# PROTOCOL AND STATISTICAL ANALYSIS PLAN

Study Title: **REVLIMID (Lenalidomide) for Therapy of Radioiodine-Unresponsive Papillary and Follicular Thyroid Carcinoma**

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| **Protocol Title:** | **Phase II Trial of REVLIMID® (Lenalidomide) for Therapy of Radioiodine-Unresponsive Papillary & Follicular Thyroid Carcinomas** |
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| **Study Agent:** | **REVLIMID® (Lenalidomide)** |
| **Celgene Protocol#:** | **RV-THYR-PI-057** |
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## PRINCIPAL INVESTIGATOR SIGNATURE PAGE

**Principal Investigator:**

_____ _____

Signature of Investigator Date

Kenneth B. Ain, M.D.

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.

## Table of Contents

1.0 **PROTOCOL ABSTRACT:**
PHASE II TRIAL OF REVLIMID® (LENALIDOMIDE) FOR THERAPY OF RADIOIODINE-UNRESPONSIVE PAPILLARY AND FOLLICULAR THYROID CARCINOMAS

1.1 **Key Personnel:**

1.1.1 Principal Investigator:

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1.1.2 Co-Investigators:

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1.2 **Objectives:** Primary objectives are to assess the anti-tumor activity of REVLIMID® (lenalidomide), administered as a single agent, in patients with distantly metastatic thyroid carcinomas which are unresponsive to systemic radioiodine, in terms of tumor response and response duration. Secondary objectives are: 1) to assess differences in the primary objectives between papillary and follicular thyroid carcinomas, 2) to assess treatment toxicities and duration of toxic effects, and 3) to determine if parameters of angiogenesis: serum levels of vascular endothelial growth factor (VEGF-A), soluble VEGF receptors (sVEGF-1 & sVEGF-2), and thrombospondin-1, change in response to treatment and correlate with primary objectives.

1.3 **Rationale:** Thalidomide has found new uses as a tumor antiangiogenesis agent that is capable of diminishing the proliferation of angiogenesis-dependent solid malignancies. A putative mechanism relates to the ability of thalidomide to inhibit the processing of some mRNAs, including those of tumor necrosis factor-alpha (TNF-α) and vascular endothelial growth factor (VEGF). Alternative antiangiogenic mechanisms invoke thalidomide's ability to decrease the expression of beta integrin subunits, resulting in diminished cell migration. Additional effects on other cytokines affecting the immune system have prompted the designation of immunomodulatory drugs (Imids®) for thalidomide and its derivatives. Early trials have suggested clinical activity in multiple myeloma, renal carcinoma, malignant gliomas, and Kaposi's sarcomas. Distantly metastatic, unresectable medullary thyroid carcinomas, as well as dedifferentiated papillary and follicular thyroid carcinomas, which no longer concentrate radioiodine, have no known effective systemic therapies. We have verified, in the context of a completed phase 2 clinical trial (1), that thalidomide has significant activity in thyroid carcinomas that are no longer radioiodine avid and are rapidly progressive. This activity has only limited durability of around 7 months and is associated with significant toxicities of sedation, constipation and neuropathy.

REVLIMID® (lenalidomide) is an analog of thalidomide with the chemical name, alpha-(3-aminophthalimido) glutarimide. REVLIMID® is noted to be more potent than thalidomide in inhibiting the production of TNF-alpha. It has more than double the inhibition of microvessel growth at the same concentration as thalidomide in a rat aorta angiogenesis model as well as greatly enhanced activity as an IMiD. Most important, lacks much of the toxicity of thalidomide, particularly in regards to somnolenc neuropathy, or biochemical effects (2). In fact, patients with multiple myeloma, known to be resistant to thalidomide, were still seen to exhibit clinical responses to REVLIMID® (3). This makes REVLIMID® an appropriate agent to investigate in a phase 2 trial in thyroid carcinoma.

## 1.4 **Eligibility**:

### 1.4.1 Inclusion Criteria:

**1)** Histological confirmation of follicular, papillary, insular, or Hürthle-cell thyroid carcinoma. Histologic slides and/or tissue blocks must be reviewed at the University of Kentucky Medical Center.

**2)** Patients must have unresectable, distantly metastatic tumor, which does not concentrate radioactive iodine. Alternatively, follicular or papillary thyroid carcinoma patients with a large distant tumor burdens which have not sufficiently responded to more than 800 mCi I-131 cumulative therapy and are progressive (criteria #4) may be appropriate for inclusion.

**3)** No systemic chemotherapy agents within 4 weeks of initiation of therapy.

**4)** Patients must have 2 consecutive radiographic evaluations demonstrating a cumulative 30% increase in tumor volume over a period of one year or less.

**5)** Patients must be over the age of 18 years with the ability to understand and willing to sign an informed consent.

**6)** Females of childbearing potential (FCBP)[†] must have a negative serum or uri pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days prior to and again within 24 hours of starting lenalidomide 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. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendix F: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods, AND Appendix G: Education and Counseling Guidance Document.

[†] 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).

7) Karnofsky performance status ≥70.

8) Baseline Laboratory Studies: Absolute neutrophil count (ANC) >1000/mm$^3$; platelet count ≥100 K/mm$^3$; Creatinine ≤2 mg/dL, and transaminase levels (AST/SGOT, ALT/SGPT) ≤2 x ULN (or ≤5 x ULN if hepatic metastases are present).

9) Disease free of other prior malignancies for ≥5 years, with the exception of currently treated basal cell/squamous cell carcinoma of the skin or "in-situ" carcinoma of the cervix or breast.

10) TSH (thyrotropin) levels must be suppressed with sufficient levothyroxine to be kept beneath the normal range of the assay.

1.4.2 Exclusion Criteria:

1) Patients may not have had prior REVLIMID® therapy.

2) No serious concomitant medical or psychiatric illness that might interfere with informed consent or conduct of the study, including active infections that are not controlled with medication.

3) Patients must not be pregnant or breastfeeding.

4) Use of any other experimental drug or therapy within 28 days of baseline.

5) Known hypersensitivity to thalidomide.

6) The development of erythema nodosum, characterized by a desquamating rash, while taking thalidomide or similar drugs.

7) 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.

8) Concurrent use of other anti-cancer agents or treatments, with the exception of thyrotropin-suppression by levothyroxine.

9) All subjects with central nervous system involvement, with the exception of those subjects whose central nervous system metastases have been treated with either radiotherapy and/or surgery and remain asymptomatic with no evidence of active central nervous system disease (verified by CT scan or MRI) for at least 6 months.

10) Known to be positive for HIV or infectious hepatitis, type A, B, or C.

11) Patients with medullary or anaplastic thyroid carcinomas are excluded. Patients whose disease is limited to bone metastases are excluded.

1.5 **Treatment Plan**: Treatment will be initiated with REVLIMID® at 25 mg/day taken in the morning. Dose adjustments may be made to alleviate toxicities. Patients will be assessed for treatment response each 28-day cycle for the first 2 28-day cycles, then every 2 28-day cycles for a total treatment time of one year. At one year, those patients that are maintaining tumor response to REVLIMID® treatment and wish to continue these treatments will enter into the "Extended Therapy" phase. These patients may continue with extended drug therapy through the RevAssist® program see Appendix 1, in 28-day cycles with treatment response and routine tumor assessment every three months. The Celgene Corporation will supply REVLIMID® as 5 mg and 25 mg capsules and will be dispensed by the designated investigational pharmacy. REVLIMID that is provided through the RevAssist program will be supplied as 5 mg, 10 mg, 15 mg and 25 mg capsules.

Treatment will be continued, past each response assessment point (starting with the second 28-day cycle), as long as there is no evidence of disease progression at an equal or greater rate than documented for the baseline year prior to initiation of treatment. Alternatively, unacceptable toxicity will result in a dose reduction or termination of REVLIMID® therapy, as per strict criteria.

1.6 **Statistical Evaluations**: A two-stage design will be used, as described by Gehan (4), which entails the evaluation of 14 patients to determine whether there is at least one patient responsive to this treatment. Would no responders be found within 4 28-day cycles after initiating each of the 14 patients on the study drug, the study will end at that time. In the presence of at least one responder, the trial is planned to continue, accruing an additional 11 patients or sufficient patients to determine a 95% confidence interval for the true response rate. Thus, a total of 14 patients will be enrolled if there are no responders; however, up to 25 patients will be enrolled if there are responders in the initial group. Response rates of 65% have been noted in prior studies using the parent compound, thalidomide (1). Based on such activity, we anticipate that the probability of observing 'no responses' for this treatment regimen in 14 subjects is less than $4.0 \times 10^{-7}$. In essence, there is very low probability that this study will not move into the second phase given the levels of tumor activity reported previously for this treatment.

1.7 **Patient Evaluation**: (See Table 1. Schedule of Study Assessments)

1.7.1 Pre-study Evaluation:

Basic Data: Physical examination, medical history, and laboratory tests (urinalysis, electrolytes, BUN, creatinine, hepatic enzymes, bilirubin, ionized calcium, phosphorus, glucose, albumin, PT, and aPTT), basel ECG.

Tumor Assessment:
*Tumor markers*: Thyroglobulin Panel (TG & anti-TG Ab), TSH, free T4.
*Angiogenic Markers*: serum samples for VEGF-A, sVEGFR-1, sVEGFR-2, and thrombospondin-1 (TSP-1).
*Radiological Studies*: Patients must have at least one year of radiographic evidence of tumor progression with at least 2 separate x-ray studies (preferably CT or MR scans) able to define tumor volume, or similar radiographic evidence over a shorter period of time delineating greater than 30% increased tumor volume (to permit comparison of rate of tumor progression with each patient as their own control).

Toxicity Monitoring: CBC with differential/platelet count;, biochemistry panel, serum or urine ß-HCG (for female patients of childbearing potential), pregnancy counseling and pregnancy testing, if applicable, See Appendix F and Appendix G.

1.7.2 Monitoring During Treatment:

1.7.2.1 The following studies are obtained after the 1st and 2nd 28-day cycle, then every 2nd 28-day cycles while on therapy:

Tumor Assessment:
*Angiogenic Markers*: serum samples for VEGF-A, sVEGFR-1, sVEGFR-2, and TSP-1.

1.7.2.3 The following studies are obtained every 2nd 28 day cycles while on therapy:
Tumor Assessment:
*Tumor markers*: Thyroglobulin Panel (TG & anti-TG Ab), TSH, free T4.
*Radiological Studies*: CT (without contrast for lung; otherwise with contrast) of evaluable disease.

1.7.2.3 The following studies are obtained once every 28-day cycle while on therapy
Toxicity Monitoring:
Obtain CBC with differential/platelet count (weekly for the first 2 cycles); and physical examination monthly. Biochemistry panels are obtained at visits for cycles 4, 8, and 12.

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

Pregnancy tests must occur 10 – 14 days and again within 24 hours prior to initiation of lenalidomide. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 4 weeks and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at 30 Days +/- 2 days post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 4 weeks 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 F: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).

All patients must be counseled about pregnancy precautions, risks of fetal exposure and other risks. The counseling must be done at screening and on Day 1 of each cycle including Cycle 1 (or at a minimum of every 28 days). The Appendix G: Education and Counseling Checklist must be completed by a trained counselor.

1.7.3 Studies at Termination of Protocol: The following studies are obtained when terminating the protocol due to either disease progression, severe toxicity or at the conclusion of one year of REVLIMID® treatment:

Tumor Assessment:
*Tumor markers*: Thyroglobulin Panel (TG & anti-TG Ab), TSH, free T4.

*Angiogenic Markers*: serum samples for VEGF-A, sVEGFR-1, sVEGFR-2, and TSP-1.
*Radiological Studies*: CT (without contrast for lung; otherwise with contrast) of evaluable disease.

Toxicity Monitoring: CBC with differential/platelet count, biochemistry panel, and physical examination. Pregnancy test should be repeated 30 days after the last dose of study drug.

1.7.4 Studies during the "Extended Therapy" phase: The following studies are obtained after the one-year protocol has concluded and the patient is maintaining a clinical response to REVLIMID® therapy and elects to continue to receive this drug. Note that these studies are performed as "standard-of-care" assessments that are appropriate for oncologic follow-up:

Tumor Assessment (obtained at physician visits every 3 months):
*Tumor markers*: Thyroglobulin Panel (TG & anti-TG Ab), TSH, free T4.
*Angiogenic Markers*: Not done.
*Radiological Studies*: CT (without contrast for lung; otherwise with contrast) of evaluable disease.

Toxicity Monitoring (obtained every month while taking REVLIMID®):
CBC with differential/platelet count every 4 weeks.
FCBP with regular or no menstruation must have a pregnancy test every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at 30 Days +/- 2 days post the last dose of lenalidomide. Females with irregular menstruation must have a pregnar 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 F: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).

Additional standard assessments (obtained at physician visits every 3 months): biochemistry panel and physical examination.

1.8 **Outpatient Visits**: Patients will report to the University of Kentucky Clinical Research Organization (UKCRO) for outpatient evaluations by the principal investigator and UKCRO nursing staff at: time of initial enrollment, at the start of every 28 day cycle and for a final visit.

1.8.1 Study Duration: Each patient will continue on study for 12 28-day cycles or until there is evidence of disease progression (or patient withdraws from study), whichever is sooner.

1.8.2 Final Visit: Should any patient terminate participation at any time, either out of choice, disease progression, or significant toxicity, there will be a final outpatient visit. Toxicity assessment will be done approximately 30 days after last dose of study drug.

1.8.3 Extended Therapy phase: Lenalidomide (Revlimid®) will be provided to research subjects for the duration the extened phase participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with the RevAssist® program. Per standard RevAssist® 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 Celgene's RevAssist® program. Prescriptions must be filled within 7 days. **Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.**

Patients will have a CBC prior to each new cycle of Revlimid®. Standard-of-care clinical visits with the principal investigator will take place every 3 months as long as the patient is participating in the Extended Therapy phase.

1.9 **Response Criteria**:

1.9.1 Complete Response (CR): Disappearance of all radiological and clinical evidence of tumor. The patient must be free of all tumor related symptoms for at least 4 weeks.

1.9.2 Partial Response (PR): 30% or greater decrease in the sum of the longest diameter of all measured lesions (or alternatively, ≥30% reduction of calculated tumor volumes) for at least 4 weeks.

1.9.3 Minor Response (MR): For tumors with a documented rate of progression (calculated as either the linear slope of calculated tumor volumes vs. time for the immediate year prior to initiating this study or as the slope of the logarithm of tumor volumes vs. time over the same interval), a decrease in the rate of progression by ≥50%.

1.9.4 Stable Disease (SD): No change or <30% decrease in the tumor volume (calculated as in 1.9.2) for at least 4 weeks.

1.9.5 Progressive disease (PD): Less than a 50% reduction in the rate of progression (see 1.9.3), an increase of >25% in the size of any measured lesion, or the appearance of new metastatic lesions.

2.0

*Table 1: Schedule of Study Assessments*

| Procedure | Screening ≤ 21 days prior to initiating therapy | Cycle 1 | Cycle 2 | Cycle 3 | Cycle 4 | Cycle 5 | Cycle 6 | Cycle 7 | Cycle 8 | Cycle 9 | Cycle 10 | Cycle 11 | Cycle 12 or Ending Study | Extension Phase | Extension Phase: Every 1 month | Extended Therapy Phase: Every 3 months |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Complete medical history (prior treatment), ECG | X | | | | | | | | | | | | | | | |
| Physical examination, Karnofsky (clinic visit) | X | X | X | X | X | X | X | X | X | X | X | X | X | | | X |
| Prior tumor growth rate (previous year of CT scans) | X | | | | | | | | | | | | | | | |
| Record prior & concurrent medications | X | X | X | X | X | X | X | X | X | X | X | X | X | | | X |
| CT chest &/or abdomen / pelvis[3] | X[1] | | X | | X | | X | | X | | X | | X | | | X |
| CBC/diff[4] | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | |
| Comprehensive Biochemistry | X | | | | X | | | | X | | | | X | | | |
| TSH/free T4, thyroglobulin profile | X | X | X | | X | | X | | X | | X | | X | | | |
| Pregnancy test (fertile females only[2, 7, 8] | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | |
| Urinalysis, coagulation profile | X | | | | | | | | | | | | | | | |
| VEGF-A, TSP-1, sVEGFR-1, sVEGFR-2 | X | X | X | | X | | X | | X | | X | | X | | | |
| Review Education and Counseling Guidance Documents[9] | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | |
| Register Patient into RevAssist® Program[10] | | | | | | | | | | | | | | X[10] | | |
| Distribution of study drug (REVLIMID®) | | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| Prescribe lenalidomide via RevAssist®[10] | | | | | | | | | | | | | | | X[10] | |
| Response assessment[5] | | | X | | X | | X | | X | | X | | X | | | X |
| Record adverse events[6] | | X | X | X | X | X | X | X | X | X | X | X | X | | | X |
| Perform drug accountability | | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| Obtain Follow-Up anti-cancer treatments | | | | | | | | | | | | | X[7] | | | |
| Obtain Follow-Up survival information | | | | | | | | | | | | | X[7] | | | |

[1] First baseline CT scan within one week of starting study drug, volumetric evaluations to be completed at UK.
[2] Serum or urine pregnancy test.
[3] All CT / MRI scans to be performed as per guidelines of section 6.2.3.
[4] Performed weekly for first 2 Cycles, then monthly thereafter.
[5] Repeat only those evaluations with known or suspected sites of disease.
[6] Adverse events ascertained during clinic visits.
Obtain follow-up visits every three months until disease progression or initiation of a new therapy. A post therapy 30 day toxicity will be done on all patelnts that discontinue therapy for any reason.
[7] 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).
[8] Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to initiation of lenalidomide. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 4 weeks 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 4 weeks 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: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).
[9] Unless patients are registered into the Celgene RevAssist® program, all patients receiving drug through the Lenalidomide Counseling Program must be counseled about pregnancy autions, risks of fetal exposure and other risks based on Lenalidomide Counseling Program criteria. The counseling must be done on Day 1 of each cycle (or at a minimum of every 28

Days) and at drug discontinuation. The Appendix: Education and Counseling Guidance ... ment must be completed by a trained Counselor. Note: A different counseling me... exists for the RevAssist® program.

[10] Patients will be registered into the RevAssist® program. When patients are registered in the RevAssist® program, Lenalidomide (Revlimid®) must be prescribed through and in compliance with the RevAssist® program of Celgene Corporation. Prescriptions must be filled within 7 days. Consideration should be given to prescribing lenalidomide 5 to 7 days in advance of Day 1 of each cycle to allow time for required patient and prescriber surveys, and drug shipment to patient. Any unused Revlimid® (lenalidomide) should be returned to the patient for disposition in accordance with the RevAssist® program. Please see Appendix I for an example of a RevAssist® form regarding a female of child bearing potential.

## 3.0 Background and Rationale:

### 3.1 Nature of the Disease: Dedifferentiated Thyroid Epithelial Carcinomas (papillary carcinomas, follicular carcinomas, insular carcinomas):

Thyroid epithelial carcinomas are generally classified into papillary or follicular histologic types, including their respective variants (tall cell, Hürthle cell, diffuse sclerosing, and insular). In this context, functional differentiation refers to maintenance of cellular functions particular to benign thyroid follicular cells, a slow growth rate, and a low propensity to metastasize. It is also applied as a descriptive term to histologic features that are typically associated with differentiated cellular functions. Losses of thyroid-specific functions impede both diagnostic and therapeutic efforts. These efforts rely upon the expression of the sodium-iodide symporter (NIS) and thyroglobulin, permitting the use of radioiodide for tumor detection and treatment, as well as the measurement of circulating thyroglobulin as a tumor marker. In most cases, dedifferentiated tumors secrete thyroglobulin despite failing to concentrate iodide, providing important clues denoting the presence of carcinoma (5).

The fundamental failure of clinical management of such undifferentiated thyroid cancer is the absence of any demonstrably effective alternative systemic therapy. Systemic chemotherapies in patients with thyroid carcinoma have been uniformly ineffective despite numerous, usually anecdotal, trials (6). The agents and regimens used have included combinations of: doxorubicin, cisplatin and bleomycin; doxorubicin, cisplatin and vindesine (7); and single agents, including, mitoxantrone (8), aclarubicin (9), and doxorubicin (10). Although paclitaxel has significant activity in anaplastic thyroid carcinomas (ATC) (11, 12), our experiences in non-ATC, dedifferentiated thyroid cancers have been less rewarding.

The consequence of distantly metastatic, unresectable, dedifferentiated epithelial thyroid cancer, which no longer responds to radioiodine treatment, is slow inexorable disease progression with increasing morbidity and eventual death. In some cases, further tumor dedifferentiation results in precipitous increases in tumor growth rate and dissemination that are rapidly fatal. On the other hand, some patients survive for a decade or more with slowly increasing tumor burdens. All of these patients are desperate for innovative and effective systemic therapies.

### 3.2 Antiangiogenic Therapy of Malignancies:

Angiogenesis is a critical determinant of solid tumor growth. Tumor microvessels consequent to neovascularization are though to arise from increased expression of tumor-derived proangiogenic factors (13). These vessels are tortuous with arterio-venous shunts, poorly developed endothelial linings and result in sluggish unreliable blood flow to the tumors. Consequently, therapeutic efforts directed against these vessels have provided new opportunities for antineoplastic treatment.

Proangiogenic factors include: basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor-alpha (VEGF-A), interleukin 8 (IL-8), and hepatocyte growth factor (HGF) (14). Recognition of their roles in tumor development and maintenance has fostered the use of a number of

pharmacologic agents as angiogenesis inhibitors; some of which work via putative mechanisms involving inhibition of these factors (15). Some of these drugs, notably interferon alpha and thalidomide, were found to be antiangiogenic despite being originally developed for different purposes (16). Ongoing clinical trials have demonstrated the effectiveness of antiangiogenic strategies for a number of solid tumors.

A current concept of tumor angiogenesis suggests that bone-marrow-derived circulating endothelial progenitor cells (CEPs) contribute to tumor angiogenesis by seeding sites of ongoing angiogenesis after stimulation by tumor-derived growth factors (such as VEGF-A) (17, 18). CEPs can be isolated using flow-cytometric analysis of CD34+ cells from the peripheral blood mononuclear leukocyte (PBML) layer of Ficoll-Hypague gradients of blood samples from cancer patients (19). These CEPs differentiate into endothelial cells (20, 21) and are able to home-in specifically to tumor sites to create neovascularization of malignancies (22). Whereas VEGF-A appears to be a major stimulant of CEP seeding, recent evidence suggests that circulating soluble forms of VEGF receptors may function as endogenous inhibitors of tumor angiogenesis and reflect antiangiogenic drug activity (23). Likewise, additional evidence suggests that thrombospondin-1 may function as an additional endogenous inhibitor of VEGF and tumor angiogenesis with circulating levels inversely related to activity of tumor neovascularization (24, 25).

### 3.3 Thalidomide - Clinical Experience with Solid Tumors and Thyroid Carcinoma:

Thalidomide, a glutamic acid derivative, was first developed as a sedative that was withdrawn from use due to severe teratogenicity, causing dysmelia. A putative mechanism relates to the ability of thalidomide to inhibit the processing of some mRNAs, including those of tumor necrosis factor-alpha (TNF-$\alpha$) and VEGF, as well as antagonize angiogenesis induced by bFGF. Alternative antiangiogenic mechanisms invoke thalidomide's ability to decrease the expression of beta integrin subunits, resulting in diminished cell migration. This may be mechanistically related to its teratogenic effects; however, it also has been exploited as a treatment for solid tumors. There have been several published attempts to use xenograft models of human cancers to evaluate the effectiveness of thalidomide. They have had varying results, but are typically unable to predict the response evidenced in phase II clinical trials. The reason for this has become known, due to evidence that rodent hepatic microsomes are incapable of metabolizing thalidomide into the active antiangiogenic metabolite (26-28). Thus, thalidomide must be evaluated in clinical trials since species-specific activation of this agent prevents effective preclinical evaluation in xenograft studies in athymic rodents, and suitable non-rodent athymic hosts are not available.

Early phase clinical trials of thalidomide therapy for solid tumors have been successful enough to warrant additional study. In one phase II study in advanced melanoma (17 patients), renal cell carcinoma (18 patients), ovarian cancer (19 patients) and breast cancer (12 patients), thalidomide was administered at 100 mg every evening for up to one year (29). Three patients with renal cell carcinoma had a partial response with an additional 3 patients showed disease stabilization for up to 6 months with minimal toxicity. Another phase II trial in patients with recurrent high-grade gliomas, treated with 1200 mg thalidomide daily for up to one year, resulted in two partial responses, two minor responses, and 12 patients with stabilization of disease out of 39

enrolled patients. Aside from sedation and constipation, the drug was well tolerated with only one case of grade-2 peripheral-neuropathy after one year of treatment (30). A number of studies have suggested that there was no clearly defined threshold for thalidomide activity in responsive tumors, although in most studies responses were found at <800 mg daily, and that there was a wide range of variability in the occurrence toxicities. The large variety of solid tumors responsive to thalidomide validated the need to directly test this agent in any patients with solid tumors that lack effective alternative therapies.

There were no published trials of thalidomide in thyroid carcinomas; however, in a phase II trial of paclitaxel in anaplastic thyroid carcinoma, we noted that, after disease progression in one patient with a partial response to paclitaxel, an additional 6 month partial response was evoked with thalidomide, administered off protocol (12). Consequently, we performed a phase 2 clinical trial of thalidomide, administered as a single agent in rapidly progressive and radioiodine-unresponsive thyroid carcinoma, from 2001 and completed by 2003. Final publication of these results is pending; however, they were consistent with preliminary results published in late 2002. There was a greater than 50% response rate, ranging from partial responses to disease stabilization, with mean durability of response for at least 7 months (1). Unfortunately, there was significant toxicity with sedation, peripheral neuropathy and constipation. The availability of new derivatives of thalidomide with greater disease activity and fewer side effects provides an opportunity to gain greater therapeutic benefits.

### 3.4 REVLIMID®: Current clinical experience and preclinical studies:

REVLIMID® (lenalidomide) is an analog of thalidomide with the chemical name, alpha-(3-aminophthalimido) glutarimide (31). REVLIMID® is noted to be more pot than thalidomide in inhibiting the production of TNF-alpha. It has more than double i inhibition of microvessel growth at the same concentration as thalidomide in a rat aorta angiogenesis model as well as greatly enhanced activity as an IMiD. Most important, it lacks much of the toxicity of thalidomide, particularly in regards to somnolence, neuropathy, or biochemical effects (2). In fact, patients with multiple myeloma, known to be resistant to thalidomide, were still seen to exhibit clinical responses to REVLIMID® (3). This makes REVLIMID® an appropriate agent to investigate in a phase 2 trial in thyroid carcinoma.

In a phase I study of REVLIMID® with 13 melanoma patients, and 6 patients with pancreatic cancer, renal cell carcinoma, ductal breast cancer or squamous cell carcinoma, seven of the melanoma patients had a clinical response to REVLIMID® (1 PR, 6 disease stabilization) using a dose of 25 or 50 mg daily (2). Unlike thalidomide, there was no somnolence and no neurological or biochemical toxicities. Thirty-six percent of patients had grade 1 toxicities and 51% had grade 2 toxicities of: a pruritic rash, fatigue, dysgeusia, nausea, mild paresthesia, or anorexia (in decreasing order of frequency). Treatment was associated with significant increases in circulating levels of: soluble IL-2 receptor, IL-12, TNF-alpha, GM-CSF, and IL-8.

Another phase I trial of REVLIMID® in multiple myeloma patients used a dose-escalation protocol starting with 5 mg and ending at 50 mg with 25 evaluable patients (3). The investigators noted a single grade 3 neutropenia at the 10 mg daily dose and c

patient, each, with grade-3-thrombocytopenia and grade-4 neutropenia after 2 months at 25 mg daily. With 50 mg daily for more than one month, 12 of 13 patients had grade 3-4 myelosuppression, all responding to dose reduction to 25 mg. The maximal tolerated dose (MTD) was found to be 25 mg daily with the median time to best clinical response at 2 months and a median duration of response at 6 months. Bone marrow evaluation of selected patients with myelosuppression found no evidence of marrow hypoplasia, suggesting an alternative mechanism for this side effect. Kinetic analysis showed that the maximal plasma concentration was reached at 1-1.5 hrs after ingesting the dose and there was monophasic elimination with a half-life of 3.1 to 4.2 hrs. As in the other trial, there was no evidence of sedation, constipation, or neuropathy. Recent clinical experience suggests that there may be an enhanced risk of thrombotic events warranting prophylactic use of low-dose aspirin.

Additional studies have verified 25 mg as the minimal effective dose to suppress solid tumors (32). Dosing 25 mg daily is more effective than 50 mg every other day in suppressing multiple myeloma and associated with less toxicity (33, 34). Evaluation of a 15 mg dose twice daily versus a single 30 mg daily dose found that the once daily dosing was associated with less myelosuppression (35). Both thrombocytopenia and neutropenia are more common with higher doses and longer lengths of treatment; however these side effects respond to dose-reduction (36). In addition, unlike thalidomide, REVLIMID® has been shown to be non-teratogenic in the New Zealand rabbit model, the only animal model in which thalidomide-associated teratogenicity can be detected (37).

Clinical trials of REVLIMID® have been sufficiently promising that the FDA granted it orphan-drug status in October 2001. Initial reports of phase 2 and phase 3 trials resulted in the FDA granting fast-track status to CC5013 for treating refractory or relapsed multiple myeloma in February 2003. Additional fast-track status was granted for treatment of myelodysplastic syndromes in April 2003 (37). REVLIMID® (lenalidomide) was approved by the FDA in December of 2005 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.

In consideration of the demonstrated efficacy of thalidomide in aggressive thyroid carcinomas and the greater effectiveness of REVLIMID® with much less toxicity, it is appropriate to verify the activity of REVLIMID® in thyroid cancer. Preclinical studies, of human thyroid carcinoma cell line monolayers treated with REVLIMID®, show no evidence of direct tumor cell cytotoxicity. On the other hand, the same cell lines grown as xenograft tumors in nude mice, reveal significant tumor growth inhibition with the same agent (Ain, KB & Dziba, J, unpublished observations). These results support this current phase 2 clinical trial of REVLIMID® in rapidly progressive, radioiodine-unresponsive, distantly metastatic thyroid carcinomas.

## 3.5 Toxicology of REVLIMID® in Human Clinical Trials:

*Source: INVESTIGATOR'S BROCHURE (Celgene Corporation: version 10, date: 07/12/2006): CONFIDENTIAL*

A single oral dose of REVLIMID® is rapidly absorbed in the fasted state with maximal plasma levels reached in 0.5 to 2.0 hours. The mean half-life of elimination

ranges from 3.2 to 8.7 hours. Administration of REVLIMID® with food results in slower, but not diminished, absorption. Around two thirds of an oral dose is excreted in the urine within 24 hours as unchanged REVLIMID®. The pharmacokinetics of repetitive dosages of REVLIMID® are similar to those of single dosing. There is no evidence of accumulation of this drug with multiple dosing.

Single dosing studies (using dosages ranging from 5 mg to 400 mg) found no differences with placebo aside from increased risk of rhinitis, cough, pruritis and rash. None of these findings were severe and there were no serious adverse events. Despite its high rate of renal excretion, there were no effects upon renal function. Multiple dose studies have shown reductions in $CD4^+$ counts and $CD8^+$ counts. There have also been mild, clinically insignificant reductions in platelet and lymphocyte counts. The most frequently reported side effects of multiple doses of 100 mg are rash and pruritis. Some subjects were found to have elevated SGPT (less than twice the upper limit of the normal range) at the final visit of an 8-day trial. There has not been any evidence of cardiac toxicity.

Clinical trials of REVLIMID® in multiple myeloma have demonstrated that this drug can be tolerated, at dosages of 25 mg or less, for at least a year. To date (6/04) 3 subjects have been treated for periods of 2.8 to 3.1 years. Long-term studies have defined the Maximum-tolerated dose (MTD) to be 25 mg/day. The most frequently reported adverse events were leukopenia (15/27), allergic reactions (11/27), fever (9/27) and constipation (9/27). The most frequently reported Grade ≥3 toxicity was leukopenia. Thrombocytopenia was seen in 2/27 subjects. The Dose-Limiting Toxicity (DLT), defining the MTD of 25 mg daily is myelosuppression. Additional mild-grade toxicities of the 25 mg daily dose include: anemia, non-specific abdominal discomfort, backaches, diarrhea, anorexia, nausea, vomiting, fatigue, dizziness, headache, peripheral edema, cough, insomnia, and pyrexia. An inclusive list of all 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, 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. These are also available in the FDA-approved package insert (Appendix G).

REVLIMID® must not be administered to pregnant or nursing women. Fertile women must verify the absence of pregnancy by appropriate testing within 7 days of initiating this drug. Sexually active fertile patients must agree to use adequate contraception. Men are advised to wear condoms when sexually active with fertile women.

## 4.0 Objectives:

4.1 Assess the anti-tumor activity of REVLIMID®, administered as a single agent, in patients with distantly metastatic thyroid carcinomas that are unresponsive to systemic radioiodine or other therapies, in terms of tumor response and response duration.

4.2 Assess any differences in the anti-tumor activity of REVLIMID® between histiotypes of papillary (typical, tall cell, columnar cell, oxyphilic/Hürthle cell) and follicular (typical, oxyphilic/Hürthle cell, insular) thyroid carcinomas.

4.3 Evaluate treatment toxicities and duration of toxic effects.

4.4 Evaluate markers of tumor angiogenesis: serum levels of vascular endothelial growth factor (VEGF-A), soluble VEGF receptors (sVEGF-1 & sVEGF-2), and thrombospondin-1, to determine if they change in response to treatment and correlate with primary objectives and disease status.

## 5.0 Investigational Plan

### 5.1 Patient Eligibility:

#### 5.1.1 Inclusion Criteria:

1) Histological confirmation of follicular, papillary, insular, or Hürthle-cell thyroid carcinoma. Histologic slides and/or tissue blocks must have been reviewed at the University of Kentucky Medical Center.

2) Patients must have progressive, unresectable, distantly metastatic tumor, which does not concentrate radioactive iodine. Alternatively, follicular or papillary thyroid carcinoma patients with distant tumor burdens which have not sufficiently responded to more than 800 mCi I-131 cumulative therapy and are progressive (criteria #4) may be appropriate for inclusion.

3) No systemic chemotherapy agents within 4 weeks of initiation of therapy.

4) Patients must have 2 consecutive radiographic evaluations demonstrating a cumulative 30% increase in tumor volume over a time period of one year or less.

5) Patient must be over the age of 18 years with the ability to understand and willing to sign an informed consent.

6) 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 starting lenalidomide 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. All patients must b counseled at a minimum of every 28 days about pregnancy precautions and risks of feta exposure. See Appendix F: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods, AND also Appendix G: Education and Counseling Guidance Document.

† 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).

7) Karnofsky performance status ≥70 %.

8) Baseline Laboratory Studies: Absolute neutrophil count (ANC) >1000/mm$^3$; platelet count ≥100 K/mm$^3$; Creatinine ≤ 2 mg/dL, and transaminase levels (AST/SGOT, ALT/SGPT) ≤ 2 x ULN (or ≤ 5 x ULN if hepatic metastases are present).

9) Disease free of other prior malignancies for ≥ 5 years, with the exception of currently treated basal cell/squamous cell carcinoma of the skin or "in-situ" carcinoma of the cervix or breast.

10) TSH (thyrotropin) levels must be suppressed with sufficient levothyroxine to be kept beneath the normal range of the assay.

5.1.2 Exclusion Criteria:

1) Patients may not have had prior REVLIMID® therapy.

2) No serious concomitant medical or psychiatric illness that might interfere with informed consent or conduct of the study, including active infections that are not controlled with medication.

3) Patients must not be pregnant or breastfeeding.

4) Use of any other experimental drug or therapy within 28 days of baseline.

5) Known hypersensitivity to thalidomide.

6) The development of erythema nodosum characterized by a desquamating rash while taking thalidomide or similar drugs.

7) 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.

**8)** Concurrent use of other anti-cancer agents or treatments, with the exception of thyrotropin-suppression by levothyroxine.

**9)** All subjects with central nervous system involvement, with the exception of those subjects whose central nervous system metastases have been treated with either radiotherapy and/or surgery and remains asymptomatic with no evidence of active central nervous system disease (verified by CT scan or MRI) for at least 6 months.

**10)** Patients known to be positive for HIV or infectious hepatitis, type A, B, or C.

**11)** Patients with medullary or anaplastic thyroid carcinomas are excluded. Patients whose disease is limited to bone metastases are excluded.

5.2 **Treatment Plan**:

5.2.1 Therapy is administered on an outpatient basis.

5.2.2 Treatment Drugs: Patients will receive the study drug as long as there is no evidence of disease progression (as defined in section 9.0 Response Criteria) or unacceptable toxicity.

5.2.2.1 Patients must continue to take levothyroxine at a dose sufficient to suppress the TSH level ≤0.1 while avoiding significant thyrotoxicosis.

5.2.2.2 Concomitant use of other anti-cancer therapies (besides levothyroxine) or other investigational agents is not permitted while subjects are receiving study drug during the treatment phase of the study.

5.2.2.3 Patients will be informed of a possible risk of thrombotic events and will be given the option of starting prophylactic treatment with low-dose aspirin at 81 mg daily.

5.2.3 Patients will be assessed for treatment response monthly for the first 2 28-day cycles, then every 2 28-day cycles for a total treatment time of one year.

5.2.4 Treatment will be initiated with REVLIMID® at 25 mg/day taken each morning or at the same time each day. Dose adjustments will be made to deal with toxicities as described in section 5.2.5. REVLIMID® will be provided as 5 mg and 25 mg capsules for oral administration.

5.2.4.1 Drug will be provided by Celgene Corporation and will be shipped to the pharmacy at the study site in individual bottles. Bottles will contain a sufficient number of capsules to last for 28 days of dosing. The study drug must be dispensed in the original packaging and the label must be clearly visible. The study drug will be provided to each patient at his or her scheduled research clinic visit. Bottle numbers must be recorded when study drug is received and dispensed. The Study Pharmacist will maintain an inventory of each shipment of study drug received and compare it with the accompanying drug accountability form, signing and returning the form to Celgene and

maintaining a copy in the study file. Treatment through this protocol will be conducted under the aegis of the Investigational New Drug application held by Dr. Kenneth B. Ain.

5.2.4.2 Handling Revlimid®: Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened. At the discretion of the principal investigator AND only on instruction by the principal investigator capsules can be opened for patients who have extreme difficulty, or who are unable to swallow. FEMALES OF CHILD BEARING POTENTIAL SHOULD NOT HANDLE OR ADMINISTER REVLIMID® CAPSULES UNLESS THEY ARE WEARING GLOVES AND MASK.

5.2.4.3 Labeling: REVLIMID® investigational supplies that are dispensed to the patients by the investigational pharmacy are supplied in individual bottles of capsules. Each bottle that is dispensed by the investigational pharmacy will identify the contents as study medication. It will also bear Celgene's name and address, quantity contained and the standard caution statement as follows: Caution: New Drug – Limited by Federal Law to investigational use. For appropriate drug accountability, it is recommended that each bottle be marked with the institutional or Celgene protocol number (RV-THYR-PI-057) upon receipt. Additional labels must not cover the Celgene label.

5.2.4.4 Storage: The Study Pharmacist at the investigational pharmacy will store all investigational study drugs in an appropriately secure area to prevent unauthorized access. The study drug will be stored at room temperature away from direct sunlight and protected from excessive temperature ranges.

5.2.4.5 Unused Study Drug Supplies: Patients that have been provided REVLIMID® through the investigational pharmacy will be instructed to return empty bottles or unused capsules. Celgene will instruct the Investigator on the return destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the source documents. Study drug supplies will be retained by the Study Pharmacist, pending instructions for disposition by Celgene.

5.2.4.6 Record of Administration: Accurate records will be kept of all study drug administration (including dispensing and dosing).

5.2.5 Dose Modification or Interruption: Subjects will be evaluated for Adverse Events (AEs) at each visit, using the NCI Common Terminology Criteria for Adverse Events, version 3.0 (CTC; appendix C) as the guide for the grading of severity. Refer to Table 2: Revlimid® Dose Reduction Steps For Dose Modification and Table 3: Dose Modification for Revlimid® for instructions on dose modifications. Subjects who cannot tolerate a dosage of at least 5 mg daily will be discontinued from the treatment phase of this study (unless the subject has achieved a plateau phase of response to study therapy; such subjects will continue to adhere to the schedule of assessments followed during the treatment phase of the study, even though the study drug has been discontinued, until disease progression).

Once the REVLIMID® dose is initiated at 25 mg/day, taken in the morning or approximately the same time each day, it will be maintained at this dose for the duration of the study unless dose modification is necessary due to toxicity. 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.

***Table 2***

Dose adjustments will be made for toxicity as needed, until a stable tolerable dose is achieved or a dose of at least 5 mg/day is unable to be tolerated, resulting in discontinuation of REVLIMID®. If REVLIMID® is held, toxicity should be assessed weekly and if therapy cannot be resumed within 4 weeks of holding therapy, the patient will be removed from the study.

| *Table 2: Revlimid® Dose Reduction Steps* | |
|---|---|
| ***Starting Dose*** | ***25 mg daily (28-day cycles)*** |
| *Dose Level -1* | *20 mg daily every 28 days* |
| *Dose Level -2* | *15 mg daily every 28 days* |
| *Dose Level -3* | *10 mg daily every 28 days* |
| *Dose Level -4* | *5 mg daily every 28 days* |

*Table 3*

| REVLIMID® Dose Modification Criteria | | |
|---|---|---|
| **Toxicity** | **Grade** | **Dose Level Change** |
| Rash / Desquamation | Rash: II | Hold until resolution to ≤ grade I; resume at one level dose reduction. Further dose reductions are permitted to a minimum of 5 mg |
| | Rash: III | Hold until resolution to ≤ grade I; resume with 2 dose level reductions or a minimum of 5 mg. If grade III rash recurs discontinue therapy. |
| | Rash: IV or any grade desquamating (blistering) rash or erythema multiforme ≥ grade III | Discontinue drug |
| Sinus bradycardia, atrial fibrillation or other cardiac arrhythmias | II | Hold until resolution to ≤ grade I, resume at one dose level reduction. Additional dose reductions are permitted to a minimum of 5 mg. |
| | III | Discontinue drug |
| | IV | Discontinue drug |
| Neutropenia | III or IV | Hold, CBC weekly until resolution to ≤ grade II, ; resume at one dose level reduction. Additional dose reductions are permitted to a minimum of 5 mg. |
| Thrombocytopenia | III or IV | Hold, CBC weekly until resolution to ≤ grade 2, ; resume with one dose level reduction, additional dose reductions are permitted to a minimum of 5 mg. |
| Venous thrombosis or embolism | III | Hold drug & anticoagulate, restart at one dose level reduction |
| | IV | Discontinue drug & anticoagulate |
| Allergic reaction or Hypersensitivity | II | Hold until resolution to ≤ grade I; resume at one dose level reduction. Additional dose reductions are permitted to a minimum of 5 mg. |
| | III | Hold until resolution to ≤ grade I; resume at two dose level reductions to a minimum of 5 mg. If grade III recurs, discontinue therapy |
| | IV | Discontinue drug |
| Other non-hematological toxicity assessed as Revlimid-related | III | Hold until resolution to ≤ grade II; resume at one level dose reduction. Additional dose reductions are permitted to a minimum of 5 mg. |
| | IV | Discontinue drug |

G-CSF is not permitted during this study unless needed to treat severe neutropenia or neutropenic fever. Otherwise, neutropenia should be managed as outlined in the table above. Filgrastim is not provided by this study. Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, and antiemetics when appropriate. The use of radiation therapy &/or surgery to a pre-existing metastatic bone lesion may be permitted while continuing on this protocol as long as it is not an evaluable site of disease and does not represent disease progression

*In the event that the daily dose schedule of Revlimid is causing repeat hematologic toxicity that needs time to resolve, consideration may be given to modify the schedule from daily every 28 days to daily for 21 days followed by 7 days of rest each month. This modification must be discussed and approved by the Principal Investigator of the study.*

5.2.6 Extended Therapy phase: At one year after starting this protocol, those patients that are maintaining tumor response to REVLIMID® treatment and wish to continue these treatments will enter into the "Extended Therapy" phase. These patients may elect to continue with extended drug therapy in 28-day cycles through the RevAssist program see Appendix 1, with treatment response and routine tumor assessment every three months. This phase will continue, indefinitely, as long as the patient tolerates the medication and continues to manifest a tumor response. This phase may be terminated by Celgene Corporation, the principle investigator, or the patient at any time.

## 6.0 Pre-Treatment Evaluation: (Patient must sign IRB consent form)

6.1 **Basic Data:** Physical examination and medical history; Laboratory tests (urinalysis, electrolytes, BUN, creatinine, hepatic enzymes, bilirubin, ionized calcium, phosphorus, glucose, albumin, PT, aPTT), baseline electrocardiogram.

6.2 **Tumor Assessment:**

6.2.1 **Tumor markers:** thyroglobulin panel (thyroglobulin & anti-thyroglobulin antibody), TSH, free T4.

6.2.2 **Radiological Studies:** Patients must have at least one year of radiographic evidence of tumor progression with at least 2 separate x-ray studies (preferably CT or MR scans) able to define tumor volume, or similar radiographic evidence over a shorter period of time delineating greater than 30% increased tumor volume (to permit comparison of rate of tumor progression with each patient as their own control). A baseline radiological evaluation of tumor volume must be obtained within one week prior to initiating REVLIMID®.

6.2.3 **Tumor Volume Assessment Methodology**: Volumetric tissue measurements are well established for both MR and CT scans which are generally performed on an independent imaging work station (38-41). A Siemen's Magic View PACS workstation will be used to perform volumetric measurements on metastatic tumor(s) utilizing software VB 32 release B updated on 2/2000 written by Sun Microsystems. An irregular ROI (region of interest) curve will be traced around the tumor(s) on dual high-resolution 1024 x 1024 matrix monitors. All tracings

will be stored on CD-ROM for reproducibility as well as visual inspection of tumor(s) size change by superimposing the most recent study on the prior study.

CT images will be obtained with a 3 mm thick beam incremented at 1 mm intervals. The 3 mm thickness is chosen to reduce the graininess due to quantu mottling with a 1.5 mm thick beam (smallest available slice). The calculated surface area of each 1 mm thin slice contained in the irregular shaped ROI will be added to the other slices to yield a three dimensional volume. Depending on whether the evaluable disease sites require oral or IV contrast for imaging, the CT scan will be either with or without such contrast material. All CT scans will be performed on a Siemen's Somatom CT scanner.

MR images will be obtained utilizing 3D volume acquisition techniques because of the non-rectangular pulses on 2D axial images, which require a 1 mm gap between slices to reduce cross talk. Because of the 1 mm gap, inaccuracies in total volume will be introduced on the 2D techniques. All MR scans will be performed on either a 1.5 T superconductive magnet Siemen's Vision or Symphony scanner. Use of gadolinium contrast agent may be used depending on the imaging findings.

Choice of CT or MR will depend on patient cooperation. Although MR is far superior to CT in discriminating tissue types, the 3D volume technique requires that the patient be able to hold completely still for at least 8-10 minutes, whereas each CT scan slice can be obtained in less than 1 second. It is anticipated that the majority of imaging studies will be CT scans. If outside CT or MR scans are of sufficient resolution and the scanning factors are known, the hard copy scans can be digitized and thus transferred to the work station. If these are r adequate, then repeat scans will be performed at this institution. Follow up scan monitoring therapy will be reviewed for tumor volume changes, morphological changes in size, and presence of bony/cartilage invasion.

6.3 **Angiogenic Markers** (see Appendix E for sample collection/storage/methodology)

6.3.1 **Proangiogenic cytokine:** vascular endothelial growth factor-alpha (VEGF-A).

6.3.2 **Antiangiogenic factors:** soluble VEGF receptor-1 (sVEGFR-1), sVEGFR-2, and thrombospondin-1 (TSP-1).

6.4 Toxicity Monitoring: Please refer to Table 1: Schedule of Study Assessments

6. 4.1 **Hematologic**: CBC with differential/platelet count.

6. 4.2 **Biochemical**: Serum comprehensive metabolic profile

6. 4.3 **Pregnancy prevention**: Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to initiation of lenalidomide. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 4 weeks and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at 30 Days +/- 2 days post the last dose of lenalidomide.

Females with irregular menstruation must have a pregnancy test weekly for the first 4 weeks 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 F: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).

7.0 **Evaluation During Study**: Please refer to Table 1: Schedule of Study Assessments
Physical examination and history (clinic visit): monthly for the first 2 28-day cycles, then every 2 28-day cycles while on the study.

7.1 **Tumor Assessment**: The following studies are obtained every 2 28-day cycles while on therapy:

7.1.1 **Tumor markers**: thyroglobulin panel, TSH, free T4.

7.1.2 **Radiological Studies**: CT (without contrast for lung metastases; otherwise with contrast) &/or MRI of evaluable disease. Radiological studies will be financed by the research study at 28-day cycles 2, 6, & 10 (if the patient remains on the protocol for that length of time). Baseline radiological studies and those at the intervals of 28-day cycles 4, 8, &-12 will be financed by the patient &/or 3rd party payers, representing appropriate intervals of assessing progressive metastatic tumors for usual clinical standards of care.

7.2 **Angiogenic Markers:** The following studies are obtained monthly for the first 2 28-day cycles, then every 2 28-day cycles while on therapy:

7.2.1 **Proangiogenic cytokine:** VEGF-A.

7.2.2 **Antiangiogenic factors:** sVEGFR-1, sVEGFR-2, and TSP-1.

7.3 **Toxicity Monitoring**:

7.3.1 **Hematological**: Weekly: CBC with differential and platelet count for the first 2 cycles then monthly. Obtain biochemistry panel at cycles 4, 8 and 12.

7.3.2 **Pregnancy prevention** (Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to initiation of lenalidomide. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 4 weeks and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at 30 Days +/- 2 days post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 4 weeks 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 F: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).

8.0 **Evaluations at Termination of Protocol**: The following studies are obtained when terminating the protocol due to either disease progression, severe toxicity or at the conclusion of one year of REVLIMID® treatment:

8.1 **Tumor Assessment:**

8.1.1 **Tumor markers:** thyroglobulin panel, TSH, free T4.

8.1.2 **Radiological Studies:** CT (without contrast for lung; otherwise with contra &/or MRI of evaluable disease.

8.2 **Angiogenic Markers:**

8.2.1 **Proangiogenic cytokine:** VEGF-A.

8.2.2 **Antiangiogenic factors:** sVEGFR-1, sVEGFR-2, and TSP-1.

8.3 **Evaluations during "Extended Therapy" phase:** The following studies are obtained after the one-year protocol has concluded and the patient is maintaining a clinical response to REVLIMID® therapy and elects to continue to receive this drug and may receive REVLIMID through the RevAssist program. Note that these studies are performed as "standard-of-care" assessments that are appropriate for oncologic follow-up:

8.3.1 **Tumor Assessment** (obtained at physician visits every 3 months):
*Tumor markers*: Thyroglobulin Panel (TG & anti-TG Ab), TSH, free T4.
*Angiogenic Markers*: Not done.
*Radiological Studies*: CT (without contrast for lung; otherwise with contrast) of evaluable disease.
*Additional standard assessments*: biochemistry panel and physical examination.

8.3.2 **Toxicity Monitoring** (obtained every month while taking REVLIMID®): CBC with differential/platelet count, and pregnancy test every 4 weeks if regular menstruation and every 2 weeks if irregular. All patients must continue to follow the birth control guidelines.

9.0 **Response Criteria and Toxicity Assessment**: Overall responses will be assessed as described in Figure 4, below. These assessments are adapted from RECIST Criteria (referenced in Fig. 4).

9.1 **Parameters of Response:**

9.1.1 **Complete Response (CR)**: Disappearance of all radiological and clinical evidence of tumor. The patient must be free of all tumor related symptoms for at least 4 weeks.

9.1.2 **Partial Response (PR)**: 30% or greater decrease in the sum of the longest diameter of all measured lesions (or alternatively, ≥30% reduction of calculated tumor volumes) for at least 4 weeks.

9.1.3 **Minor Response (MR)**: For tumors with a documented rate of progression (calculated as either the linear slope of calculated tumor volumes vs. time for the immediate year prior to initiating this study or as the slope of the logarithm of

tumor volumes vs. time over the same interval), a decrease in the rate of progression by ≥50%.

9.1.4 **Stable Disease (SD)**: No change or <30% decrease in the tumor volume (calculated as in 9.1.2) for at least 4 weeks.

9.1.5 **Progressive disease (PD)**: Less than a 50% reduction in the rate of progression (see 9.1.3), an increase of >20% in the size of target lesions, or the appearance of new metastatic lesions.

**Figure 4.** Overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions* (Adapted from Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG 2000 New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205-16)

| Target lesions | Non-target lesions | New lesions | Overall response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Incomplete response/MR/SD | No | PR |
| PR | Non-PD | No | PR |
| MR | Non-PD | No | MR |
| SD | Non-PD | No | SD |
| PD | Any | Yes or no | PD |
| Any | PD | Yes or no | PD |
| Any | Any | Yes | PD |

*CR= complete response; PR= partial response; MR= minor response; SD= stable disease; and PD= progressive disease.

9.2 **Toxicity Assessment**: This will be performed at intervals defined in section 7.0 using criteria defined in appendices A, B, & C.

10.0 **Criteria for Discontinuing Therapy**:

10.1 Progressive Disease is an indication to discontinue therapy.

10.2 Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of the study drug.

10.3 Non-compliance by the patient with protocol requirements.

10.4 Patient desire to discontinue therapy.

10.5 Evidence of pregnancy.

10.6 Withdrawal of consent.

10.7 Lost to follow-up.

10.8 Death

11.0 **Statistical Parameters**: A two-stage design will be used, as described by Gehan (4), which entails the evaluation of 14 patients to determine whether there is at least one patient responsive to this treatment. Would no responders be found within 4 28-day cycles after initiating each of the 14 patients on the study drug, the study will end at that time. In the presence of at least one responder, the trial is planned to continue, accruing an additional 11 patients or sufficient patients to determine a 95% confidence interval for the true response rate. Thus, a total of 14 patients will be enrolled if there are no responders; however, up to 25 patients will be enrolled if there are responders in the initial group. Response rates of 65% have been noted in prior studies using the parent compound, thalidomide (1). Based on such activity, we anticipate that the probability of observing 'no responses' for this treatment regimen in 14 subjects is less than $4.0 \times 10^{-7}$. In essence, there is very low probability that this study will not move into the second phase given the levels of tumor activity reported previously for this treatment.

12.0 **Protocol Management and Data Collection**: All data will be collected and entered into the study database by the Nursing Staff of the University of Kentucky Clinical Research Organization (UK-CRO), Drs. Ain and Lee, and the research support staff of the University of Kentucky Thyroid Oncology Program. Clinical decisions regarding study subjects, as well as protocol decisions, will be the responsibility of the Principal Investigator. The Markey Cancer Center Data and Safety Monitoring System (DSMS) will be used to monitor this study (see section 13.6).

12.1 **Investigator responsibilities**: Investigator responsibilities are set out in the IC guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations (CFR). The Investigator will permit study-related monitoring visits and audits by Celgene or it's 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 data entry system, and to all other study documents. The Investigator, or a designated member of the Investigator's staff, must be available at some time during monitoring visits 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.

12.2 **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.

12.3 **Premature discontinuation of study**: Both this study's investigators and the supporter, Celgene, have the right to discontinue this study at any time for reasonable medical

administrative reasons. Possible reasons for termination of the study could be, but are not limited to:

- o Unsatisfactory enrollment with respect to quantity or quality.
- o Inaccurate or incomplete data collection.
- o Falsification of records. ..
- o Failure to adhere to the study protocol.

13.0 **Reporting Requirements**: This section outlines the protocol for reporting Serious Adverse Events (SAEs).

13.1 **Investigator Reporting to the FDA:** The sponsor (for this protocol, the principal investigator) shall also notify FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but in no event later than 7 calendar days after the sponsor's initial receipt of the information. Each telephone call or facsimile transmission to FDA shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. A clear description of the suspected reaction will be provided along with an assessment as to whether the event is drug or disease related. The phone number is 301-594-5778. The address is: FDA, Division of Oncology, HFD – 150, 1451 Rockville Pike, Rockville, MD 20852-1448.

If the results of the sponsor's investigation show that an adverse drug experience, not initially determined to be reportable under the preceding paragraph of this section is so reportable, the sponsor shall report such experience in a written safety report as soon as possible, but in no event later than 15 calendar days after the determination is made.

13.2 **Serious Adverse Event (SAE) Reporting**: A serious adverse event is one that at any dose (including overdose):

- o Results in death
- o Is life-threatening[1]
- o Requires inpatient hospitalization or prolongation of existing hospitalization
- o Results in persistent or significant disability or incapacity[2]
- o Is a congenital anomaly or birth defect
- o Is an important medical event[3]
- o Positive 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.

13.3 **Report of Adverse Events to Celgene Corporation:** Serious adverse events (SAE) are defined above. The investigator should inform Celgene of any **SAE** within 24 hours of being aware of the event. This must be documented on Celgene SAE form or a FDA 3500 or MEDWATCH form. This form must be completed and supplied to Celgene within 24 hours/1 business day at the latest on the following working day. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up MEDWATCH. The Celgene protocol number (RV-THYR-PI-057) should be included on SAE reports to Celgene

13.3.1 **Pregnancies:**

Pregnancies occurring while the subject is on study drug or within 4 weeks after the subject's last dose of study drug are considered Expedited reportable events. If the subject is on study drug the study drug is to be discontinued immediately and the subject is to be instructed to return any unused portion of the study drug to the Investigator. The pregnancy must be reported to Celgene Corporation Worldwide Drug Safety Surveillance (WWDSS) within 24 hours of the Investigator's knowledge of the pregnancy by phone and facsimile using the SAE Form.

The Investigator will follow the subject until completion of the pregnancy, and must notify Celgene Corporation Worldwide Drug Safety Surveillance (WWDSS) of the outcome as specified below. The Investigator will provide this information as a follow-up to the initial SAE.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting SAEs (i.e., report the event to Celgene Corporation Worldwide Drug Safety Surveillance (WWDSS) by facsimile within 24 hours of the Investigator's knowledge of the event).

Any suspected fetal exposure to lenalidomide must be reported to Celgene within 24 hours of being made aware of the event. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects is related to the *in utero* exposure to the study drug should also be reported.
In the case of a live "normal" birth, Celgene Corporation Worldwide Drug Safety Surveillance (WWDSS) should be advised as soon as the information is available.

**13.4** Celgene Contact Information..
Celgene Corporation
Worldwide Drug Safety Surveillance (WWDSS)
86 Morris Avenue
Summit, N.J. 07901

Toll Free: (800)-640-7854

Phone: (908) 673-9667
Fax: (908) 673-9115
e-mail: drugsafety@celgene.com

**13.5 Report of Adverse Events to the Institutional Review Board**: The principal Investigator is required to notify his/her Institutional Review Board (IRB) by facsimile using the UK INTERNAL UNANTICIPATED PROBLEM/ADVERSE EVENT REPORTING FORM. All internal (i.e. UK) problems/adverse events that are serious and unanticipated and which are possibly, probably or definitely associated with study procedures must be reported to the IRB, if applicable, the IBC and GCRC using this form within the following timeframe:

1. Any **death** of a subject occurring on a UK study that is possibly, probably or definitely associated with study procedures should be reported immediately (i.e. within 48 hours).

2. A problem/event experienced by a subject that is **life threatening** and possibly, probably or definitely related to the study procedures, should be reported within 7 calendar days (1 week) of investigator's receipt of information:

- All other internal **serious** and **unanticipated problems/events** that are possibly, probably or definitely related to study procedures, must be reported within 14 calendar days (2 weeks) of investigator's receipt of information.
- An **unanticipated problem** is any event that affects the rights, safety, or welfare of subjects or others. The event could be physical, such as an **adverse experience**. The event also could involve social harm or risk (i.e., a breach in confidentiality or harm to a subject's reputation) or psychological or legal harm or risk. Examples of unanticipated problems include, but are not limited to, breach of confidentiality, protocol violations and deviations, and complaints about the research procedures or treatment by key personnel on the research study.
- A **serious unanticipated problem** is any event that results in significant harm to or increased risk for the subject or others.
- If there is insufficient information to determine if the event is associated, it should be reported.

**13.6 Markey Data and Safety Monitoring System (DSMS)**: The Markey Cancer of the University of Kentucky has established a system for following clinical oncology trials. This mechanism will be used as the Plan for monitoring this trial.

**13.6.1 Components:** Quality Assurance Committee (QAC);Protocol Review Committee (PRC).

**13.6.2 Quality Assurance Committee (QAC):** The QAC provides oversight and monitoring of clinical trials. The Committee is responsible for reviewing data to identify patient safety and protocol compliance issues. The Markey Protocol Review Committee (PRC) assigns studies a QAC timeline based on the phase, origination of the study and known safety issues.

13.6.3 **QAC Membership:** The members of the QAC consists of Medical Oncologists, a Pharmacist, a Nurse Manager, a Certified Clinical Research Professional and a

Reporter. These members are selected based on their experience, reputation for objectivity and knowledge of clinical trial methodology. All member view themselves as representing the interest of the study patients and not that of the institution.

**13.6.4 QAC Review:** At each meeting, the following study data is reviewed by the QAC: treatment issues, serous adverse events (SAE's) per FDA's definition, dose levels, dose modifications, and responses as applicable.

The QAC reviews protocols to assure the following:

- progress of the trial and safety of participants,
- compliance with requirements regarding the reporting of severe adverse events,
- that any action resulting in a temporary of permanent suspension of this clinical trial is reported to the responsible program director, and
- data accuracy and protocol compliance.

**13.6.4.2 Study Suspension:** The Markey Quality Assurance Committee, the responsible disease-specific CCART and/or the UK/VA IRB are empowered to immediately suspend accrual to a study for any of the following: Failure to comply with AE/SAE reporting requirements, poor study enrollment, protocol violations, or issues related to patient safety.

13.7 **Reporting by supporter to investigator concerning 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 study 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 (sponsor) must keep copies of all AE information, including correspondence with Celgene and the IRB/EC, on file (see Section 13.8 for records retention information).

13.8 **Study Records Requirements**: The Investigator (sponsor) will ensure that all records and documents pertaining to the conduct of the study and the distribution of the study drug, 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; 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 study 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.

13.9 **Subject confidentiality and supporter access to information**: The Investigator and the supporter, Celgene, affirm the subject's right to protection against invasion of privacy. In compliance with United States federal regulations, Celgene requires the Investigator to permit Celgene's representatives 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.

14.0 **Protocol amendments**: Any amendment to this protocol must be agreed to by the Principal Investigator (sponsor) and reviewed by Celgene. Written verification of IRB/EC approval will be obtained before any amendment, which affects subject safety or efficacy, is implemented.

15.0 **References**:


1. **Ain KB, Lee C, Williams K** 2002 Phase II trial of thalidomide for therapy of radioiodine-unresponsive papillary and follicular thyroid carcinomas and medullary thyroid carcinomas: preliminary results. Cancer Invest 21:Suppl 1, 38-9
2. **Bartlett JB, Michael A, Clarke IA, et al.** 2004 Phase I study to determine the safety, tolerability and immunostimulatory activity of thalidomide analogue REVLIMID® in patients with metastatic malignant melanoma and other advanced cancers. Br J Cancer 90:955-61
3. **Richardson PG, Schlossman RL, Weller E, et al.** 2002 Immunomodulatory drug REVLIMID® overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. Blood 100:3063-7
4. **Gehan EA** 1961 The determination of the number of patients required in a follow-up trial of a new chemotherapeutic agent. J Chronic Dis 13:346-353
5. **Ozata M, Suzuki S, Miyamoto T, Liu RT, Fierro-Renoy F, DeGroot LJ** 1994 Serum thyroglobulin in the follow-up of patients with treated differentiated thyroid cancer. J Clin Endocrinol Metab 79:98-105
6. **Ain KB** 1999 Management of poorly differentiated thyroid cancer. In: Braunwald E, Fauci AS, Isselbacher KJ, Hauser SL, Longo DL, Jameson JL (eds) Harrison's Online. McGraw-Hill, New York
7. **Scherubl H, Raue F, Ziegler R** 1990 Combination chemotherapy of advanced medullary and differentiated thyroid cancer. Phase II study. J Cancer Res Clin Oncol 116:21-3
8. **Schlumberger M, Parmentier C** 1989 Phase II evaluation of mitoxantrone in advanced non anaplastic thyroid cancer. Bull Cancer 76:403-406
9. **Samonigg H, Hossfeld DK, Spehn J, Fill H, Leb G** 1988 Aclarubicin in advanced thyroid cancer: a phase II study. Eur J Cancer Clin Oncol 24:1271-1275
10. **Maheshwari YK, Hill Jr CS, Haynie III TP, Hickey RC, Samaan NA** 1981 I-131 therapy in differentiated thyroid cancer: M. D. Anderson Hospital experience. Cancer 47:664-71
11. **Ain KB, Tofiq S, Taylor KD** 1996 Antineoplastic activity of taxol against human anaplastic thyroid carcinoma cell lines in vitro and in vivo. J Clin Endocrinol Metab 81:3650-3
12. **Ain KB, Egorin MJ, DeSimone PA** 2000 Treatment of anaplastic thyroid carcinoma with paclitaxel: phase 2 trial using ninety-six-hour infusion. Collaborative Anaplastic Thyroid Cancer Health Intervention Trials (CATCHIT) Group. Thyroid 10:587-94

13. **Brown JM, Giaccia AJ** 1998 The unique physiology of solid tumors: opportunities (and problems) for cancer therapy. Cancer Res 58:1408-1416
14. **Fidler IJ** 1999 Critical determinants of cancer metastasis: rationale for therapy. Cancer Chemother Pharmacol 43:S3-10
15. **Kerbel R, Folkman J** 2002 Clinical translation of angiogenesis inhibitors. Nat Rev Cancer 2:727-39
16. **Kerbel RS, Viloria-Petit A, Klement G, Rak J** 2000 'Accidental' anti-angiogenic drugs. anti-oncogene directed signal transduction inhibitors and conventional chemotherapeutic agents as examples. Eur J Cancer 36:1248-57
17. **Reyes M, Dudek A, Jahagirdar B, Koodie L, Marker PH, Verfaillie CM** 2002 Origin of endothelial progenitors in human postnatal bone marrow. J Clin Invest 109:337-46
18. **Bagley RG, Walter-Yohrling J, Cao X, et al.** 2003 Endothelial precursor cells as a model of tumor endothelium: characterization and comparison with mature endothelial cells. Cancer Res 63:5866-73
19. **Garrity T, Pandit R, Wright MA, Benefield J, Keni S, Young MR** 1997 Increased presence of CD34+ cells in the peripheral blood of head and neck cancer patients and their differentiation into dendritic cells. Int J Cancer 73:663-9
20. **Young MR** 2004 Tumor skewing of CD34+ progenitor cell differentiation into endothelial cells. Int J Cancer 109:516-24
21. **Asahara T, Murohara T, Sullivan A, et al.** 1997 Isolation of putative progenitor endothelial cells for angiogenesis. Science 275:964-7
22. **Moore XL, Lu J, Sun L, Zhu CJ, Tan P, Wong MC** 2004 Endothelial progenitor cells' "homing" specificity to brain tumors. Gene Ther 11:811-8
23. **Ebos JM, Bocci G, Man S, et al.** 2004 A naturally occurring soluble form of vascular endothelial growth factor receptor 2 detected in mouse and human plasma. Mol Cancer Res 2:315-26
24. **Lawler J, Detmar M** 2004 Tumor progression: the effects of thrombospondin-1 and -2. Int J Biochem Cell Biol 36:1038-45
25. **Bocci G, Francia G, Man S, Lawler J, Kerbel RS** 2003 Thrombospondin 1, a mediator of the antiangiogenic effects of low-dose metronomic chemotherapy. Proc Natl Acad Sci U S A 100:12917-22
26. **Bauer KS, Dixon SC, Figg WD** 1998 Inhibition of angiogenesis by thalidomide requires metabolic activation, which is species-dependent. Biochem Pharmacol 55:1827-1834
27. **Chung F, Lu J, Palmer BD, et al.** 2004 Thalidomide pharmacokinetics and metabolite formation in mice, rabbits, and multiple myeloma patients. Clin Cancer Res 10:5949-56
28. **Hansen JM, Carney EW, Harris C** 1999 Differential alteration by thalidomide of the glutathione content of rat vs. rabbit conceptuses in vitro. Reprod Toxicol 13:547-54
29. **Fine HA, Figg WD, Jaeckle K, et al.** 2000 Phase II trial of the antiangiogenic agent thalidomide in patients with recurrent high-grade gliomas. J Clin Oncol 18:708-15
30. **Juliusson G, Celsing F, Turesson I, Lenhoff S, Adriansson M, Malm C** 2000 Frequent good partial remissions from thalidomide including best response ever in patients with advanced refractory and relapsed myeloma. Br J Haematol 109:89-96
31. **Mitsiades CS, Mitsiades N** 2004 REVLIMID® (Celgene). Curr Opin Investig Drugs 5:635-47
32. **Zangari M, Tricot G, Zeldis J, Eddlemon P, Saghafifar F, Barlogie B** 2001 Results of phase I study of REVLIMID® for the treatment of multiple myeloma (MM) patients who relapse after high dose chemotherapy (HDCT). Blood 98:3226a
33. **Barlogie B, Shaughnessy J, Tricot G, et al.** 2004 Treatment of multiple myeloma. Blood 103:20-32
34. **Barlogie B** 2003 Thalidomide and REVLIMID® in multiple myeloma: the University of

Arkansas experience. Semin Hematol 40:33-8
35. **Anderson KC** 2003 The role of immunomodulatory drugs in multiple myeloma. Semin Hematol 40:23-32
36. **Richardson PG, Jagannath S, Schlossman R, et al.** 2002 A multi-center, randomized, phase II study to evaluate the efficacy and safety of two CDC-5013 dose regimens when used alone or in combination with dexamethasone (Dex) for the treatment of relapsed or refractory multiple myeloma (MM). Blood 100:386a
37. **Bartlett JB, Dredge K, Dalgleish AG** 2004 The evolution of thalidomide and its IMiD derivatives as anticancer agents. Nat Rev Cancer 4:314-22
38. **Bigler ED, Blatter DD, Anderson CV, et al.** 1997 Hippocampal volume in normal aging and traumatic brain injury [see comments]. AJNR Am J Neuroradiol 18:11-23
39. **Blatter DD, Bigler ED, Gale SD, et al.** 1995 Quantitative volumetric analysis of brain MR: normative database spanning 5 decades of life [see comments]. AJNR Am J Neuroradiol 16:241-51
40. **Insausti R, Juottonen K, Soininen H, et al.** 1998 MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. AJNR Am J Neuroradiol 19:659-71
41. **Kidron D, Black SE, Stanchev P, et al.** 1997 Quantitative MR volumetry in Alzheimer's disease. Topographic markers and the effects of sex and education. Neurology 49:1504-12