mouth ulceration); Gastrointestinal hemorrhage[14], Hemorrhoids; Ileus; Oral pain; Pancreatitis; Periodontal disease; Proctitis; Rectal pain; Small intestinal obstruction; Stomach pain; Typhlitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema trunk; Facial pain; Gait disturbance; Injection site reaction; Localized edema; Malaise; Multi-organ failure; Sudden death NOS
HEPATOBILIARY DISORDERS - Hepatic failure
IMMUNE SYSTEM DISORDERS - Anaphylaxis
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Fracture; Postoperative hemorrhage; Vascular access complication; Wound complication
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood bilirubin increased; CD4 lymphocytes decreased; INR increased (potential interaction with Coumadin); Investigations - Other (BUN increased); Investigations - Other (lactic dehydrogenase increased); Lipase increased; Lymphocyte count increased; Serum amylase increased; Weight gain
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hyperuricemia; Hypoalbuminemia; Hypoglycemia; Hypomagnesemia; Hyponatremia; Metabolism and nutrition disorders - Other (albuminuria) ; Metabolism and nutrition disorders - Other (blood urea increased);
Metabolism and nutrition disorders - Other (hypoproteinemia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Avascular necrosis; Bone pain; Chest wall pain; Generalized muscle weakness; Joint effusion; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (muscle cramps); Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Leukemia secondary to oncology chemotherapy; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (carcinoma of the lung); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (lymphoma); Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Dizziness; Dysesthesia; Hydrocephalus; Intracranial hemorrhage; Lethargy; Neuralgia; Paresthesia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Reversible posterior leukoencephalopathy syndrome; Seizure; Somnolence; Spasticity; Stroke; Syncope
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Mania; Psychiatric disorders - Other (bipolar disorder); Psychosis
RENAL AND URINARY DISORDERS - Bladder spasm; Cystitis noninfective; Hematuria; Hemoglobinuria; Proteinuria; Renal hemorrhage; Urinary frequency; Urinary retention; Urinary tract pain; Urinary urgency
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Female genital tract fistula; Hematosalpinx; Irregular menstruation; Menorrhagia; Ovarian hemorrhage; Prostatic hemorrhage; Spermatic cord hemorrhage; Testicular disorder; Testicular hemorrhage; Testicular pain; Uterine hemorrhage; Vaginal discharge; Vaginal dryness; Vaginal fistula; Vaginal hemorrhage; Vaginal inflammation
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome;

Allergic rhinitis; Bronchopulmonary hemorrhage; Bronchospasm; Hiccups; Hypoxia; Nasal congestion; Pharyngolaryngeal pain; Pleuritic pain; Productive cough; Pulmonary edema; Pulmonary fibrosis; Pulmonary hypertension; Respiratory failure; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Erythema multiforme; Hyperhidrosis; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Photosensitivity; Skin and subcutaneous tissue disorders - Other (angioneurotic edema); Skin ulceration; Stevens-Johnson syndrome
VASCULAR DISORDERS - Flushing; Phlebitis; Superficial thrombophlebitis; Visceral arterial ischemia

Note: Intracerebral Bleeding: Subjects with central nervous system (CNS) tumors (primary CNS tumors or metastases) and/or receiving anticoagulation therapy may be at an increased risk of intracerebral bleeding (including fatal outcomes) while receiving therapy with temsirolimus (CCI-779, Torisel).

Note: Temsirolimus (CCI-779, Torisel) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Lenalidomide (CC-5013, NSC 703813)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 4081 patients.* Below is the CAEPR for lenalidomide (CC-5013).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.6, December 24, 2015[1]

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 4.0 Term) [n= 4081]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
CARDIAC DISORDERS			
		Myocardial infarction[2]	
ENDOCRINE DISORDERS			
	Hypothyroidism		***Hypothyroidism (Gr 3)***
GASTROINTESTINAL DISORDERS			
Constipation			***Constipation (Gr 3)***
Diarrhea			***Diarrhea (Gr 3)***
	Nausea		***Nausea (Gr 3)***
		Pancreatitis	
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 4.0 Term) [n= 4081]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Chills		***Chills (Gr 2)***
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatic failure	
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis	
		Immune system disorders - Other (graft vs. host disease)[3]	
INFECTIONS AND INFESTATIONS			
	Infection[4]		***Infection (Gr 3)[4]***
INVESTIGATIONS			
		Lipase increased	
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 3)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 3)***
Platelet count decreased			***Platelet count decreased (Gr 3)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		
	Musculoskeletal and connective tissue disorders - Other (muscle cramp/muscle spasm)		***Musculoskeletal and connective tissue disorders - Other (Muscle cramp/muscle spasm) (Gr 2)***
	Myalgia		***Myalgia (Gr 2)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy[5]	
		Myelodysplastic syndrome[5]	
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor flare)[6]	
		Treatment related secondary malignancy[5]	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		
		Stroke[2]	
		Leukoencephalopathy	
PSYCHIATRIC DISORDERS			
	Insomnia		***Insomnia (Gr 2)***
RENAL AND URINARY DISORDERS			

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 4.0 Term) [n= 4081]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	
	Hyperhidrosis		***Hyperhidrosis (Gr 2)***
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (pyoderma gangrenosum)		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
SURGICAL AND MEDICAL PROCEDURES			
		Surgical and medical procedures - Other (impaired stem cell mobilization)[7]	
VASCULAR DISORDERS			
	Thromboembolic event[8]		***Thromboembolic event[8] (Gr 2)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Myocardial infarction and cerebrovascular accident (stroke) have been observed in multiple myeloma patients treated with lenalidomde and dexamethasone.

[3]Graft vs. host disease has been observed in subjects who have received lenalidomide in the setting of allo-transplantation.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[5]There has been an increased frequency of secondary malignancies (including AML/MDS) in multiple myeloma patients being treated with melphalan, prednisone, and lenalidomide post bone marrow transplant.

[6]Serious tumor flare reactions have been observed in patients with chronic lymphocytic leukemia (CLL) and lymphoma.

[7]A decrease in the number of stem cells (CD34+ cells) collected from patients treated with >4 cycles of lenalidomide has been reported.

[8]Significantly increased risk of deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis has been observed in patients with multiple myeloma receiving lenalidomide with dexamethasone.

[9]Gastrointestinal hemorrhage includes: Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper

gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[10]Gastrointestinal obstruction includes: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Obstruction gastric, Rectal obstruction, and Small intestinal obstruction under the GASTROINTESTINAL DISORDERS SOC.

[11]Osteonecrosis of the jaw has been seen with increased frequency when lenalidomide is used in combination with bevacizumab, docetaxel (Taxotere®), prednisone, and zolendronic acid (Zometa®).

NOTE: While not observed in human subjects, lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of contraception.

Adverse events reported on Lenalidomide (CC-5013) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Lenalidomide (CC-5013) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (eosinophilia); Blood and lymphatic system disorders - Other (monocytosis); Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Febrile neutropenia; Hemolysis; Spleen disorder
CARDIAC DISORDERS - Acute coronary syndrome; Atrial fibrillation; Atrial flutter; Atrioventricular block first degree; Cardiac arrest; Cardiac disorders - Other (cardiovascular edema); Cardiac disorders - Other (ECG abnormalities); Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Palpitations; Pericarditis; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus
ENDOCRINE DISORDERS - Cushingoid; Hyperthyroidism
EYE DISORDERS - Blurred vision; Conjunctivitis; Dry eye; Flashing lights; Retinopathy
GASTROINTESTINAL DISORDERS - Abdominal distension; Abdominal pain; Anal mucositis; Ascites; Colonic perforation; Dry mouth; Dyspepsia; Dysphagia; Flatulence; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (Crohn's disease aggravated); Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (pale feces); Gastrointestinal hemorrhage[9]; Gastrointestinal obstruction[10]; Ileus; Mucositis oral; Rectal mucositis; Small intestinal mucositis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - General disorders and administration site conditions - Other (edema NOS); Malaise; Multi-organ failure; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Cholecystitis
IMMUNE SYSTEM DISORDERS - Allergic reaction; Immune system disorders - Other (angioedema)
INFECTIONS AND INFESTATIONS - Infections and infestations - Other (Opportunistic infection associated with >=grade 2 lymphopenia)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Fall; Fracture; Hip fracture; Vascular access complication
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Cholesterol high; Creatinine increased; Electrocardiogram QT corrected interval prolonged; INR increased; Investigations - Other (hemochromatosis)
METABOLISM AND NUTRITION DISORDERS - Acidosis; Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Bone pain; Chest wall pain; Generalized muscle weakness; Joint effusion; Muscle weakness lower limb; Musculoskeletal and connective tissue disorders - Other (rhabdomyolysis); Neck pain; Osteonecrosis of jaw[11]; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysgeusia; Dysphasia; Edema cerebral; Encephalopathy; Intracranial hemorrhage; Ischemia cerebrovascular; Memory impairment; Myelitis; Nervous system disorders - Other (hyporeflexia); Nervous system disorders - Other (spinal cord compression); Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence;

Syncope; Transient ischemic attacks; Tremor
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Psychosis
RENAL AND URINARY DISORDERS - Urinary frequency; Urinary incontinence; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Reproductive system and breast disorders - Other (hypogonadism); Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Atelectasis; Bronchopulmonary hemorrhage; Epistaxis; Hypoxia; Laryngeal mucositis; Pharyngeal mucositis; Pleural effusion; Pneumonitis; Pulmonary hypertension; Respiratory failure; Tracheal mucositis; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Nail loss; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (Sweet's syndrome); Urticaria
VASCULAR DISORDERS - Hot flashes; Hypertension; Hypotension; Phlebitis; Vascular disorders - Other (hemorrhage NOS)

Note: Lenalidomide (CC-5013) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 ADVERSE EVENT CHARACTERISTICS

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

NOTE: HIV-positive patients will be carefully monitored. Once 5 patients with HIV-positive disease have been accrued, CTEP and the PI will discuss toxicity and efficacy, with a consideration of reintroducing anti-retroviral therapy.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (Cancer Therapy Evaluation Program Adverse Event Reporting SystemCTEP-AERS accessed via the CTEP Web site (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 The following text is required for multi-institutional studies only and may be deleted for single institution studies.

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for

other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational

agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:
- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

- For **Hospitalization** only – Any medical event equivalent to CTC Grade 3, 4, or 5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of designation as expected or unexpected and attribution.

- Telephone reports to the Investigational Drug Branch at 301-230-2330 available 24 hours daily (recorder between 5 P.M. and 9 A.M. EST).

- In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to NCI by telephone at: 301-897-7497, or 301-897-7402 for CIP studies. An electronic report MUST be submitted immediately upon re-establishment of internet connection", for the reason that all paper CTEP-AERS forms have been removed from the CTEP website and will no longer be accepted.

Pregnancy Reporting Requirements
Females of Childbearing Potential:

- Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject or the partner of a male subject occurring while the subject is on lenalidomide or within 28 days after the subject's last dose, are considered immediately reportable events. Lenalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported via CTEP-AERS as a **grade 4** event under: SOC pregnancy, puerperium and perinatal conditions; adverse event: **pregnancy, puerperium and perinatal conditions-other, fetal exposure.**
  - *The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.*
- The Investigator will follow the female subject until completion of the pregnancy, and must make an amendment to the initial pregnancy report immediately regarding the outcome of the pregnancy and neonatal status (either normal or abnormal outcome).
- If the outcome of the pregnancy was abnormal (including spontaneous or therapeutic abortion, fetal demise and congenital abnormalities), the

Investigator should report the abnormal outcome as an amendment to the initial pregnancy report as soon as the as the Investigator has knowledge of the outcome.

- All neonatal deaths and neonatal complications that occur within 28 days of birth should be reported, without regard to causality, as an amendment to the initial pregnancy report. In addition, any infant death after 28 days that the Investigator suspects is related to the *in utero* exposure to the lenalidomide should also be reported as an amendment within 24 hours of the Investigator's knowledge of the event.

Male Subjects

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

CTEP-AERS provides a copy feature for other e-mail recipients. AE notification **must** be sent to:

The Cancer Clinical Trials Office to:
Quality Assurance Operations Manager
University of Chicago
Cancer Clinical Trials Office
5841 S. Maryland, MC1140
Chicago, IL 60637
qaccto@bsd.uchicago.edu

The UC Principal Investigator, if UC is not the lead institution.

Use the NCI Protocol Number on all reports.

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through CTEP-AERS must also be reported in routine study data submissions.**

7.5 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). Investigators are required to report cases of secondary malignancies, including AML/MDS occurring on or following treatment on NCI-sponsored chemotherapy protocols via CTEP-AERS with CTCAE 4.0. Refer to the "CTEP website http://ctep.cancer.gov) for additional information about secondary AML/MDS reporting.

- All new malignant tumors must be reported through CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported including solid tumors (including non-melanoma skin malignancies), hematologic malignancies, Myelodysplastic Syndrome (MDS)/Acute Myelogenous Leukemia (AML), and *in situ* tumors.
- Using CTCAE v4.0, the event(s) may be reported as one of the following: (1) Leukemia secondary to oncology chemotherapy; (2) Myelodysplastic syndrome; (3) Treatment-related secondary malignancy; or (4) Neoplasm other, malignant (grade 3 or 4).
- These events should be reported for the duration of the study treatment and during any protocol-specified follow-up periods.

7.6-Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

8.0- PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 7.1.

8.1-TEMSIROLIMUS (TORISEL®, NSC 683864)

Chemical Name: Sirolimus 42-ester with 2,2-bis (hydroxymethyl)-propionic acid

Other Names: CCI-779, Torisel®, Rapamycin analog, WAY-130779

Classification: Cell cycle inhibitor

Molecular Formula: $C_{56}H_{87}NO_{16}$ **M.W.:** 1030.30 daltons

Mode of Action: Temsirolimus [an ester of the immunosuppressive compound sirolimus, (rapamycin, Rapamune®)] blocks cell cycle progression from the G1 to the S phase by binding to the intracellular cytoplasmic protein, FK506 binding protein (FKBP)12. This complex inhibits activity of the enzyme mTOR (mammalian target of rapamycin), inhibiting translation of several key proteins that regulate progression through the G1 phase in response to growth factors. Sirolimus, temsirolimus's major metabolite, also binds to FKBP12.

How Supplied: TORISEL (temsirolimus) is supplied as a commercially labeled kit consisting

of the following:

- TORISEL (temsirolimus) injection (25 mg/mL). The TORISEL vial includes an overfill of 0.2 mL. Inert ingredients in the drug vial include dehydrated alcohol, d,l-alpha-tocopherol, propylene glycol, and anhydrous citric acid.

- DILUENT for TORISEL. The DILUENT vial includes a deliverable volume of 1.8 mL. The diluent vial contains polysorbate 80 NF, polyethylene glycol 400 NF, and absolute alcohol USP.

Preparation:

Protect from excessive room light and sunlight during preparation.

Follow this two step dilution process (TORISEL should only be diluted with the supplied diluent):

Step 1
Inject 1.8 mL of DILUENT for temsirolimus into the vial of temsirolimusconcentrate for injection (25 mg/mL). A total volume of 3 mL (10mg/mL) will be obtained. Mix well by gentle inversion of the vial. DO NOT SHAKE. Allow sufficient time for air bubbles to subside. The solution should be clear to slightly turbid, colorless to light-yellow in color and free from visual particulates.

Step 2
Withdraw the required amount of temsirolimus from the 10 mg/mL concentrate/diluent mixture prepared in Step 1. For doses less than 10mg, filter the concentrate/diluents mixture using a syringe filter unit before measuring required volume. Further dilute with 0.9% sodium chloride injection in glass or polyolefin containers to a final concentration between 0.04 mg/mL and 1mg/mL. Mix by inversion of the bag and avoid excessive shaking. Inspect for visual particulates and discoloration prior to administration.

Storage: Refrigerate intact temsirolimus kit at 2º-8ºC and protect from light.

Stability: The 10 mg/mL drug solution/diluent mixture is stable for 24 hours at room temperature.

Administer within 6 hours of the final dilution in 0.9% NaCl. Store at room temperature (20º-25ºC) and protect from light.

Route of Administration: Intravenous with an appropriate in-line filter (i.e. 0.2 to 5 micron) for all temsirolimus doses equal to or greater than 10 mg. To avoid drug loss, prepare doses less than 10mg by filtering the concentrate/diluents mixture as noted previously between steps 1 and 2 using a syringe filter unit.

Incompatibilities: Avoid contact of the diluted product with polyvinyl chloride (PVC) equipment or devices that are plasticized with di- (2-ethylhexyl)pthalate (DEHP) to prevent DEHP leaching. Store diluted temsirolimus solutions in bottles (glass) or plastic bags (polyolefin or polypropylene).

Temsirolimus is compatible with most infusion sets that are acceptable with paclitaxel.

Infusion sets which have been qualified for use with temsirolimus include the following:

- •Baxter vented paclitaxel set
- •Baxter unvented paclitaxel set
- •Abbott #11947 tubing set
- •Alaris #72953 tubing set

Other non-PVC tubings can be used with the following in-line filters:

- •IV 6200 Disposable I.V. Filter 0.2 micron by EPS®, Inc
- •IV 6120 Disposable I.V. Filter 1.2 micron by EPS®, Inc
- •LV 5000 Large Volume 5 micron Conical Filter by B.Braun
- •Baxter Paclitaxel IV 0.2 micron filter set (2C7555)
- •Codan 5 micron monofilter
- •Alaris extension filter set #20350E
- *Other polyethersulfone filters may be used.*

Potential Drug Interactions:
Temsirolimus is a CYP3A4 substrate. Avoid concomitant treatment of temsirolimus with potent CYP3A4 inhibitors and agents that have CYP3A4 induction potential.

The combination of temsirolimus and sunitinib resulted in dose limiting toxicity at low doses of both agents. Avoid concomitant sunitinib during temsirolimus treatment.

Temsirolimus and warfarin may interact to increase INR. Monitor warfarin patient's PT/INR after starting and stopping temsirolimus.

The combination of temsirolimus and ACE inhibitors resulted in angioedema-type reactions (including delayed reactions occurring up to 2 months after initiation of therapy).

Patient Care Implications: For hypersensitivity prophylaxis, give diphenhydramine 25-50 mg I.V. (or comparable antihistamine) approximately 30 minutes before starting temsirolimus infusion. Infuse over 30 minutes.

If a patient develops a hypersensitivity reaction despite diphenhydramine pretreatment, stop the infusion and wait 30 to 60 minutes (depending upon the reaction severity). At the physician's discretion, it may be possible to resume treatment by administering an H2 blocker approximately 30 minutes before restarting the infusion. The manufacturer recommends famotidine 20 mg IV, rather than cimetidine, because it lacks reported drug interactions. If famotidine is unavailable, administer ranitidine 50 mg IV. Re-attempt infusion at a slower rate, possibly over one hour.

Vaccinations: Avoid the use of live vaccines during temsirolimus treatment.

Agent Accountability and Ordering
NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

8.2-Lenalidomide (CC-5013, NSC # 703813)

Black Box warning

NOTE:
Before lenalidomide is dispensed, patients must 1) have a negative pregnancy test (if applicable) and 2) be counseled by a trained counselor. Pharmacists may be trained counselors (see Lenalidomide Counselor Program Site Counselor Identification Form in the protocol). The counseling requirements for investigational-use lenalidomide are separate from the RevAssist program. Only a 28-day supply may be dispensed to a patient at one time.

Lenalidomide (α-[3-aminophthalimido] glucaride, Revlimid™ "(formerly known as Revimid™, CC-5013) (NSC # 703813)

Chemical Name: 3-(4'-amino-1,3-dihydro-1-oxo-2*H*-isoindol-2-yl)-2,6-piperidinedione

Other Names: CC-5013, Revlimid™, CDC-501

Classification: Immunomodulatory Agent

CAS Registry Number: 191732-72-6

Molecular Formula: $C_{13}H_{13}N_3O_3$ **M.W.:** 259.25

Mode of Action: Lenalidomide, a thalidomide analog, is an immunomodulatory agent with a spectrum of activity that is still under investigation. Some of its effects include inhibition of inflammation, inhibition of angiogenesis, inhibition of hematopoetic tumor cell proliferation, modulation of stem cell differentiation and upregulating responses of T cells and NK cells.

How Supplied: Celgene supplies and CTEP, NCI, DCTD distributes lenalidomide 2.5 mg (size 4), 5 mg (size 2) and 25 mg (size 0) hard gelatin capsules in tamper-evident, child-resistant, opaque, high density polyethylene (HDPE) bottles with HDPE caps Bottles contain 100 capsules per container. The capsules also contain anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

Storage: Store capsules at room temperature (25°C). Excursions are permitted (to 15-30°C).

Stability: Refer to the package labeling for expiration date. Lenalidomide stability is adequate for at least 28 days after transferring to a pharmacy vial.

Route of Administration: Take lenalidomide by mouth with or without food. Do not crush, chew or open capsules.

Dispensing: Only a 28-day supply may be dispensed at one time. Sites may not mail lenalidomide to patients.

Patient Care Implications and Counseling

Risks Associated with Pregnancy

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.

Definition of female of childbearing potential (FCBP)

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

Before starting study drug:

Female Subjects:

- FCBP must have two negative pregnancy tests (minimum sensitivity of 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10-14 days prior to the start of study drug and the second pregnancy test

must be performed within 24 hours prior to the start of study drug. The subject may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative.

Male Subjects:

- Must agree to use a latex condom during sexual contact with females of childbearing potential while participating in the study and for at least 28 days following discontinuation from the study even if he has undergone a successful vasectomy.

All Subjects:

- Only enough lenalidomide for one cycle of therapy may be dispensed with each cycle of therapy.

- If pregnancy or a positive pregnancy test does occur in a study subject or the partner of a male study subject during study participation, lenalidomide must be immediately discontinued.

Counseling

- In investigational studies where lenalidomide is supplied by the NCI, patients will be counseled by a qualified healthcare professional (including but not limited to, nurses, pharmacists and physicians). Two healthcare professionals at each site will be trained by Celgene in requirements specific to counseling of subjects (investigators cannot counsel patients as part of this requirement). Refer to specific protocol sections for more information about training requirements.
- Once trained, these healthcare staff will counsel subjects prior to medication being dispensed to ensure that the subject has complied with all requirements including use of birth control and pregnancy testing (FCBP) and that the subject understands the risks associated with lenalidomide. This step will be documented with a completed Lenalidomide Education and Counseling Guidance Document (Appendix J) and no drug will be dispensed until this step occurs. Counseling includes verification with the female patient that required pregnancy testing was performed and results were negative. A Lenalidomide Information Sheet (Appendix K) will be supplied with each medication dispense.
- If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up. Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

TOXICITY

The most common toxicity reported with lenalidomide to date is myelosuppression. In a phase I dose-finding trial, grade 3 neutropenia was seen in 60% and grade 4 in 15% of 25 patients. Grade 3 thrombocytopenia occurred in 20%. Myelosuppression frequently occurred after the first 28 days of single daily dose treatment. It has been suggested that myelosuppression may not be completely reversible in heavily pretreated patients. No other grade 3 or 4 toxicities were noted

in this trial. Mild (grade 1) lightheadedness, fatigue, rash, and leg cramps were reported in as many as 40% of patients. Abnormal kidney function and thyroid function tests have been noted. In contrast to thalidomide, lenalidomide is thought not to cause significant somnolence, constipation, or neuropathy. Rarely, tumor lysis syndrome (TLS) has been seen. In trials with lenalidomide, in a small number of patients, cardiac arrhythmias have been described. Preliminary data also indicate that anemia may occur, in addition to thrombocytopenia and neutropenia, and may be severe. In addition, a small increase in the risk of arterial thrombosis (e.g., myocardial infarction, CNS thromboembolic events) has been reported. Lenalidomide is a derivative of thalidomide, however, studies in animal models have not as yet demonstrated that lenalidomide is a teratogen.

Recent data indicate that like thalidomide, lenalidomide may be associated with an increased risk of venous thrombosis and pulmonary embolism. It appears that this risk is increased when lenalidomide is used concurrently with dexamethasone or epoetin. Prophylactic aspirin or low molecular weight heparin are to be given for patients with a high risk of developing DVT/PE or arterial thromboses unless contraindicated. High risk will be defined as a history of DVT/PE, significant family history, performance status ≥ 2, smoking history, use of oral contraceptives, and concurrent use of epoetin. Patients with diabetes mellitus or coronary artery disease are considered to be at high risk for arterial thromboembolic events.

Agent Ordering

NCI-supplied agents may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that the agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Note that mailed and faxed Clinical Drug Requests (CDRs) are no longer accepted. Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account https://eapps-ctep.nci.nih.gov/iam/ and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

Agent Accountability

Agent Inventory Records – The investigator, or a responsible party designated by the

investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the CTEP home page at http://ctep.cancer.gov for the Procedures for Drug Accountability and Storage and to obtain a copy of the DARF and Clinical Drug Request form.).

8.3-Commercial Agent(s)

N/A

9.0-BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1-Biomarker Studies

N/A

9.2-Laboratory Correlative Studies

A critical component of this trial is the collection and analysis of primary tumor and surrogate tissue patient samples. Our prior experience with these agents suggests a heterogeneity of response that may be explained by biologic features. The overarching hypothesis is that baseline biologic features of these pathways influence response rate and progression-free survival, and that genetic, epigenetic and pharmacodynamic changes in specific drug targets correlate with outcome in patients treated with temsirolimus plus lenalidomide. Specifically, we propose to evaluate the mTOR pathway, angiogenic processes, and immune status in patients treated in this phase I/II clinical trial of temsirolimus plus lenalidomide. A summary of sample collection is in the table below. The pre-treatment/diagnostic tissue block collection is required unless there is insufficient material; all other correlative studies are optional.

Sample type	**Sample Collection Time Points**					
	Prior to initiation of therapy (Baseline)	**Cycle 1 Day 1**		**Cycle 1 Day 15**	**Cycle 2 Day 1**	**Day 1 of all subsequent cycles**
		Prior to infusion (Hour 0)	**After infusion (Hour 4)**			
Tissue block for TMA	**X***					
Plasma for cytokine analysis (red and green tops)		**X**	**X**	**X**	**X**	**X**
Peripheral blood for flow cytometry and lymphocyte subsets (purple top)		**X**		**X**	**X**	**X**
Peripheral blood for methylation, DNA		**X**				

analysis (purple top)

* Consenting patients may also opt for a second tumor biopsy just prior to Cycle 2 Day 1.

Evaluation of mTOR pathway activation in pre-treatment tumor tissue and target inhibition in peripheral blood.

Background: The heterogeneity of clinical response to single agent temsirolimus suggests biologic features that are potentially predictive of outcome. Identification of these biologic features and correlation with outcome will aid future applications of temsirolimus plus lenalidomide on specific patient populations with a higher likelihood of response. Response to temsirolimus plus lenalidomide therapy should correlate with baseline activation status of mTOR pathway, i.e. PTEN, pAkt, p70 S6K/S6K1, 4E-BP1, pmTOR and rpS6 as assessed by immunohistochemistry (IHC) in tissue microarray (TMA) of pre-treatment paraffin embedded tumor specimens.

Methods: mTOR pathway analysis will be performed on primary tissue via a TMA of pre-treatment lymphoma tissue. The TMA will be constructed from paraffin tissue blocks of diagnostic biopsies in all patients enrolled to study. Paraffin embedded tumor blocks will be obtained in collaboration with the department of pathology at the University of Chicago medical center. In cases where fresh biopsies are not available, archived samples will be used and noted. Tumor tissue arrays will be generated using all available samples. TMA or paraffin tissue sections (when blocks are not available for punching cores) will be analyzed for the following target proteins: PTEN/phospo-PTEN (Ser380), AKT (pan)/phospho-AKT(Ser473), mTOR (pan)/phospho- mTOR (Ser2448), p70 S6 Kinase(total)/phospho-p70 S6 Kinase (Thr389), S6 ribosomal protein (total)/phospho-S6 ribosomal protein (Ser 235/236) and phospho-S6 ribosomal protein (Ser 240/244), 4E-BP1 (total)/phospho-4E-BP1 (Th37/46), (Cell Signalling Technology). **Analysis**:.Analysis will be descriptive in nature.

Primary tumor sample vascular phenotype assessment (angiogenesis)

Background. Both mTOR inhibitors and immune modulatory drugs have anti-angiogenic activity. Angiogenic cytokine mediators such as VEGF and HIF1□ are downstream of the mTOR pathway. Inhibition of mTOR, then, results in the downregulation of angiogenic cytokines. Immune modulatory drugs such as lenalidomide impact tumor microenvironments as well as angiogenesis. Therefore, combination therapy with these novel anti-lymphoma agents are expected to have potent anti-angiogenic activity. In order to understand the potential anti-vascular activity of these agents, a detailed analysis of the vascular structures of primary tumor samples will be performed.

Methods: 1. Tissue microarray of primary tumor samples. Paraffin embedded tumor blocks will be obtained in collaboration with the department of pathology at the University of Chicago medical center. In cases where fresh biopsies are not available, archived samples will be used and noted. Tumor tissue arrays will be generated using all available samples. Microvessel density will be analyzed by staining samples with an anti-CD34 antibody. Hypervascular

interfollicular areas and hypovascular follicular areas will be analyzed separately. Anti-podoplannin antibodies will be used to assess lymphatic vascular density. An anti-CD68 antibody will be used to assess for macrophage infiltration. Antibody staining will be visualized with a secondary detection system. Staining intensity will be quantitated by blinded pathological assessment as well as digital image analysis using an Acid Chromavision system.

2. Plasma and serum samples for assessment of circulating levels of pro-angiogenic cytokines.

Peripheral blood samples will be drawn from patients as per the table above. Samples will be analyzed by ELISA. Please see section 7.5 for sampling handling detais. Commercial ELISA assays will be used and supplied protocols followed. The following ELISA assays from R&D Systems will be used: anti-VEGF, anti-CXCL12/SDF-1, anti-PDGF-beta, and anti-bFGF. Samples will be run in duplicate. Cytokine concentration data will be correlated with pre-treatment disease state and vascular density, and will in addition be correlated with response to therapy during and after completion of therapy.

3. Flow cytometry to assess the effect of therapy on circulating angiogenic cells

Peripheral blood samples will be drawn from patients as per the table above. One purple top tube (EDTA) will be drawn and transferred on wet ice to Dr. Cohen's laboratory for processing. Samples will be stained with antibody cocktails and analyzed by flow cytometry as previously described.[65] except with the following modifications. Blood will be diluted 1:1 with PBS. Diluted blood will be layered on top of 5mls ficoll (Amersham Pharmacia Biotech). Specimens will be spun at 350g for 20 minutes at room temperature. The buffy coat layer containing mononuclear cells will be collected and washed two times with PBS. Mononuclear cells will then be frozen in 90% fetal calf serum/10% DMSO and stored in liquid nitrogen. For flow cytometric analysis, cells will be thawed, washed, and resuspended in 5mLs of PBS/0.5%BSA/1mM EDTA. 500ul aliquots will be delivered to flow cytometry tubes. Samples will undergo FcR blocking with anti-CD16/32 (Fc block, Pharmingen) for 10 minutes at room temperature. Samples will then be stained with the following antibodies: CD31-FITC/CD133-PE/CD45-PerCP/CD34-APC or CD31-FITC/KDR-PE/CD45-PerCP/CD34-APC. After staining samples will be fixed in 2% paraformaldehyde. Stained samples will be analyzed by flow cytometry using a FacsCanto (BD) and data analyzed using FlowJo software (Treestar). Circulating endothelial cell phenotypes will be defined as CD31+bright/CD34+dim/CD45-. Circulating progenitor cells will be defined as CD34+bright/CD31+dim/CD45+dim. Circulating endothelial progenitor cells will be defined as CD34+/KDR+. Circulating cell population data will be correlated with pre-treatment disease state and vascular density, and will in addition be correlated with response to therapy during and after completion of therapy.

Evaluation of immune components of the lymphoma microenvironment.

Background. Microenvironmental immune components in pre-tumor tissue biopsies and changes in these populations in peripheral blood may correlate with response to combination therapy. It is expected that patients with increased macrophage infiltration and decreased T-cell infiltration will respond best to microenvironmental targeted therapy.

Methods: IHC will be performed on pre-treatment (and post-treatment when available) samples using a panel of antibodies. T-cell subsets and Tregs will be analyzed using CD3, CD4, CD8, CD25, and FoxP3. Infiltrating macrophages will be marked with CD68 while follicular dendritic

cells will be marked with CD21. NK subpopulations will be marked with CD16, CD56, and CD57. Given the expected paucity of post-treatment tissue biopsies, peripheral blood samples will be collected as above to assess changes in these populations over time.

Analysis: Differences in pre- and post-treatment levels, as well as comparisons between tissue and blood samples, will be compared using a paired t-test. Changes in levels of responders versus non-responders will be analyzed using a non-parametric Wilcoxon rank-sum test.

Evaluation of gene expression profile and methylation patterns in DLBCL and FL patients (groups A and B, respectively)

Background: differences in gene expression profiles (GEP) may help predict resistance to agents that inhibit the Mammalian Target of Rapamycin (mTOR), and may help to identify combinations of drugs capable of overcoming this resistance[66,67] In addition, there are profound changes in distribution of DNA methylation across the genome in NHLs, including DLBCL[68] and FL[69,70]. The genes affected by changes in methylation involve critical intracellular processes like transcription, cell cycle and cell survival. Integrated analysis of genome-wide methylation and expression can yield biological insights and identify patient subgroups that are not apparent from either GEP or methylation analyses alone. We therefore hypothesize that integrated high-resolution analysis of DNA methylation and gene expression can identify key epigenomic determinants of clinical outcomes in patients with relapsed and refractory NHL. If this is successful in developing a predictive model for response, this information will be applied to pre-treatment tumor specimens for patients enrolled in group C.

Methods: Pre-treatment FFPE tumor biopsies will be used for RNA extraction and for DNA analysis. This will allow analysis of miRNA promoter regions and differentially methylated sites identified in tumor versus normal tissue.

Analysis: To determine association between gene expression or methylation and clinical response, patients will be divided based on response to combination mTORi and IMID therapy: responders (those with partial response [PR] or complete response [CR]), versus non-responders (those with stable disease [SD] or progressive disease [PD]). The differences will be assessed using a conventional T-test, followed by a modified T-test employed using the eBayes function in limma (R version 9.2).[71,72]

Handling of Specimens
All tumor specimens must be accompanied by a specimen transmission (Appendix H) form that includes:

- Patient name
- Hospital record number
- NCI protocol number
- Sample type (aspirate, surgical specimen, core biopsy, etc)
- Date when biopsy was obtained; site of tumor tissue (e.g. primary tumor, metastatic site)

Shipping of Specimens (see also Appendix H)

The shipment of all human tissue samples (for blood samples see 7.6) must comply with appropriate regulations as specified by the carrier. Samples should be frozen and sent on dry ice except for one lavender top tube which will be sent on wet ice. At a minimum, all samples must be packaged within two containers with absorbent material between containers to control any spill or leakage. The outer container must be puncture resistant (e.g., cardboard mail tube, corrugated cardboard box). A biohazard sticker must be affixed to both the inner and outer containers.

All tumor blocks must be accompanied by a pathology report and a sample transmission form (appendix H) and shipped the following address:

Jose Zavala
University of Chicago
5841 S. Maryland Ave.
M/C 2115
Chicago, IL 60637
Phone: 773-834-5358
Fa x : 773-702-4889
jzavala@bsd.uchicago.edu

***Prior to shipment** (serum, plasma, tissue and purple tops/DNA) please email Sara Chung to notify that the samples have been sent, and email the FedEX bill number to him.

Blood Draws (Appendix F): Serum and Plasma and DNA Preparation:

All patients consenting to phlebotomy for correlative studies will have samples as described by the chart above (Section 9.0) and in Appendices F, G, and H. Samples will be drawn by an experienced phlebotomist: One 6ml red top (serum) tube processed into two 1ml aliquots, one 6ml green top (plasma) tube processed into two 1ml aliquots, and TWO 10ml purple tops (whole blood). Serum (red tops) will be used to assess for cytokine levels by ELISA assay.

Red top (Serum): The specimen will be allowed to clot for one hour after collection time in the refrigerator. The collection time should be written on the tube or accompanying paperwork. It will then be placed, along with a balancing falcon tube (15 ml) containing water, in holders inside the centrifuge. They will be spun for 10 minutes at 3000 rpm. The red top tube will be removed. Using a plastic pipette, 1 ml of supernatant (serum) will be siphoned individually into clear, plastic **1.8 ml vials, and labeled as serum, patient ID number, Cycle number/Day and date in indelible ink**.

Green top (Plasma): The specimen will be allowed to clot for one hour after collection time in the refrigerator. The collection time should be written on the tube or accompanying paperwork. It will then be placed, along with a balancing falcon tube (15 ml) containing water, in holders inside the centrifuge. They will be spun for 10 minutes at 3000 rpm. The green top tube will be removed. Using a plastic pipette, 1 ml of supernatant (plasma) will be siphoned individually into clear, plastic **1.8 ml vials and labeled as plasma, patient ID number, Cycle number/Day and date in indelible ink**.

Purple Tops (Whole Blood): Two purple tops will be collected. One purple top tube will be aliquoted into 4 separate 1.8mL plastic vials and labeled as "Whole Blood, Patient ID number, cycle number/Day, date" in indelible ink and frozen at -80C after appropriate labeling. These tubes should be transferred to Dr. Cohen's lab on dry ice.

The second purple top tube will be collected and transferred to Dr. Cohen's lab on wet ice. This second tube should not be frozen on dry ice as doing so will lyse both red and white blood cells. In Dr. Cohen's lab, blood will be diluted 1:1 with PBS. Diluted blood will be layered on top of 5mls ficoll (Amersham Pharmacia Biotech). Specimens will be spun at 350g for 20 minutes at room temperature. The buffy coat layer containing mononuclear cells will be collected and washed two times with PBS. Mononuclear cells will then be frozen in 90% fetal calf serum/10% DMSO and stored in liquid nitrogen.

Storage/Batching: The blood samples will be stored and batched over time throughout the patient's treatment as in Appendices G and I at -80C. When samples are drawn, the appendix G will be filled out and faxed to study coordinator listed on face sheet of protocol for EACH BLOOD DRAW at ***773-702-4889*, to document that each blood draw is collected.**

Shipping: They will be batch shipped by overnight carrier on dry ice to the address noted in Appendices G and H. (only on Mondays, Tuesdays, or Wednesdays – to ensure receipt before the weekend at the University of Chicago by study coordinator). Each vial must be labeled with patient ID number, Cycle number/Day, sample type (serum or plasma) and date in indelible ink. Another 'Master' Appendix G form (separate from the ones faxed in real-time during therapy at each time point) will be included and filled out to indicate what samples are included in the shipment.

Handling of Specimens

All blood specimens must be accompanied by a specimen transmission (Appendix G) form that includes:

- Patient name
- Hospital record number
- NCI protocol number
- Date/time of blood draw
- Indication of the timepoint of the draw (ie C2D1)

Shipping of Blood Samples (see also Appendix I)

All blood samples must be accompanied by a sample transmission form (appendix G) and shipped to the following address:
Jose Zavala
University of Chicago
5841 S. Maryland Ave.
M/C 2115
Chicago, IL 60637

Phone: 773-834-5358
Fa x : 773-702-4889
jzavala@bsd.uchicago.edu

9.3-Special Studies

See section above.

10 STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done 4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Study	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**Wk 9**	**Wk 10**	**Wk 11**	**Wk 12**	**Off Study**
Temsirolimus		A	A	A	A	A	A	A	A	A	A	A	A	
Lenalidomide[g,j]		X				X				X				
Informed consent	X													
Demographics	X													
Medical history	X													
Concurrent meds	X	X----------											----------X	
Physical exam[h]	X	X				X				X				X
Vital signs	X	X				X				X				X
Height	X													
Weight	X	X				X				X				X
Performance status	X	X				X				X				X
CBC w/diff, plts	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EKG (as indicated)	X													
HIV[f]	X													
Adverse event evaluation		X----------											----------X	X
Tumor measurements	X	Tumor measurements are repeated after Week 8, then every 3 cycles (i.e. every 12 weeks). Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X
Radiologic evaluation	X	Tumor measurements are repeated after Week 8, then every 3 cycles (i.e. every 12 weeks). Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X
B-HCG[b,c]	X[b]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	
Bone marrow aspirate and biopsy	X[d]													
Correlative studies	X[e]													

A: Temsirolimus 25 mg on D1, D8, D15, D22 of a 28 day cycle.
B: Lenalidomide 20 daily on Days 1-21 of a 28 day cycle.
a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, triglycerides, cholesterol panel (cholesterol, HDL, LDL), magnesium on Day 1 of each cycle. For all subsequent days: CMP, LDH, Mg.
b: Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

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

d: Bone marrow aspirate and biopsy should be performed within 6 weeks of starting therapy. If positive, it must be repeated to document response as per Section 9.0.
e: See Section 7.0 for summary of correlative studies.
f: HIV testing is NOT required for study entry. However, if a patient with known HIV disease is enrolled as per Section 3.1.10, then baseline CD4 count, viral load, and record of recent anti-retroviral therapy must be documented as per Appendix D.
g: All patients must be considered for prophylaxis against thromboembolic events as per Section 4.3.2 and Appendix D.
h: Physical exam must be documented on Day 1 of each cycle at a minimum
i: The Lenalidomide Education and Counseling Guidance Document (Appendix _J_) must be completed and signed by a trained counselor at the participating site prior to each dispensing of lenalidomide treatment. A copy of this document must be maintained in the patient records. The Lenalidomide Information Sheet (Appendix _K_) will be given to each patient receiving lenalidomide treatment. The patient must read this document prior to starting lenalidomide study treatment and each time they receive a new supply of study drug.
j: Only enough lenalidomide for 21 days or one cycle of study treatment (whichever is shorter) may be provided to the patient each cycle.

11.0 MEASUREMENT OF EFFECT

Eligible patients with measurable disease will be assessed by revised lymphoma response criteria.[73] For the purposes of this study, patients should be reevaluated at week 8, then every 3 cycles (12 weeks). Confirmatory scans are recommended at least 4 weeks following initial documentation of an objective response.

11.1-Definition of Response

11.1.1-Complete Response (CR):

- Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.
- In patients with no pre-treatment PET scan, or if the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET-negative. NOTE: mTOR inhibitors are known to affect cellular metabolism and may confound the interpretation of post-treatment PET images. Patients who are considered by the treating physician to be responding but who still have a PET-avid focus should have the PET scan images submitted to the PI (Sonali Smith, MD) for review.
- The spleen and/or liver, if considered enlarged prior to therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.
- If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry, but that demonstrates a small population of clonal lymphocytes by flow cytometry, will be considered a CR until data become available demonstrating a clear difference in patient outcome.

11.1.2-Partial Response(PR):

- At least a 50% decrease in the sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: a) they should be clearly measurable in at least two perpendicular dimensions; b) if possible, they should be from disparate regions of the body; and c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
- No increase should be observed in the size of other nodes, liver, or spleen.
- Splenic and hepatic nodules must regress by ≥ 50% in their SPD, or, for single nodules, in the greatest transverse diameter.
- With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
- Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement, will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.
- No new sites of disease should be observed.
- For patients with no pre-treatment PET scan, or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site. NOTE: mTOR inhibitors are known to affect cellular metabolism and may confound the interpretation of post-treatment PET images. Patients who are considered by the treating physician to be responding but who still have a PET-avid focus should have the PET scan images submitted to the PI (Sonali Smith, MD) for review.

11.1.3-Stable Disease (SD):

- Patient fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see below). The PET should be positive at prior sites of disease, with no new areas of involvement on the post treatment CT or PET.

11.1.4-Progression (PD) or Relapse:

- Lymph nodes should be considered abnormal if the long axis is > 1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is > 1.0. Lymph nodes ≤ 1.0 cm by ≤ 1.0 cm will not be considered as abnormal for relapse or progressive disease.
- Appearance of any new lesion > 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

- At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of < 1.0 cm must increase by ≥ 50% and to a size of 1.5 x 1.5 cm, or > 1.5 cm in the long axis.
- At least a 50% increase in the longest diameter of any single previously identified node > 1.0 cm in its short axis.
- Lesions should be PET-positive if a typical FDG-avid lymphoma or the lesion was PET-positive prior to therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

11.2-Guidelines for Evaluation of Measureable Disease

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

Clinical Lesions will only be considered measurable when they are superficial (e.g. skin nodules, palpable lymph nodes).
Chest X-ray: Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen, and pelvis. Head & neck and extremities usually require specific protocols.
Ultrasound (US) should not be used to measure tumor lesions that are clinically not easily accessible when the primary endpoint of the study is objective response evaluation. It is a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
Duration of Response
Duration of response is defined as the time interval between when criteria for response (PR or CR) are first met until the first documentation of relapse or progressive disease.
Definition of Survival
Progression-free survival (PFS) is defined as the time from study entry until disease progression or death from any cause. Overall survival (OS) is defined as the time from study entry until death from any cause.
Response Criteria for Waldenstrom's Macroglobulinemia
Responses for WM will be categorized using the Consensus recommendations for response. Progressive disease will be measured as a confirmed 25% increase in the monoclonal protein from baseline [69].

11.3-Other Response Parameters

N/A

12.0-DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1-Data Reporting

12.1.1-Method

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis, either by FTP burst of data or via the CDS web application. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

12.1.2-Responsibility for Data Submission

N/A

12.2-CTEP Multicenter Guidelines

Suggested text is provided below which can be modified as necessary. If this study is being performed within a single institution, this section should be marked "N/A" and the text below deleted.

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix B.

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

12.3-Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI

under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group

studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13.0-STATISTICAL CONSIDERATIONS

13.1-Study Design/Endpoints

The primary objective of the phase I portion of the trial is to determine safety and tolerability of the combination of temsirolimus and lenalidomide in relapsed and refractory Hodgkin and non-Hodgkin lymphoma patients. The phase I study will utilize a traditional "3+3" design. Groups of 3 subjects will be treated per cohort beginning at dose level 1. If 0 of 3 patients experience DLT, the dose will be escalated for the next cohort. The definition of DLT is outlined in Section 4.2. If 1 of 3 patients experiences a DLT, 3 more patients will be treated at the same dose level, and if no further DLTs are observed the dose will be escalated. If 2 or more DLTs occur at any dose level the MTD will have been exceeded. A minimum of 6 patients will be treated at the MTD (recommended phase II dose) before proceeding to the second phase of the study. There will be no intra-patient dose escalation. Patients in the phase I portion of trial who were treated at the eventual phase II dose will be rolled into the phase II efficacy analysis.
The primary objective of the phase II portion will be to evaluate the complete and overall response rate, and the secondary endpoints will be progression free survival and overall survival. Patients will be accrued in a two-stage, phase II "mini-max" design. This design, which has larger first-stage sample sizes than the "optimal" designs, is justified due to the high anticipated activity of the treatment combination. Separate analyses will be performed for each lymphoma

subtype, with alpha=0.1 and power=90%. For FL subtypes: we will test the hypothesis that the response rate is <= 50% vs. the alternative that it is >=70%. 11 or fewer responses with the drug combination in the first 23 patients per subtype will result in termination of the trial due to lack of activity. Otherwise, an additional 16 patients will be enrolled per subtype. If there are 24 or more responders (≥61%) the treatment will be considered worthy of further study. Response criteria will be per updated international definitions.[67] For DLBCL and NOS lymphoma patients: we will test the hypothesis that the response rate is <= 30% vs. the alternative that it is >=50%. Here 7 or fewer responses in the first 28 patients will result in early termination. Otherwise, an additional 11 patients will be enrolled and if there are 16 or more responders (≥ 41%) the treatment will be considered sufficiently active to warrant further study. For the two sets of designs, the probability of early stopping under the null hypothesis is 0.50 and 0.36, respectively.

13.2-Sample Size/Accrual Rate

The proposed sample size is 9-18 patients for the phase I dose-finding portion of the study. The proposed sample size for the phase II portion of the study ("mini-max" two-stage design) is up to 121 patients. At an estimated 4 patients/month, the study will take approximately 34 months for accrual.

13.3-Stratification Factors

Patients will by stratified into histologically-based cohorts for the phase II portion of the study as described in Section 11.1. Patients with DLBCL will be further stratified based on immunophenotype (germinal center vs. non-germinal center), but comparison of these two subgroups will be descriptive in nature and will not change the total accrual goal for this subgroup.

13.4-Analysis of Secondary Endpoints

Kaplan-Meier curves will be generated for progression-free (PFS) and overall survival (OS) stratified by histology; median PFS and OS times will be determined and 90% confidence intervals derived as described in Brookmeyer and Crowley[74]. Correlative data will be analyzed using paired t and nonparametric tests as described above. Baseline levels and early changes will also be correlated with PFS using the Cox[75] regression model.

13.5-Reporting and Exclusions

13.5.1-Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with Temsirolimus and Lenalidomide.

13.5.2-Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

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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.

APPENDIX B CTEP MULTICENTER GUIDELINES

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  - Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
  - Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

CTEP-assigned Protocol #_____8309____

APPENDIX C PATIENT'S MEDICATION DIARY- LENALIDOMIDE

Today's date _____ **Agent** ___**Lenalidomide**

Patient Name_____ (*initials acceptable)* **Patient Study ID** _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 4 week-period while you take **Lenalidomide**.
2. You will take your dose of **Lenalidomide** each day in the morning. You will take 5 mg or 25 mg capsules. You may take the capsules with or without food as you wish.
3. Record the date, the number of capsules of each size you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please return this form to your physician when you go for your next appointment.

Day	Date	Time of daily dose	# of capsules taken		Comments
			5 mg	25 mg	
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
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17					
18					
19					
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21					
22					
23					
24					
25					
26					
27					
28					

Physician's Office will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study_____
3. Patient's planned total daily dose_____
4. Total number of capsules taken this month (each size)_____
5. Physician/Nurse/Data Manager's Signature _____

Patient's signature

_____

APPENDIX D BASELINE LYMPHOMA DATA FORM

Study: NCI# 8309 Phase I/II Trial of Temsirolimus plus Lenalidomide in relapsed lymphomas
Local IRB#:

Patient ID#: Study drug start date:_____

_____

Patient initials:

_____

Assignment of germinal center (GCB) vs. non-germinal center (NGCB) phenotype for DLBCL pts (Group A)--CIRCLE ONE

	GC	NGCB
MARKER	**POS/NEG**	**not done**
CD10		
Bcl6		
MUM1		
Other_____		

Inclusion of patients with HIV-associated lymphoma

	Result
HIV (yes/no)	
CD4 count at study entry	
viral load at study entry	
recent anti-retroviral use (<14d)	

Prophylaxis for thromboembolic events
****Patients with any one of the following risk factors require prophylaxis against thromboembolic events****

Risk factor	yes/no
FH of DVT/PE	
Personal history of DVT/PE	
Performance status >2	
Smoking history	
Oral contraceptive use	
Concurrent epoietin use	
Diabetes mellitus	
Coronary artery disease	
Chronic steroid use	

Prophylaxis initiated? y/n
Type of prophylaxis_____
_____
If not, why?
_____
_____

Investigator signature: _____

Date: _____

APPENDIX E: LYMPHOMA RESPONSE ASSESSMENT FORM

Study: NCI# 8309 Phase I/II Trial of Temsirolimus plus Lenalidomide in relapsed lymphomas

Local IRB#:
Patient ID#: _____
Patient initials: _____

Study drug start date:_____
Study drug end date: _____
cycles delivered: _____

Response to most recent regimen prior to study entry (circle one)

CR/CRu PR SD PD

List all measurable and assessable sites to be used for response:

Measurable sites (cm)	Date of evaluation:					
Site for response	Type of Scan	Measurement	Measurement	Measurement	Measurement	Measurement
1.						
2.						
3.						
4.						
5.						
			% inc/dec	% inc/dec	% inc/dec	% inc/dec
Total Tumor Size						

Assessable sites (e.g. liver, spleen) and Response status (present, no change, incr., decr., absent, or indeterminate)

Site for response	Date of evaluation: Means of evaluation					
		Assessment	Assessment	Assessment	Assessment	Assessment
1.						
2.						
3.						
Total Tumor Size						
Bone marrow biopsy	Date of evaluation:					
	Result (pos, neg, indet)					
PET scan	Date of evaluation:					
	Result (pos, neg, incr., decr.)					
Overall Response Status (CR/CRu, PR, SD, PD)						

Investigator signature: _____

Date: _____

APPENDIX F
The University of Chicago
Blood Sample Collection Form

Protocol
8309

Clinician/Research Nurse: Please Fill Out

Blood Samples

Patient Name: _____ **Cycle#** **Day#_____**

Patient Protocol ID #:_____ **Date Blood Obtained: _____**

Date of Birth: _____ **Attending Physician: _____**

Institution:* _____** ***Cross-over samples (COS)? (circle): yes / no

Date consent was signed: _____ ***if YES Cross-over samples: label COS-CXDX on tubes***

Day started on clinical protocol:_____ **Diagnosis:_____**

Visit	Collection Tubes to use:	Date Drawn	Processing	Please check all sent samples
C1 Day 1	**One 6ml Red (serum) Top pretreatment and 4h after infusion**		Two 1 ml aliquots	
	One 6ml Green (plasma) Top pretreatment and 4h after infusion		Two 1 ml aliquots	
	One 10ml Purple (whole blood) Top		~~No processing purple tops~~	
	One 10mL Purple (whole blood) top		Four 1.8mL aliquots	
			No processing for second purple top	
C1 Day 15	**One 6ml Red (serum) Top**		Two 1 ml aliquots	
	One 6ml Green (plasma) Top		Two 1 ml aliquots	
	One 10ml Purple (whole blood) Tops		No processing purple tops	
C2D1	**One 6ml Red (serum) Top**		Two 1 ml aliquots	
	One 6ml Green (plasma) Top		Two 1 ml aliquots	
	One 10ml Purple (whole blood) Tops		No processing purple tops	
C3D1	**One 6ml Red (serum) Top**		Two 1 ml aliquots	
	One 6ml Green (plasma) Top		Two 1 ml aliquots	
	One 10ml Purple (whole blood) Tops		No processing purple tops	
C4D1	**One 6ml Red (serum) Top**		Two 1 ml aliquots	
	One 6ml Green (plasma) Top		Two 1 ml aliquots	
	One 10ml Purple (whole blood) Tops		No processing purple tops	
C5D1	**One 6ml Red (serum) Top**		Two 1 ml aliquots	
	One 6ml Green (plasma) Top		Two 1 ml aliquots	
	One 10ml Purple (whole blood) Tops		No processing purple tops	
C6D1	**One 6ml Red (serum) Top**		Two 1 ml aliquots	
	One 6ml Green (plasma) Top		Two 1 ml aliquots	
	One 10ml Purple (whole blood) Tops		No processing purple tops	
Progression	**One 6ml Red (serum) Top**		Two 1 ml aliquots	
	One 6ml Green (plasma) Top		Two 1 ml aliquots	
	One 10ml Purple (whole blood) Tops		No processing purple tops	

APPENDIX G

The University of Chicago
Archived Tissue Acquisition Form

Protocol #8309

Clinician/Research Nurse: Please Fill Out

Lymphoma Tissue (blocks/unstained slides)

Patient Name: _____

Patient Protocol ID #:_____ **Date Tissue Obtained: _____**

Date of Birth: _____ **Attending Physician: _____**

Origin of Tissue: **_____** ***Institution:*** **_____**

Date consent was signed: _____ **Diagnosis:_____**

Day started on clinical protocol:_____

Researcher: Please Fill Out
Date Samples received: _____ **Data entered into Database: Yes**

No

Name of Data Manager informed: _____ Date Informed:_____

Approximate size of tissue: _____

Notes:

APPENDIX H
SHIPPING INSTRUCTIONS

All shipments must contain a completed Sample Identification form and Tracking form.

******Each site will be required to pay for shipping using their per patient amounts, and really should only batch ship once per patient.**

*** Purple , Red, and Green top tubes should be collected and processed as per Section 7 (see also Appendix F). Paraffin sections can be sent at room temperature**. The blood samples should be labeled with the patient protocol ID#, Cycle and Day identifiers and stored throughout treatment at -80C at your institution, and then shipped to the below address:

Jose Zavala
University of Chicago
5841 S. Maryland Ave.
MC2115
Chicago, IL 60637
Phone: 773-834-5358
Fa x : 773-702-4889
jzzvala@bsd.uchicago.edu

*****Prior to shipment** (serum, plasma, tissue and purple tops/DNA) please call UC study coordinator to notify that the samples have been sent.
*** Please ship preferentially on Monday, Tuesday or Wednesday, to allow for arrival prior to weekends.

Instructions for Shipping Specimens

The Federal Aviation Administration (FAA) is an arm of the Department of Transportation (DOT). The DOT requires that anyone involved in the transport of hazardous materials (such as infectious substances, diagnostic specimens, genetically modified organisms, biological products, and dry ice) needs to comply with the Federal transportation law (49 CFR 172.700). These regulations are applicable to anyone who handles, offers for transport, and transports dangerous goods or causes dangerous goods to be transported. Please comply with federal regulations 49 CFR and IATA 1.5.

Helpful Hints for Shipping

Dry Ice: Packing Instruction

Processed plasma, serum, and whole blood aliquots

1. *Please fill cooler at least half full with dry ice and cover specimen bag with dry ice to prevent thawing*.
2. Enclose embedded tissue or serum/plasma vial in a sealed biohazard bag.
3. Include an absorbent pad within primary sealed biohazard bag.
4. Place the primary bag in a secondary bag.
5. Box (cooler) must be able to release gas build-up.
6. Indicate the dry ice weight in kg on both the waybill and on the box.
7. Include the marking "Dry Ice, UN1845" on the box.

8. Place a Class 9 label on the box.

*These are only a few helpful hints to aide in shipping. Please refer to CFR 49 for exact criteria.

Unprocessed whole blood (purple top tube)

1. Enclose embedded tissue or serum/plasma vial in a sealed biohazard bag.
2. Include an absorbent pad within primary sealed biohazard bag.
3. Place the primary bag in a secondary bag.
4. Fill cooler with half full with ice in a contained bag.

Training courses and additional information about shipping requirements can be also found at:
http://www.saftpak.com/
http://hazmat.dot.gov

Whole Blood (10ml Purple Top aliquoted into four 1.8 mL plastic freezing vials)

-Please write the study number, patient initials, cycle number, and date on tubes.

*-Store at –80C**. If -80C is not available, please store at-20C.***

Whole Blood (10mL Purple Top, unprocessed)

-Please send to Dr. Cohen's lab as described above on wet ice.

Serum (Red Top Tubes: Two 1ml aliquot Tubes)

Red top (Serum): Allow the specimen to clot for one hour after collection time in the refrigerator. The collection time should be written on the tube or accompanying paperwork. Then place the tube, along with a balancing falcon tube (15 ml) containing water, in holders inside the centrifuge. Spin them for 10 minutes at 3000 rpm. Remove the red top tube. Using a plastic pipette, siphon 0.5 ml of supernatant (serum) individually into clear, plastic 1.8 ml vials.

Plasma (Green Top Tubes: Two 1ml aliquot Tubes)

Green top (Plasma): Allow the specimen to clot for one hour after collection time in the refrigerator. The collection time should be written on the tube or accompanying paperwork. Then place the tube, along with a balancing falcon tube (15 ml) containing water, in holders inside the centrifuge. Spin them for 10 minutes at 3000 rpm. Remove the green top tube. Using a plastic pipette, siphon 0.5 ml of supernatant (plasma) individually into clear, plastic 1.8 ml vials.

Tissue

Preferably, whole Tissue blocks sent to University of Chicago and processed. Blocks will be returned.

Alternatively, please process paraffin embedded tissue as follows:

*1. For IHC- Unstained formalin fixed paraffin embedded tissue sections should be cut at **4-5 micron** thickness. Cut **20** serial sections and store at room temperature.*

*2a. For DNA extraction **-10 micron** thick sections in approximately **25** curls should be placed in a sterile eppendorf tube and labeled with appropriate identifiers; do this for a total of 5 tubes.*

*2b) Alternatively to 2a, please cut **10 micron** thick sections onto slides for a total of **20** slides.*

APPENDIX I: LENALIDOMIDE PACKET (4 DOCUMENTS)

1- Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods
2- Lenalidomide Education and Counseling Guidance
3- Lenalidomide Information Sheet
4- Lenalidomide Counseling Program

1- Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Risks Associated with Pregnancy

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.

Criteria for females of childbearing potential (FCBP)

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

Counseling

For a female of childbearing potential, lenalidomide is contraindicated unless all of the following are met (i.e., all females of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol

- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

The investigator must ensure that for females of childbearing potential:

- Complies with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Acknowledge the aforementioned requirements

For a female NOT of childbearing potential, lenalidomide is contraindicated unless all of the following are met (i.e., all females NOT of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

Traces of lenalidomide have been found in semen. Male patients taking lenalidomide must meet the following conditions (i.e., all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a female of childbearing potential.

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; 3) during dose interruptions; and 4) for at least 28 days after study treatment discontinuation.

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

Highly effective methods:

- Intrauterine device (IUD)
- Hormonal (birth control pills, injections, implants)
- Tubal ligation
- Partner's vasectomy

Additional effective methods:

- Male condom
- Diaphragm
- Cervical Cap

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 females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting study drug

Female Patients:

FCBP must have two negative pregnancy tests (minimum sensitivity of 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10 to 14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The patient may not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative.

Male Patients:

Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following study drug discontinuation

Female Patients:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following study drug discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following study drug discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a study patient, study drug must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study treatment must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.

Male Patients:

- Counseling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to lenalidomide must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

Additional precautions

- Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.
- Female patients should not donate blood during treatment and for at least 28 days following discontinuation of lenalidomide.
- Male patients should not donate blood, semen or sperm during treatment or for at least 28 days following discontinuation of lenalidomide.
- Only enough study drug for 28 days or one cycle of therapy (whichever is shorter) may be dispensed with each cycle of therapy.

2- Lenalidomide Education and Counseling Guidance Document

Protocol Number: _____

Patient Name (Print): _____ DOB: _____/_____/_____ (mm/dd/yyyy)

Female: ☐

If female, check one:

FCBP (Female of childbearing potential): sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal (**amenorrhea following cancer therapy does not rule out childbearing potential**) for at least 24 consecutive months (i.e., has had menses at any time during the preceding 24 consecutive months)

- ☐ NOT FCBP

Male: ☐

To be completed prior to each dispensing of lenalidomide.

Do Not Dispense lenalidomide if:

- **The patient is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The patient states she did not use TWO reliable methods of birth control (unless practicing complete abstinence of heterosexual intercourse) [at least 28 days prior, during dose interruption, and 28 days after discontinuation of lenalidomide].**

FCBP:

1. I verified that the required pregnancy tests performed are negative.

2. I counseled FCBP regarding the following:

- Potential risks of fetal exposure to lenalidomide: If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking lenalidomide. The teratogenic potential of lenalidomide in humans cannot be ruled out. FCBP must agree not to become pregnant while taking lenalidomide.
- Using TWO reliable methods of birth control at the same time or complete abstinence from heterosexual intercourse [at least 28 days prior, during dose interruption and 28 days after discontinuation of lenalidomide].
- Continuation of TWO reliable methods of birth control or complete abstinence if therapy is interrupted.
- **That even if she has amenorrhea she must comply with advice on contraception**
- Use of one highly effective method and one additional method of birth control AT THE SAME TIME. 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
- Pregnancy tests before and during treatment, even if the patient agrees not to have reproductive heterosexual intercourse. Two pregnancy tests will be performed prior to receiving study drug, one within 10-14 days and the second within 24 hours of the start of lenalidomide.

- Frequency of pregnancy tests to be done:
    - Every week during the first 28 days of this study and a pregnancy test every 28 days during the patient's participation in this study if menstrual cycles are regular or every 14 days if cycles are irregular.
    - If the patient missed a period or has unusual menstrual bleeding.
    - When the patient is discontinued from the study and at day 28 after study drug discontinuation if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at days 14 and 28 after study drug discontinuation.

- Stop taking lenalidomide immediately in the event of becoming pregnant and to call their study doctor as soon as possible.
- NEVER share lenalidomide with anyone else.
- Do not donate blood while taking lenalidomide and for 28 days after stopping lenalidomide.
- Do not breastfeed a baby while participating in this study and for at least 28 days after study drug discontinuation.
- Do not break, chew, or open lenalidomide capsules.
- **Return unused lenalidomide to the investigator.**

3. Provide Lenalidomide Information Sheet to the patient.

FEMALE NOT OF CHILDBEARING POTENTIAL (NATURAL MENOPAUSE FOR AT LEAST 24 CONSECUTIVE MONTHS, A HYSTERECTOMY, OR BILATERAL OOPHORECTOMY):

1. I counseled the female NOT of child bearing potential regarding the following:

- Potential fetal harm (Refer to item #2 in FCBP)
- NEVER share lenalidomide with anyone else.
- Do not donate blood while taking lenalidomide and for 28 days after stopping lenalidomide.
- Do not break, chew, or open lenalidomide capsules
- **Return used lenalidomide capsules to the Investigator.**

2. Provide Lenalidomide Information Sheet to the patient.

MALE:

1. I counseled the Male patient regarding the following:

- Potential fetal harm (Refer to item #2 in FCBP).
- To engage in complete abstinence or use a condom when engaging in sexual intercourse (including those who have had a vasectomy) with a female of childbearing potential, while taking lenalidomide, during dose interruptions and for 28 days after stopping lenalidomide.

- Males should notify their study doctor when their female partner becomes pregnant and female partners of males taking lenalidomide should be advised to call their healthcare provider immediately if they get pregnant

- NEVER share lenalidomide with anyone else.

- Do not donate blood, semen or sperm while taking lenalidomide and for 28 days after stopping lenalidomide.
- Do not break, chew, or open lenalidomide capsules.
- **Return unused lenalidomide capsules to the investigator.**

2. Provide Lenalidomide Information Sheet to the patient.

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____

Maintain a copy of the Education and Counseling Guidance Document in the patient records.

3- Lenalidomide Information Sheet

FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

Please read this Lenalidomide Information Sheet before you start taking lenalidomide and each time you get a new supply, since there may be new information. This Lenalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about lenalidomide?

Lenalidomide may cause birth defects (deformed babies) or death of an unborn baby.

Lenalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Lenalidomide has not been tested in pregnant women but may also cause birth defects. Findings from a monkey study indicate that lenalidomide caused birth defects in the babies of female monkeys who received the drug during pregnancy**.**

If you are a woman who is able to become pregnant:

Do not take study drug if you are pregnant or plan to become pregnant

Either do not have sexual intercourse at all or use two reliable, separate forms of effective birth control at the same time:

- for 28 days before starting lenalidomide
- while taking lenalidomide
- during dose interruptions of lenalidomide
- for 28 days after stopping lenalidomide

You must have pregnancy testing done at the following times:

- within 10 to 14 days and again 24 hours prior to the first dose of lenalidomide
- weekly for the first 28 days
- every 28 days after the first month or every 14 days if you have irregular menstrual periods
- if you miss your period or have unusual menstrual bleeding
- 28 days after the last dose of lenalidomide (14 and 28 days after the last dose if menstrual periods are irregular)

Stop taking study drug if you become pregnant during treatment

- If you suspect you are pregnant at any time during the study, you must stop lenalidomide immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to the National Cancer Institute and the pharmaceutical collaborator, Celgene Corporation**.**

Do not breastfeed while taking study drug

The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not of childbearing potential:

In order to ensure that an unborn baby is not exposed to lenalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a man:

Lenalidomide is detected in trace quantities in human semen. The risk to the fetus in females of child bearing potential whose male partner is receiving lenalidomide is unknown at this time.

Men (including those who have had a vasectomy) must either abstain from sexual intercourse or use a condom during sexual contact with a pregnant female or a female that can become pregnant:

- While you are taking lenalidomide
- During dose interruptions of lenalidomide
- For 28 days after you stop taking lenalidomide

Men should not donate sperm or semen while taking study drug and for 28 days after stopping lenalidomide.

If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to the National Cancer Institute and the pharmaceutical collaborator, Celgene Corporation. Your partner should call their healthcare provider immediately if she gets pregnant.

Restrictions in sharing lenalidomide and donating blood:

Do not share lenalidomide with other people. It must be kept out of the reach of children and should never be given to any other person.

Do not donate blood while you take lenalidomide and for 28 days after stopping study drug.

Do not break, chew, or open study drug capsules.

You will get no more than a 28-day supply of lenalidomide at one time.

Return unused study drug capsules to your study doctor.

Additional information is provided in the informed consent form and you can ask your study doctor for more information.

4-Lenalidomide Counseling Training Request Form

Celgene Corporation	**Celgene Pregnancy Prevention & Counseling Program** **Site Counselor Identification Form** **for NCI Studies** **NCI Protocol #:** _____

- Please identify at least two (2) counselors and fax back to 888-314-2392
- Use one form per counselor.
- Identified counselors must be licensed healthcare professionals (e.g. RN, PA, RPh, PhD, LPN, CNP, or MD) and must not be the principal investigator.
- If you have any questions, please email (coop_ma@celgene.com)

General Information

Principal Investigator: _____ Institution Name: _____

Counselor Information

CTEPpersonID: _____ CTEPsiteID: _____

First Name: _____ Middle Initial:_____ Last Name: _____

License Type: (circle one) MD PhD PA CNP RN LPN RPh Other:_____

Email Address: _____

Phone: _____ Fax: _____

Institution Street Address: _____

City: _____ State/Region: _____

Zip/Post Code: _____ Country: _____

Previously approved as a Counselor? □ No □ Yes

If no, please list all the protocols #(s), corresponding CTEPsiteID(s) and institution names(s) that you *plan to provide* counseling for:

If yes, please list the protocols #(s), corresponding CTEPsiteID(s) and institution names(s) *for protocols Celgene has already associated you with*:

Protocol#:	CTEPsiteID	Institution