Protocol Title: Phase I Study of Everolimus (RAD001) in Combination with Lenalidomide in Patients with Advanced Solid Malignancies Enriched for Renal Cell Carcinoma

SPONSOR	**Emory University Winship Cancer Institute**
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Novartis Tracking #:	**CRAD001LUS141T**
DRAFT VERSION:	**July 13, 2009**
DATE FINAL:	**January 4, 2010**
AMENDMENT:	**June 10, 2014**

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Principal Investigator:	**June 10, 2014**
Signature of Investigator	Date
Taofeek K. Owonikoko, MD, PhD	
Printed Name of Investigator	

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, instructions from Celgene representatives, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

STUDY PERSONNEL

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List of Changes to Amended protocol from 06/10/2014

Pages 2 -3: Update the list of investigators and study staff

Page 9: Update the study synopsis to include adenoidcystic carcinoma and neuroendocrine tumors as eligible for treatment at the defined MTD.

Page 12: Update footnote 11 to specify the correct time points to collect samples for correlative analysis

Page 22: Update the overall study design to include adenoidcystic carcinoma and neuroendocrine tumors as eligible for treatment at the defined MTD

Page 23: Update the dose escalation schema table to include adenoidcystic carcinoma and neuroendocrine tumors as eligible for expansion cohort treated at MTD

Page 24: Delete Kevin Kim who is no longer a co-investigator on the study and update shipping instruction for collected tissue samples.

Page 29: Update the prescribing information for lenalidomide

Page 37: correct typographical error regarding the total number of patients to be enrolled from 39 to 45

Page 39: Update the inclusion criteria related to registration in the REMS program and adherence to pregnancy testing using the mandatory language by pharmaceutical supporter, Celgene.

Page 45: Clarification for treatment discontinuation or resumption of therapy following delayed recovery from toxicity.

Page 46: Update dose modification criteria for thrombocytopenia in line with updated guidelines from Celgene

Page 58: Update the guidleines for managing occurrence of pregnancy or suspected pregnancy in patients on lenalidomide

Page 59: Update Celgene drug safety contact information

List of Changes to Amended protocol from 06/11/2012

Page 40, line 22 – update the disease free interval exclusion period from previously treated malignancy to 3 years instead of 5 years.

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1 Protocol Synopsis

PROTOCOL TITLE: Phase I Study of Everolimus (RAD001) in Combination with Lenalidomide in Patients with Advanced Solid Malignancies Enriched for Renal Cell Carcinoma	
DATE PROTOCOL FINAL:	June 11, 2012 (Version 5)
INDICATION:	**Advanced Refractory Solid Malignancies**
STUDY PHASE:	**I**

BACKGROUND AND RATIONALE:

The mammalian target of rapamycin (mTOR) signaling pathway is a clinically relevant target in many solid and hematologic malignancies. Preclinical studies showed that the abrogation of mTOR signaling leads to tumor growth inhibition due to the involvement of mTOR pathway in myriad cellular processes including cell growth, cell survival, protein synthesis and angiogenesis. Many investigational agents targeting the mTOR pathway are in advanced stage of clinical evaluation for cancer therapy. Clinical significance of mTOR signaling inhibition was validated by temsirolimus, a derivative of rapamycin, which, produced improved survival outcome and is now approved for the treatment of poor risk renal cell carcinoma patients. Although the combination of temsirolimus and interferon achieved better response rate than the comparative single agent arms (4.6% vs. 8.6% vs. 8.1% for interferon, temsirolimus and the combination respectively), this did not result in survival advantage due to the additive toxicities leading to overall reduced dose intensity for temsirolimus in the combination arm. Everolimus is an orally bioavailable derivative of rapamycin with significant anti-tumor activity in refractory renal cell carcinoma and with improved toxicity profile compared to temsirolimus. When administered at 10mg daily continuous dosing in a phase II trial enrolling patients either previously untreated or treaed with no more than 1 prior regimen, everolimus achieved a 14% response rate. This promising clinical activity and its tolerable toxicity profile make everolimus a preferred mTOR inhibitor to combine with potentially synergistic agents in early phase clinical trial.

Lenalidomide is a second generation immunomodulatory agent with better toxicity profile and greater cytotoxicity than the original compound, thalidomide. Although the exact mechanism of action of lenalidomide remains to be fully elucidated, studies using multiple myeloma cell lines have shown that lenalidomide action on cancer cell-stromal interaction and its modulation of angiogenesis and tumor directed immunity are central to its cytotoxicity. Lenalidomide induces cell cycle arrest and apoptosis and also stimulates T cell specific immune response and promotes expansion and enhanced cytotoxicity of natural killer (NK) cells. Lenalidomide has been tested in phase II clinical trial enrolling patients with refractory renal cell carcinoma. It achieved a complete response of 3%, partial response of 8% and stable disease in 53% of patients when administered at the standard approved dose of 25mg.

In preclinical studies, cell exposure to mTOR inhibitor results in increased expression of AKT protein, which in turn activates downstream signaling through alternative pathways

including forkhead transcription factor (FKHR) and glycogen synthase kinase (GSK)-3 that can bypass the mTOR complex. Immunomodulatory agents such as lenalidomide can overcome cellular tolerance of mTOR inhibition through as yet poorly understood mechanism. It is however, plausible that this results from their pleiotropic effects on these alternative signaling molecules. In fact, the combination of lenalidomide and rapamycin was synergistic in *in vitro* experiments using multiple myeloma cell lines. We hypothesize that the combination of lenalidomide and everolimus will produce improved clinical outcome in renal cell carcinoma as well as in many other solid tumor types where these agents have demonstrable clinical activity as single agents. The two drugs are well tolerated individually and would therefore be safe and tolerable in combination due to their non-overlapping toxicities.

STUDY OBJECTIVES:

Primary:

- Determine the maximum tolerated dose (MTD) and define the phase II recommended dose (P2RD) for the combination
- Assess the safety and tolerability of the combination of everolimus and lenalidomide in patients with advanced solid malignancies

Secondary:

- Assess for drug-drug interaction through pharmacokinetic analysis for everolimus and lenalidomide
- Identify preliminary evidence of efficacy by assessing the clinical benefit rate (CR+PR+SD) achieved in an expanded cohort of renal cell carcinoma patients
- Assess preliminary efficacy in an expanded cohort of patients with adenoid cystic carcinoma

Correlative Objectives

- Assess for the predictive ability of mTOR pathway protein expression in archival diagnostic tissue for the clinical activity of everolimus
- Determine the predictive ability of changes in inflammatory and immunologic markers in paired blood samples as pharmacodynamic evidence of target modulation by escalating doses of lenalidomide
- Correlate changes in level of cathepsin G in plasma with escalating doses of lenalidomide and with incidence of venous thromboembolism
- Correlate myb protein expression with the efficacy of the combination of everolimus and lenalidomide in patients with adenoidcystic carcinoma.
- Assess the predictive value of myb gene alteration in patients with adenoidcystic cancer

STUDY DESIGN:

This is a phase I, open-label, single institution, non-randomized study of escalating doses of daily, orally administered lenalidomide in combination with standard doses of everolimus, an orally available mTOR inhibitor. The trial is open to patients with advanced solid malignancies who have failed or are intolerant of available standard treatment options for their disease. Dose escalation will proceed in a modified Fibonacci 3+3 fashion with the requirement that dose escalation to the next level can only proceed if 0 of 3 or ≤1 of 6 patients experience a dose limiting toxicity (DLT). Five escalating dose cohorts and three deescalating dose cohorts (if DLT is encountered with the starting dose) will be used to evaluate different doses of lenalidomide and everolimus starting with the approved and or clinically relevant doses of both agents. The proposed starting dose level 1 is 10mg of lenalidomide in combination with 5mg of everolimus both administered on a once daily continuous dosing schedule for 28 days respectively in a 28-day cycle. A serial de-escalation to 10mg of lenalidomide (21 of 28 days) and 5mg of everolimus every other day will be carried out if DLT is observed in ≥ 33% of patients enrolled to the starting dose cohort. The MTD is the highest dose level of lenalidomide and everolimus (up to a maximum dose of 25mg and 10mg respectively) at which <33% of the dose cohort experiences DLT after 1 cycle (28 days) of therapy. The established MTD will be the recommended dose for follow-up phase II study. To obtain preliminary evidence of potential clinical benefit of this combination, an expanded cohort of 15 patients with clear cell renal cell carcinoma, adenoidcystic carcinoma and neuroendocrine tumors will be treated at the defined MTD.

A parallel expansion cohort of 9 patients with adenoidcystic cancer will be treated at the RP2D

STUDY ENDPOINTS

Primary:

- The MTD is the maximum doses of both drugs that can be administered without inducing DLT in ≥33% of the treated patient cohort.
- Safety will be assessed according to NCI CTCAE 4.0v
- Assessment of DLT will be performed during the first cycle only and the following will constitute DLT in this study:
    - Grade 4 hematological toxicity lasting more than 7 days
    - Grade 4 Neutropenia of any duration in the presence of fever ≥ 38.5 c
    - Grade ≥3 nausea and or vomiting in spite of standard supportive therapy
    - Grade ≥3 non-hematologic toxicity (excluding alopecia)
    - Inability to re-treat patient within 2 wks of scheduled treatment due to treatment-related adverse event
    - Inability to deliver all doses of Lenalidomide and or Everolimus during the first cycle due to an unexpected drug-related toxicity (if toxicity is an

expected toxicity as per current package insert, then it will not be considered a DLT). These subjects should be discontinued from the study

In the event of study discontinuation prior to completing the entire first treatment cycle for reasons other than DLT, the affected subject will be considered inevaluable for toxicity and will be replaced by another subject to be treated at the same dose-level.

Secondary:

- Significant drug-drug interaction will be determined through pharmacokinetic analysis for parent drug and metabolites (the following PK parameters will be estimated and reported for each agent according to dose level – ($AUC_{0\rightarrow t}$) Area under the concentration-time curve from the time of dosing to the time of the last observation; ($AUC_{0\rightarrow\infty}$) Area under the concentration-time curve from the time of dosing extrapolated to infinity; (C_{max}) Maximum serum concentration observed postdose; (T_{max}) Time point at which the C_{max} occurs; ($t_{½}$) Elimination half-life, determined as $0.693/\lambda z$)
- The frequency of achieving a complete plus partial response to the 2 drug combination by dose cohort. Response will be assessed by cross sectional imaging after every 2 cycles and will be categorized according to RECIST 1.1 criteria.

Correlative:

- Mean change in immunological biomarkers at baseline, after 1 cycle of protocol directed therapy and at disease progression by dose cohort
- Mean change in plasma levels of inflammatory markers at baseline, after 1 completed cycle of therapy and at disease progression
- Plasma level of cathepsin G at baseline, after 1 cycle of therapy and following the first diagnosis of venous thromboembolic disease

STUDY DURATION: 18-24 months	**TOTAL SAMPLE SIZE:** 45
DOSING REGIMEN(S): According to dose cohort: Lenalidomide once daily days 1-28 of a 28 day cycle Everolimus once daily continuously (day 1-28)	**DRUG SUPPLIES:** For study participants, Celgene Corporation will provide lenalidomide at no charge through the RevAssist® program. Everolimus will be supplied by Novartis Pharmaceuticals Corporation and dispensed through the Investigational Drug Pharmacy

2 Schedule of Study Assessments *

Procedure	Screening ≤ 28 days from Baseline (First day drug administration)	Cycle 1				Cycles 2, 4, 6, 8	Cycles 3, 5, 7, 9	Discontinuation From Protocol Therapy	Follow-Up Phase
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 1		Not indicated
Record prior medications, treatments	X								
Record prior anti-cancer therapies	X								
Physical examination, vital signs, weight	X	X[9]				X	X	X	
ECOG performance status	X	X[9]				X	X	X	
CT or MRI of the chest & abdomen / pelvis	X					X[7]		X	
Chest x-ray [1]	X [1]					X[1]		X[1]	
Bone scan [2]	X [2]					X[2]		X[2]	
CT or MRI of the brain	X [3]					X[3]		X[3]	
ECG	X							X	
Hematology	X	X[9]		X		X	X	X	
Serum chemistry [4]	X	X[9]		X		X[4]	X[4]	X	
Pregnancy testing[5]	X[6]	X	X	X	X	X[6]	X[6]	X[6]	
Register patient into RevAssist® program	X								
Baseline lesion assessment	X								
Dispense everolimus via IDS Prescribe lenalidomide via RevAssist® [10]		X[10]				X[10]	X[10]		
Response assessment [7]						X[7]		X	
Record adverse events[8]			X		X	X	X	X[8]	
Record concomitant therapies/procedures			X		X	X	X	X	
Obtain Follow-Up anti-cancer treatments									X
Obtain Follow-Up survival information									X
Obtain Archival Tissue Block	X								
Collect Blood Sample for Correlative Assay	X[11]	X[11]				X[11]		X[11,12]	
Fresh Tumor Biopsy[13]	X[13]					X[13]			

* Variations of ± 3 days of the scheduled visit are permitted.

If Physical examination, vital signs, weight and ECOG performance status were done within 7 days of Day 1, they do not need to be repeated at Study Day 1.

An unscheduled visit can occur at any time during the study. Source must be maintained for these unscheduled visits. The date for the visit and any data generated must be recorded on the appropriate CRF. Source documents for these unscheduled visits must also be maintained.

[1] Not needed if Chest CT scan has been obtained.

[2] May repeat as clinically indicated if subject had previously positive bone scan or if symptoms suggest metastases.

[3] If symptoms raise suspicion of CNS lesions.

[4] To include Thyroid Stimulating Hormone (TSH) at Screening, every 16 weeks and at treatment discontinuation. T3 and T4 levels may be assessed as clinically indicated.

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

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

[7] Based on RECIST 1.1 criteria, PRs and CRs do not require separate confirmatory scans. Duration of response will be determined with the results of the regular restaging scans to be obtained after every 2 cycles.

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

[9] If screening assessments were done within 7 days of Day 1, they do not need to be repeated at Study Day 1.

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

[11]Baseline samples for correlative assays may be collected up to 3 days prior to dosing. See Appendix D for directions on blood collection and preparation. Samples for inflammatory and immunologic markes will be collected with the first 2 restaging scans i.e. end of cycle 2 (samples should be collected on day 1 cycle 3 ± 2days) and at the time of disease progression if different than any of the afore-listed time points.

[12] Collect at the time of documented disease progression

[13] Fresh tumor biopsy to be obtained at baseline and at the end of cycle 1. This is optional and will be limited to patients enrolled in the expansion cohort after obtaining a separate informed consent for the procedures.

3 Background and Rationale

3.1 Introduction

3.2 Lenalidomide

Lenalidomide is a proprietary IMiD™ compound of Celgene Corporation. IMiD™ compounds have both immunomodulatory and anti-angiogenic properties which could confer antitumor and antimetastatic effects. Lenalidomide has been demonstrated to possess anti-angiogenic activity through inhibition of bFGF, VEGF and TNF-alpha induced endothelial cell migration, due at least in part to inhibition of Akt phosphorylation response to bFGF.[1] In addition, lenalidomide has a variety of immunomodulatory effects. Lenalidomide stimulates T cell proliferation, and the production of IL-2, IL-10 and IFN-gamma, inhibits IL-1-beta and IL-6 and modulates IL-12 production.[2] Up regulation of T cell derived IL-2 production is achieved at least in part through increased AP-1 activity.[3] Although the exact antitumor mechanism of action of lenalidomide is unknown, a number of mechanisms are postulated to be responsible for lenalidomide's activity against multiple myeloma. Lenalidomide has been shown to increase T cell proliferation, which leads to an increase in IL-2 and IFN-gamma secretion. The increased level of these circulating cytokines augment natural killer cell number and function, and enhance natural killer cell activity to yield an increase in multiple myeloma cell lysis.[4] In addition, lenalidomide has direct activity against multiple myeloma and induces apoptosis or G1 growth arrest in multiple myeloma cell lines and in multiple myeloma cells of patients resistant to melphalan, doxorubicin and dexamethasone.[5]

3.3 Everolimus:

Everolimus is a derivative of rapamycin, which acts as a signal transduction inhibitor. Its target is mammalian target of rapamycin (mTOR), a key serine-threonine kinase regulating protein synthesis and ultimately cell growth, cell proliferation, angiogenesis and survival.[6] Downstream of PI3/AKT, mTOR is a component of the PI3K/AKT/mTOR pathway known to be dysregulated in numerous human malignancies. Molecular epidemiological studies demonstrate that, in addition to a high frequency in specific cancers, activation of the PI3K/AKT/mTOR pathway is frequently a characteristic of worsening prognoses (through increased aggressiveness), resistance to treatment, extension of disease and progression. Preclinical studies have confirmed the role of this pathway in tumor development. Gain of function models demonstrate that constitutive activation of kinases such as AKT can lead to the inexorable development of malignancies resembling those seen in patients characterized by frequent activation of the same kinase. This complemented the demonstration of the antitumor activity of kinase inhibitors acting *in vitro* and *in vivo*.

Experiments carried out in Novartis laboratories, as well as elsewhere, show that everolimus is capable of inhibiting the proliferation and growth of a wide spectrum of tumor cell lines and tumors, respectively. The antiproliferative effects of everolimus are achieved at nanomolar concentrations; which is easily achieved in patients treated at the doses used in clinical trials. An

important aspect of the antitumor effect of everolimus is its potential to act on tumor cells by directly inhibiting growth and indirectly by inhibiting angiogenesis.[6] The observation of *in vivo* sensitivity of xenografts raised from cells demonstrating resistance to everolimus *in vitro* is attributable to the drug's potential to act on the vascular component of the supporting peritumoral stroma.[6] The antiangiogenic property of everolimus was confirmed through experiments demonstrating the effect of everolimus in countering VEGF-induced proliferation of human umbilical endothelial cells (HUVEC) *in vitro*,[7] VEGF-driven angiogenesis in a chamber implant murine model and revascularization in a murine orthotopic melanoma model.

Although everolimus shows antitumor activity by itself, objective responses are quite modest. There is therefore an increasing focus on the potential for increased anti tumor activity when combined with other antitumor therapies. The PI3K/AKT pathway is downstream of numerous other effectors known to play a role in cancer cell proliferation and or survival, most notably growth factor receptor protein tyrosine kinase and hormone receptors. Therefore, there is great potential that everolimus may be combined with antibody-based therapy such as trastuzumab (Herceptin®) blocking HER2/ErbB2, bevacizumab (Avastin®) sequestering vascular endothelial growth factor, and rituximab (Rituxan®/MabThera®) directed against CD20, a B lymphocyte-specific antigen); and small molecule inhibitors such as erlotinib (Tarceva®) and gefitinib (Iressa®) inhibiting EGFR/ErbB1, PTK787 inhibiting the VEGF receptor (VEGFr), bortezomib (Velcade®) an inhibitor of the proteosome, and vorinostat (SAHA) a histone deacetylase inhibitor.

3.4 Rationale for Treatment in this Setting

The mammalian target of rapamycin (mTOR) signaling pathway is a clinically relevant target in many solid malignancies. Preclinical studies showed that the abrogation of signaling through this pathway leads to tumor growth inhibition. Clinical significance of mTOR signaling inhibition was validated by temsirolimus, a derivative of rapamycin which produced improved survival outcome leading to its approval for the treatment of poor risk renal cell carcinoma patients.[8] Although the combination of temsirolimus and interferon combination achieved better response rate than the comparative single agent arms (4.6% vs. 8.6% vs. 8.1% for interferon, temsirolimus and the combination respectively), this did not result in survival advantage due to the reduced dose intensity necessitated by the additive toxicity observed with temsirolimus in the combination arm.[8] Everolimus is an orally bioavailable derivative of rapamycin with significant anti-tumor activity in various solid malignancies, most notably refractory renal cell carcinoma. It has an improved toxicity profile over temsirolimus. When administered at 10mg daily continuous dosing in a phase II study of patients previously untreated or treated with only one prior regimen, everolimus achieved a 14% response rate and a 57% disease stability rate.[9] A phase III study in previously treatedrenal cell carcinoma patients produced a 1% response rate and 63% stable disease rate[10] suggesting that prior therapy with other targeted agents may lead to acquired resistance to mTOR targeting agents. Nonetheless, on the basis of the superior progression free survival compared to placebo treatment, everolimus received FDA approval for the treatment of patients with clear cell renal cell carcinoma. The demonstrated clinical activity of everolimus in solid malignancies and its tolerable toxicity profile recommend it as the

preferred mTOR inhibitor in early phase clinical trial of potentially synergistic combination regimen in solid tumors.

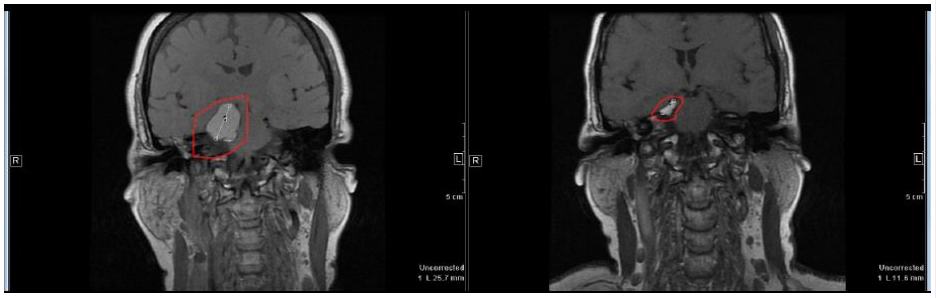
Lenalidomide is a second generation immunomodulatory agent with better toxicity profile and greater cytotoxicity than the original compound, thalidomide. Although the exact mechanism of action of lenalidomide remains to be fully elucidated, studies using multiple myeloma and NHL cell lines have shown that lenalidomide action on cancer-stroma interaction and its modulation of angiogenesis and tumor directed immunity are central to its cytotoxicity.[11-13] Lenalidomide induces cell cycle arrest and apoptosis and also stimulates T cell specific immune response and promotes expansion and enhanced cytotoxicity of natural killer (NK) cells.[11] In preclinical studies, exposure of cells to mTOR inhibitor resulted in a compensatory escape reaction with increased expression of AKT protein,[14] which in turn activates downstream signaling through alternative pathways including forkhead transcription factor (FKHR) and glycogen synthase kinase (GSK)-3 that can bypass the mTOR complex. Immunomodulatory agents such as lenalidomide can overcome mTOR inhibitor resistance through as yet poorly understood mechanism probably through their pleiotropic effects on multiple alternative signaling molecules. In preclinical studies with multiple myeloma cell lines, the combination of lenalidomide and rapamycin was capable of overcoming the protective effect of IGF1 and IL-6 against the cytotoxic effect of rapamycin (Figure 1). This interaction was associated with increased apoptosis (Figure 2) and resulted in a synergistic cytotoxic effect (Figure 3).[15] Lenalidomide has been tested in phase II clinical trial enrolling patients with refractory renal cell carcinoma. It achieved a complete response of 3%, partial response of 8% and stable disease in 53% of patients when administered at the standard approved dose of 25mg.

Cytotoxicity and acquired resistance following single agent therapy with lenalidomide and everolimus may occur through a shared mechanism involving modulation of tumor directed immunity and tumor associated angiogenesis. The co-administration of both agents may therefore result in maximal pathway modulation leading to increased efficacy and delayed acquisition of the resistance phenotype by the tumor cells. Because the two drugs are well tolerated individually and have non-overlapping toxicities we anticipate that they would be safe and tolerable in combination. We therefore hypothesize that the combination of lenalidomide and everolimus will be safe, tolerable and will produce synergistic clinical outcome in solid malignancies such as renal cell carcinoma as well as other solid malignancies where these agents have shown single agent clinical activity.

Adenoidcystic carcinoma:

Adenoidcystic carcinoma is the second most common type of salivary gland neoplasm. It presents as a locally aggressive type of cancer that arise commonly in minor and major salivary glands. This cancer has a very poor long-term prognosis with no established FDA-approved therapeutic intervention. Recent research work showed that a chromosomal translocation involving the genes encoding the transcription factors, MYB and NFIB, is frequently observed in this tumor type. A balanced translocation between MYB and NFIB is present in 49% of adenoid cystic carcinomas but is not identified in other salivary gland tumors or nonsalivary gland neoplasms. Strong Myb immunostaining is detected in upto 65% of all cases and is very specific for adenoid cystic carcinomas (West et al. PMID:21164292 and Brill et al. 2011; PMID:21572406). Adenoidcystic cancer with MYB translocation tend to have poorer prognosis with higher local relapse rates. While it is very likely that this translocation may mediate a key driver event in the development of this type of cancer, there is as yet no specific therapeutic agent that is specific for this putative oncogenic aberration. It is also unclear whether this chromosomal aberration will predict for response to novel targeted therapy; however, it is worthwhile correlating the presence of this translocation with the clinical outcome of patients especially in the early drug development phase where we observe very intriguing signs of efficacy. .

We enrolled five patients with salivary gland tumor in the escalation phase of this study. Four of the five patients completed at least 2 cycles of therapy and all of them obtained meaningful clinical benefit. A heavily pretreated patient with adenoidcystic carcinoma has achieved near partial response (>25% tumor shrinkage by RECIST criteria; supplemental figure S1). She remains on protocol treatment after completing 7 cycles of treatment. This intriguing observation justifies a more focused evaluation of the combination of lenalidomide and everolimus in this patient population.



Supplemental figure S1: MRI of the brain showing dramatic reduction in intracranial tumor growth following 6 cycles of treatment with lenalidomide and everolimus in a patients with salivary gland adenoidcystic carcinoma

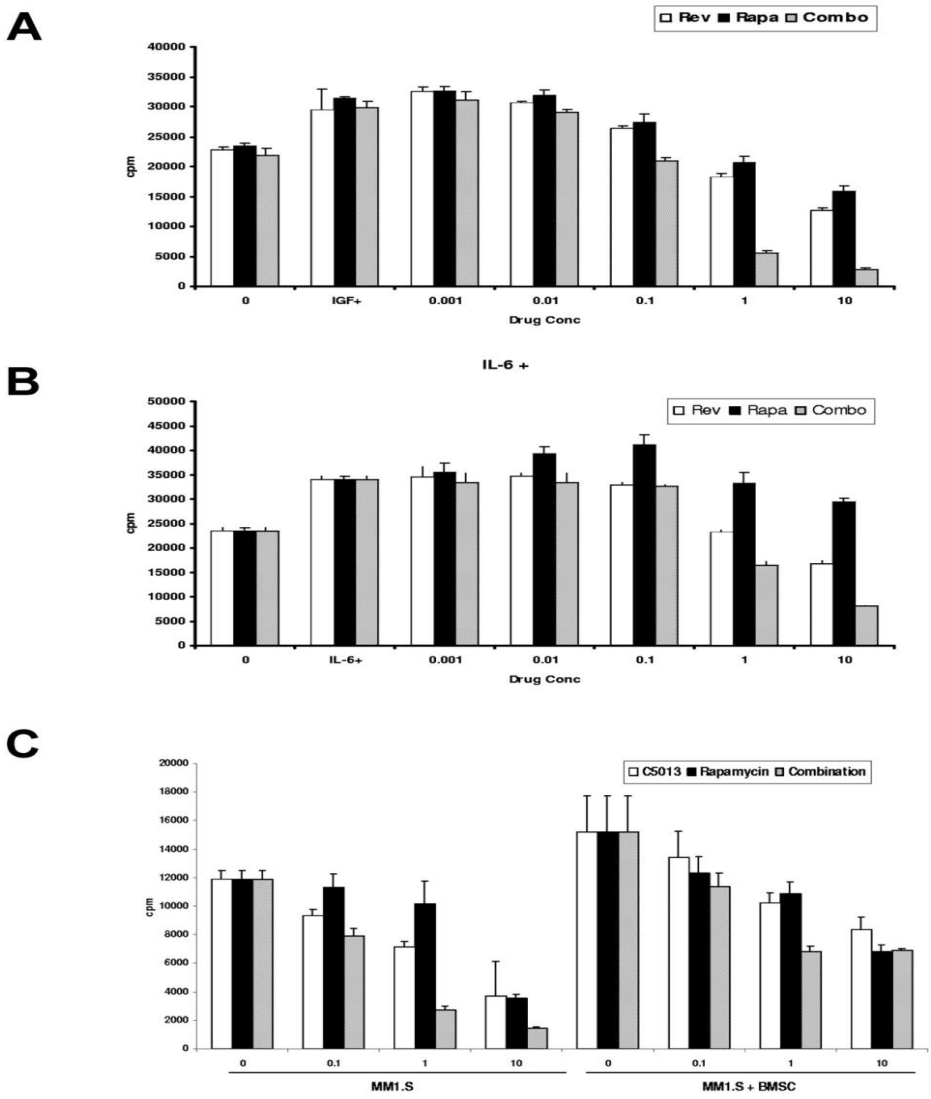


Figure 1

Combination of lenalidomide (CC-5013) and rapamycin overcomes the protective effect of IL-6, IGF-1, and adherence to the bone marrow microenvironment. Rapamycin-induced cytotoxicity is abrogated in the presence of cytokines, but the combination of CC-5013 with rapamycin overcomes the protective effects of (A) IL-6 and (B) IGF-1. (C) Combined therapy was also effective at inhibiting DNA synthesis in MM1.S cells adherent to BMSCs. Raje et al. Blood, 104 (13): 4188-4193, 2004[15]

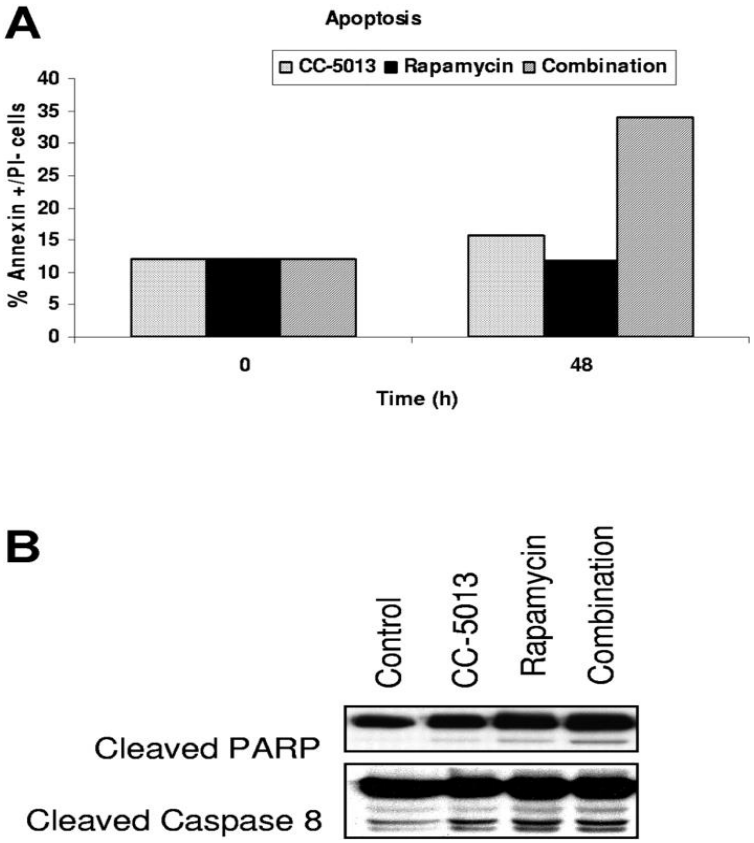


Figure 2

Combination CC-5013 and rapamycin induces apoptosis in MM1.S cells. (A) Increase in the apoptotic cells (Annexin$^+$ PI$^-$) after exposure to CC-5013 (1 μM) and rapamycin (1 nM) for 48 hours, (B) associated with caspase 8 and PARP cleavage. Raje et al. Blood, 104 (13): 4188-4193, 2004[15]

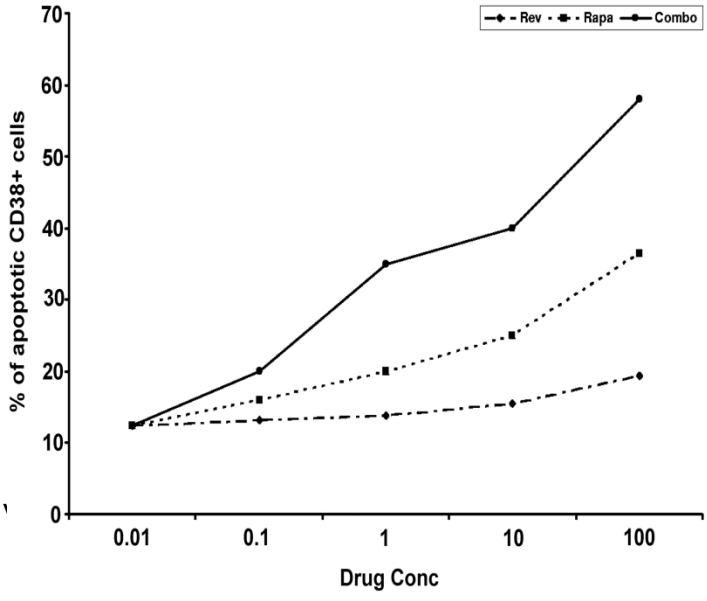


Figure 3

Effect of CC-5013, rapamycin, and combination on patient myeloma cells. A dose-dependent increase in the percentage of apoptotic patient MM cells, evidenced by Apo 2.7 staining of bright CD38-positive cells, was noted after exposure to combination CC-5013 and rapamycin treatment. Raje et al. Blood, 104 (13): 4188-4193, 2004[15]

3.4.1 LENALIDOMIDE INDICATIONS AND USAGE:

Revlimid® (lenalidomide) is available in 5 mg, 10 mg, 15 mg and 25 mg capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The 5 mg capsule shell contains gelatin, titanium dioxide and black ink. The 10 mg capsule shell contains gelatin, fd&c blue #2, yellow iron oxide, titanium dioxide and black ink.

Revlimid® (lenalidomide) is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. Revlimid® is also approved in combination with dexamethasone for the treatment of patients with multiple myeloma that have received at least one prior therapy. All other uses are considered investigational.

3.4.2 EVEROLIMUS INDICATIONS AND USAGE:

AFINITOR® (everolimus) is indicated for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib. The recommended dose of AFINITOR for treatment of advanced renal cell carcinoma is 10 mg, to be taken once daily at the same time every day, either with or without food. AFINITOR tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed. Continue treatment as long as clinical benefit is observed or until unacceptable toxicity occurs.

3.5 Adverse Events

3.3.1 Lenalidomide

Most frequently reported adverse events reported during clinical studies with lenalidomide in oncologic and non-oncologic indications, regardless of presumed relationship to study medication include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting and diarrhea, dehydration, rash, itching, infections, sepsis, pneumonia, UTI, Upper respiratory infection, cellulites, atrial fibrillation, congestive heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, CVA, convulsions, dizziness, spinal cord compression, syncope, disease progression, death not specified and fractures.

Complete and updated adverse events are available in the Investigational Drug Brochure and the IND Safety Letters.

3.3.2 Everolimus

The data described below reflect exposure to AFINITOR (n=274) and placebo (n=137) in a randomized, controlled trial in patients with metastatic renal cell carcinoma who received prior treatment with sunitinib and/or sorafenib. The median age of patients was 61 years (range 27-85), 88% were Caucasian, and 78% were male. The median duration of blinded study treatment was 141 days (range 19-451) for patients receiving AFINITOR and 60 days (range 21-295) for those receiving placebo. The most common adverse reactions (incidence ≥30%) were stomatitis, infections, asthenia, fatigue, cough, and diarrhea. The most common grade 3/4 adverse reactions (incidence ≥3%) were infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and asthenia. The most common laboratory abnormalities (incidence ≥50%) were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine. The most common grade 3/4 laboratory abnormalities (incidence ≥3%) were lymphopenia, hyperglycemia, anemia, hypophosphatemia, and hypercholesterolemia. Deaths due to acute respiratory failure (0.7%), infection (0.7%) and acute renal failure (0.4%) were observed on the AFINITOR arm but none on the placebo arm. The rates of treatment-emergent adverse events (irrespective of causality) resulting in permanent discontinuation were 14% and 3% for the AFINITOR and placebo treatment groups, respectively. The most common adverse reactions (irrespective of causality) leading to treatment discontinuation were pneumonitis and dyspnea. Infections, stomatitis, and pneumonitis were the most common reasons for treatment delay or dose reduction. The most common medical interventions required during AFINITOR treatment were for infections, anemia, and stomatitis.

4 Study Objectives and Endpoints

4.1 Objectives

4.1.1 Primary objectives

- Determine the maximum tolerated dose (MTD) and define the phase II recommended dose (P2RD) for the combination of lenalidomide and everolimus in patients with advanced solid malignancies
- Assess the safety and tolerability of the combination of everolimus and lenalidomide in patients with advanced solid malignancies

4.1.2 Secondary study objectives

- Assess for drug-drug interaction through pharmacokinetic analysis for everolimus and lenalidomide
- Identify preliminary evidence of efficacy by assessing the clinical benefit rate (CR+PR+SD) achieved in an expanded cohort of renal cell carcinoma patients
- Assess preliminary efficacy in an expanded cohort of patients with adenoid cystic carcinoma

4.1.3 Correlative Objectives

- Correlate mTOR pathway protein expression in archival diagnostic tumor tissue with the clinical activity of everolimus
- Determine the predictive ability of changes in inflammatory and immunologic markers in paired blood samples as pharmacodynamic evidence of target modulation by escalating doses of lenalidomide
- Correlate changes in level of cathepsin G in plasma with escalating doses of lenalidomide and with incidence of venous thromboembolism
- Correlate myb protein expression with the efficacy of the combination of everolimus and lenalidomide in patients with adenoidcystic carcinoma.
- Assess the predictive value of myb gene alteration in patients with adenoidcystic cancer

4.2 Endpoints

4.2.1 Primary Endpoint

Maximum tolerated dose (MTD) of the combination of lenalidomide and everolimus

Safety will be assessed according to NCI CTCAE 4.0 (Appendix C)

Assessment of DLT will be performed during the first cycle only and the following will constitute DLT in this study:

- Grade 4 hematologic toxicity lasting more than 7 days
- Grade 4 Neutropenia of any duration with fever ≥ 38.5c
- Grade ≥3 nausea and or vomiting in spite of standard supportive therapy
- Grade ≥3 non-hematologic toxicity (exclude alopecia)
- Inability to re-treat patient within 2 wks of scheduled treatment due to treatment-related toxicity
- Inability to deliver all doses of Everolimus during the first cycle due to an unexpected drug-related toxicity (if everolimus related toxicity is an expected toxicity as per current package insert, then it will not be considered a DLT). These subjects should be discontinued from the study.
- Discontinuation of the study prior to completing the entire first treatment cycle for reasons other than DLT, a subject will be added to that dose-level cohort.
- The occurrence of one of the above drug-related toxicities will result in a clinical and/or laboratory assessment to be performed within 7 days following the initial finding to examine the subject for resolution of the toxicity. Lack of resolution of any of these toxicities according to the guidelines above will be considered a DLT and result in discontinuation of that subject

4.2.2 Secondary Endpoints

- The frequency of achieving a complete plus partial response or disease stabilization with the 2 drug combination by dose cohort. (Response will be assessed by cross sectional imaging after every 2 cycles and will be categorized according to RECIST 1.1 criteria)

4.2.3 Correlative Endpoints

- Immunoscore of mTOR pathway protein expression (S6, pS6, 4E-BP1, p-4E-BP1, eI4F, Akt, pAkt, raptor, rictor, PRAS40, mSin1, FKBP38, and IRS-1 and HIF1-α) in archival biopsy sample for all patients and in paired fresh tumor biopsy specimens in up to 15 patients treated at P2RD if a separate informed consent is obtained.
- Immunoscore of myb protein expression in archival tissue samples in patients with adenoidcystic cancer.
- Serum level of inflammatory and immunologic markers (IL-6, IL-8, IL-12, IFN-γ, TNF-α, sIL-2R-α, CD4+ and CD8+ T-cell, NK cell and Treg cells); markers of angiogenesis (circulating VEGF and soluble VEGFR) and level of the potent platelet aggregator, cathepsin G, will be performed in serial blood samples collected at baseline, at the end of cycle 1 and at the time of disease progression or first diagnosis of venous thromboembolism (in the case of cathepsin G) and correlated with lenalidomide therapy by dose cohort.

5 Investigational Plan

5.1 Overall design

This is a phase I, open-label, single institution, non-randomized study of escalating doses of daily, orally administered lenalidomide in combination with standard doses of everolimus, an orally available mTOR inhibitor. The trial is open to patients with advanced solid malignancies who have failed or are intolerant of available standard treatment options for their disease. Dose escalation will proceed in a modified Fibonacci 3+3 fashion with the requirement that dose escalation to the next level can only proceed if 0 of 3 or ≤1 of 6 patients experience a dose limiting toxicity (DLT). Four escalating dose cohorts and three deescalating dose cohorts will be used to evaluate different doses of lenalidomide and everolimus starting with the approved and or clinically relevant doses of both agents. The proposed starting dose level 1 is 10mg of lenalidomide (days 1 – 28) in combination with 10mg of everolimus (days 1 - 28) in a 28-day cycle. A serial de-escalation to 10mg of lenalidomide (days 1-21 of a 28 day cycle) and 5mg of everolimus will be carried out if DLT is observed in ≥ 33% of patients enrolled to the starting dose cohort. The MTD is the highest dose level of lenalidomide and everolimus (up to a maximum dose of 25mg and 10mg respectively) at which <33% of the dose cohort experiences DLT after 1 cycle (28 days) of therapy. The established MTD will be the recommended dose for follow-up phase II study. To obtain preliminary clinical benefit of this combination, an expanded cohort of 15 patients with clear cell renal cell carcinoma, adenoidcystic carcinoma and neuroendocrine tumors will be treated at the define MTD. To allow for assessment of drug-drug interaction using PK analysis, lenalidomide will be administered alone on day 1 of the first cycle followed by both agents on day 2 cycle 1. Both drugs will be started simultaneously on day 1 of all subsequent cycles.

In addition, a parallel cohort of 9 additional patients with adenoidcystic cancer will be treated at the RP2D. This is to enable us to obtain further evidence in support of the efficacy of this regimen in patients with adenoidcystic cancer as observed in the limited number of patients with this cancer type who were enrolled in the escalation phase of the study.

Table 1

Dose Level	Lenalidomide (day 1 to 28)	Everolimus (day 1-28)	Patient Enrolment	Remarks
-2	10mg Days 1-21	5mg every other day	3 + 3	If DLT, study will close without defining a MTD
-1	10mg Days 1-21	5mg	3 + 3	Deescalate to level -2 if ≥ 1 of 6 patients experience DLT, otherwise declare as MTD and expand the cohort
Starting Dose 1	10mg	5mg	3 + 3	Escalate to level 2 if 0 of 3 or 1 of 6 patients experience DLT, otherwise deescalate 1 level
2	15mg	5mg	3 + 3	Escalate to level 3 if 0 of 3 or 1 of 6 patients experience DLT, otherwise deescalate 1 level
3	20mg	5mg	3 + 3	Escalate to level 4 if 0 of 3 or 1 of 6 patients experience DLT, otherwise deescalate 1 level
4	25mg	5mg	3 + 3	if ≥ 1 of 6 patients experience deescalate 1 level, otherwise declare as MTD
5	25mg	10	3 + 3	if ≥ 1 of 6 patients experience deescalate 1 level, otherwise declare as MTD
MTD	TBD	TBD	15	Expanded cohort of 15 patients restricted to patients with renal cell carcinoma, adenoidcystic carcinoma and neuroendocrine tumors

5.1.1 Blood Sample Collection:

Blood samples will be collected in heparinized green top tubes (3 mls for PK samples and 7 mls for PBMC collection), red top tube (7 mls to obtain serum sample for cytokine assay). PBMC will be purified using standard Ficoll-Paque gradient centrifugation according to the instructions of the manufacturer (Amersham Pharmacia, Uppsala, Sweden). All samples must be stored away within 1 hour of collection by refrigeration at -80oC until ready for assay.

5.1.2 PK Analysis –

PK Analysis will not be performed in this study. This information will be obtained in a separate ongoing phase I study of this combination in patients with hematologic malignancies where everolimus and lenalidomide concentrations will be assayed in blood with a liquid chromatography/mass spectroscopy assay as previously described.[18,19].

5.1.3 Immunohistochemistry for mTOR pathway protein –

Archival paraffin embedded tissue collected at the time of patient screening will be shipped to the lab of the PI, Taofeek K. Owonikoko, MD, PhD at the Winship Cancer Institute. After obtaining a separate informed consent from trial subjects, CT -guided biopsy will be performed using either fine-needle aspiration for lung metastases or a 17 gauge biopsy gun for all other organ sites. Biopsies will be directed by a specialist from the Interventional Radiology department. Accessible lesions may also be biopsied by a preferred surgeon or other specialist as appropriate for the site. Submitted material obtained by various biopsy methods will be embedded in paraffin. Archival and fresh tumor biopsies will be stored until the end of the trial when all samples will be analyzed in a single batch. Immunohistochemical detection of the mTOR pathway proteins will be carried out with the avidin-biotin technique using specific monoclonal antibodies in the laboratory of the principal investigator, Dr. Taofeek Owonikoko in collaboration with Shi-Yong Sun, PhD. Paired fresh tumor biopsy will be limited to patients enrolled in the expansion cohort. The final decision to proceed with fresh biopsy will however, be based on the experience in the escalation phase of the study and will require express approval of celgene.

Assess for myb protein expression by IHC in patients with adenoidcystic cancer and correlate with response to therapy.

5.1.4 Flow Cytometry for Detection and Quantification of T-cell Subsets -

At the appropriate time points as specified in the treatment schema (baseline, with the first 2 restaging assessment and at disease progression), 7 mls of anticoagulated whole blood sample will be collected and sent to the lab of Dr. Edmund Waller, a collaborator at the Winship Cancer Institute, who will perform flow cytometry for the detection of different subsets of circulating T and B lymphocytes.

5.1.5 ELISA Assay for Circulating Cytokine and Angiogenesis Mediators -

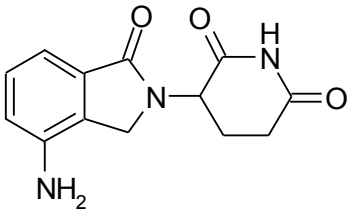
ELISA detection and quantification of the cytokines of interest will be performed using previously published methods. Samples will be collected at baseline, with the first 2 restaging assessment and at disease progression. Samples will be loaded onto a 96-well microtiter plate coated with monoclonal antibody specific for the cytokine of interest. After a blocking step, samples will be diluted into a buffer and incubated with the primary antibody. After a washing step, antisera specific for the cytokine is added followed by additional incubation. Another washing step will be performed to be followed by the addition of peroxidase-conjugated secondary antibody. The concentrations of the respective cytokines will be determined in triplicate for each serum samples using an ELISA plate reader. A set of calibrators and assay controls will be run with each assay. The ELISA assays will be performed by Dr. Owonikoko's lab.

5.2 Protocol Therapy

5.2.1 Lenalidomide Description

REVLIMID® (lenalidomide), a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2*H*-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:

Chemical Structure of Lenalidomide



3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione

The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3.

Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

5.2.2 Clinical pharmacology

Mechanism of action:

Lenalidomide is a proprietary IMiD™ compound of Celgene Corporation. IMiD™ compounds have both immunomodulatory and anti-angiogenic properties which could confer antitumor and antimetastatic effects. Lenalidomide has been demonstrated to possess anti-angiogenic activity through inhibition of bFGF, VEGF and TNF-alpha induced endothelial cell migration, due at least in part to inhibition of Akt phosphorylation response to bFGF. In addition, lenalidomide has a variety of immunomodulatory effects. Lenalidomide stimulates T cell proliferation, and the production of IL-2, IL-10 and IFN-gamma, inhibits IL-1 beta and IL-6 and modulates IL-12 production. Upregulation of T cell derived IL-2 production is achieved at least in part through increased AP-1 activity.

Although the exact antitumor mechanism of action of lenalidomide is unknown, a number of mechanisms are postulated to be responsible for lenalidomide's activity against multiple myeloma. Lenalidomide has been shown to increase T cell proliferation, which leads to an increase in IL-2 and IFN-gamma secretion. The increased level of these circulating cytokines augment natural killer cell number and function, and enhance natural killer cell activity to yield an increase in multiple myeloma cell lysis. In addition, lenalidomide has direct activity against

multiple myeloma and induces apoptosis or G1 growth arrest in multiple myeloma cell lines and in multiple myeloma cells of patients resistant to melphalan, doxorubicin and dexamethasone. Lenalidomide inhibited the secretion of pro-inflammatory cytokines and increased the secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells. Lenalidomide inhibited cell proliferation with varying effectiveness (IC50s) in some but not all cell lines. Of cell lines tested, lenalidomide was effective in inhibiting growth of Namalwa cells (a human B cell lymphoma cell line with a deletion of one chromosome 5) but was much less effective in inhibiting growth of KG-1 cells (human myeloblastic cell line, also with a deletion of one chromosome 5) and other cell lines without chromosome 5 deletions. Lenalidomide inhibited the expression of cyclooxygenase-2 (COX-2) but not COX-1 in vitro.

Clinical Pharmacokinetics and Pharmacodynamics

Absorption:

Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. Co-administration with food does not alter the extent of absorption (AUC) but does reduce the maximal plasma concentration (Cmax) by 36%. The pharmacokinetic disposition of lenalidomide is linear. Cmax and AUC increase proportionately with increases in dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.

Pharmacokinetic analyses were performed on 15 multiple myeloma patients treated in the phase I studies. Absorption was found to be rapid on both Day 1 and Day 28 with time to maximum blood levels ranging from 0.7 to 2.0 hours at all dose levels (5mg, 10mg, 25mg, and 50mg). No plasma accumulation was observed with multiple daily dosing. Plasma lenalidomide declined in a monophasic manner with elimination half-life ranging from 2.8 to 6.1 hours on both Day 1 and 28 at all 4 doses. Peak and overall plasma concentrations were dose proportional over the dosing range of 5mg to 50mg. Exposure (AUC) in multiple myeloma patients is 57% higher than in healthy male volunteers.

Distribution:

In vitro (^{14}C)-lenalidomide binding to plasma proteins is approximately 30%.

Metabolism and excretion:

The metabolic profile of lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore is partially or entirely active. Half-life of elimination is approximately 3 hours.

Clinical experience

A phase I study in subjects with refractory or relapsed multiple myeloma was conducted to identify the maximum tolerated dose (MTD) and to evaluate the safety of lenalidomide given orally for up to 4 weeks at 5 mg/day, 10 mg/day, 25 mg/day and 50 mg/day. Secondary objectives included evaluation of response to lenalidomide, as well as pharmacokinetics and identification of surrogate markers to aid in defining mechanisms of action. Subjects who tolerated study drug with acceptable toxicity and were without disease progression were permitted to continue on therapy beyond 28 days as part of an extension phase for over 1 year. Twenty-seven subjects were enrolled, of whom 15 had undergone prior autologous stem cell transplantation and 16 had received prior thalidomide, with a median of 3 prior regimens (range 2-6). All subjects had relapsed MM and 18 (72%) were refractory to salvage therapy. Two subjects were removed from study on the first day of treatment due to rapid disease progression, which resulted in renal dysfunction and rendered them ineligible. The first group of 3 subjects were treated for 28 d at 5 mg/d without any dose limiting toxicity (DLT). The second cohort of 3 subjects commenced therapy at 10 mg/day. In one subject, DLT was encountered with grade 2 fever as well as grade 3 leukopenia and neutropenia, resulting in removal from study before day 28. Two subjects tolerated drug. Three additional subjects were treated at 10 mg/day with no attributable toxicity within the first 28 days. In the third cohort of 3 subjects at 25mg/day, drug was well tolerated within the first 28 days but grade 3 thrombocytopenia and grade 3 and 4 neutropenia occurred during the second month, resulting in 2 subjects being removed from study. In the fourth cohort at 50mg/day, the first 3 subjects tolerated treatment without DLT in the first 28 days and a subsequent 10 subjects also tolerated drug without DLT within the first 28 days. However, subsequent grade 3 thrombocytopenia and grade 3/4 neutropenia in the extension phase has prompted dose reduction and GCSF support in all subjects. No significant somnolence, constipation or neuropathy has been seen in any cohort. Median duration of therapy is currently 4 months [range 2 weeks – 14 months] and 11 subjects continue on treatment. Maximal protein reductions seen during therapy in subjects who have received $\geq$ 28d of treatment are summarized below:

Table 2: Monoclonal protein reductions in a phase I study with lenalidomide

dose	pts [n]	< 25%	$\geq$ 25% <50%	>50%	Progression
5	3	-	2	1	-
10	5	-	-	1	4
25	3	1	2	-	-
50	13	3	5	4	1
Subtotals	24	4 (17%)	9 (37%)	6 (25%)	5 (21%)

Thus, best responses in protein of $\geq$ 25% have been seen in 15 of 24 evaluable pts (63%), and a <25% reduction has been seen in 4 subjects to achieve stable disease or better in 19 of 24 (79%). Pharmacokinetics [days 1-4, and 28] have been completed in 24 subjects and reveal rapid absorption (t max: 1-1.5 h); monophasic elimination (t ½: 3.1-4.2 h), and low to moderate inter-subject variability for AUC (11-52%) and Cmax (3-33%). Furthermore, there was no significant accumulation by day 28. In conclusion, these studies suggest lenalidomide at the dose levels

studied has anti-tumor activity, Continuous pharmacokinetics with convenient daily oral dosing and acceptable toxicity in subjects with relapsed and refractory multiple myeloma. Given the myelosuppression beyond day 28 seen in all subjects at 50 mg/day, this dose was considered to be the DLT, and thus the 25 mg/day dose level as a continuous daily schedule of administration was considered MTD. Given the activity of the drug seen at lower dose levels and the PK characteristics observed, 30 mg/day in divided or single daily dose was assessed for activity and safety, and to determine whether a divided dose schedule is superior. In addition, a 3-week on and one-week off schedule was assessed to determine if a cycling schedule would decrease the myelosuppression that was observed in earlier trials with daily dosing. In this phase II study, 70 subjects with relapsed and refractory myeloma were enrolled at several centers in the U.S. Richardson et al reported that 26% of subjects required dose reduction due to myelosuppression in this study. Responses that were observed included 4% of subjects with complete responses, 17% with partial responses and 33% with minimal responses. Progressive disease occurred in 15% of subjects.[17] It was concluded that daily dosing was better tolerated than twice daily dosing because of a lower incidence and severity of myelosuppression.

Data from two phase III trials comparing lenalidomide + dexamethasone to single agent dexamethasone in patients with relapsed and/or refractory multiple myeloma were presented at the 10th international multiple myeloma workshop in Sydney Australia (Weber et al., 2005; Dimopoulos et al., 2005). Patients who had received 1-3 prior therapies, and progressing on their last therapy were randomized to receive lenalidomide, 25 mg/d x 21 d, placebo d22-28 plus dexamethasone, 40 mg, d 1-4, 9-12, 17-20, q 28d or placebo daily x 28 d plus dexamethasone, 40 mg, d 1-4, 9-12, 17-20, q28d. Anemia, thrombocytopenia, neutropenia, fatigue, neuropathy, and constipation were also observed more often in lenalidomide + dexamethasone group compared to dexamethasone only group, however these events were generally manageable.

Supplier(s)

Celgene Corporation will supply Revlimid® (lenalidomide) to study participants at no charge through the RevAssist® program.

Dosage form

Lenalidomide will be supplied as capsules for oral administration.

Packaging

Lenalidomide will be shipped directly to patients. Bottles will contain a sufficient number of capsules for one cycle of dosing**.**

Storage

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

5.2.3 Prescribing Information

Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with the Celgene Corporation's Revlimid REMS® program. Per standard Revlimid REMS® program requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in, and must comply with, all requirements of the Revlimid REMS® program.

Drug will be shipped on a per patient basis by the contract pharmacy to the clinic site for IND studies. **Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.**

Pregnancy Testing

Must follow pregnancy testing requirements as outlined in the Revlimid REMS® program material.

Special populations:

Patients with renal insufficiency: the pharmacokinetics of lenalidomide in solid tumor patients with renal dysfunction has not been determined. In multiple myeloma patients, those with mild renal impairment had an AUC 56% greater than those with normal renal function. (see precautions: renal impairment).

Patients with hepatic disease: the pharmacokinetics of lenalidomide in patients with hepatic impairment has not been studied.

Age: the effects of age on the pharmacokinetics of lenalidomide have not been studied.

Pediatric: no pharmacokinetic data are available in patients below the age of 18 years.

Gender: the effects of gender on the pharmacokinetics of lenalidomide have not been studied.

Race: pharmacokinetic differences due to race have not been studied.

Deep Venous Thrombosis and Pulmonary Embolism

Lenalidomide has demonstrated a significantly increased risk of DVT and PE in patients with multiple myeloma who were treated with Revlimid® (lenalidomide) combination therapy. Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Prophylactic anticoagulation or antiplatelet therapy prescribed in conjunction with Revlimid® (lenalidomide) may be required for patients enrolled in this current trial.

Other adverse events

Most frequently reported adverse events reported during clinical studies with lenalidomide in oncologic and non-oncologic indications, regardless of presumed relationship to study medication include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting and diarrhea, dehydration, rash, itching, infections, sepsis, pneumonia, uti, upper respiratory infection, atrial fibrillation, congestive heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, cva, convulsions, dizziness, spinal cord compression, syncope, disease progression, death not specified and fractures.

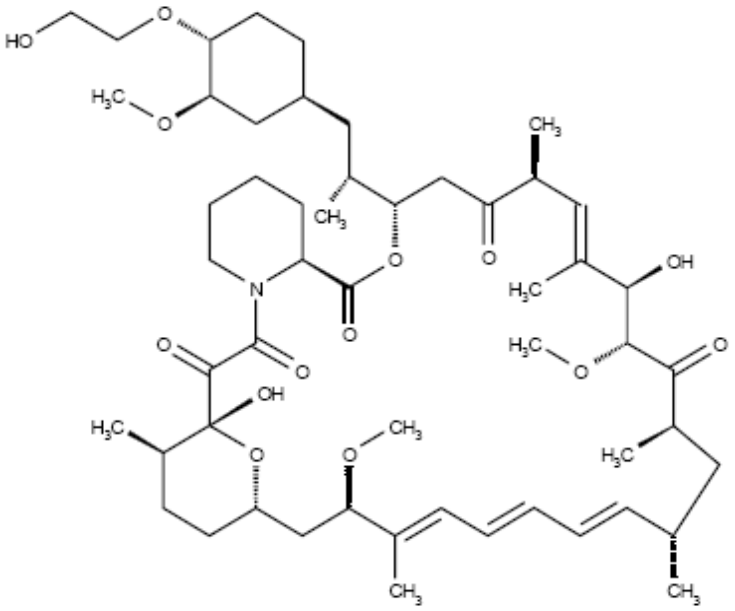
Complete and updated adverse events are available in the investigational drug brochure and the IND safety letters.

5.3 Everolimus Description

AFINITOR (everolimus), an inhibitor of mTOR, is an antineoplastic agent. The chemical name of everolimus is (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.04,9]hexatriaconta-16,24, 26,28-tetraene-2,3,10,14,20-pentaone.

The molecular formula is C53H83NO14 and the molecular weight is 958.2.

The structural formula is



AFINITOR is supplied as tablets for oral administration containing 5 mg and 10 mg of everolimus together with butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone and lactose anhydrous as inactive ingredients.

5.3.1 Indication and Administration

AFINITOR is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib. The recommended dose of AFINITOR for treatment of advanced renal cell carcinoma is 10 mg, to be taken once daily at the same time every day, either with or without food. AFINITOR tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed.

5.3.2 CLINICAL PHARMACOLOGY

Mechanism of Action

Everolimus is an inhibitor of mTOR (mammalian target of rapamycin), a serine-threonine kinase, downstream of the PI3K/AKT pathway. The mTOR pathway is dysregulated in several human cancers. Everolimus binds to an intracellular protein, FKBP-12, resulting in an inhibitory complex formation and inhibition of mTOR kinase activity. Everolimus reduced the activity of

S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4E-BP), downstream effectors of mTOR, involved in protein synthesis. In addition, everolimus inhibited the expression of hypoxia-inducible factor (e.g., HIF-1) and reduced the expression of vascular endothelial growth factor (VEGF). Inhibition of mTOR by everolimus has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in in vitro and/or in vivo studies.

Pharmacodynamics

QT/QTc Prolongation Potential - In a randomized, placebo-controlled, crossover study, 59 healthy subjects were administered a single oral dose of AFINITOR (20 mg and 50 mg) and placebo. There is no indication of a QT/QTc prolonging effect of AFINITOR in single doses up to 50 mg. Markers of protein synthesis show that inhibition of mTOR is complete after a 10 mg daily dose.

Pharmacokinetics

Everolimus is rapidly absorbed with a median Tmax of 1-2 hours. The bioavailability of the drug is believed to be 11% or greater. The steady-state $AUC_{0-\tau}$ is dose-proportional over the dose range between 5 to 70 mg in the weekly regimen and 5 and 10 mg in the daily regimen. Cmax is dose-proportional between 5 and 10 mg for both the weekly and daily regimens. At doses of 20 mg/week and higher, the increase in Cmax is less than dose-proportional. The coefficient of variation between patients is approximately 50%. Trough levels (24 hour post-dose) correlate well with AUC0-τ at steady-state during daily administration. About 20% of the drug in blood is in plasma, the remainder being sequestered in blood cells. The unbound fraction in plasma is about 26%. Everolimus is extensively metabolized in the liver, and eliminated in the bile. Major metabolites are inactive. Everolimus is a substrate of CYP3A4 and a substrate and moderate inhibitor of P-glycoprotein and so its metabolism is sensitive to drugs which modify these enzymes. Competitive inhibition could occur when everolimus is combined with drugs which are also CYP3A4 or P-glycoprotein substrates. The elimination half-life is approximately 30 hours.

Absorption

In patients with advanced solid tumors, peak everolimus concentrations are reached 1 to 2 hours after administration of oral doses ranging from 5 mg to 70 mg. Following single doses, Cmax is dose-proportional between 5 mg and 10 mg. At doses of 20 mg and higher, the increase in Cmax is less than dose-proportional, however AUC shows dose-proportionality over the 5 mg to 70 mg dose range. Steady-state was achieved within two weeks following once-daily dosing.

Food effect: Based on data in healthy subjects taking 1 mg everolimus tablets, a high-fat meal reduced Cmax and AUC by 60% and 16%, respectively. No data are available with AFINITOR 5 mg and 10 mg tablets.

Distribution

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5000 ng/mL, is 17% to 73%. The amount of everolimus confined to the plasma is approximately 20% at blood concentrations observed in cancer patients given AFINITOR 10 mg/day. Plasma protein binding is approximately 74% both in healthy subjects and in patients with moderate hepatic impairment.

5.3.3 Metabolism

Everolimus is a substrate of CYP3A4 and PgP. Following oral administration, everolimus is the main circulating component in human blood. Six main metabolites of everolimus have been detected in human blood, including three monohydroxylated metabolites, two hydrolytic ring-opened products, and a phosphatidylcholine conjugate of everolimus. These metabolites were also identified in animal species used in toxicity studies, and showed approximately 100-times less activity than everolimus itself. In vitro, everolimus competitively inhibited the metabolism of CYP3A4 and was a mixed inhibitor of the CYP2D6 substrate dextromethorphan. The mean steady state Cmax following an oral dose of 10 mg daily is more than 12-fold below the Ki-values of the in vitro inhibition. Therefore, an effect of everolimus on the metabolism of CYP3A4 and CYP2D6 substrates is unlikely.

5.3.4 Excretion

No specific excretion studies have been undertaken in cancer patients. Following the administration of a 3 mg single dose of radiolabelled everolimus in patients who were receiving cyclosporine, 80% of the radioactivity was recovered from the feces, while 5% was excreted in the urine. The parent substance was not detected in urine or feces. The mean elimination half-life of everolimus is approximately 30 hours.

Patients with Renal Impairment

Approximately 5% of total radioactivity was excreted in the urine following a 3 mg dose of [14C]-labeled everolimus. In a population pharmacokinetic analysis which included 170 patients with advanced cancer, no significant influence of creatinine clearance (25 – 178 mL/min) was detected on oral clearance (CL/F) of everolimus

Patients with Hepatic Impairment

The average AUC of everolimus in eight subjects with moderate hepatic impairment (Child-Pugh class B) was twice that found in eight subjects with normal hepatic function. AUC was positively correlated with serum bilirubin concentration and with prolongation of prothrombin time and negatively correlated with serum albumin concentration. A dose reduction for patients with Child-Pugh class B hepatic impairment is recommended. AFINITOR should not be used in patients with severe (Child-Pugh class C) hepatic impairment as the impact of severe hepatic impairment on everolimus exposure has not been assessed.

Effects of Age and Gender

In a population pharmacokinetic evaluation in cancer patients, no relationship was apparent between oral clearance and patient age or gender.

Ethnicity

Based on a cross-study comparison, Japanese patients (n = 6) had on average exposures that were higher than non-Japanese patients receiving the same dose. Based on analysis of population pharmacokinetics, oral clearance (CL/F) is on average 20% higher in Black patients than in Caucasians. The significance of these differences on the safety and efficacy of everolimus in Japanese or Black patients has not been established.

5.3.5 Non Clinical Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Administration of everolimus for up to 2 years did not indicate oncogenic potential in mice and rats up to the highest doses tested (0.9 mg/kg) corresponding respectively to 4.3 and 0.2 times the estimated clinical exposure (AUC0-24h) at the recommended human dose of 10 mg daily. Everolimus was not genotoxic in a battery of in vitro assays (Ames mutation test in Salmonella, mutation test in L5178Y mouse lymphoma cells, and chromosome aberration assay in V79 Chinese hamster cells). Everolimus was not genotoxic in an in vivo mouse bone marrow micronucleus test at doses up to 500 mg/kg/day (1500 mg/m2/day, approximately 255-fold the recommended human dose, based on the body surface area), administered as two doses, 24 hours apart. Based on non-clinical findings, male fertility may be compromised by treatment with AFINITOR. In a 13-week male fertility study in rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm count, and plasma testosterone levels were diminished at 5 mg/kg, which resulted in infertility at 5 mg/kg. Effects on male fertility occurred at the AUC0-24h values below that of therapeutic exposure (approximately 10%-81% of the AUC0-24h in patients receiving the recommended dose of 10 mg daily). After a 10-13 week non-treatment period, the fertility index increased from zero (infertility) to 60% (12/20 mated

females were pregnant). Oral doses of everolimus in female rats at ≥ 0.1 mg/kg (approximately 4% the AUC0-24h in patients receiving the recommended dose of 10 mg daily) resulted in increases in pre-implantation loss, suggesting that the drug may reduce female fertility. Everolimus crossed the placenta and was toxic to the conceptus.

In safety pharmacology studies, everolimus was devoid of relevant effects on vital functions including the cardiovascular, respiratory and nervous systems. Everolimus had no influence on QT interval prolongation. Furthermore, everolimus showed no antigenic potential. Although everolimus passes the blood-brain barrier, there was no indication of relevant changes in the behavior of rodents, even after single oral doses up to 2000 mg/kg or after repeated administration at up to 40 mg/kg/day. Based on these findings, the potential of everolimus to affect vital functions in patients is low.

Everolimus has no genotoxicity or carcinogenicity potential. All significant adverse events observed in preclinical toxicology studies with everolimus in mice, rats, monkeys and minipigs were consistent with the anticipated pharmacological action as an antiproliferative and immunosuppressant and at least in part reversible after a two or four week recovery period, with the exception of the changes in male reproductive organs, most notably testes. Ocular effects (lenticular disorders) observed in rats were not observed in any other species and are considered to be a species-specific disorder. The known pharmacokinetic half-life of 30 hours in patients, and the prolonged pharmacodynamic effect of several days demonstrated preclinically, justified initial use of a weekly regimen in patients as a means of investigating safety at doses higher than those used in previous transplant studies. At the same time, analysis of changes in a non-tumoral, blood borne biomarker of activity in patients permitted pharmacokinetic-pharmacodynamic modeling with extrapolation from preclinical findings to predict the likely effect of everolimus on its intracellular target in tumors, at different doses for both the weekly and daily regimens.

5.3.6 Clinical Studies

Everolimus has been investigated in various indications, including solid organ transplantation, hematologic and non-hematologic malignancies, and rheumatoid arthritis. Efforts to evaluate everolimus in the setting of rheumatoid arthritis have since been discontinued. Everolimus has been in clinical development for solid organ transplantation since 1996 and obtained marketing authorization in 2003 under the trade name Certican®. Certican® is indicated for prophylaxis of rejection in renal and cardiac transplantation in over 60 countries, including the majority of the European Union. Certican® is commercially available in tablets strengths of .25, .5, .75 and 1 mg. In the United States Certican® is an investigational new drug in development for the indication of transplantation. Everolimus has been in development for patients with various

hematologic and nonhematologic malignancies since 2002, and has been evaluated either as a single agent or in combination with other antitumor agents, tyrosine kinase inhibitors, antibodies and aromatase inhibitors. Patients with metastatic renal cell carcinoma (mRCC) who failed a previous vascular endothelial growth factor receptor (VEGFr) tyrosine kinase inhibitor (TKI), advanced breast cancer patients, carcinoid neuroendocrine tumors, pancreatic islet cell tumors (pNET), hematologic malignancies including chronic myelogenous leukemia (CML) non-Hodgkin's and mantle cell lymphoma, hepatocellular, gastric, colorectal, gastrointestinal stromal tumors (GIST), prostate and other indications including sarcoma, head, neck, lung and glioblastoma multiforme conducted in investigator sponsored studies have or are being conducted. A Phase III, randomized, double blind, placebo controlled study in patients with mRCC who progressed on a VEGFr TKI recently demonstrated that everolimus, administered daily at an oral dose of 10 mg administered provides positive clinical benefit.[10] Median progression free survival (PFS) was prolonged from 1.87 months for patients receiving placebo to 4.01 months for everolimus treated patients, assessed by central independent review blinded to clinical data (hazard ratio 0.30, 95% CI 0.22-0.40, p<0·0001). Median PFS was prolonged from 1.87 months for patients receiving placebo to 4.9 months for everolimus treated patients, assessed by central independent review blinded to clinical data (hazard ratio 0.33, 95% CI 0.25-0.43, p<0.001). Additionally, two Phase III combination studies are ongoing for patients with advanced pNET receiving best supportive care, and one in carcinoid tumors with Sandostatin LAR® Depot.

An international, multicenter, randomized, double-blind trial comparing AFINITOR 10 mg daily and placebo, both in conjunction with best supportive care, was conducted in patients with metastatic renal cell carcinoma whose disease had progressed despite prior treatment with sunitinib, sorafenib, or both sequentially. Prior therapy with bevacizumab, interleukin 2, or interferon-α was also permitted. Randomization was stratified according to prognostic score1 and prior anticancer therapy.

Progression-free survival (PFS), documented using RECIST (Response Evaluation Criteria in Solid Tumors) was assessed via a blinded, independent, central radiologic review. After documented radiological progression, patients could be unblinded by the investigator: those randomized to placebo were then able to receive open-label AFINITOR 10 mg daily. In total, 416 patients were randomized 2:1 to receive AFINITOR (n=277) or placebo (n=139). Demographics were well balanced between the two arms (median age 61 years; 77% male, 88%

Caucasian, 74% received prior sunitinib or sorafenib, and 26% received both sequentially). AFINITOR was superior to placebo for progression-free survival. The treatment effect was similar across prognostic scores and prior sorafenib and/or sunitinib. The overall survival (OS) results were not mature and 32% of patients had died by the time of cut-off.

Supplier(s)

Novartis Pharmaceuticals Corporation will supply everolimus (Afinitor^{R}) to study participants at no charge.

Drug Handling

Procedures for proper handling and disposal of anticancer drugs should be considered. AFINITOR tablets should not be crushed. Direct contact of crushed tablets with the skin or mucous membranes should be avoided. If such contact occurs, wash thoroughly as outlined in the references. Personnel should avoid exposure to crushed tablets.

Dosage form

Everolimus will be supplied as tablets for oral administration.

Packaging

Everolimus will be provided to patients through the Investigational Drug Supply Pharmacy at the Winship Cancer Institute at the beginning of each cycle. Blister packets will contain sufficient number of capsules for one cycle of dosing**.**

Storage

Store AFINITOR (everolimus) tablets at 25° C (77°F); excursions permitted between 15°–30°C (59°–86°F). Store in the original container, protect from light and moisture. Keep this and all drugs out of the reach of children.

5.4 Screening and Eligibility

The Investigator is responsible for keeping a record of all subjects who sign an Informed Consent Form for entry into the study. All subjects will be screened for eligibility. Screening procedures are outlined in Section 2, Schedule of Study Assessments and unless otherwise specified, must take place within 28 days prior to initiation of therapy.

Approximately 45 subjects with advanced refractory solid malignancies will be screened for enrollment and must meet the eligibility criteria below.

Subjects must meet the following inclusion/exclusion criteria to be eligible for the study.

5.4.1 Inclusion Criteria

- Subjects must meet the following inclusion/exclusion criteria to be eligible for the study.
- Ability to understand and willingness to voluntarily sign an informed consent form.
- Histologic or cytologic confirmation of a solid malignancy
- Age ≥18 years at the time of signing the informed consent form. Because no dosing or adverse event data are currently available on the use of everolimus in combination with lenalidomide in patients <18 years of age, children are excluded from this study.
- Able to adhere to the study visit schedule and other protocol requirements.
- Patients must have at least one measurable site of disease according to RECIST 1.1 criteria that has not been previously irradiated. If the patient has had previous radiation to the marker lesion(s), there must be evidence of progression since the radiation.
- Diagnosed with advanced refractory solid malignancies or intolerant of standard therapy for the stage of the disease (because there is currently no standard approved therapy for adenoidcystic carcinoma, therefore there is no requirement of prior therapy for this patient population).
- All previous cancer therapy, including radiation, hormonal therapy and surgery, must have been discontinued at least 4 weeks prior to treatment in this study. A minimum of 6 weeks treatment break is required in case of nitrosoureas or mitomycin C.
- ECOG performance status of 0 - 2 at study entry (see Appendix A).
- Able to receive prophylactic anticoagulation with aspirin, warfarin or low molecular weight heparin when required for lenalidomide administration
- Fasting serum cholesterol ≤300 mg/dL OR ≤7.75 mmol/L AND fasting triglycerides ≤ 2.5 x ULN. NOTE: In case one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication.

- Laboratory test results within these ranges:
    - Absolute neutrophil count 1500 ≥ /mm³
    - Platelet count ≥ 100,000/mm³
    - Hb ≥9 g/dL
    - Creatinine within institutional limits of normal or Creatinine clearance ≥ 60 ml/min/m^2 if elevated creatinine (see Appendix F: Cockcroft-Gault estimation of CrCl):

- Total bilirubin < 2.0 mg/dL or < 1.5.0 x ULN for the institution whichever is higher
- AST (SGOT) and ALT (SGPT) < 2.x ULN or < 5 x ULN if hepatic metastases are present.

- All study participants must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of the REMS® program.
- Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.
- Females of childbearing potential (FCBP)[†] must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days prior to and again within 24 hours of prescribing lenalidomide (prescriptions must be filled within 7 days) and 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 she starts taking 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. See Appendix B: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

5.4.2 Exclusion criteria

- 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 including signing the informed consent form.
- Pregnant or breast feeding females. (Lactating females must agree not to breast feed while taking lenalidomide).

[†] A female of childbearing potential 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).

- Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.
- Use of any other experimental drug or therapy within 28 days of baseline.
- Known hypersensitivity to thalidomide or everolimus (including other rapamycins, sirolimus and temsirolimus).
- The development of erythema nodosum if characterized by a desquamating rash while taking thalidomide or similar drugs.
- Prior treatment with lenalidomide or everolimus
- Concurrent use of other anti-cancer agents or treatments.
- Patients known to be positive for HIV or infectious hepatitis, type B or C requiring active therapy (hepatitis B seropositivity due to Hep B virus vaccine is not an exclusion). Patients on combination antiviral therapy are ineligible because of the potential for pharmacokinetic interactions with everolimus and or lenalidomide. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in this patient population.
- Liver disease such as cirrhosis or severe hepatic impairment (Child-Pugh class C).
    - History of liver disease, such as cirrhosis or chronic active hepatitis B and C.
    - Presence of Hepatitis B surface antigen (HbsAg)
    - Presence of Hepatitis C antibody test (anti-HCV)
    - Note: A detailed assessment of Hepatitis B/C medical history and risk factors must be done at screening for all patients. HBV DNA and HCV RNA PCR testing are required at screening for all patients with a positive medical history based on risk factors and/or confirmation of prior HBV/HCV infection.
- Symptomatic brain metastasis. Patients with treated brain metastasis must be completely weaned off of steroid therapy for at least 14 days prior to starting protocol therapy
- Patients receiving chronic, systemic treatment with corticosteroids or another immunosuppressive agent. (Topical or inhaled corticosteroids are allowed).
- Patients should not receive immunization with attenuated live vaccines within one week of study entry or during study period

- Diagnosed venous thromboembolic disease within the preceding 6 months (patient on full dose or prophylactic anticoagulation are eligible)
- Patients receiving any medications or substances that are inhibitors or inducers of CYP450 enzyme(s) are ineligible. Lists of excluded medications and substances known or with the potential to interact with theCYP450 enzyme(s) are provided in Appendix E.
- History of other malignancies except: (i) adequately treated basal or squamous cell carcinoma of the skin; (ii) curatively treated, a) in situ carcinoma of the uterine cervix, b) prostate cancer, or c) superficial bladder cancer; or (iii) other curatively treated solid tumor with no evidence of disease for ≥ 3 years
- Patients, who have had a major surgery or significant traumatic injury within 4 weeks of start of study drug, patients who have not recovered from the side effects of any major surgery (defined as requiring general anesthesia) or patients that may require major surgery during the course of the study
- Patients with an active, bleeding diathesis

5.4.3 Inclusion of Women and Patients of Ethnic Minority Background

Both men and women of all races and ethnic groups are eligible for this trial.

5.5 Visit schedule and assessments

Screening Assessments and all on study scheduled visits and assessments are outlined in Section 2 Table of Study Assessments.

At treatment discontinuation, subjects will undergo off study evaluations per the Schedule of Assessments, Section 2. In addition, a safety assessment will be done approximately 30 days post the last dose of protocol therapy.

5.6 Drug Administration

5.6.1 Treatment assignments

Patient will be assigned to dose cohort in the order they enter the study using the modified Fibonacci dose escalation schema as detailed in Table 1, section 5.1.

5.6.2 Dosing regimen

The planned starting dose of lenalidomide for investigation is 10 mg/day, orally on days 1 - 28 (28 day cycle). Dosing will be in the morning at approximately the same time each day. Prescriptions must be filled within 7 days. Subjects deemed by the Principal Investigator to be at heightened risk of venous thromboembolism will receive prophylaxis with daily aspirin (81mg or 325 mg) or low molecular weight heparin if intolerant to ASA. Coumadin should be used with caution and close monitoring of INR required.

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.

The planned starting dose of everolimus (RAD001) is an approved dose of 5 mg/day on a continuous basis, days 1- 28. RAD001 will be self-administered (by the patients themselves). The investigator will instruct the patient to take the study drug exactly as specified in the protocol. RAD001 will be administered orally as once daily dose of 5 mg or 10 mg (one or two 5 mg tablets) starting from study day 2, cycle 1 until progression of disease or unacceptable toxicity. Patients will be instructed to take RAD001 in the morning, at the same time each day.

RAD001 may be taken with or without food.

If vomiting occurs, no attempt should be made to replace the vomited dose.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded.

Medication labels will comply with US legal requirements and be printed in English. They will supply no information about the patient. The storage conditions for study drug will be described on the medication label.

RAD001 will be provided by Novartis. RAD001 is formulated as tablets for oral administration of 5mg strength. Tablets are blister-packed under aluminum foil in units of 10 tablets, which should be opened only at the time of administration as drug is both hygroscopic and light-sensitive.

Subjects experiencing adverse events may need study treatment modifications (See section 5.7).

5.6.3 Special Handling Instructions

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

5.6.4 Record of administration

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

5.7 Dose Continuation, Modification and Interruption

Subjects will be evaluated for adverse events (AEs) at each visit with the NCI CTCAE v4.0 (Appendix C: NCI CTCAE v4.0) used as a guide for the grading of severity. Sections below describe dose reduction steps, instructions for initiation of a new cycle of therapy and dose modifications during a cycle of therapy.

5.7.1 Dose Reduction Steps

This dose reduction steps will guide dose modification for Lenalidomide and Everolimus in patients who either experienced a DLT or who develop treatment related toxicity beyond cycle 1 of therapy. The decision for dose escalation or deesclation for dose cohorts will however proceed according to the dose escalation schema (Table 1, Section 5.1).

Table 3: LENALIDOMIDE Dose Reduction Steps

If toxicity occurred at	Reduce dose to

25 mg	20 mg daily
20 mg	15 mg daily
15 mg	10 mg daily
10 mg	10 mg daily on Days 1-21 every 28 days
10 mg daily on Days 1 – 21 of 28	5 mg daily on Days 1-21 every 28 days

Table 4: Everolimus Dose Reduction Steps

If the Toxicity occurred at --- (MG/DOSE):	Reduce dose to --- (MG/DOSE):
0 (starting dose)	10 mg daily
-1	5 mg daily
-2	5 mg every other day

5.7.2 Instructions for initiation of a New Cycle

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

- The ANC is ≥ 1500/mm³;
- The platelet count is 100,000≥ /mm³; (If held during the previous cycle for low platelet count, prophylactic anti-coagulation should be re-started when platelet count is ≥75,000)
- Any drug-related rash or neuropathy that may have occurred has resolved to ≤ grade 1 severity;
- Any other drug-related adverse events that may have occurred have resolved to ≤ grade 2 severity.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of treatment will not be initiated until the toxicity has resolved as described above. If a lenalidomide or everolimus dose reduction was taken during the previous cycle, and the cycle was completed without requiring further dose modification, then the next cycle will start at the same reduced dose. **If drug dosing was omitted for the remainder of the previous cycle or if the new cycle is delayed due to toxicity newly encountered on the scheduled Day 1**, then the

new cycle will be started with a one-level dose reduction of the drug to which the toxicity was attributed.

5.7.3 Instructions for dose modifications or interruption during a cycle

This information is meant to assist in dose modification for individual study participant who experienced a treatment-related toxicity. The dose escalation schema for the study cohort will proceed as described under the escalation schema (refer Table 1, Section 5.1).

In the event of treatment interruption due to study-drug related toxicity, both agents will be held until the patient is able to resume further therapy. At the time of dosing resumption, alternate dose reduction strategy will be employed if the dose reduction is necessitated by hematologic toxicity. This alternate dose reduction will always start with Lenalidomide (not required if already at the minimum dose of 5mg) followed by Everolimus if further reduction is still necessary. In the case of non-hematological toxicity, dose reduction will be limited to the drug with the highest likelihood of attribution. In case of equal likelihood of attribution or where clear attribution is impossible, simultaneous reduction of both drugs will be effected at resumption of therapy.

NB: Patients unable to resume treatment within the allotted time period for recovery from treatment-related toxicities detailed in Table 5 and Table 6 may be allowed to resume treatment with express approval of the study sponsor provided they have evidence of clinical benefit from treatment and the toxicity has resolved to a level considered safe for further treatment with everolimus or lenalidomide. Also, patient may be allowed to continue on only one study drug if a permanent discontinuation of the other study drug is mandated by a unique treatment-related toxicity e.g. discontinuation of lenalidomide for desquamating rash.

Table 5: Dose Modifications NOTE: Please consider altering threshold hematologic toxicity criteria for dose modifications depending on specific disease and patient population involved in study, and with consideration given to the Inclusion Criteria and the Instructions for Initiation of a New Cycle. Also consider whether the use of G-CSF is permitted as outlined in the neutropenia row. For combination therapy trials, please consider the following recommendations/issues: 1) it is highly recommended that appropriate dose modifications (holding and reductions as needed) for other drugs in the regimen are incorporated into this table, 2) whether the holding of 1 drug requires other drugs to be held, 3) for drugs with overlapping toxicities (hematologic toxicities, for example) please consider, if appropriate, alternating dose reductions by episode (reduce 1 drug for the first episode and then another drug for the second episode and continuing to alternate which drug is reduced for subsequent reductions as needed, and 4) whether dose modifications for the category "other non-hematologic toxicities ≥ grade 3" should be based on attribution (this is recommended).

NCI CTC Toxicity Grade	Dose Modification Instructions
Grade 3 neutropenia associated with fever (temperature ≥ 38.5º C) or Grade 4 neutropenia	• Hold (interrupt) lenalidomide dose. • Follow CBC weekly. • If neutropenia has resolved to ≤ grade 2 within 14 days, restart lenalidomide at next lower dose level and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the lenalidomide dose maintained prior to considering dose reduction for Everolimus.
Thrombocytopenia ≥Grade 3 (platelet count < 50,000/mm³)	• Hold (interrupt) lenalidomide dose. • Follow CBC weekly. • If thrombocytopenia resolves to ≤ grade 2 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up.
Platelet count < 50,000/mm³	• Hold prophylactic anti-coagulation, if applicable. • Restart prophylactic anti-coagulation when platelet count is ≥ 75,000/mm³.
Non-blistering rash **Grade 3** **Grade 4**	• If Grade 3, hold (interrupt) lenalidomide dose. Follow weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 28, restart lenalidomide at next lower dose level and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. • If Grade 4, discontinue lenalidomide. Remove patient from study.
Desquamating (blistering) rash- any Grade	• Discontinue lenalidomide. Remove patient from study.

Table 5: Dose Modifications NOTE: Please consider altering threshold hematologic toxicity criteria for dose modifications depending on specific disease and patient population involved in study, and with consideration given to the Inclusion Criteria and the Instructions for Initiation of a New Cycle. Also consider whether the use of G-CSF is permitted as outlined in the neutropenia row. For combination therapy trials, please consider the following recommendations/issues: 1) it is highly recommended that appropriate dose modifications (holding and reductions as needed) for other drugs in the regimen are incorporated into this table, 2) whether the holding of 1 drug requires other drugs to be held, 3) for drugs with overlapping toxicities (hematologic toxicities, for example) please consider, if appropriate, alternating dose reductions by episode (reduce 1 drug for the first episode and then another drug for the second episode and continuing to alternate which drug is reduced for subsequent reductions as needed, and 4) whether dose modifications for the category "other non-hematologic toxicities ≥ grade 3" should be based on attribution (this is recommended).

NCI CTC Toxicity Grade	Dose Modification Instructions
Neuropathy **Grade 3**	• If Grade 3, hold (interrupt) lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 28, restart lenalidomide at next lower dose level and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up.
Grade 4	• If Grade 4, discontinue lenalidomide. Remove patient from study.
Venous thrombosis/embolism ≥ Grade 3	• Hold (interrupt) lenalidomide and start anticoagulation; restart lenalidomide at investigator's discretion (maintain dose level). • Omit lenalidomide for remainder of cycle. See Anticoagulation Consideration (Section 5.7.2)
Hyperthyroidism or hypothyroidism	• Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. • Resume lenalidomide at the same dose for 1st occurrence • Reduce dose of lenalidomide with 2nd occurrence • See Instructions for Initiation of a New Cycle
other non-hematologic toxicity ≥ Grade 3	• Hold (interrupt) lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 2 prior to Day 28, restart lenalidomide and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle. Omitted doses are not made up. For toxicity attributed to lenalidomide, reduce the lenalidomide dose by 1 dose level when restarting lenalidomide.

Table 6: Dose Interruption/Modification Guidelines for Everolimus

Please note that in case of hematological toxicity, Everolimus dose reduction should be considered only if the dose reduction for lenalidomide has been effected as per Table 5 above and found to be ineffective or insufficient to allow the patient to safely resume therapy per protocol guidelines

Toxicity	Actions
Non-hematological toxicity	
Grade 2 (except pneumonitis – refer to Table 3-2)	If the toxicity is tolerable to the patient, maintain the same dose. If the toxicity is intolerable to patient, interrupt RAD001 until recovery to grade ≤1. Then reintroduce RAD001 at same dose. If event returns to grade 2, then interrupt RAD001 until recovery to grade ≤1. Then reintroduce RAD001 at the lower dose level.
Grade 3 (except hyperlipidemia*) (except pneumonitis – refer to Table 3-2)	Interrupt RAD001 until recovery to grade ≤1. Then reintroduce RAD001 at the lower dose level. For pneumonitis consider the use of a short course of corticosteroids.
Grade 4	Discontinue RAD001.
Hematological toxicity	
Grade 2 Thrombocytopenia (platelets <75, ≥ 50x10^9/L)	Interrupt RAD001 until recovery to grade ≤1 (>75 x10^9/L). Then reintroduce RAD001 at initial dose. If thrombocytopenia again returns to grade 2, interrupt RAD001 until recovery to grade ≤1. Then reintroduce RAD001 at the lower dose level.
Grade 3 Thrombocytopenia (platelets <50, ≥ 25 x10^9/L)	Interrupt RAD001 until recovery to grade ≤1 (platelets ≥ 75 x10^9/L). Then resume RAD001 at one dose level lower. If grade 3 thrombocytopenia recurs, discontinue RAD001.
Grade 4 Thrombocytopenia (platelets < 25 x10^9/L)	Discontinue RAD001.
Grade 3 Neutropenia (neutrophils <1, ≥0.5 x10^9/L)	Interrupt RAD001 until recovery to grade ≤1 (neutrophils ≥ 1.5 x 10^9/L). Then resume RAD001 at the initial dose. If ANC again returns to Grade 3, hold RAD001 until the ANC ≥ 1.5 x 10^9/L. Then resume RAD001 dosing at the lower dose level. Discontinue patient from study therapy for a third episode of grade 3 neutropenia.
Grade 4 Neutropenia (neutrophils < 0.5 x10^9/L)	Interrupt RAD001 until recovery to grade ≤ 1 (neutrophils ≥ 1.5 x 10^9/L). Then resume RAD001 at the lower dose level. If grade 3 or grade 4 neutropenia occurs despite this dose reduction, discontinue RAD001.
Grade 3 febrile neutropenia (not life-threatening)	Interrupt RAD001 until resolution of fever and neutropenia to grade ≤ 1. Hold further RAD001 until the ANC ≥ 1,500/mm^3 and fever has resolved. Then resume RAD001 at the lower dose level. If febrile neutropenia recurs, discontinue RAD001.
Grade 4 febrile neutropenia (life-threatening)	Discontinue RAD001.
Any hematological or non-hematological toxicity requiring interruption for ≥ 3 weeks	Discontinue RAD001

Grade 3 hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia) should be managed using medical therapies (see Sec. 3.2.5.2).

5.7.4 Monitoring of RAD001 suspected toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value suspected to be related to RAD001 must be followed at least weekly until the adverse event or abnormal laboratory resolves or returns to grade 1. If a patient requires a dose delay of > 21 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study.

5.7.5 Known Undesirable Side Effects of RAD001

Overall, the most frequent adverse effects suspected to be related to RAD001 have been stomatitis, rash, anemia, fatigue, asthenia, diarrhea, anorexia, nausea, hypercholesterolemia, mucosal inflammation, vomiting, hypertriglyceridemia, cough, peripheral edema, dry skin, epistaxis, pruritus and dyspnea. The most common Grade 3 or 4 adverse reactions suspected to be related to treatment were anemia, infections, hyperglycemia, stomatitis, fatigue, lymphopenia, hypercholesterolemia, pneumonitis, and elevated gammaglutamyltransferase concentrations.

The principal DLT in Phase 1 trials has been Grade 3 stomatitis. For guidance on management of stomatitis refer to Section 5.7.6.

Hyperlipidemia was reported as a serious adverse reaction. It is a recognized side-effect of rapamycins. Use of lipid-lowering drugs should be associated with dietary recommendations. Monitoring of blood lipid levels requires patients to be fasting so that this aspect must be verified when interpreting results. For guidance on management of hyperlipidemia refer to Section 5.7.7.

Hyperglycemia was reported as a serious adverse reaction. Similarly, the fasting state of patients should be verified when interpreting results. For guidance on management of hyperglycemia refer to Section 5.7.7.

Pneumonitis is a recognized adverse effect of rapamycins (sirolimus, temsirolimus, and everolimus). Numerous case reports in the literature suggest that rapamycin-associated pneumonitis is relatively unaggressive, limited in extent, and reversible upon drug discontinuation. The term ‘pneumonitis’ is used here to describe non-infectious, non-malignant infiltration in the lungs which is evident radiologically. More precise diagnosis should follow histocytological examination following lung biopsy, generally during bronchoscopy which may or may not be symptomatic. Advice on the management of pneumonitis has been provided in Table 7.

In oncology studies with RAD001, severe pneumonitis suspected as drug-related has been reported as a serious adverse event on 13 occasions and additionally in the following associated preferred terms including acute respiratory distress syndrome (n=2), alveolitis (n=1) and allergic alveolitis (n=1), interstitial lung disease (n=10), lung infiltration (n=23), cryptogenic organizing pneumonia, lung consolidation, pulmonary alvealoar haemorrhage, pulmonary toxicity and pulmonary fibrosis (n=1, each). One fatal case of drug-related pneumonitis was reported for a patient with metastatic infiltrating ductal carcinoma of the breast treated with 10 mg/day, which

developed approximately two months after starting RAD001. Cytology for both the pleural and pericardial fluids were positive for malignancy. The death was considered possibly related to the underlying late stage tumor and study drug. Additionally, one patient treated with 10 mg/day died due to severe acute respiratory distress syndrome and septic shock. Thoracic CT scan demonstrated condensation in the majority of the left lower lobe and frosted glass appearance in the left upper lobe, lingula, and right lung.

Along with the cases of non-infectious pneumonitis, serious opportunistic infections have also been reported in cancer patients treated with RAD001: mycobactrium, aspergillus, and fatal candidal sepsis, and fatal pneumocystis carnii in particular. Because RAD001, as other rapamycins, inhibits proliferation of activated lymphocytes and reduces neutrophil counts, treatment with RAD001 must be considered as predisposing patients to the risk of infection. This risk will be higher in patients severely immunocompromised because of their underlying disease and/or co-medications. Outcome may be fatal in case of serious infections.

A reduction in blood cell counts is frequent when RAD001 therapy is initiated. Without clinical significance and infrequently, anemia and thrombocytopenia have been reported. In heavily pretreated patients with aggressive lymphoma, the incidence of grade 3 anemia, neutropenia, and thrombocytopenia was reported to be 11%, 16%, and 30%, respectively. Serious, suspected drug-related hemorrhages have been exceptional. Nevertheless, RAD001 should be considered as predisposing patients to hemorrhage, potentially fatal, should they develop severe drug-related thrombocytopenia.

Discrete, reversible changes in liver enzymes have been found to occur in numerous patients during treatment with RAD001 in oncology clinical studies, and in a study in rheumatoid arthritis. In oncology studies, these changes may be evident only in patients without severe underlying morbidity. The increase in transaminase's (AST and ALT) generally appears after 4 weeks of treatment. In all but a few cases it does not exceed Grade 1 ($\leq$ 2.5 x ULN). Similarly, mild increases in alkaline phosphatases can coexist. Spontaneous corrections or intermittent correction with continued treatment can occur. Serum bilirubin is not increased. In studies of patients with advanced cancers, clinically relevant changes in liver enzymes have been invariably associated with the presence of liver metastases and/or progression of the underlying cancer.

Renal failure has been reported in five suspected cases to date. One patient with no alternative explanation made a complete recovery following study drug adjustment and no treatment/therapy for the event. The rest or the patients had concurrent morbidities, which might have contributed to the reported events.

Hypophosphatemia, hypomagnesemia, hyponatremia and hypocalcemia have been reported as serious adverse reactions. Electrolytes should be monitored in patients treated with RAD001.

Table 6 provides general recommendations for the management of patients, with suspected drug toxicities while on treatment with RAD001 as single-agent therapy.

More detailed information regarding RAD001 reported suspected toxicities and individual cases is provided in the [Investigator's Brochure].

5.7.6 Management of stomatitis/oral mucositis/mouth ulcers

Stomatitis/oral mucositis/mouth ulcers due to RAD001 should be treated using local supportive care. Please note that investigators in earlier trials have described the oral toxicities associated with RAD001 as mouth ulcers, rather than mucositis or stomatitis. If your examination reveals mouth ulcers rather than a more general inflammation of the mouth, please classify the adverse event as such. Please follow the paradigm below for treatment of stomatitis/oral mucositis/mouth ulcers:

1. For mild toxicity (Grade 1), use conservative measures such as **non-alcoholic mouth wash or salt water (0.9%) mouth wash** several times a day until resolution.
2. For more severe toxicity (Grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or Grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are **topical analgesic mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol)** with or without **topical corticosteroids,** such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).
3. Agents containing hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.
4. Antifungal agents must be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all patients due to their strong inhibition of RAD001 metabolism, thereby leading to higher RAD001 exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed. Similarly, antiviral agents such as acyclovir should be avoided unless a viral infection is diagnosed.

Note: Stomatitis/oral mucositis should be appropriately graded using the functional grading given on the NCI-CTC for adverse events, version 3.0.

5.7.7 Management of hyperlipidemia and hyperglycemia

Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits. Blood tests to monitor hyperlipidemia must be taken in the fasting state. Grade 2 hypercholesterolemia (> 300 mg/dL or 7.75 mmol/L) or Grade 2 hypertriglyceridemia (>2.5 x ULN) should be treated with a 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitor (e.g., atorvastatin, pravastatin) or appropriate lipid-lowering medication, in addition to diet. Patients should be monitored clinically and through serum biochemistry for the development of rhabdomyolysis and other adverse events as required in the product label/data sheets for HMG-CoA reductase inhibitors.

Note: Concomitant therapy with fibrates and an HMG-CoA reductase inhibitor is associated with an increased risk of a rare but serious skeletal muscle toxicity manifested by rhabdomyolysis, markedly elevated creatine kinase (CPK) levels and myoglobinuria, acute renal failure and sometimes death. The risk versus benefit of using this therapy should be determined for individual patients based on their risk of cardiovascular complications of hyperlipidemia.

Grade 3 **hyperglycemia** has been observed in patients receiving RAD001 therapy. In many cases in study RAD001 C2222, the affected patients had an abnormal fasting glucose at baseline.

Based on this finding, it is suggested that optimal glucose control should be achieved before starting a patient on RAD001 and should be monitored during RAD001 therapy.

5.7.8 Management of non-infectious pneumonitis

Both asymptomatic radiological changes (grade 1) and symptomatic non-infectious pneumonitis (grade 2 = not interfering with activities of daily living or grade 3 = interfering with activities of daily living and oxygen indicated) have been noted in patients receiving RAD001 therapy. Non-infectious pneumonitis has been associated with RAD001 and other mTOR inhibitors (Atkins 2004). In order to monitor for asymptomatic (grade 1) pulmonary infiltrates, a chest X-ray is required if a CT scan of chest is not used for bi-monthly disease evaluations. Additional chest CT scans may be performed, when clinically necessary. If non-infectious pneumonitis develops, a consultation with a pulmonologist should be considered. If the patient develops grade 3 pneumonitis, treatment with RAD001 should be interrupted and the patient should be treated as medically indicated (short course corticosteroids, oxygen, etc).

Management of non-infectious pneumonitis suspected to be associated with RAD001 and dose modifications instructions are provided in Table 3-2

Table 7 Management of non-infectious pneumonitis

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	RAD001 Dose Adjustment
Grade 1	**CT scans with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O_2 saturation at rest. Repeat chest x-ray/CT scan every 2 Cycles until return to baseline.**	**No specific therapy is required**	**Administer 100% of RAD001 dose.**
Grade 2	**CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O_2 saturation at rest. Repeat each subsequent Cycle until return to baseline. Consider bronchoscopy ***	**Symptomatic only. Prescribe corticosteroids if cough is troublesome.**	**Reduce RAD001 dose until recovery to ≤ Grade 1. RAD001 may also be interrupted if symptoms are troublesome. Patients will be withdrawn from the study if they fail to recover to ≤ Grade 1 within 3 weeks.**
Grade 3	**CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O_2 saturation at rest.; Repeat each subsequent Cycle until return to baseline. Bronchoscopy is recommended ***	**Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.**	**Hold treatment until recovery to ≤ Grade 1. May restart protocol treatment within 2 weeks at a reduced dose (by one level) if evidence of clinical benefit. Patients will be withdrawn from the study if they fail to recover to ≤ Grade 1 within 2 weeks.**
Grade 4	**CT scan with lung windows and required pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat each subsequent Cycle until return to baseline. Bronchoscopy is recommended *.**	**Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.**	**Discontinue treatment.**

***A bronchoscopy with biopsy and/or bronchoalveolar lavage is recommended.**

All interruptions or changes to study drug administration must be recorded.

5.8 Treatment compliance

Research center personnel will review the dosing instructions with subjects. Subjects will be asked to maintain a diary to record the drug administration (Appendix Y). Subjects will be asked to bring any unused drug and empty drug containers to the research center at their next visit. Research personnel will count and record the number of used and unused drug at each visit and reconcile with the patient diary.

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

Any unused everolimus pills should be returned to the IDS pharmacy for appropriate handling and destruction.

5.9 Concomitant therapy-Lenalidomide

5.9.1 Recommended concomitant therapy

Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, and antiemetics when appropriate

5.9.2 Anticoagulation Consideration

Lenalidomide increases the risk of thrombotic events in patients who are at high risk or with a history a thrombosis, in particular when combined with other drugs known to cause thrombosis. When lenalidomide is combined with other agents such as steroids (e.g. dexamethasone, prednisone), anthracyclines (Doxil, Adriamycin) and erythropoietin the risk of thrombosis is increased.

Subjects deemed by the principal investigator at heightened risk of venous thrombosis will receive prophylactic anticoagulation with the use of aspirin (81 or 325 mg) or some other form of prophylaxis as deemed appropriate. Low molecular weight heparin may be utilized in patients that are intolerant to ASA. Coumadin should be used with caution and close monitoring of INR.

Prophylactic anti-coagulation should be held for platelet counts $\leq$ 50,000, and then restarted when platelet counts are $\geq$ 75, 000.

5.9.3 Prohibited concomitant therapy

Concomitant use of other anti-cancer therapies outside of the study drugs, including radiation or other investigational agents is not permitted while subjects are receiving protocol therapy during the treatment phase of the study.

5.10 Concomitant Therapy – Everolimus (RAD001)

Patients will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the investigator. At each visit, the investigator will ask the patient about any new medications he/she is or has taken after the start of the study drug.

All Concomitant medications/Significant non-drug therapies taken $\leq$ 30 days prior to start and after start of study drug, including physical therapy and blood transfusions, should be recorded.

The following restrictions apply during the entire duration of the study:

- No other investigational therapy should be given to patients.
- No anticancer agents other than the study medication should be given to patients. If such agents are required for a patient then the patient must first be withdrawn from the study.

- Co-administration with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) or P-glycoprotein (PgP) should be avoided
- Seville orange, star fruit, grapefruit and their juices affect P450 and PgP activity. Concomitant use should be avoided
- Co-administration with moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole) or PgP inhibitors should be used with caution. If patient requires co-administration of moderate CYP3A4 inhibitors or PgP inhibitors, reduce the dose of RAD001 to 5 mg daily. Additional dose reductions to 5 mg every other day may be required to manage toxicities. If the inhibitor is discontinued the RAD001 dose should be returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor.
- Avoid the use of strong CYP3A4 inducers. If patient requires co-administration of strong CYP3A4 inducers (i.e., phenytoin, carbamazepine, rifampin, rifabutin, Phenobarbital, St. John's wort)**, the patient should be monitored as per protocol and discontinued from study treatment if progression occurs.** An increase in the dose of RAD001 from 10 mg up to 20 mg daily should be considered, using 5 mg increments. Enzyme induction usually occurs within 7-10 days, therefore RAD001 dose should be increased to 15 mg daily, 7 days after the start of the inducer therapy. If no safety concerns are seen within the next 7 days, the dose can be increased again to 20 mg daily. This dose of RAD001 is intended to achieve similar AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the RAD001 dose should be returned to the dose used prior to initiation of the strong CYP3A4/PgP inducer.
- No chronic treatment with systemic steroids or another immunosuppressive agents. Topical or inhaled corticosteroids are allowed.
- RAD001 may affect the response to vaccinations making the response to the vaccination less effective. Live vaccines should be avoided while a patient is treated with RAD001.

Oral anticoagulants such as warfarin are CYP2C9 substrates and, as such, no interaction with RAD001 is expected. However, drug-drug interaction studies between macrolide antibiotics and warfarin have produced mixed outcomes and the disparity in these findings has led to the conclusion that multiple factors may alter the clearance of warfarin. The coadministration of RAD001 and oral anticoagulants is possible but should be subject to verification of coagulation (INR) once steady state is reached (after one week's treatment).

Examples are provided in Table 8. A comprehensive list of cytochrome P450 isoenzymes and CYP3A4 inhibitors, inducers, and substrates can be found at http://medicine.iupui.edu/flockhart. This website is continually revised and should be checked frequently for updates.

Table 8 Examples of clinically relevant drug interaction: substrates, inducers and inhibitors of isoenzyme CYP3A.

Substrates (competitive inhibition)	
Antibiotics[1]: clarithromycin* erythromycin telithromycin* Anti-arrhythmics: quinidine Benzodiazepines: alprazolam diazepam midazolam triazolam Immune Modulators: cyclosporine tacrolimus (FK506) HIV Protease Inhibitors: indinavir* ritonavir* saquinavir* Prokinetic: cisapride Antihistamines: astemizole chlorpheniramine_	Calcium Channel Blockers: amlodipine diltiazem felodipine nifedipine nisoldipine nitrendipine verapamil HMG CoA Reductase Inhibitors[2]: atorvastatin cerivastatin lovastatin simvastatin Miscellaneous: aprepitant buspirone haloperidol methadone pimozide quinine sildenafil tamoxifen trazodone vincristine
Inducers	
Carbamazepine Phenobarbital Phenytoin* Rifabutin*	Rifampin* St John's wort Troglitazone
Inhibitors	
Amiodarone Cimetidine Clarithromycin Delaviridine Diltiazem Erythromycin Fluvoxamine* Grapefruit juice Sevilla orange	Indinavir Itraconazole* Ketoconazole* Voriconazole* Posaconazole* Mibefradil Nefazodone* Nelfinavir* Troleandomycin Verapamil

Based on: Ingelman-Sundberg M, Human drug metabolising cytochrome P450 enzymes: properties and polymorphisms, Naunyn Schmiedebergs Arch Pharmacol. 2004 Jan;369(1):89-104. and [http://www.medicine.iupui.edu/flockhart/clinlist.htm as of July 13, 2006]

* asterisk denotes strong inhibition/ induction

Please note:

- strong inhibitor implies that it can cause ≥5-fold increase in AUC or ≥80% decrease in clearance of sensitive CYP substrates
- moderate inhibitor implies that it can cause 2 to 5-fold increase in AUC values or 50-80% decrease in clearance of sensitive CYP substrates.

  (Distinction is not always categorical as interaction can vary according to conditions).

1. Macrolide antibiotics: Azithromycin is not a CYP3A substrate. It may therefore be employed where

antibiotherapy with a macrolide is desirable in a patient being treated with RAD001

2. Statins: Atorvastatin and pravastatin may be associated with RAD001, since a PK interaction study has shown that there is no relevant PK interaction.

5.11 Discontinuation of Study Treatment

Treatment will continue at the prescribed dose level until the occurrence of any of the following events.

- Disease progression
- Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of the treatment regimen.
- Intolerance of lenalidomide or everolimus for any reason.
- Major violation of the study protocol.
- Withdrawal of consent
- Lost to follow up
- Death
    - Suspected pregnancy or positive pregnancy

5.12 Follow-Up

Subjects who discontinue treatment for any reason, will not be followed if they have no residual toxicity (≥ grade 3) attributable to the study drugs at the time of the final safety assessment planned for approximately 30 days post the last dose of protocol therapy. If otherwise indicated by persistent grade ≥ 3 toxicity, patients will be followed by telephone contact every 30 days. In addition off study evaluations per the Schedule of Assessments, Section 2 will be done.

6 Adverse events

6.1 Serious Adverse Event (SAE) Definition

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

· Results in death

· Is life-threatening[1]

Requires inpatient hospitalization or prolongation of existing hospitalization

· Results in persistent or significant disability or incapacity[2]

· Is a congenital anomaly or birth defect

· Is an important medical event[3]

· Pregnancy

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

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

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

6.2 Adverse Drug Reaction Reporting - Lenalidomide

Toxicity will be scored using CTCAE Version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP homepage (HTTP://CTEP.INFO.NIH.GOV
OR
HTTP://CTEP.CANCER.GOV/PROTOCOLDEVELOPMENT/ELECTRONIC_APPLICATIONS/DOCS/CTCAEV4.PDF). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

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

6.2.1 Pregnancies

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

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should

report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

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

Male Subjects

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

6.2.2 Celgene Drug Safety Contact Information:

Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

6.3 Adverse events – RAD001

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. the severity grade (mild, moderate, severe) or (grade 1-4)

2. its relationship to the study drug(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. whether it constitutes a serious adverse event (SAE)

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the [Investigators' Brochure]. This information should be included in the patient informed consent and should be discussed with the patient during the study as needed.

Serious adverse events

A serious adverse event is an undesirable sign, symptom or medical condition which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

To ensure patient safety, every SAE, **regardless of suspected causality**, occurring

- after the patient has provided informed consent and until 4 weeks after the patient has stopped study treatment/participation
- after the patient is randomized and until 4 weeks after the patient has stopped study treatment

- after the patient begins taking study drug and until 4 weeks after the patient has stopped study treatment
- after protocol-specified procedures begin (e.g., placebo run-in, washout period, double-blind treatment, etc.) and until 4 weeks after the patient has stopped study treatment
- after the start of any period in which the study protocol interferes with the standard medical treatment given to a patient (e.g., treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication) and until 4 weeks after the patient has stopped study treatment

must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this 4-week period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

The investigator must assess and record the relationship of each SAE to each specific study drug (if there is more than one study drug), complete the SAE Report in English, and send the completed, signed form by fax (888-299-4565) within 24 hours to the Novartis Clinical Safety and Epidemiology Department.

The original copy of the SAE Report and the fax confirmation sheet must be kept within the Trial Master File at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the [Investigator's Brochure] or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a Clinical Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

Novartis instructions for rapid notification of serious adverse events

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Novartis Pharmaceuticals Clinical Safety and Epidemiology Department (CS&E).

All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form).

All events must be reported, by FAX (888-299-4565), to Novartis Pharmaceuticals CS&E Department within 24 hours of learning of it's occurrence. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days.

Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).

Serious adverse events occurring more than 4 weeks after study discontinuation need only be reported if a relationship to the Novartis study drug (or therapy) is suspected.

For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer by the investigator.

Pregnancies

Any pregnancy that occurs during study participation should be reported. To ensure patient safety each pregnancy must also be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

6.3.1 Novartis Drug Safety Contact Information:

CS&E Department
Novartis Pharmaceuticals Corporation
Fax: 888-299-4565

6.4 Investigator Reporting Responsibilities

The conduct of the study will comply with all FDA safety reporting requirements.

IND Annual Reports

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33

provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Celgene Corporation and Novartis Pharmaceuticals as supporters of this study as follows.

Celgene Corporation
Attn: Medical Affairs Operations
Connell Corporate Park
400 Connell Drive Suite 700
Berkeley Heights, NJ 07922
Tel: (908) 673-9000

And

CS&E Department
Novartis Pharmaceuticals Corporation
180 Park Avenue
Florham Park, NJ 07932
Fax: 888-299-4565

All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (i.e. mild, moderate, severe), relationship to drug (i.e. probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and as defined above are present. The investigator is responsible for reporting adverse events to Celgene as described below.

6.4.1 Expedited reporting by investigator to Celgene

Serious adverse events (SAE) are defined above. The investigator must inform the study supporters, Novartis Pharmaceuticals and Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s) if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (RV-ST-PI-0558) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

6.4.2 Report of Adverse Events to the Institutional Review Board

The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

6.4.3 Investigator Reporting to the FDA

Serious adverse events (SAEs) that are **unlisted/unexpected, and at least possibly associated to the drug,** and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) by telephone or by fax. Fatal or life threatening SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 7 calendar days after awareness of the event. All other SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 15 calendar days after awareness of the event. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related. In accordance with 21CFR312.32, adverse events associated with the use of investigational use will be reported to the FDA. The PI is responsible for notifying the FDA and all other participating investigators in a written IND safety report of any AE that is both serious and unexpected.

6.5 Adverse Event Updates/IND Safety Reports

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

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

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

The Investigator must keep copies of all AE information, including correspondence with Celgene and the IRB/EC, on file (see Section 11.4 for records retention information).

7 Response Criteria

Baseline lesion assessments must occur within ≤ 28 days of protocol therapy initiation or as indicated in Section 2, Schedule of Study Assessments.

Efficacy assessments are scheduled to occur after every 2 cycles of protocol therapy or approximately every 8 weeks (as detailed in Schedule of Study Assessments Table). All partial and complete responses will be confirmed with another efficacy assessment in no less than 4 weeks apart.

Measurement of Effect

Measurable Disease - the presence of at least one measurable lesion at baseline is only mandatory for the expansion cohort. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable Lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm using conventional techniques or ≥10 mm with spiral CT scan.

Non-measurable Lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and:

All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

7.1.1 Methods of Measurement

• CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. 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 tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

• Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

• Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

• Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline Documentation of "Target" and "Non-Target" Lesions

• All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline.

• Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

• A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

• All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

7.1.2 Response Criteria

Evaluation of Target Lesions

Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD)	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of Non Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

7.1.3 Confirmation

The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

8 Protocol Amendments/Deviations

8.1 Protocol amendments

Any amendment to this protocol must be agreed to by the Principal Investigator and reviewed by Celgene. Amendments should only be submitted to IRB/EC after consideration of Celgene review. Written verification of IRB/EC approval will be obtained before any amendment is implemented.

8.2 Protocol deviations

When an emergency occurs that requires a deviation from the protocol for a subject, a deviation will be made only for that subject. A decision will be made as soon as possible to determine whether or not the subject (for whom the deviation from protocol was effected) is to continue in the study. The subject's medical records will completely describe the deviation from the protocol and state the reasons for such deviation. In addition, the Investigator will notify the IRB/EC in writing of such deviation from protocol.

Non-emergency minor deviations from the protocol will be permitted with approval of the Principal Investigator.

9 Data Management

9.1 Analyses and Reporting

Data will be analyzed and reported within 3 months of enrolment of the last patient in the expansion cohort.. All subsequent data collected will be analyzed and reported in a follow-up clinical report.

9.2 Publication of results

Any formal presentation or publication of data from this trial may be published after review and comment by Novartis and Celgene Corporation and prior to any outside submission. Novartis and Celgene Corporation must receive copies of any intended communication in advance of publication (at least fifteen working days for presentational materials and abstracts and thirty working days for manuscripts). These requirements acknowledge Celgene Corporation and Novartis' responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. Principal Investigation/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of Novartis and Celgene Corporation and, in accord with the trial contract and shall not permit disclosure of Novartis and Celgene Corporation confidential or proprietary information.

9.3 Data Monitoring Committee

The institution data safety monitoring committee will review the outcome of the study at regular intervals as mandated by institutional policy or more frequently if deemed necessary by the Principal Investigator. The Data Monitoring Committee (DMC) will be composed of medical and statistical independent reviewers and will meet to review the efficacy and safety data and determine a risk/benefit analysis in this subject population. The purpose of the DMC is to advise on serious safety considerations, lack of efficacy and any other considerations within the charge to the Committee. The DMC may request additional meetings or safety reports as deemed necessary upon discussion with Celgene and its representatives. The DMC may stop the study following review of results from each interim analysis. Appropriate efficacy and safety data summaries will be provided to the DMC after each interim analysis.

In addition, the principal investigator will review the toxicities as they occur and/or are reported. The approval of the principal investigator or designee is necessary for accrual of all patients. Toxicity information will be reviewed at the weekly Phase I meetings attended by all PIs, clinical coordinators and research nurses involved in all ongoing phase I clinical trials at WCI If the data review reveals a change in the risk/benefit ratio, the investigator will notify the IRB. The principal investigator and co-investigators will review the data and forward any changes or protocol amendments to the IRB. All serious adverse events will be immediately reported to the IRB as outlined in the full protocol. All study participant information will be kept in a confidential manner by the assigning of a random number to each study participant. All data will be kept confidential as per institutional guidelines and policies. Any breach of confidentiality is a serious matter and conflicts with institutional policies and will be reported to the IRB. A cumulative summary of all adverse events occurring on this study and a report of the data safety and monitoring plan will be submitted to the IRBs with the annual renewal reports.

9.4 Study auditing

9.4.1 Investigator responsibilities

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations.

Investigators must enter study data onto CRFs or other data collection system. The Investigator will permit study-related audits by Celgene or its representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

The Investigator, or a designated member of the Investigator's staff, must be available at some time during audits to review data and resolve any queries and to allow direct access to the subject's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The data collection must be completed prior to each visit and be made available to the Celgene representative so that the accuracy and completeness may be checked.

10 Biostatistical Analysis

10.1 Overview

All data will be listed individually by subject. Continuous variables will be summarized using descriptive statistics: mean, standard deviation, median, and minimum and maximum values. Categorical variables will be summarized using number of subjects and proportion expressed as percentage. Baseline value for any specified variable is the last valid measurement before the administration of the study drug. Unless otherwise indicated, statistical significance will be declared if the two-sided p value is ≤ 0.05.

10.2 Datasets to be analyzed

Demographics

Subject demographics including age, sex, race, ethnicity, height, weight, disease information, and medical conditions will be summarized by cohort using descriptive statistics.

Extent of Drug Exposure

The total number of doses of lenalidomide and everolimus (mg), and total number of treatment cycles delivered will be summarized by dose level using descriptive statistics.

Efficacy Endpoints

The secondary endpoint of the trial is response rate. The best overall response rate as defined by the proportion of subjects who have had a CR or PR will be summarized by dose level. Any subject treated in the expansion phase with overall response assessment of partial or complete response will have the response confirmed by repeat assessment no less than 4 weeks after the criteria for response are first met. The RR will be summarized by dose level using descriptive statistics along with a 95% confidence interval.

Pharmacokinetic Parameters

Serum concentration of study drug will be determined by a validated method according to assessment schedules. The pharmacokinetic parameters will be summarized using descriptive statistics.

The concentrations of everolimus, lenalidomide and their clinically significant metabolic product will be summarized by dose level using descriptive statistic. The mean concentration for each dose level will be plotted on scheduled sample time. The following pharmacokinetic parameters will be estimated and reported for each agent according to dose level.

$AUC_{0\rightarrow t}$ Area under the concentration-time curve from the time of dosing to the time of the last observation; $AUC_{0\rightarrow\infty}$ Area under the concentration-time curve from the time of dosing extrapolated to infinity; C_{max} Maximum serum concentration observed postdose; T_{max} Time point at which the C_{max} occurs; t½ Elimination half-life, determined as $0.693/\lambda z$.

Pharmacodynamic Correlates

The levels of mTOR pathway proteins, inflammatory cytokines and lymphocyte subsets at each specified time point will be reported in a descriptive manner for each dose schedule and analyzed by tumor type, when appropriate. Data will also be explored graphically. The PK and

pharmacodynamic data will be used to describe potential relationships between plasma levels of everolimus and or lenalidomide and changes in serum protein, toxicities, and tumor response.

10.3 Statistical Methodology

All data will be listed individually by subject. Continuous variables will be summarized using descriptive statistics: mean, standard deviation, median, and minimum and maximum values. Categorical variables will be summarized using number of subjects and proportion expressed as percentage. Baseline value for any specified variable is the last valid measurement before the administration of the study drug. Unless otherwise indicated, statistical significance will be declared if the two-sided p value is ≤ 0.05.

The estimation of pharmacokinetic parameters will be performed using WinNonlin® Version 5.0 or higher. All statistical analyses will be performed using SAS® Version 9.13 or higher.

Changes in immunological markers between baseline and C2D1 samples will be compared for each patient and for each dose cohort. In addition, mTOR pathway protein expression in baseline diagnostic biopsy samples will be assessed by Immunohistochemistry (IHC) and correlated with response. The dynamic changes in biomarker expression before and after one cycle of treatment with the drug combination will be summarized using summary statistics mean and standard deviation. Comparisons between the two time points will be presented graphically and subjected to statistical analysis using the Pearson's correlation coefficient.

Missing Data Handling

Unresolved missing data may be imputed when the analysis integrity is affected. The conservative principle will be used for data imputation. For example, if an adverse event onset day is missing but the adverse event onset year and month can not exclude this adverse event as a TEAE, the adverse event will be flagged as a TEAE.

10.4 Safety evaluation

Data from all subjects who receive any protocol therapy will be included in the safety analyses. Subjects who entered the study and did not receive any protocol therapy and had this confirmed, will not be evaluated for safety.

The severity of the toxicities will be graded according to the NCI CTCAE v4.0 whenever possible. The safety analysis will be conducted on all enrolled patient population. The following safety parameters will be evaluated:

Adverse Events

A treatment-related adverse event (TRAE) is defined as a sign or symptom that emerges during treatment or within 30 days after the last dose of study drug, having been absent pre-treatment or that has worsened relative to the pretreatment state. Any adverse events deemed related to study drug will also be considered a TRAE regardless of the elapsed time since the last dose of study drug. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) to categorize the event to a system organ class and a preferred term. The number of subjects who experienced at least 1 adverse event, severe (≥ Grade 3) adverse event, study drug-

related adverse event, serious adverse event, and the number of subjects discontinued due to adverse events will be summarized by dose level. For each system organ class and preferred term, summaries will be made with respect to the number and proportion of subjects having at least 1 occurrence of an adverse event during the study. The incidence of adverse events will be presented overall, by system organ class and preferred term, intensity (based on CTCAE Version 4.0), TRAEs, and additional grouping by severity and relationship to study drug. An individual listing of adverse events will be provided. DLTs and study drug-related ≥ Grade 2 adverse events will be listed individually.

10.5 Interim analyses

No interim efficacy analysis is planned. However, safety and toxicity analysis will be conducted on an ongoing basis by the Winship Cancer Institute DSMC.

10.6 Sample size and power considerations

The sample size of up to 30 patients is required to establish the MTD and the RP2D based on the proposed modified Fibonacci dose escalation schema assuming that each dose cohort requires the maximum of 6 subjects . Up to 6 subjects will be enrolled at each dose level. If no DLTs occur, a total of 15 subjects will be needed to complete the dose escalation part of the study. To further characterize safety and efficacy, fifteen additional subjects will be enrolled at the MTD in an expansion cohort. In order to perform preliminary evaluation of anti-tumor activity, the sample size at the MTD or highest dose level cohort is determined by a power analysis. It is assumed that the subjects would have no response if they would not have received any therapy and that response rate for subjects in the MTD or highest dose level cohort would be 10%. Based on this assumption, a sample size of 15 subjects in the MTD cohort will provide more than 79% power in a one-sample exact binomial test at the significance level of 0.05. We anticipate accrual of 2-3 patients per month for the escalation phase and approximately 1-2 patients per month for the expansion phase, which is restricted to patients with clear cell renal cell carcinoma. At this accrual rate, we expect total accrual and study completion within 18-24 months.

A parallel expansion cohort of 9 patients with adenoidcystic carcinoma will also be evaluated. An objective response in at least 3 of 9 patients will be considered sufficient evidence to explore the benefit of this regimen in a larger phase II efficacy trial. The expected maximum overall sample size of 45 patients will still be maintained with the addition of this parallel cohort because only 21 of the maximum expected 30 patients were required in the dose escalation of the study.

11 Regulatory Considerations

11.1 Institutional Review Board/Ethics Committee approval

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

The Investigator will be responsible for preparing documents for submission to the relevant IRB/EC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

Any amendments to the protocol after receipt of IRB/EC approval must be submitted by the Investigator to the IRB/EC for approval. The Investigator is also responsible for notifying the IRB/EC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

Any advertisements used to recruit subjects for the study must be reviewed and approved by the IRB/EC prior to use.

11.2 Informed consent

The Investigator must obtain informed consent of a subject or his/her designee prior to any study related procedures as per GCPs as set forth in the CFR and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files.

11.3 Subject confidentiality

Celgene affirms the subject's right to protection against invasion of privacy. In compliance with United States federal regulations, Celgene requires the Investigator to permit representatives of Celgene Corporation and, when necessary, representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws.

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

11.4 Study records requirements

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the protocol therapy, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; SAE reports, pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

11.5 Premature discontinuation of study

The Principal Investigator, institution and Celgene have the right to discontinue this study at any time for reasonable medical or administrative reasons. Possible reasons for termination of the study could be but are not limited to:

Unsatisfactory enrollment with respect to quantity or quality.

Inaccurate or incomplete data collection.

Falsification of records.

Failure to adhere to the study protocol.

Any possible premature discontinuation would be documented adequately with reasons being stated, and information would have to be issued according to local requirements (e.g., IRB/EC, regulatory authorities, etc.).

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13 Appendices

13.1 Appendix A – ECOG Performance Status Scale

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

13.2 Appendix B: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Risks Associated with Pregnancy

The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of the lenalidomide on human eggs and sperm. The risks to a fetus are not known. However, because lenalidomide is related to thalidomide, and thalidomide is known to cause severe birth defects, the following requirements must be observed.

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

Females of childbearing potential (FCBP)[†] must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) while participating in the study; and 3) for at least 28 days after discontinuation from the study. The two methods of reliable contraception must include one highly effective method (i.e. intrauterine device (IUD), hormonal [birth control pills, injections, or implants], tubal ligation, partner's vasectomy) and one additional effective (barrier) method (i.e. latex condom, diaphragm, cervical cap). FCBP must be referred to a qualified provider of contraceptive methods if needed.

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

Before starting lenalidomide:

Female Subjects:

- FCBP must have two negative pregnancy tests (sensitivity of at least 50 mIU/mL) prior to prescribing lenalidomide. The first pregnancy test must be performed within 10-14 days

[†] A female of childbearing potential 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).

prior to prescribing lenalidomide and the second pregnancy test must be performed within 24 hours prior to prescribing lenalidomide (prescriptions must be filled within 7 days). The subject may not receive lenalidomide 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.

During study participation and for 28 days following discontinuation from the study:

All Subjects:

- 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.

Female Subjects:

- 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 discontinuation from the study. 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 discontinuation from the study.
- In addition to the required pregnancy testing, the Investigator must confirm with FCBP that she is continuing to use two reliable methods of birth control at each visit.
- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide treatment must be discontinued during this evaluation.

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.

13.3 Appendix C NCI CTC Version 4.0

TOXICITY WILL BE SCORED USING NCI CTC VERSION 4.0 FOR TOXICITY AND ADVERSE EVENT REPORTING. A COPY OF THE NCI CTC VERSION 4.0 CAN BE DOWNLOADED FROM THE CTEP HOMEPAGE: (HTTP://CTEP.INFO.NIH.GOV**) OR HTTP://CTEP.CANCER.GOV/PROTOCOLDEVELOPMENT/ELECTRONIC_APPLICATIONS/DOCS/CTCAEV4.PDF .**
ALL APPROPRIATE TREATMENT AREAS HAVE ACCESS TO A COPY OF THE CTC VERSION

13.4 Appendix D – Blood Sample Collection and Processing

Pharmacokinetic and Pharmacodynamic Studies

PK samples will not be collected during this study.

Flow Cytometry:

All patients will have blood samples collected for assessment of circulating lymphocytes as a pharmacodynamic endpoint for lenalidomide therapy. Samples will be collected at baseline and with the first 2 restaging scans for response assessment (on day 1 cycle 3 ± 2days and day 1 cycle 5 ± 2days;) and at the time of disease progression. Collect 5mls of whole blood in purple-topped tubes and invert gently several times to ensure appropriate mixing of blood and anticoagulant. Samples should be transported at room temperature to Ned Wallers lab on the 4th floor of the Winship Cancer Institute building (Attn: Hillary Rosenthal, MT, ASCP; Tel - 404-727-3086).

ELISA Assay for circulating cytokines:

Samples for ELISA test should be collected in two red-topped tubes at baseline and with the first 2 restaging scans (day 1 cycle 3 ± 2days and day 1 cycle 5 ± 2days;) and at the time of disease progression if different than any of the aforelisted time points. Please transport samples on ice to the laboratory of Shi-Yong Sun, PhD on the 3rd floor of the Winship Cancer Institute building, (Attention: Guojing Zhang or Ping Yue).

Tumor Biopsy

Patients enrolled in the expansion cohort must sign a separate informed consent form for research tumor tissue biopsy. Surgical tumor tissue and needle biopsies (collected by 18-gauge or larger needles), should be collected in pre-cooled cryovials and immediately flash frozen in liquid nitrogen, then stored at -80 degrees C. Samples will be sent to the laboratory of Shi-Yong Sun, PhD (Attention: Guojing Zhang or Ping Yue) on the 3rd floor of the Winship Cancer Institute building.

13.5 Appendix E – List of CYP450 and PgP Interacting Drugs

Agents that may Increase Everolimus Blood Concentrations

CYP3A4 Inhibitors and PgP Inhibitors: In healthy subjects, compared to everolimus treatment alone there were significant increases in everolimus exposure when coadministered with: ketoconazole (a strong CYP3A4 inhibitor and a PgP inhibitor) - Cmax and AUC increased by 3.9- and 15.0-fold, respectively; erythromycin (a moderate CYP3A4 inhibitor and a PgP inhibitor) - Cmax and AUC increased by 2.0- and 4.4-fold, respectively; verapamil (a moderate CYP3A4 inhibitor and a PgP inhibitor) - Cmax and AUC increased by 2.3-and 3.5-fold, respectively. Concomitant strong or moderate inhibitors of CYP3A4 and PgP inhibitors should not be used. Due to significant increases in exposure of everolimus, co-administration with strong or moderate inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, amprenavir, indinavir, nelfinavir, delavirdine, fosamprenavir, voriconazole, aprepitant, erythromycin, fluconazole, grapefruit juice, verapamil or diltazem) or P-glycoprotein (PgP) should be avoided.

Agents that may Decrease Everolimus Blood Concentrations

CYP3A4 Inducers: In healthy subjects, co-administration of everolimus with rifampin, a strong inducer of CYP3A4, decreased everolimus AUC and Cmax by 64% and 58% respectively, compared to everolimus treatment alone. An increase in the everolimus dose is recommended when co-administered with a strong CYP3A4 inducer (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital.

Agents whose Plasma Concentrations may be Altered by Everolimus

Studies in healthy subjects indicate that there are no clinically significant pharmacokinetic interactions between everolimus and the HMG-CoA reductase inhibitors atorvastatin (a CYP3A4 substrate) and pravastatin (a non-CYP3A4 substrate) and population pharmacokinetic analyses also detected no influence of simvastatin (a CYP3A4 substrate) on the clearance of everolimus

Drug Interactions with Lenalidomide

Results from human in vitro metabolism studies and nonclinical studies show that lenalidomide is neither metabolized by nor inhibits or induces the cytochrome P450 pathway suggesting that lenalidomide is not likely to cause or be subject to P450-based metabolic drug interactions in man. Co-administration of multiple doses of 10 mg of lenalidomide had no effect on the single dose pharmacokinetics of R- and S-warfarin. Co-administration of single 25-mg dose warfarin had no effect on the pharmacokinetics of total lenalidomide. Expected changes in laboratory assessments of PT and INR were observed after warfarin administration, but these changes were not affected by concomitant lenalidomide administration. When digoxin was co-administered with lenalidomide the digoxin AUC was not significantly different, however, the digoxin Cmax was increased by 14%. Periodic monitoring of digoxin plasma levels, in accordance with clinical

judgment and based on standard clinical practice in patients receiving this medication, is recommended during administration of lenalidomide.

13.6 Appendix F: Estimated creatinine clearance rate (eC_{Cr}) using Cockcroft-Gault formula

In men, this is: GFR= (140 - age) x weight (kg) / (72 x serum creatinine)

In women, multiply this result by .85 i.e. GFR= [(140 - age) x weight (kg) / (72 x serum creatinine)] x 0.85

13.7 Appendix X - RevAssist Program

RevAssist® for Prescribers Prescribing REVLIMID® (lenalidomide)

REVLIMID® is available only under a restricted distribution program called RevAssist®.

Healthcare providers must register with RevAssist® to prescribe REVLIMID® for their patients.

RevAssist® for Patients

- To avoid fetal exposure, REVLIMID® (lenalidomide) is only available under a special restricted distribution program called RevAssist®.
- Only prescribers registered with RevAssist® can prescribe REVLIMID®.
- Only RevAssist® contract pharmacies can dispense REVLIMID®.
- In order to receive REVLIMID®, patients must enroll in RevAssist® and agree to comply with the requirements of the RevAssist® program.

Information about REVLIMID® and the RevAssist® program can be obtained by calling the Celgene Customer Care Center toll-free at 1-888-423-5436. FAX: 1-888-432-9325; 86 Morris Avenue, Summit, NJ 07901

13.8 Appendix Y – Pill Diary

Study Title	Phase I Study of Everolimus (RAD001) in Combination with Lenalidomide in Patients with Advanced Solid Malignancies Enriched for Renal Cell Carcinoma	
Pill Diary		
Subject Initials		
Subject ID		
Cycle #		
Research Coordinator Name: Phone: Pager: e-mail:		
Cohort#	Original Everolimus Dose ……	Original Lenalidomide Dose …….
# of Dose Reductions	Current Daily Everolimus Dose: ……..	Current Daily Lenalidomide Dose: ……

Instructions:
1. Please take the prescribed pills as instructed

2. Please record the date and time you take your medications. On visit days, medications should be taken in the clinic unless otherwise instructed

3. Please bring medication and pill diary to each study visit.

Day	Date	Everolimus (Y/N)	Lenalidomide (Y/N)	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				

13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				
Patient Signature		……		Date:

This section to be completed by a Research Personnel (Investigator, Research Nurse / Research Coordinator)		
Dosing Cycle Start Date:	Dosing Cycle End Date:	
Everolimus Lot Number: ……	# of Bottles / # of Tablets Dispensed : ____5mg ____10mg	Any Interruptions? (Yes/No)
Lenalidomide Lot Number …..……	# of Bottles / # of Tablets Dispensed : ____5mg ____10mg	Any Interruptions? (Yes/No)
Length of Dose Interruption:		
Reason for Interruption:		
Reason for Dose Reduction:		
Additional Comments:		