FOX CHASE CANCER CENTER
TEMPLE HEALTH

A Phase I Study of Lenalidomide plus Pembrolizumab in Patients with Relapsed and/or Refractory Solid Tumors with Phase II Expansion in Non-Small Cell Lung Cancer

Supported by Merck and Celgene

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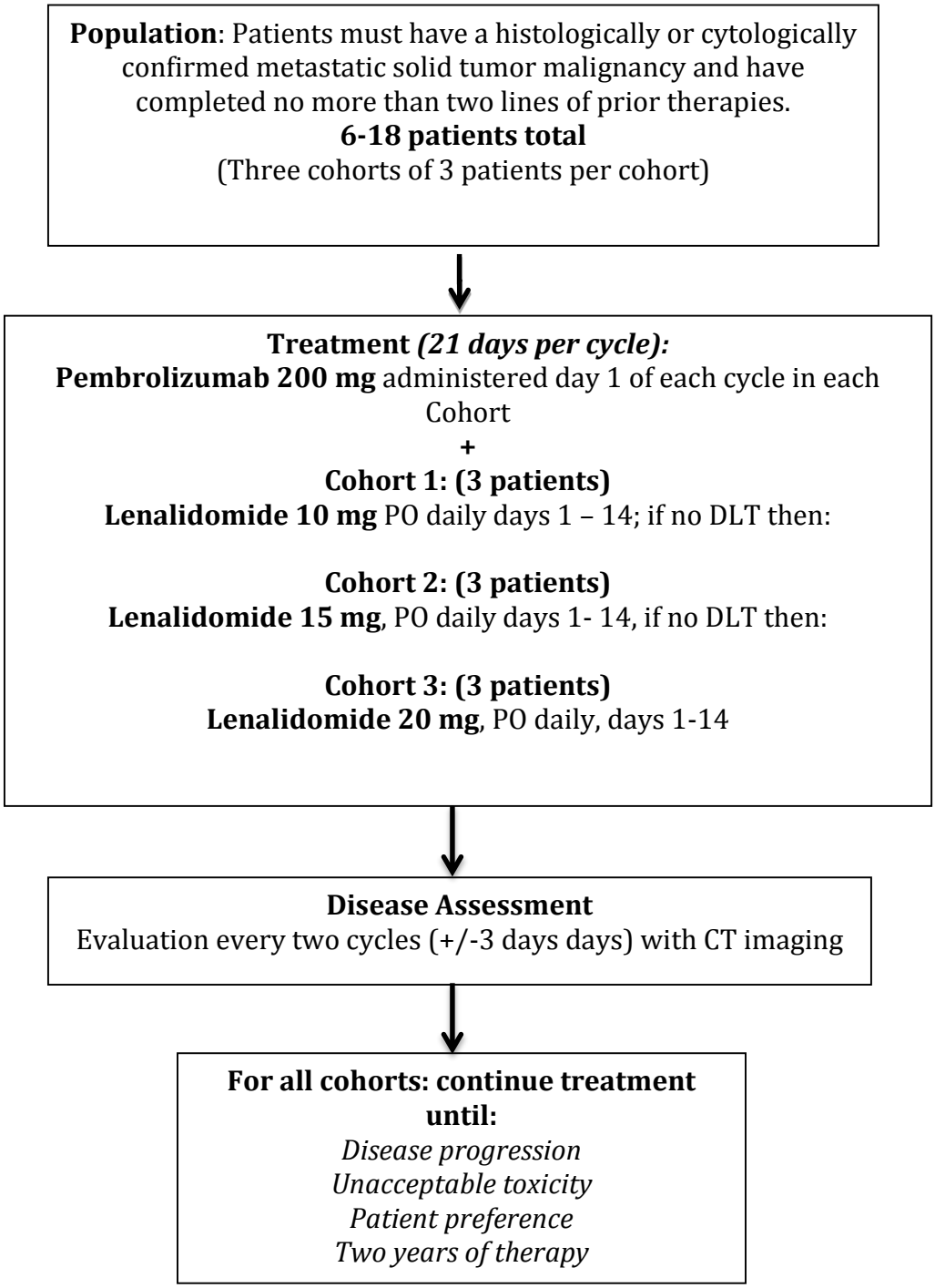
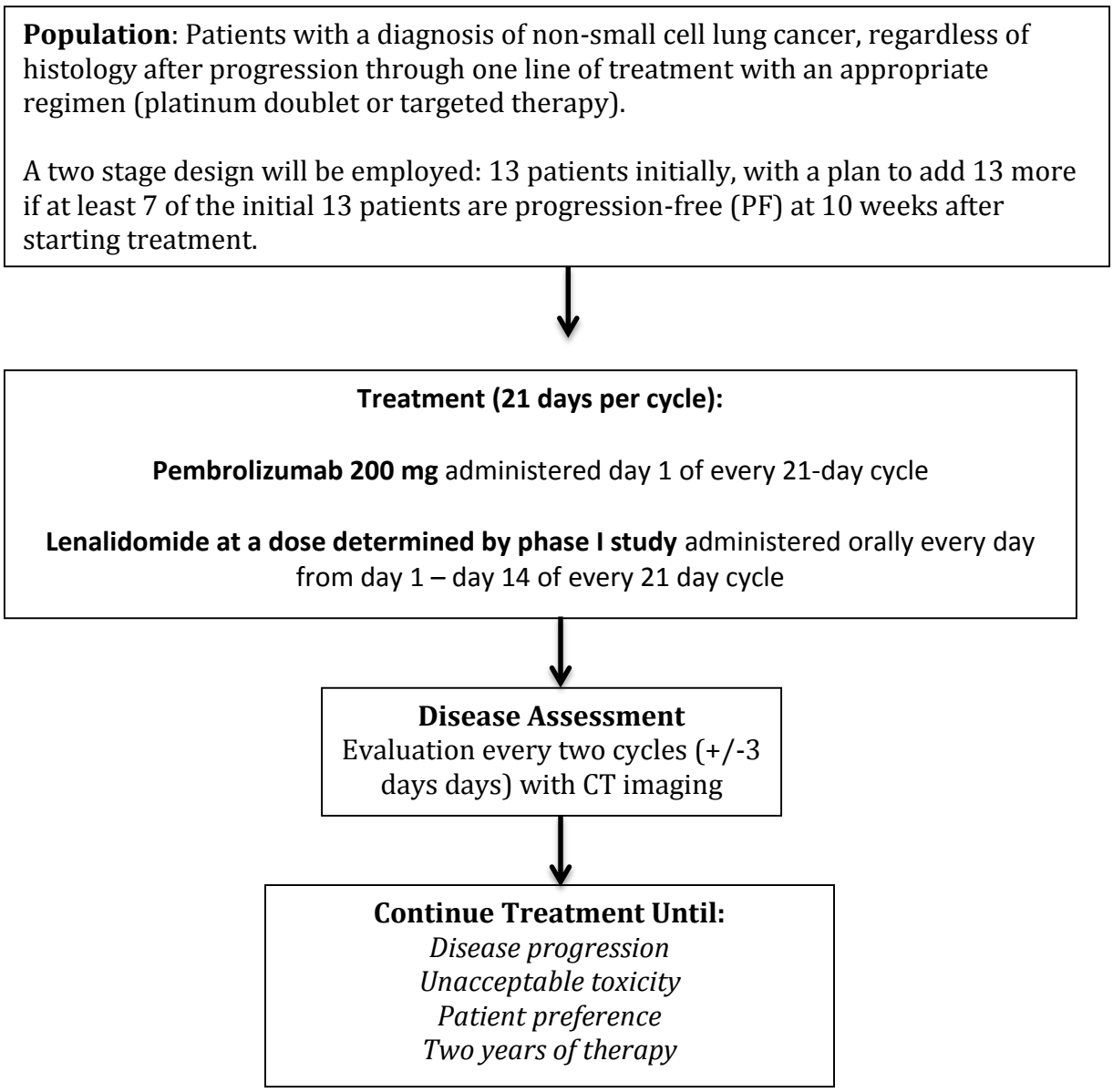
Table of Contents

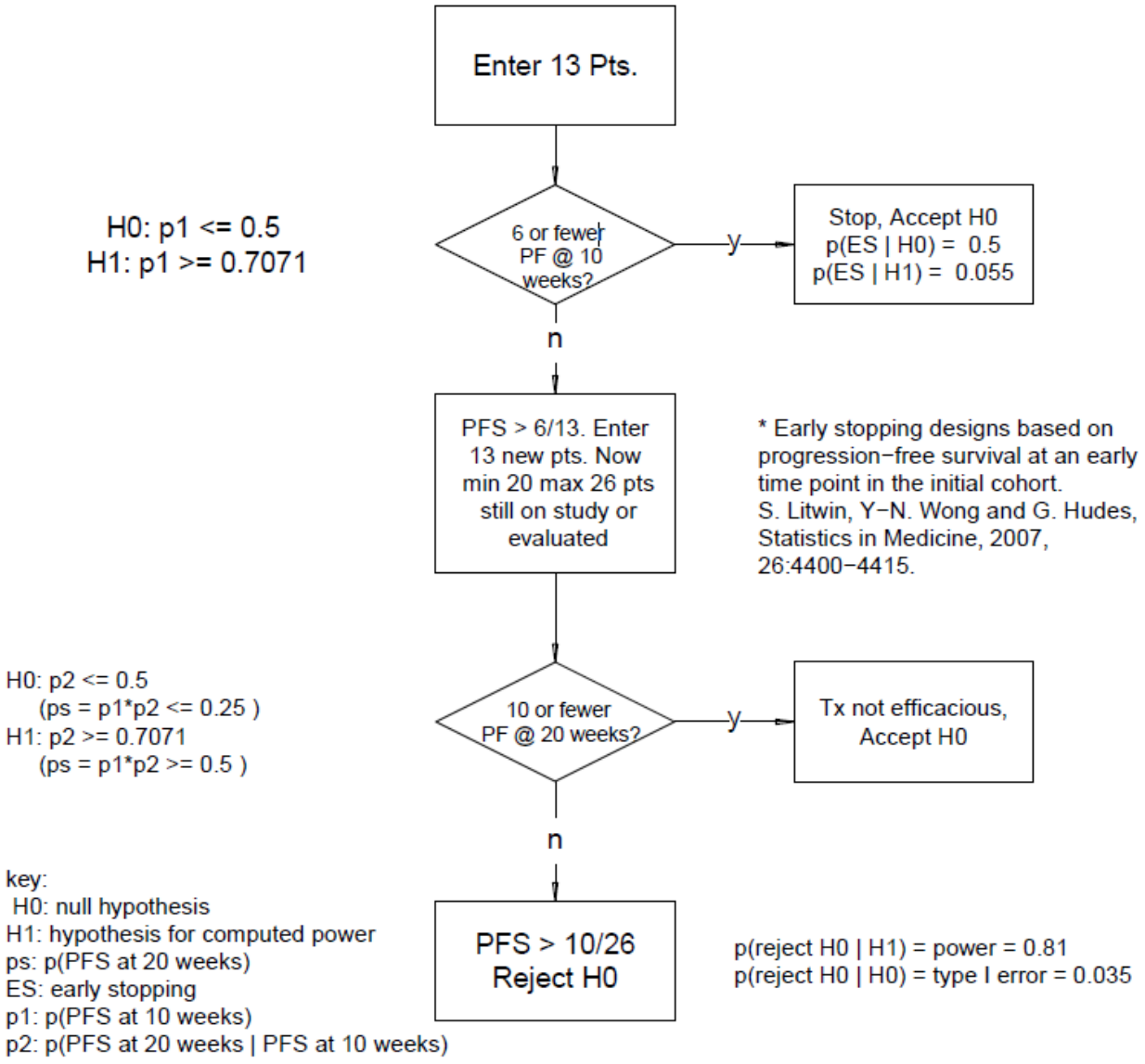
Phase I Schema



Phase II Schema



Study Flowchart



1.0 Introduction

1.1 Study Disease

The prognosis for patients with relapsed and/or refractory metastatic solid tumor malignancies remains generally poor, and new drugs and drug combinations are needed for this group of patients. Ideally, these drugs and combinations will have a limited side effect profile. With the recent development of novel immunotherapeutic agents, such as the anti-programmed death 1 (PD-1) antibodies, new combinations are possible (i.e. combining new agents with older therapies). We propose to explore a novel drug combination for patients with relapsed and/or refractory advanced solid tumors, with a plan to pursue further study in an expansion phase II cohort in patients with advanced non-small cell lung cancer (NSCLC). We have chosen NSCLC based on recent data showing significant responses to anti-PD1 antibody therapies.[1,2]

1.2 Non-Small Cell Lung Cancer

Lung cancer is affecting an ever increasing number of patients, and remains one of the world's leading causes of cancer-related deaths. There have been many developments in the management of lung cancer, especially in Non-Small Cell Lung Cancer (NSCLC). These new treatments take into account the histology and molecular characteristics of the tumor as well as patient characteristics.

The management of NSCLC has historically relied on the use of cytotoxic chemotherapy and responses have been modest. Advances in our understanding of the tumor biology, along with identification of specific molecular alterations, have allowed a more personalized approach for treatment of some patients with this disease.

In advanced NSCLC, use of platinum doublets has been the accepted standard of care for many years. Studies such as ECOG 1594 and SWOG 9509 compared several platinum based doublet regimens and found them to be equally effective, with minor differences in toxicity profile.[3,4] The median progression free survival has remained at approximately five months.[5] None of these studies reported a particular advantage in any of the subgroups analyzed with the exception of pemetrexed-based treatment in non-squamous histology where survival appears to be better.[5]

For a subset of patients with molecularly defined disease, such as those with an activating EGFR mutation or an EML4-ALK translocation, we now have effective first, second and third line treatment options.[6] It appears that in this small sub-population emergence of newer drugs and the ability to define the resistance mechanisms and the availability of specific agents for these resistance mechanisms has led to an improvement in the overall survival of these patients.[7]

For patients with advanced lung cancer who do not have a molecularly defined aberration, the activity of immune checkpoint inhibitors has been welcomed news. A number of antibodies targeting either the programed death-1 (PD-1) pathway or the cytotoxic T lymphocyte antigen-4 (CTLA-4) have captured the attention of many in the field. Nivolumab (BMS), an anti PD-1 antibody, is approved for treatment of patients with squamous cell

carcinoma of the lung after disease progression following treatment with a platinum doublet. This approval is based on the superior survival of this agent as compared with standard of care docetaxel in this population in a randomized phase III trial.[2] A similar study recently reported a survival benefit for nivolumab over docetaxel in patients with non-squamous histology and led to FDA approval of this agent for the non-squamous patient population as well.[8]

Pembrolizumab (Merck) is also an anti PD-1 antibody with significant activity in NSCLC as demonstrated by a large single arm study that examined several different dose ranges and schedules of this agent.[1] This study reported data on 495 patients treated with pembrolizumab. In addition to evaluating for safety and side effect profile, the investigators also sought to define separate cohorts using a PD-L1 assay as a biomarker to predict drug efficacy. This study revealed an overall response rate (ORR) of 19.4%, with 84.4% of responding patients without disease progression at the time of data analysis. Median duration of response was 12.4 months in all patients and median overall survival (OS) was 12.0 months (16.2 months for previously untreated patients). When the patients were divided into groups based on degree of PD-L1 staining positivity in tumor samples – PD-L1 < 1%, PD-L1 1-49%, PD-L1 > 50% - the degree of PD-L1 positivity correlated strongly with response. Patients in the highest expressing group of PD-L1 (50% or greater) had a response rate of 45.2%, and patients with no prior treatment had the best response ratesand longest duration of response. These exciting results have led to many further trials evaluating the role of pembrolizumab in patients with NSCLC, including combination therapy trials with many different classes of agents. On October 2, 2015, the FDA granted regulatory approval for this agent in patients with PD-L1 expressing NSCLC regardless of histology.

1.3 Agents under Investigation

Pembrolizumab is a humanized IgG4 monoclonal antibody which targets the PD-1 receptor, thus inhibiting the interaction between PD-1 and its ligands, PD-L1 and PD-L2 respectively. It is administered as an IV infusion. This drug has several studies in patients with solid tumors and currently has an FDA indication for use in patients with melanoma and non-small cell lung cancer.

Lenalidomide is a thalidomide analogue with immunomodulatory, anti-angiogenic, and antineoplastic effects. It is administered as a pill taken orally. It has completed phase III study evaluation and has FDA indications for use in certain patients with multiple myeloma, myelodysplastic syndrome, and mantle cell lymphoma.

1.4 Background

Considerable excitement has developed in recent years regarding the use of immune checkpoint blockade agents for the treatment of patients with solid and hematologic malignancies.[9,10] The concept that tumors evade immune surveillance through a variety of mechanisms, and that activating the immune system can lead to tumor regression in a variety of tumor types has been known for decades.[11] The hypothesis which led to the development of immune checkpoint blockade agents was that inhibition of the biologic pathways which serve to dampen immune response (serving as “checkpoints” to ensure immune homeostasis and preventing deleterious autoimmune effects), would lead to uninhibited immune

activation and subsequent anti-tumor effects. The first immune checkpoint receptor to be clinically targeted was cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), a Type I transmembrane protein of the Ig superfamily expressed on activated T cells which helps to regulate immune responses and prevent autoimmune reactions. [12,13] The anti-CTLA-4 monoclonal antibody (mAb) ipilimumab (Yervoy; Bristol-Myers Squibb, NJ) was developed due to promising preclinical studies, and became the first FDA approved checkpoint blockade agent in March 2011, based on results of two phase III studies in advanced melanoma which showed an improvement in overall survival (OS).[14,15]

The second immune checkpoint pathway to be clinically targeted was programmed cell death protein 1 (PD-1) and its associated ligands (PD-L1 and PD-L2). PD-1, like CTLA-4, is also a Type I transmembrane protein of the Ig superfamily, but it is expressed on a wider variety of cells including T cells, NK cells and B cells among others. The ligands for PD-1 (e.g. PD-L1 and PD-L2) are expressed on a wide variety of cells, including non-hematopoietic cells, and expression can be upregulated based on various stimuli. The primary function of PD-1 is believed to be inhibition of T cell effector responses within peripheral tissues (including tumors), as opposed to CTLA-4 which primarily regulates early T cell activation phases (primarily in lymph tissue).[16,17] One of the first anti-PD-1 agents to enter clinical trials was nivolumab (Opdivo; Bristol-Myers Squibb, NJ), a fully human IgG4 mAb targeted to PD-1; phase I trials with this drug revealed responses not only in the typical immune-responsive malignancies (known to respond to treatment with IL-2 and interferon-a) such as melanoma and renal cell carcinoma (RCC), but also in non-small cell lung cancer (NSCLC).[18,19] Subsequent studies of nivolumab in advanced melanoma led to accelerated FDA approval in December 2014.[20,21] In March 2015, nivolumab was approved for use in the second-line setting in patients with squamous cell NSCLC; nivolumab subsequently obtained approval for use in the second line setting for patients with non-squamous NSCLC in October 2015. Pembrolizumab (Keytruda; Merck, NJ) is a humanized IgG4 mAb targeted to PD1 which has also been studied in a variety of tumor types with impressive clinical responses; the most mature data are in advanced melanoma and pembrolizumab received FDA approval for treatment of this disease in September 2014.[22,23] This agent received FDA approval for treatment of PD-L1 expressing NSCLC regardless of histology in the second line setting on October 2, 2015.

Though the response rate to treatment with these checkpoint blockade agents in the setting of advanced solid tumor malignancies is encouraging, even more exciting is the durability of some of the responses, including some which are ongoing for years.[21] Though these three drugs (ipilimumab, nivolumab, pembrolizumab) are the only checkpoint blockade agents currently FDA approved in the United States, many more are in the development pipeline.[24] Based on the efficacy of checkpoint blockade agents in other tumor types (most mature data in RCC, NSCLC and melanoma, encouraging early data in bladder cancer, breast cancer, Hodgkin lymphoma, among others) other FDA approved indications are expected in 2016 and 2017.

In contrast to these novel immune activating drugs, thalidomide (Thalomid, Celgene, NJ), an agent with immunomodulatory properties, was being used and investigated in the 1940s as an antiemetic and sedative. After largely disappearing following the tragic era of its use as an

antiemetic in pregnant women leading to teratogenicity (dysmelia), this drug and related agents have returned to clinical medicine within the past ten years. This class of drugs – the immunomodulatory agents (IMiDs), developed by Celgene - include thalidomide, lenalidomide (Revlimid, Celgene, NJ) and pomalidomide (Pomalyst, Celgene, NJ); have received regulatory approval by the FDA for treatment of a variety of hematologic malignancies, including multiple myeloma (all three agents), myelodysplastic syndrome and mantle cell lymphoma (lenalidomide) and erythema nodusum leprosum (thalidomide).

The IMiDs have multiple mechanisms of action, including stimulation of T cell activation, augmentation of cytotoxic T and NK effector cell functions, anti-angiogenic properties, and epigenetic alterations, among others.[25,26] The ability of the IMiDs to activate T cells – cytotoxic T cells and T helper cells – by utilizing the B7/CD28 pathway is intriguing, as this pathway involves the checkpoint receptors discussed above; one study specifically indicates the ability of an IMiD to overcome CTLA-4 mediated inhibition.[27] Lenalidomide has been studied as a phase I single agent and in combination with chemotherapy in many different solid tumor types, including NSCLC, with multiple responses noted.[28] However, thus far there have been no clinical studies exploring the combination of a checkpoint blockade agent with an IMiD in solid tumor malignancies.

Lenalidomide has been shown to enhance CD4 and CD8 T cell co-stimulation, and to induce T cell proliferation much more potently than its precursor drug thalidomide.[29] Part of this process includes increased release of the pro-inflammatory cytokine interleukin-2 (IL-2) by T cells. Recent research suggests a mechanism for this change in the inflammatory milieu: lenalidomide regulates ubiquitination and degradation of two key lymphoid transcription factors, IKZF1 and IKZF3. IKZF3 binds to the gene promoter of IL-2 and represses the transcription of IL-2 in T-cells, thus a lenalidomide-induced decrease in IKZF3 levels yields downstream increased production of IL-2, with its subsequent immunomodulatory effects.[30] Lenalidomide also inhibits the function of T regulatory cells (Treg), which are known to play a key role in helping tumors evade immune evasion by increasing tolerance and downregulating immune activation.[31]

Given that both of these classes of drugs – IMiDs and anti-PD1 antibodies - induce anti-tumor effects through T cell activation, utilizing different mechanisms of action, it is reasonable to propose that combining a drug from each class together in one treatment regimen could have significant anti-tumor effect, perhaps greater than either might have alone. We propose to open a phase I trial for patients with advanced solid tumor malignancies to explore the maximum tolerated dose (MTD) of an IMiD (lenalidomide) in combination with a fixed and approved dose of an anti-PD1 agent (pembrolizumab), followed by an expansion cohort phase II trial in non-small cell lung cancer. We prefer to study an anti-PD-1 agent versus an anti-CTLA-4 agent given the wider range of tumor types responsive to anti-PD-1 therapy and because the anti-PD-1 drugs are typically better tolerated than the anti-CTLA-4 drugs. Patients with advanced, refractory solid tumors need better therapeutic options, and we hope that utilizing the above proposed combination immunotherapy regimen may offer hope for meaningful and durable responses.

It is important to emphasize that due to a lack of an appropriate mouse model, it is not

possible to test this combination in the preclinical setting. Moreover, the safety profile of both agents is well known. The dose modifications schema for lenalidomide is well established and this agent has been given, either alone or in combination with other drugs, safely and effectively to thousands of patients around the world.

An abstract presented at the most recent American Society of Hematology Annual Meeting in December 2015 reported data from a phase I study of pembrolizumab in combination with lenalidomide and dexamethasone for relapsed/refractory multiple myeloma.[32] Data from 17 patients who were treated during the dose determination and dose confirmation phase was presented. Sixteen patients experienced at least one AE of any grade, and 10 patients experienced at least one AE of grade 3 or 4. However, no deaths or treatment discontinuation for toxicity was noted. The most frequently noted AEs (> 25%) were thrombocytopenia (47%), neutropenia (41%), and fatigue (29%). Of note, this was a heavily pretreated population (53% had ≥3 treatments, and 41% had IMiD-refractory disease) and the therapy combination was well-tolerated. No thromboembolic events were reported. The MTD/MAD was defined as pembrolizumab 200 mg fixed dose in combination with lenalidomide 25 mg and low-dose dexamethasone 40 mg. Objective response rate was 76%. This data from this study suggests that this combination of drugs is well tolerated, and will likely be tolerated in the context of patients with advanced solid tumors, as we propose in this trial.

1.5 Rationale

It has become clear in recent years that drugs aimed at enhancing and modifying immune responses to tumor cells will be an essential and growing component of oncology's armamentarium. There is data to show that anti-PD-1 antibodies can have impressive anti-tumor effects as single agents, in a wide variety of primary cancers. Future studies will seek to investigate the optimal therapeutic timing of these agents (e.g. first-line versus nth line) as well as novel drug combinations which will seek to augment efficacy. There are currently combination trials involving pembrolizumab and at least nine different classes of drugs. However, there has been no study using pembrolizumab in combination with an IMiD, a class of drugs which has pleotropic immunomodulatory effects which may synergize with the effect of an anti-PD-1 agent, in solid tumors. Activating the anti-tumor effects of T cells utilizing the multiple pathways of both pembrolizumab and lenalidomide is an endeavor which merits investigation.

Our hypothesis is that this combination will be well-tolerated, without significant toxicities or adverse events. Numerous studies have found the anti-PD-1 agents to be well-tolerated, and lenalidomide has also been shown to have relatively minimal side effects.[28,33] We expect that we will reach dose level 2 of lenalidomide (20 mg) without experiencing dose-limiting toxicities (DLT). We intend to capitalize on the immune-modulatory effects of lenalidomide in combination with pembrolizumab. Since the population enrolled in this trial are pre-treated with standard agents, we would like to minimize the potential myelosuppresive effects of this agent. We also believe that we can achieve maximal immune modulation with doses selected. Therefore, we did not incorporate higher doses of lenalidomide in this trial. Toxicity grading will be recorded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4.0. Doses for lenalidomide were selected on the basis of previously published early phase trials for patients with solid tumor malignancies, as well as the approved dosing levels for

hematologic malignancies (e.g. myeloma, MDS).[28] The fixed dose of pembrolizumab was determined based on prior studies, including a recently published study in patients with NSCLC.[1]

The primary endpoint for the phase I component of this protocol will be determining the maximum tolerated dose (MTD) of lenalidomide in combination with pembrolizumab.

The primary endpoint for the phase II component of this protocol will be determining efficacy as measured by progression free survival (PFS), and our hypothesis is that this novel drug combination will improve PFS as described below.

2.0 Objectives

2.1 Primary Objective

Phase I: To determine the safety, tolerability, and the maximum tolerated dose (MTD) of lenalidomide in combination with a fixed dose of pembrolizumab in subjects with relapsed and/or refractory solid tumors.

Phase II (in NSCLC): To determine efficacy as measured by progression free survival (PFS).

2.2 Secondary Objectives

Phase I/II:

a) Assess antitumor activity of the combination as measured by objective response rate.

b) Preliminary assessment of immune correlates, including T and NK cell subset frequency and activation phenotype, cytokine profiles, and specific T and NK cell responses.

c) Assessment of PD-L1 expression and correlation with responses.

d) Explore potential to overcome resistance in patients previously treated with an anti-PD1 antibody.

3.0 Study Plan

3.1 Description of Study Design, Population and Duration of Study Therapy

For the phase I component of our trial we will utilize a classic 3 + 3 dose escalation design, with a fixed dose of pembrolizumab and an escalating dose of the lenalidomide (see Schema above). The patient population will all have histologically confirmed advanced solid tumor malignancy with at least one lesion that is measurable by RECIST 1.1 criteria, ECOG performance status of 0-1, either one or two lines of prior therapy, and adequate liver, kidney and bone marrow function as described in section 4.0. Previous surgery, adjuvant chemotherapy and or radiation therapy will be allowed. The baseline pathologic specimen will be assessed for PD-L1 staining. Baseline blood samples will be collected for immunologic correlates prior to treatment on Day 1 of Cycle 1 and post treatment at 2, 4, 24 hours. Samples will also be collected prior to treatment on Day 1 of Cycle 2, and at time of

progression. Baseline CT scan of the chest and abdomen will be obtained within 30 days prior to the initiation of cycle 1. CT scan with contrast or MRI with contrast of the brain will also be obtained within 30 days prior to the initiation of cycle 1.

The study will plan to enroll 3 patients in an initial cohort, to receive the dose level 1 of lenalidomide (10 mg PO) on days 1-14 of a 21-day cycle, and pembrolizumab (200 mg IV) on day 1. Patients will be evaluated for toxicities after initiation of treatment. If there are no DLTs for the initial 3 patients after one cycle, the next dosing cohort will open, with another 3 patients. Similarly, if the second cohort of patients receives the dose level 2 of lenalidomide (15 mg) for one cycle without DLT, then the third and final cohort will open. When the third cohort testing the dose level 3 of lenalidomide (20 mg) has completed one cycle, the phase I component of the trial will be completed. Standard phase I, 3 + 3 design rules will be utilized as follows: if 1 out of 3 patients experiences a DLT at certain dose level, then 3 more patients will be enrolled at the same level. If 2 out of 6 patients experience DLT at a certain dose level, 3 additional patients are added at the next lower level. Dose reduction is continued until at most 1 of 6 patients experiences DLT. The highest level with at most 1 of 6 patients DLT will be declared MTD. If no dose level achieves this criterion the trial will be discontinued for excess toxicity.

At Fox Chase Cancer Center, we see roughly 10,000 new patients annually, and enroll approximately 200 patients annually, on phase I trials. 6-18 patients will be enrolled to complete the phase I component of this protocol, and we should be able to accrue this number within 6 months (1-2 patients per month). Patients will continue to be followed every 21 days on the first day of each new cycle for the first 12 months on this protocol. Patients who remain on study after the initial 12 months will be evaluated once every 2 cycles until disease progression, unacceptable toxicity or withdrawal of consent.

The phase II component of this trial will utilize a two stage design as described in the statistical section, initially enrolling 13 patients, followed by 13 more patients if the early stopping criteria are not met (See statistics section). This population will include patients with histologically confirmed diagnoses of non-small cell lung carcinoma, regardless of histologic subtype; who have completed one line of standard therapy. Previous surgery, adjuvant chemotherapy and or radiation therapy will be allowed. Patients with molecular targets (EGFR, ALK, ROS1) who have progressed on targeted agents and are not eligible for other treatments or trials specific for this population will be allowed to participate. A pre-treatment (archival) and fresh tumor sample will be needed for participation in trial. PD-L1 expression levels in both samples will be determined to assess the role of chemotherapy on expression level and pattern of this biomarker. Baseline blood samples will be collected for immunologic correlates prior to treatment on Day 1 of Cycle 1 and post treatment at 2, 4, 24 hours. Samples will also be collected prior to treatment on Day 1 of Cycle 2, and at time of progression. Baseline CT scan of the chest and abdomen will be obtained within 30 days prior to the initiation of cycle 1. CT scan with contrast or MRI with contrast of the brain will also be obtained within 30 days prior to the initiation of cycle 1. Time to progression will be measured with disease imaging following every 2 cycles of therapy with a three-day window (+ or -). Patients will continue treatment until disease progression or unacceptable toxicity or two years of therapy. Overall survival will be assessed every 3 months during long term

follow up. Accrual of the required 26 patients will likely take 12 months.

As another exploratory analysis, we intend to treat 10 additional patients with prior treatment with any of the anti PD-1/PD-L1 antibodies and subsequent progression on this protocol. The intent is to explore the possibility of overcoming PD-1 axis resistance through inhibition of Treg activity.

4.0 Patient Selection Inclusion & Exclusion

4.1 Inclusion Criteria

4.1.1 Patients must have a histologically or cytologically confirmed metastatic solid tumor malignancy for the phase I component. The phase II component will require patients to have histologically or cytologically confirmed non-small cell lung carcinoma regardless of histology.

4.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension in accordance with RECIST criteria v. 1.1 as described in detail in section 11.0.

4.1.3 **For participation in the Phase II portion**, patients must have completed at least one line of prior therapy.

For participation in the Phase I portion, patients must have completed either one or two lines of prior therapy.

Treatment on this protocol may begin as long as the patient has recovered from toxicities of prior therapy at the discretion of the treating physician. Patients with NSCLC harboring an EGFR, ALK or ROS-1 alteration must have progressed through at least one prior therapy with appropriate molecularly targeted agents.

4.1.4 Age > 18 years.

4.1.5 ECOG performance status 0 or 1.

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

Absolute neutrophil count	> 1,500/mcL
Hemoglobin	≥ 9.0 mg/ml
Platelets	> 100,000/mcL
Total bilirubin	within normal institutional limits
AST/ALT (SGOT/SGPT)	< 2 times institutional normal limits, or up to 5 times institutional normal limits if the patient has liver metastases
Creatinine OR Creatinine clearance	within normal institutional limits OR > 60 Ml/min/1.73 m2 for patients with creatinine levels above institutional normal
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

4.1.7 Ability to understand and willingness to sign a written informed consent and HIPAA consent document.

4.1.8 Palliative radiation for treatment of painful bone metastasis, control of hemoptysis or treatment of small asymptomatic brain metastasis that become symptomatic during on protocol treatment is allowed. Protocol treatment will be delayed until recovery from radiation at the discretion of the treating physician.

4.1.9 A core tumor biopsy obtained after progression on the last treatment must be available at study entry for the phase II portion of the study. Any available archival tissue (for both phase I and II) will also be collected.

4.1.10 Female subject of childbearing potential must have a negative serum pregnancy 10-14 days prior to registration, and again within 24 hours prior to the first dose of Lenalidomide,

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

4.1.12 Female subject of childbearing potential must have a negative serum pregnancy 10-14 days prior to registration, and again within 24 hours prior to the first dose of lenalidomide, Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.

4.1.13 Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in Section 4.4.1 – Contraception, for the course of the study through 120 days after the last dose of study medication.

4.1.14 Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in Section 4.4.1- Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

4.1.15 Ten patients with a diagnosis of NSCLC who have disease progression per investigator's assessment who are on anti PD-1 or PD-L1 therapies will be allowed to enroll in the phase II part of this study but must be switched to treatment per this protocol.

4.2 Exclusion Criteria

4.2.1 Patients who have had chemotherapy or radiotherapy within14 days prior to entering the study. Patients may not be currently receiving any other investigational agents or immunomodulatory agents (e.g. ipilimumab).

Patients treated with prior PD-1 or PD-L1 directed therapies are ineligible for the phase I portion.

4.2.2 Patients who, at the discretion of the treating physician, have not recovered from adverse events due to agents administered earlier.

4.2.3 Patients with active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

4.2.4 Patients with untreated symptomatic brain metastases. Patients with treated brain metastases will be allowed if brain imaging obtained within 30 days of trial enrollment reveals stable disease. Patients with small asymptomatic brain metastasis are allowed to enroll. Patients on steroids doses higher than 10 mg of prednisone (or its equivalent) are excluded.

4.2.5 Patients with interstitial lung disease or active, noninfectious pneumonitis.

4.2.6 Patient who have received a live vaccine within 30 days prior to Cycle 1 Day 1.

4.2.7 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection (including HIV, hepatitis B, hepatitis C), symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, cirrhosis, or psychiatric illness/social situations that would limit compliance with study requirements.

4.2.8 Patients with known hypersensitivity to thalidomide or lenalidomide or pomalidomide.

4.2.9 Patients with peripheral neuropathy of grade ≥3. Patients with painful grade 2 neuropathy are also excluded.

4.2.10 Pregnant or breast-feeding. Refer to section 4.4 for further detail.

4.3 Inclusion of Women and Minorities

Men and women, regardless of race, ethnic group or sexual orientation are eligible for this study.

4.4 Pregnancy

Lenalidomide is an analogue of thalidomide, which is an agent known to have significant teratogenic effects; for this reason, women of child-bearing potential (WOCBP) and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of treatment, and for at least 120 days after the completion of treatment. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

Prior to study enrollment, WOBCP must be advised of the importance of avoiding pregnancy

during trial participation and the potential risk factors for an unintentional pregnancy. In additional, men enrolled on this study should understand the risks to any sexual partner of childbearing potential.

All WOCBP must have two negative pregnancy tests - within 10-14 days prior to receiving the first dose of Lenalidomide, and within 24 hours prior to the first dose of Lenalidomide. If the pregnancy test is positive, the patient must not receive protocol treatment and must not be enrolled in the study.

WOCBP is defined as follows: Any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or a bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea > 12 consecutive months, or women on hormone replacement therapy (HRT) with documented plasma follicle-stimulating hormone (FSH) level > 35 mIU/ml). Even women who are using oral, implanted, or injectable contraceptive hormones or mechanical products (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g. vasectomy), should be considered to be WOCBP.

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported within 24 hours to the sponsor. The sponsor will report this outcome, within 24 hours, to Merck and Celgene if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor investigator, Merck, and Celgene.

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor investigator. If a male subject impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor investigator, Merck, and Celgene.

4.4.1 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, or bilateral salpingectomy at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.
Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are:

Single method (one of the following is acceptable):
- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):
- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic

abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

4.4.2 Lenalidomide pregnancy prevention plan (REMS Program)

The Pregnancy Prevention Plan (PPP) applies to all subjects receiving lenalidomide within a clinical trial. The following PPP documents are included:

1. The Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document provides the following information:

- Potential risks to the fetus associated with lenalidomide exposure
- Definition of female of childbearing potential (FCBP)/female not of childbearing potential (FNCBP)
- Requirements for counseling of all subjects receiving lenalidomide about pregnancy precautions and the potential risks of fetal exposure to lenalidomide
- Acceptable birth control methods for both female subjects of childbearing potential and male subjects receiving lenalidomide in the study
- Pregnancy testing requirements for subjects receiving lenalidomide who are FCBP

2. The Lenalidomide Education and Counseling Guidance Document for each gender (female and male) must be completed and signed by a trained counselor at the participating clinical center prior to each dispensing of lenalidomide. A copy of this document must be maintained in the subject's records for each dispense.

3. The Lenalidomide Information Sheet will be given to each subject receiving lenalidomide. The subject must read this document prior to starting lenalidomide and each time the subject receives a new supply of lenalidomide.

Please see the Lenalidomide Pregnancy Risk Minimization Plan in Appendix A for additional information

4.5 Patient Registration

Participants may be registered from 8:00 am to 4:00 pm EST excluding holidays by emailing the Investigator-Sponsored Research Unit (ISRU) at: **FCCC.MONITOR@fccc.edu.** Eligible participants will be entered on study centrally once the following items have been received by email:

- Completed registration form
- Consent and HIPAA signature pages
- Eligibility checklist
- Lenalidomide Education and Counseling Guidance Document (Section 3 or 4 of Appendix A, as applicable)

Following registration, participants must begin protocol treatment within 14 calendar days of registration. Issues that would cause treatment delays must be discussed with the Sponsor-Investigator. If a registered participant does not receive protocol therapy following registration, the participant will be recorded as withdrawn from study. The Study Monitor must be notified as soon as possible if a participant does not begin protocol treatment as scheduled. For additional registration questions, please email FCCC.MONITOR@fccc.edu or call **(215) 728-5544.**

The FCCC ISRU will notify the site by email once registration is confirmed and the sequence number has been assigned. Participants must be registered and have received a sequence number prior to the initiation of treatment.

Exceptions to the current registration policies will not be permitted.

5.0 Treatment Plan

Patients will be stratified by age, primary malignancy, and performance status. Treatment will be administered on an outpatient basis. Treatment will be administered as described below. Dose delays and modifications should only be done following protocol guidelines described in section 6.0. Missed days will not be made up. If treatment delays are > 21 days; the study therapy will be discontinued.

5.1 Treatment Administration

The treatment will be given on a 21-day cycle, with a dose of pembrolizumab given on day 1, and doses of lenalidomide given on days 1-14. The dose of pembrolizumab will be fixed at 200 mg, whereas the dose of lenalidomide will depend upon the patient cohort as noted above and below. Day 1 of each cycle can be initiated +/- 3 days.

Regimen description					
Agent	**Premedications, precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Pembrolizumab	None	200 mg in 50 mL NSS	IV over 30 minutes	Day 1	3 weeks (21 days)
Lenalidomide	None	10, 15, or 20 mg	PO	Days 1-14	

Lenalidomide and steroid combination is thought to increase the chance of deep vein thrombosis (DVT). This risk is seen mainly in patients with hematologic malignancies. Since steroid dose is prohibited (except for small doses), the risk of a DVT on this protocol is thought to be low. The rate of this toxicity, if it occurs, will be monitored carefully.

5.2 Concomitant Medications, Supportive Care, Excluded Therapies and Restrictions

Patients should receive full supportive care therapies concomitantly during the study

including transfusions of blood and blood products as well as antibiotics when appropriate. Palliative radiation therapy is permitted for irradiating small areas of painful bony metastases that cannot be managed adequately using systemic or local analgesics, as long as the presence of these osseous metastases was recorded at baseline prior to study initiation and there is no definite evidence of objective disease progression at the site based on RECIST criteria v1.1. Any disease progression requiring other forms of specific anti-tumor therapy will be cause for early discontinuation of study treatment.

The following concomitant therapies warrant special attention:

- The use of erythropoietin, colony stimulating factors (per ASCO guidelines) are allowed.
- Bisphosphonates, or other approved agents for bone metastases and anti-emetics are allowed.
- Non-steroidal anti-inflammatory drugs (Ibuprofen (400 mg qid) can be administered in patients with normal renal function (Cr clearance>80 mL/min).
- Patients with mild to moderate renal insufficiency (Cr clearance from 45 to 79 mL/min) should avoid taking salicylates or NSAIDs with long elimination half-lives).
- The concomitant use of hormones or other chemotherapeutic agents will result in the patient's removal from the study. An exception can be made for steroids (at doses higher than 10 mg of prednisone or its equivalent) administered for adrenal failure or as temporizing measure for symptomatic pain or breathing, rash, or at the treating physician's discretion for symptom management, or hormones administered for non-disease related conditions, e.g., insulin for diabetes. Glucocorticosteroids may be used as antiemetics and megestrol acetate may be used for appetite.

5.2.1 Prohibited during the study:

Use of surgery, anti-neoplastic or anti-tumor agents not part of the study therapy, including chemotherapy, radiation therapy (except as stated above), immunotherapy, and hormonal anticancer therapy and steroid use (>10 mg prednisone or equivalent), unless as specified above, is not permitted while participating in this study.

Use of concurrent investigational agents is not permitted.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse events
- Treatment held >21 days beyond scheduled next cycle
- Patient becomes pregnant
- Patient decides to withdraw from the study or
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator
- 24 months of therapy completed with pembrolizumab

5.4 Duration of Follow up

Patients will be followed every 3 months for one year after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events that are related to the study treatment will be followed until resolution or stabilization of the adverse events.

5.5 DLT Definition

Toxicity will be evaluated according to the NCI CTCAE, version 4.0. These criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

DLT will be defined as any of the following events that are considered by the Investigator to be related to therapy with this combination

- Grade 4 neutropenia (ANC < 500 cells/mm^3) lasting more than 14 consecutive days
- Grade 4 neutropenia associated with coincident fever (where fever is defined as an oral or ear temperature ≥ 38.5°C)
- Grade 4 thrombocytopenia (plt < 25,000 cells/mm^3) lasting more than 14 consecutive days or platelet count less than 10,000 cells/mm^3
- Grade 3 or 4 thrombocytopenia with clinically significant bleeding.
- Delay in the initiation of the subsequent therapy by more than 21 days (eg, one full cycle) due to treatment-related toxicity
- ≥ Grade 4 non-hematological toxicity except the following: a) Grade 4 nausea or emesis, or both, that occurs in the absence of optimal antiemetic therapy [5-HT_3 serotonin receptor antagonist]; b) Grade 4 diarrhea that occurs in the absence of optimal supportive therapy
- Grade 4 rash
- Grade 3 fatigue lasting greater than 21 days continuously
- Grade 4 non-hematologic toxicity

6.0 Dose Modifications

6.1 General Principles

Dose modifications should be made based only on the guidelines described in this section. Dose reductions are permanent; there are no dose re-escalations. Patients requiring > 2 dose reductions must discontinue protocol treatment. Missed doses are not to be made up. Patients requiring treatment to be held > 21 days for recovery from toxicity must discontinue protocol treatment.

6.2 Dose Level Adjustment Table

Dose level	Lenalidomide Dose	Pembrolizumab Dose
-1 dose level	5 mg PO	200 mg IV
1 (Starting dose)	10 mg PO	200 mg IV

2 Escalation	15 mg PO	200 mg IV
3 Escalation	20 mg PO	200 mg IV

6.3 Specific Toxicities and Modifications

6.3.1 Dose modifications for lenalidomide

- Stop lenalidomide for any grade 3 or 4 toxicity not noted in the tables below. If the toxicity resolves to grade 2 or less in 21 days, treatment may resume as follows:
    - Patients with grade 4 toxicities may resume treatment on the next lower dose once the toxicity resolves to a grade 2 or lower within the 21 day window allowed.
    - Patients with first occurrence of any grade 3 toxicity may resume treatment at the same dose level if the toxicity has resolved to a grade 2 or lower within the 21 day window allowed.
    - In the event of a second grade 3 toxicity, treatment at a lower dose of lenalidomide may resume once toxicity resolves to a grade 2 or lower within the allowed 21 day window.
    - No more than two dose reductions are allowed.

The table below is to be used for management of lenalidomide related hematologic adverse events.

Toxicity	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation / Dosing Continuation
Neutropenia	3	Toxicity resolves to ≤ Grade 2	Discontinue if toxicity does not resolve within 21 days of last dose If toxicity resolved within 21 days of the last dose, restart treatment at the current dose level. If grade 3 toxicity reoccurs after resolution, reduced dose by one level OR if the current dose level is -1 (5mg) discontinue. No more than 2 dose reductions are permitted.
	4	Toxicity resolves to ≤ Grade 2	Discontinue if toxicity does not resolve within 21 days of last dose If toxicity resolved within 21 days of the last dose, dose reduce by one dose level and restart treatment. If grade 4 toxicity reoccurs after dose reduction; discontinue treatment.
Thrombocytopenia	3	Toxicity resolves to ≤ Grade 2	Discontinue if toxicity does not resolve within 21 days of last dose If toxicity resolved within 21 days of the last dose, restart treatment at the current dose level. If grade 3 toxicity reoccurs after resolution and treatment with the reduced dose by one level OR if the current dose level is -1 (5mg) discontinue. No more than 2 dose reductions are permitted.
	4	Toxicity resolves to ≤ Grade 2	Discontinue if toxicity does not resolve within 21 days of last dose If toxicity resolved within 21 days of the last dose, dose reduce by one dose level and restart treatment. If grade 4 toxicity reoccurs after dose reduction; discontinue treatment

The table below is to be used for management of lenalidomide related non-hematologic adverse events.

Toxicity	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation / Dosing Continuation
Thromboembolic event	2	Toxicity resolves to Grade 0 or 1	Discontinue if toxicity does not resolve within 21 days of last dose If toxicity resolved within 21 days of the last dose, restart treatment at the current dose level. If grade 2 toxicity reoccurs after resolution and treatment with the reduced dose by one level OR if the current dose level is -1 (5mg) discontinue. No more than 2 dose reductions are permitted.
	3 or 4	Permanently discontinue	Permanently discontinue
Treatment related secondary malignancy		Permanently discontinue	Permanently discontinue

Toxicity	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation / Dosing Continuation
INR or PT Increased	≥2	Toxicity resolves to baseline	Discontinue if toxicity does not resolve within 21 days of last dose If toxicity resolved within 21 days of the last dose, Dose reduce by one dose level and restart treatment. If ≥2 toxicity reoccurs after resolution and treatment with the reduced dose by one level OR if the current dose level is -1 (5mg) discontinue. No more than 2 dose reductions are permitted.
Activated partial thromboplastin time prolonged aPTT	≥2	Toxicity resolves to baseline	Discontinue if toxicity does not resolve within 21 days of last dose If toxicity resolved within 21 days of the last dose, Dose reduce by one dose level and restart treatment. If ≥2 toxicity reoccurs after resolution and treatment with the reduced dose by one level OR if the current dose level is -1 (5mg) discontinue. No more than 2 dose reductions are permitted.
Tumor Lysis Syndrome	3 or 4	Permanently discontinue	Permanently discontinue
AST / ALT (SGOT/SGPT)	3	Toxicity resolves to ≤ Grade 2	Discontinue if toxicity does not resolve within 21 days of last dose If toxicity resolved within 21 days of the last dose, restart treatment at the current dose level. If grade 3 toxicity reoccurs after resolution, reduced dose by one level OR if the current dose level is -1 (5mg) discontinue. No more than 2 dose reductions are permitted.
	4	Toxicity resolves to ≤ Grade 2	Discontinue if toxicity does not resolve within 21 days of last dose If toxicity resolved within 21 days of the last dose, dose reduce by one dose level and restart treatment. If grade 4 toxicity reoccurs after dose reduction; discontinue treatment.
All Other Drug-Related Toxicity[c]	3	Toxicity resolves to ≤ Grade 2	Discontinue if toxicity does not resolve within 21 days of last dose If toxicity resolved within 21 days of the last dose, restart treatment at the current dose level. If grade 3 toxicity reoccurs after resolution, reduced dose by one level OR if the current dose level is -1 (5mg) discontinue. No more than 2 dose reductions are permitted.
	4	Toxicity resolves to ≤ Grade 2	Discontinue if toxicity does not resolve within 21 days of last dose If toxicity resolved within 21 days of the last dose, dose reduce by one dose level and restart treatment. If grade 4 toxicity reoccurs after dose reduction; discontinue treatment.

6.3.2 Dose Modifications for Pembrolizumab

- Dose modifications for Pembrolizumab are not allowed

The table below is to be used for management of pembrolizumab related adverse events.

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when patients are clinically and metabolically stable
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.

[c] Patients with intolerable or persistent Grade 2 drug-related AEs, may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

- For some grade 3 or 4 toxicities, re-evaluate prior to the next cycle dose; if the toxicity resolves to grade 2 or less, resume treatment

- For severe autoimmune reactions, initiation of corticosteroids will be recommended
- Permanently discontinue Pembrolizumab for any severe or Grade 3 drug-related AE that recurs or any life-threatening event

6.4 Toxicities and AE management.

Note: It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of a toxicity (or an adverse event)..

- **Pneumonitis**:
  - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
  - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
  - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- **Diarrhea/Colitis**:

  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

  - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For **Grade 2 diarrhea/colitis,** administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Diabetes/Hyperglycemia:**

  Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA).
  - For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:
    - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
    - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hyperthyroidism or Hypothyroidism**:

  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

    - **Grade 2** hyperthyroidism and **Grade 2-4** hypothyroidism events:
        - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
        - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
    - **Grade 3-4** hyperthyroidism
        - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hepatic**:
    - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
        - Treat with IV or oral corticosteroids.
    - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
    - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- **Renal Failure or Nephritis**:
    - For **Grade 2** events, treat with corticosteroids.
    - For **Grade 3-4** events, treat with systemic corticosteroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion

of infusion.

Table 1 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 1 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

7.0 Study Agent Information

7.1 Lenalidomide Information

7.1.1 Formulation

This medication comes in an oral capsule preparation.

7.1.2 Availability

This medication will be supplied by Celgene.

Because of the embryo-fetal risk, lenalidomide is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS), the REVLIMID REMS program (formerly known as the RevAssist program) in the United States and for study sites outside of the United States through country specific risk minimization programs.

Required components of the REVLIMID REMS program include the following:

- Prescribers must be certified with the REVLIMID REMS program by enrolling and complying with the REMS requirements.

- Subjects must sign a Patient-Physician agreement form and comply with the REMS requirements. In particular, female subjects of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements and males must comply with contraception requirements.

- Pharmacies must be certified with the REVLIMID REMS program, must only dispense to subjects who are authorized to receive lenalidomide and comply with REMS requirements.

Drug will be shipped on a per patient basis by the contract pharmacy to the clinic site.

Further information about the Revlimid REMS® program is available at www.celgeneriskmanagement.com.

7.1.3 Solution preparation

N/A

7.1.4 Storage requirements

Store at 20°C - 25°C (68°F - 77°F); excursions permitted to 15°C - 30°C (59°F - 86°F).

7.1.5 Stability

This agent is stable at room temperature.

7.1.6 Route of administration

Oral

7.2 Pembrolizumab Information

7.2.1 Formulation

This medication is supplied in a carton containing 100 mg lyophilized powder in one single-use vial.

7.2.2 Availability

This medication will be supplied by Merck.

7.2.3 Solution preparation

To be reconstituted and diluted prior to IV infusion.

7.2.4 Storage requirements

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F).

7.2.5 Stability

Stable when refrigerated.

7.2.6 Route of administration

Intravenous

7.3 Drug Ordering, Storage and Handling

Following submission and approval of the required regulatory documents, participation in the study initiation meeting and receipt of the site activation letter from the OCR Regulatory Coordinator, the initial order may be placed.

Drug order forms and ordering procedure will be presented at the site initiation meeting.

7.4 Destruction of Drug

At the time of study closure, the unused, used and expired study drug will be destroyed at the site per Institutional SOPs unless otherwise specified.

7.5 Records to be kept at Site; Dispensing and Accountability

It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs (supplied by OCR) must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number.
- Dates and initials of person responsible for each investigational product inventory entry/movement.
- Amount dispensed to and returned by each patient, including unique patient identifiers.
- Amount transferred to another area for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).

8.0 Correlative / Special Studies

We will assess PD-LI status (when possible) via immunohistochemistry on initial tumor samples collected from an archival tissue sample and fresh biopsy taken prior to cycle 1 day 1. We will also analyze pretreatment serum samples for soluble PD-L1. We will then correlate the PD-L1 status of tumors for treatment efficacy.

We will assess baseline immunophenotypic profiles from the peripheral blood with follow-up sampling at established time points throughout the study, including the following:

1) General proportions of blood immune cells and activation markers by flow cytometry: CD45, CD3, CD4, CD8 (T cells), CD19 (B cells), CD14, CD16 (monocytes), CD56 (NK cells), CD11c, HLA-DR, CD303, CD66b (myeloid – DCs and granulocytes). Differentiation status of CD4 and CD8 T cells (naïve/effector memory/central memory/regulatory/γδ TCR) as defined by: CD62L, CD45RA, CD127, CD25. Activation markers will include CD69, CD25, HLA-DR, IL-15Ra, perforin, Ki67, NKp44, CD57. Immune checkpoint receptors: PD-1, CLTA-4, LAG-3, TIM-3. Due to pembrolizumab blockade of PD-1 in treated patients, both pretreatment and post-treatment samples will be saturated with pembrolizumab, washed, and stained with fluorophore-conjugated anti-human IgG4, which we have found to efficiently stain PD-1 on leukocytes. For these studies we will collect samples prior to treatment on Day 1 of Cycle 1, prior to treatment on Day 1 of Cycle 2, and at the time of progression

2) NK cell degranulation assay by flow cytometry: CD107A expression after 2 hour co-culture with the EBV-transformed B cell line, 721.221, without and with rituximab (ADCC conditions).

3) Assays to measure cytokines and chemokines (Luminex; available at FCCC) associated with Th1/Tc1 responses (e.g. IFN-g, TNF, IL-2), Th2/Tc1 responses (e.g. IL-4, IL-5, IL-10), pro-inflammatory innate responses (e.g. IFN-α, IL-1β, IL-6, IL-17), homeostatic lymphocyte expansion (e.g. IL-7, IL-15) and chemotaxis of immune cells (e.g. IP-10, MCP-1, MIP-1α, MIP-1β, RANTES). For these studies samples will be collected prior to treatment on Day 1 of Cycle 1 and post treatment at 2, 4, 24 hours. Samples will also be collected prior to treatment on Day 1 of Cycle 2, and at time of progression.

4) Using Nanostring® technology (available at FCCC) we intend to interrogate the immune composition of tumors using their PanCancer Immune Profiling Panel as an exploratory endpoint.

5) Evaluation of stromal activation status in the tumor microenvironment (Cukierman's lab) by using simultaneous multi-channel immunofluorescent analysis (SMIA) immunohistological approach on available tumor biopsies and gather qualitative and quantitative data indicative of levels of desmoplastic occurrences and fibroblastic activation (i.e., myofibroblastic) via newly written batch analysis software, "SMIA-CUKIE," which is publicly available online at https://github.com/cukie/SMIA-CUKIE .

6) We will store the remaining blood and tissue samples for future studies.

9.0 Study Calendar

	Pre-Study [B]	Cycle 1			Cycle 2			Cycles 3 + 4			Cycle 5 +			Off Study	Follow up [F]
		Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15		
Informed consent & HIPAA [A]	X														
Medical history	X														
Height	X														
Weight	X	X			X			X			X			X	
β-HCG	X [D]	X [D]	X [D]	X [D]	X [D]			X [D]			X [D]			X [D]	X [D]
Physical exam	X	X			X			X			X			X	
Concurrent meds	X														
EKG (as indicated)	X														
Vital signs (T, P, R, BP)	X	X			X			X			X			X	
Performance status	X	X			X			X			X			X	
CBC w/diff, plts	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry [C]	X	X	X	X	X	X	X	X	X	X	X			X	
TSH[K]	X	X[K]						X[K]							
PT, aPTT and INR	X	X			X			X			X			X	
Correlative Blood Samples		X [H]			X [H]									X [H]	
Tumor Tissue Collection	X [I]														
Lenalidomide Pregnancy Prevention Counseling	X	X			X			X			X				
Adverse event evaluation		X													X [G]
Tumor Imaging[J]	X	Imaging is repeated every 6 weeks regardless of dose delays. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X [E]	

A: Informed consent must be signed within 30 days of registration. If signature is outside that window the patient must sign a new consent.

B: Pre-study H&P and all labs must be ≤ *30 days* prior to Day 1 of Cycle 1. Tumor measurements and radiologic evaluations must be ≤ *30 days* prior to Day 1 of Cycle 1.

C: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

D: Serum pregnancy test (women of childbearing potential) must be completed 10-14 days prior to registration, within 24 hours prior to the first dose of Lenalidomide, and then weekly through Cycle 2, Day 1. To be repeated on Day 1 of every Cycle thereafter, at time of discontinuation, and 28 days after the final dose of Lenalidomide is administered.

E: Off-study evaluation. If PD documented during scheduled on-study assessment, tumor measurements and radiologic staging do not need to be repeated.

F: Follow up for PD, resolution of treatment related toxicities, survival should be conducted every 3 months for 1 year or until death, whichever occurs first.

G: AE and ECI follow-up shall continue until 90 days after the last treatment or until the next treatment begins whichever is less. Pregnancy will be followed for up to 120 days after the completion of lenalidomide.

H: Sample for general proportions of blood immune cells and activation markers by flow cytometry will be collected prior to treatment on Day 1 of Cycle 1, prior to treatment on Day 1 of Cycle 2, and at the time of progression.

Sample for assays to measure cytokines and chemokines associated with Th1/Tc1 responses will be collected prior to treatment on Day 1 of Cycle 1 and post treatment at 2, 4, 24 hours. Samples will also be collected prior to treatment on Day 1 of Cycle 2, and at time of progression.

I: Both an archival tumor tissue sample and fresh biopsy will be collected after eligibility is confirmed and prior to the first study treatment on Day 1 of Cycle 1

J: CT scan of the chest and abdomen will be done at baseline and every 6 weeks regardless of dose delays. A brain CT scan with contrast, or brain MRI with contrast, must be done at baseline. Brain imaging does not need to be repeated unless clinically indicated.

K: TSH will be done every 2 cycles starting cycle 1, with free T4 and free T3 done only if TSH is abnormal. If TSH is done at pre-study visit within 30 days of C1D1, it does not need to be repeated.

10.0 Adverse Events & Events of Clinical Interest

10.1 Definitions

Adverse Events (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, treatment or procedure regardless of whether it is considered related to the medical treatment or procedure *(NCI CTEP Guidelines March 28, 2011)*.

Serious Adverse Event (SAE) is an AE that is fatal or life threatening, requires inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours), persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly/ birth defect, or results in any important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent any of the above outcomes. A "life-threatening" adverse event places the patient at immediate risk of death in the judgment of the investigator or sponsor.

10.1.1 Severity Rating

The investigator will evaluate the severity of each adverse event. NCI Common Terminology Criteria for Adverse Events (CTCAE v.4.0) or study specific toxicity tables provided in the protocol define severity. If not included in CTCAE v.4.0, severity is expressed in numerical grade using the following definitions:

1. Grade 1: Mild-asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2. Grade 2: Moderate-minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL.
3. Grade 3: Severe-severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4. Grade 4: Life-threatening consequences; urgent intervention indicated.
5. Grade 5: Death related to AE

10.1.2 Attribution/Relationship to study drug

1. Definite – clearly related
2. Probable – likely related
3. Possible – may be related
4. Unlikely – doubtfully related
5. Unrelated – clearly not related

10.1.3 Expectedness

An Expected Adverse Event is one where the specificity or severity is consistent with the current information available from the resources.

An Unexpected Adverse Event is one where the nature, severity, or frequency of the event is related to participation in the research is not consistent with either:

1. The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package insert, or

2. The expected natural progression of any underlying disease, disorder, or condition of the subject (s) experiencing the adverse event and the subjects(s) predisposing risk factor profile for the adverse event.
(OHRP Guidance on reviewing unanticipated problems 2007)

10.1.4 Events of Clinical Interest

Events of clinical interest (ECI) for this trial include:

1. An overdose of the Merck product.

2. An elevated AST or ALT lab value that is:
   a. Greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal

   AND

   b. An alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

10.2 Recording and Reporting Responsibilities

10.2.1 Investigative site recording responsibilities:

1. Upon identification of an AE, ECI or SAE, the site investigator will utilize the above definitions to properly classify the event. Each category listed above must be recorded for each event.

2. All AEs, ECIs and SAEs will be recorded in the "AE case report forms" (CRF) and in progress reports with details about the grade and attribution of each episode, action taken with respect to the study drug, and the patient's outcome will be recorded in the CRF. The study period during which all AEs, ECIs, and SAEs must be reported begins at the initiation of study treatment. All events will be recorded on case report forms for the duration of the study until they resolve.

3. All ECI and SAEs will be recorded on the FDA MedWatch form 3500a. After submitting the initial report it may be necessary to submit follow up reports to the OCR, Sponsor and the FDA should the event require further investigation.

10.2.2 Investigative site reporting responsibilities:

1. From the time of the first treatment, the investigator/site is responsible to report all SAEs and ECIs that occur on or after the first day of study treatment to the Investigator-Sponsored Research Unit (ISRU) within 24 hours of becoming aware of the event. SAE and ECI monitoring shall continue until 90 days after the last dose of study drug.

2. Each investigator is responsible to report all AEs/SAEs to their local IRB following guidelines set by that IRB. The FCCC OCR reserves the right to request an event be reported to the IRB at their discretion. Copies of events reviewed by the IRB must be sent email to the IST Regulatory Specialist at SAE.FCCC@fccc.edu.

3. If the investigator or IRB feels the event warrants a revision to the informed consent that was not already initiated by the OCR, draft revisions will be made in track changes and submitted to the OCR for consideration. Any consent revisions must receive OCR approval **prior** to submission to the IRB.

4. Any investigator who is in doubt of whether a particular AE needs to be reported is directed to call the Study Monitor for confirmation with the Sponsor Investigator.

5. If the results of an investigator or OCR investigation show an adverse event not initially determined to be reportable is so reportable, the investigator will report the event following the above guidelines based on the date the determination is made.

6. Copies of all related correspondence and reporting documents must be submitted to the OCR Regulatory Coordinator and will be maintained in a regulatory file.

Participating sites should report events to:

Investigator-Sponsored Research Unit
Office of Clinical Research
Fox Chase Cancer Center
215-214-1439
SAE.FCCC@fccc.edu

10.2.3 OCR Reporting Responsibilities:

1. Adverse events which meet all of the following criteria must be reported to all participating institutions for IRB submission within 2 weeks of notification of the event:

    i. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related

documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

ii. Possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

iii. Serious (refer to above definition) or otherwise one that suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

2. If the adverse event requires modification of the study protocol and informed consent, these changes will be provided to all participating institutions in the form of an amendment from the OCR for each site's IRB of record along with the report of the adverse event.

3. Copies of all related correspondence and reporting documents will be maintained in a centralized regulatory file for this study at OCR.

4. SAEs that are related, unexpected, fatal, or life-threatening are reportable through the Food and Drug Administration (FDA) MedWatch program by telephone or fax no later than 7 calendar days after initial receipt of the information. Further information on the timing of submissions are as directed by FDA guidelines (http://www.fda.gov/medwatch/index.html). Serious, unexpected events that suggest significant clinical risk will be submitted to within 15 calendar days after initial receipt of this information.

Food and Drug Administration:
Telephone 1-800-332-1088
Fax 1-800-332-0178
http://www.fda.gov/medwatch/report.htm

10.2.4 OCR Reporting to Merck

The ISRU will report ECIs and SAEs to Merck global safety within 2 business days of learning of the event, regardless of relationship to pembrolizumab. Reports must be sent to:

Merck Global Safety.
Attn: Worldwide Product Safety
FAX 215 993-1220

10.2.5 Expedited Reporting by Sponsor-Investigator to Celgene

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events of being related to lenalidomide based on the Investigator

Brochure. In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours. The initial report must be as complete as possible, including 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 report. A final report to document resolution of the SAE is required. The Celgene tracking number (**RV-CL-NSCLC-PI-005750**) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records

10.2.5.1 Overdose

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

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of lenalidomide assigned to a given patient, regardless of any associated adverse events or sequelae.

PO	any amount over the protocol-specified dose
IV	10% over the protocol-specified dose
SC	10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate. Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

Celgene Drug Safety Contact Information:

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

10.3 Pregnancy

10.3.1 Pregnancy Reporting for Pembrolizumab

All WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

In the event of a confirmed pregnancy in a patient participating in the study, the Investigator must immediately notify the Fox Chase Cancer Center Study Monitor who will notify Dr. Hossein Borghaei.

Pregnancies and lactations that occur from the time of treatment allocation through 120 days following cessation of pembrolizumab, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor Investigator. The ISRU will report such events within 2 working days to Merck Global Safety.

10.3.2 Pregnancy Reporting for Lenalidomide

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on lenalidomide, or within 28 days of last dose of lenalidomide, are considered immediately reportable events. Lenalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female subject may be referred to an obstetrician-gynecologist (not necessarily one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug

Safety immediately by facsimile, or otherappropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

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

Male Subjects

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

11.0 Measures of Effect

Response Evaluation Criteria in Solid Tumors (RECIST)

The Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria will be used for objective tumor response assessment. Assessments will be performed after every six weeks of treatments. Once protocol treatment has been completed subjects will be assessed every three months or sooner as indicated and judged by treating physicians.

11.1 Definitions

Evaluable for adverse events. All patients will be evaluable for adverse events from the time of their first treatment with pembrolizumab and lenalidomide.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least two cycles of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

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

11.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$20 mm by chest x-ray, as $\geq$10 mm with CT scan, or $\geq$10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 30 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is

preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation

is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

Effusions: The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.4 Response Criteria

11.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.4.3 Evaluation of Best Overall Response

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

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD /not evaluated	No	PR	
SD	Non-CR/Non-PD /not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response

CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

11.5 Duration of Response

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

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

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

11.6 Progression-Free Survival

Progression-free survival (PFS) will be used in the phase II component of this study. PFS is defined as the duration of time from start of treatment to time of disease progression or death, whichever occurs first.

12.0 Statistical Considerations

12.1 Study Design/Endpoints

The primary endpoint for the phase I component of this protocol will be determining the maximum tolerated dose (MTD) of lenalidomide in combination with pembrolizumab. Our hypothesis is that the drugs pembrolizumab and lenalidomide will be well-tolerated in combination, without significant toxicities or adverse events.

The primary endpoint for the phase II component of this protocol will be determining efficacy as measured by progression free survival (PFS), and our hypothesis is that this novel drug combination will improve PFS as described below. We will test the null hypothesis that at most 25% of patients will be progression free for 20 weeks. Our alternative will be that at least 50% of them will with our combination therapy. Using the assumption of exponential PFS we would expect 50% or 71% to survive for 10 weeks under the null or alternative respectively. We will initially enter 13 patients to a two-stage design with early stopping in both time and patient number. If at least 7 of these 13 patients are PF for 10 weeks then we will enter 13 new patients to the study. In this case PF patients from the initial cohort will stay on study and, finally, if at least 11 of 26 patients are PF for 20 weeks we will reject the null hypothesis. If 6 or fewer patients are PF at 10 weeks we will not recruit additional

patients, terminate the study for lack of efficacy and accept the null hypothesis. The study has 81% overall power and 3.5% type I error. The chance of early stopping in both time and patient number is 50% under the null and 5.5% in error.

12.2 Toxicity

In the phase I part of the study, a '3+3" standard design, the chance of dose escalation, given the true toxicity is shown in the following table. For example, if the true toxicity is 50% the chance of dose escalation is 17.2%.

ptox	0.1	0.2	0.3	0.4	0.5	0.6	0.7
p(escalate)	0.906	0.709	0.494	0.309	0.172	0.082	0.032

We consider 18% rate of DLTs acceptable and 40% excessive. If 6 of the initial 13 phase II patients experience DLTs, the trial will be halted and dose reduction considered. Finally, if ever 9 patients of the 26 patients experience DLTs, the treatment will be considered too toxic. The chance of early halting when the true toxicity is 40% is 44% and is 1.8% when the true toxicity is only 18%. The toxicity design has 80% power to declare the treatment too toxic when it is, and 4.2% chance of this declaration in error.

12.3 Sample Size/Accrual Rate

The planned sample size for the phase I component will be 6-18 patients; we will plan to accrue 1-2 patients per month.

The planned sample size for the phase II component is 26 patients; we will plan to accrue 2-4 patients per month

12.4 Stratification Factors

Patients in the phase I component of the study will not be stratified.

Patients in the phase II component of the study will be stratified by subtype of lung cancer (e.g. adenocarcinoma, squamous cell carcinoma) and number of prior lines of therapy.

12.5 Analysis of Secondary Endpoints

95% confidence bounds will be computed for the tumor response rate. Frequencies of T and NK cell subsets will be tabulated with 95% confidence bounds. Activation phenotypes will be tabulated with corresponding 95% confidence bounds. The association of PD-L1 expression level (above or below the grand median) with tumor response will be submitted to Fisher's exact test.

12.6 Reporting and Exclusions

12.6.1 Evaluation of toxicity

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

12.6.2 Evaluation of response

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

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

13.0 Data and Safety Monitoring Plan

13.1 Monitoring Plan

FCCC OCR will monitor the medical and study records of each participant accrued throughout the course of the study. In addition, the OCR will collect and report data to the Sponsor Investigator who will review these data on a regular basis at a rate dependent on subject accrual. All serious adverse events (SAEs) will be reviewed on a real time basis first by the study site PI and subsequently by the OCR and Sponsor Investigator as applicable.

13.2 Data Safety Monitoring Committee

Interim analysis of toxicity, outcome and ongoing scientific investigations may be performed at least every 6 months by the Fox Chase Cancer Center Data Safety Monitoring Committee (FCCC DSMC). In this capacity the FCCC DSMC will serve as an advisory committee to the OCR. The FCCC DSMC will review those aspects of this trial that are outlined in the responsibilities section of the Data and Safety Monitoring Plan (DSMP). If the committee decides that changes should be made to this trial, it will make recommendations in writing to the Sponsor Investigator, the Associate Director of Clinical Research, and the Protocol Management Executive Committee, which, in turn, have the authority to approve or disapprove these recommendations. These changes will be discussed with the Sponsor Investigator before they are implemented. These changes may include early termination of accrual. Other changes might include altering the accrual goals or changing the eligibility criteria for the trial.

14.0 Administrative

This study will be conducted in accordance will local, state and Federal regulations and according to accepted good clinical practice guidelines.

14.1 Data Reporting

The FCCC Study Monitor will request case report forms to be completed within 2 weeks of the protocol visit. Participating sites are responsible to respond to queries prior to the next scheduled monitoring visit.

The ERP Data Manager is responsible for compiling and submitting data to the sponsor investigator and statistician on an ongoing basis for monitoring as described in the data safety monitoring plan and reporting to the Data and Safety Monitoring Committee.

All patient information will be stored in an EDC system accessible only to the study team members for the purpose of entering, reviewing and analyzing data. Any paper records, such as case report files, produced will be stored in a secure location.

The IST Regulatory Specialist is responsible for distributing and tracking review of all IND Action Letters, Safety Reports, study specific Serious Adverse Events.

14.2 Retention of Records

Time points for the retention of records are described in detail in the contract between the grantor and the OCR and passed on to the participating site. Please refer to the study specific terms for specific time points. In all cases the Study Monitor must be notified of any plans to move records to an offsite location prior to doing so.

14.3 Study Agents

Any study agent supplied through the OCR from the manufacturer or a third party distributor may not be used for any purpose outside the scope of this protocol. The agent may not be transferred to any party not participating in the clinical trial.

14.4 Informed Consent

The IRB approved informed consent documents must be signed by the patient, or the patient's legally authorized representative, before his or her participation in the study. The case history for each patient shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent documents must be provided to the patient or the patient's legally authorized representative. If applicable, they will be provided in a certified translation of the local language.

Original signed consent forms must be filed in each patient's study file or medical record with a copy in the study file.

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16.0 Appendix A: Lenalidomide Pregnancy Prevention Plan

1. LENALIDOMIDE PREGNANCY PREVENTION PLAN FOR SUBJECTS IN CLINICAL TRIALS

The Pregnancy Prevention Plan (PPP) applies to all subjects receiving lenalidomide within a clinical trial. The following PPP documents are included:

1. The Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Section 2) provides the following information:
   - Potential risks to the fetus associated with lenalidomide exposure
   - Definition of female of childbearing potential (FCBP)/female not of childbearing potential (FNCBP)
   - Requirements for counseling of all subjects receiving lenalidomide about pregnancy precautions and the potential risks of fetal exposure to lenalidomide
   - Acceptable birth control methods for both female subjects of childbearing potential and male subjects receiving lenalidomide in the study
   - Pregnancy testing requirements for subjects receiving lenalidomide who are FCBP
2. The Lenalidomide Education and Counseling Guidance Document for each gender (female and male; Section 3 and Section 4 respectively) must be completed and signed by a trained counselor at the participating clinical center prior to each dispensing of lenalidomide. A copy of this document must be maintained in the subject's records for each dispense.
3. The Lenalidomide Information Sheet (Section 5) will be given to each subject receiving lenalidomide. The subject must read this document prior to starting lenalidomide and each time the subject receives a new supply of lenalidomide.

2. LENALIDOMIDE RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

2.1. Risks Associated with Pregnancy

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. A teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a pregnancy prevention program must be followed.

2.1.1. Definition of Females of Childbearing Potential

A FCBP is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

2.1.2. Definition of Females Not of Childbearing Potential

Females who do not meet the above definition of FCBP should be classified as FNCBP.

2.2. Counseling

2.2.1. Females of Childbearing Potential

For a FCBP, lenalidomide is contraindicated unless all of the following are met (ie, all FCBP must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting lenalidomide, throughout the entire duration of lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide
- She understands and agrees to inform the Investigator if a change or stop of method of contraception is needed
- She must be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence lenalidomide as soon as it is dispensed following a negative pregnancy test

- She understands and accepts the need to undergo pregnancy testing based on the frequency outlined in this plan (Section 2.4) and in the Informed Consent
- She acknowledges that she understands the hazards lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of lenalidomide.

The Investigator must ensure that a FCBP:

- Complies with the conditions of the pregnancy prevention plan, including confirmation that she has an adequate level of understanding
- Acknowledges the aforementioned requirements.

2.2.2. Females Not of Childbearing Potential

For a FNCBP, lenalidomide is contraindicated unless all of the following are met (ie, all FNCBP must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She acknowledges she understands the hazards lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of lenalidomide.

2.2.3. Males

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

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

2.3. Contraception

2.3.1. Female Subjects of Childbearing Potential

Females of childbearing potential enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) while taking lenalidomide; 3) during dose interruptions; and 4) for at least 28 days after the last dose of lenalidomide.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. If the below contraception methods are not appropriate for

the FCBP, she must be referred to a qualified provider of contraception methods to determine the medically effective contraception method appropriate to the subject. The following are examples of highly effective and additional effective methods of contraception:

- Examples of highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])
  - Tubal ligation
  - Partner's vasectomy
- Examples of additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

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

2.3.2. Male Subjects

Male subjects must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.

2.4. Pregnancy Testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for FCBP.

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

Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking lenalidomide, at study discontinuation, and at Day 28 following the last dose of lenalidomide.

Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking lenalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of lenalidomide.

2.5. Pregnancy Precautions for Lenalidomide Use

2.5.1. Before Starting Lenalidomide

2.5.1.1. Female Subjects of Childbearing Potential

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

Females of childbearing potential must use two reliable forms of contraception simultaneously, or practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact for at least 28 days before starting lenalidomide.

2.5.1.2. Male Subjects

Male subjects must agree to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.

2.5.2. During and After Study Participation

2.5.2.1. Female Subjects

- Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking lenalidomide, at study discontinuation, and at Day 28 following the last dose of lenalidomide.
- Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking lenalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of lenalidomide.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control if not committing to complete abstinence, or confirm commitment to complete abstinence.
- If a FCBP considers the need to change or to stop a method of contraception, the Investigator must be notified immediately.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a subject, lenalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding while taking lenalidomide and for at least 28 days after the last dose of lenalidomide.

2.5.2.2. Male Subjects

- Must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.
- Must not donate semen or sperm while receiving lenalidomide, during dose interruptions or for at least 28 days after the last dose of lenalidomide.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.

- If pregnancy or a positive pregnancy test does occur in the partner of a male subject while taking lenalidomide, the Investigator must be notified immediately.

2.5.3. Additional Precautions

- Subjects should be instructed to never give lenalidomide to another person.
- Subjects should be instructed to return any unused capsules to the study doctor.
- Subjects should not donate blood while receiving lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
- No more than a 28-day lenalidomide supply may be dispensed with each cycle of lenalidomide.

3. LENALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR FEMALE SUBJECTS

To be completed prior to each dispensing of lenalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

Check one risk category:

- ☐ FCBP (Female of childbearing potential): a female who: 1) has achieved menarche (first menstrual cycle) at some point, 2) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months)
- ☐ NOT FCBP

3.1. Female of Childbearing Potential:

1. I have verified and counseled the subject regarding the following:

- ☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking lenalidomide. Females of childbearing potential must agree not to become pregnant while taking lenalidomide.
- ☐ That the required pregnancy tests performed are negative.
- ☐ The subject confirmed that she is using TWO reliable methods of birth control at the same time, or complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact (at least 28 days prior to receiving lenalidomide, while receiving lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide).

  One highly effective method and one additional method of birth control must be used AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:

  - Examples of highly effective methods:
    - Intrauterine device (IUD)
    - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])

- Tubal ligation
- Partner's vasectomy

– Examples of additional effective methods:

- Male condom
- Diaphragm
- Cervical Cap

☐ The subject confirmed that even if she has amenorrhea she must comply with advice on contraception.

☐ Pregnancy tests before, during administration of lenalidomide and at the last dose of lenalidomide, even if the subject agrees not to have reproductive heterosexual contact.

☐ Frequency of pregnancy tests to be done:

– Two pregnancy tests will be performed prior to receiving lenalidomide, one within 10 to 14 days, and a second within 24 hours of the start of lenalidomide.

– Every week during the first 28 days of this study and a pregnancy test every 28 days while the subject is taking lenalidomide if menstrual cycles are regular.

– Every week during the first 28 days of this study and a pregnancy test every 14 days while the subject is taking lenalidomide if menstrual cycles are irregular.

– If the subject missed a period or has unusual menstrual bleeding.

– When the subject is discontinued from the study and at Day 28 after the last dose of lenalidomide if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at Days 14 and 28 after the last dose of lenalidomide.

☐ The subject confirmed that she will stop taking lenalidomide immediately in the event of becoming pregnant and to call her study doctor as soon as possible.

☐ The subject confirmed that she has not and will not breastfeed a baby while taking lenalidomide and for at least 28 days after the last dose of lenalidomide.

☐ The subject has not and will never share lenalidomide with anyone else.

☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.

☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.

☐ The subject confirmed that she will return unused lenalidomide capsules to the study doctor.

2. I have provided the Lenalidomide Information Sheet to the subject.

3.2. Female Not of Childbearing Potential (Natural Menopause for at Least 24 Consecutive Months, a Hysterectomy, or Bilateral Oophorectomy):

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
   - ☐ The subject has not and will never share lenalidomide with anyone else.
   - ☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
   - ☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.
   - ☐ The subject confirmed that she will return unused lenalidomide capsules to the study doctor.
2. I have provided the Lenalidomide Information Sheet to the subject.

Do Not Dispense Lenalidomide if:

- **The subject is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The subject states she did not use TWO reliable methods of birth control (unless practicing complete abstinence from heterosexual contact) at least 28 days prior to receiving lenalidomide, while receiving lenalidomide and during dose interruptions.**
- **The subject stated that she has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

4. LENALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR MALE SUBJECTS

To be completed prior to each dispensing of lenalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
   - ☐ The subject confirmed that he has practiced complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or used a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or FCBP, while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
   - ☐ The subject confirmed that he has not impregnated his female partner while in the study.
   - ☐ The subject confirmed that he will notify his study doctor if his female partner becomes pregnant and the female partner of a male subject taking lenalidomide confirmed that she will call her healthcare provider immediately if she becomes pregnant.
   - ☐ The subject has not and will never share lenalidomide with anyone else.
   - ☐ The subject confirmed that he has not donated and will not donate semen or sperm while taking lenalidomide or during dose interruptions and that he will not donate semen or sperm for at least 28 days after the last dose of lenalidomide.
   - ☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
   - ☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.
   - ☐ The subject confirmed that he will return unused lenalidomide capsules to the study doctor.
2. I have provided the Lenalidomide Information Sheet to the subject.

Do Not Dispense Lenalidomide if:

- **The subject stated that he has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

5. LENALIDOMIDE INFORMATION SHEET

For subjects enrolled in clinical research studies

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

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

1. **Lenalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Lenalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects.

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

   - **Do not take lenalidomide if you are pregnant or plan to become pregnant**
   - **You must practice complete abstinence from sexual contact with a male or use two reliable, separate forms of effective birth control at the same time:**
     - for 28 days before starting lenalidomide
     - while taking lenalidomide
     - during breaks (dose interruptions) of lenalidomide
     - for at least 28 days after the last dose of lenalidomide
   - **You must have pregnancy testing done at the following times:**
     - within 10 to 14 days prior to the first dose of lenalidomide
     - 24 hours prior to the first dose of lenalidomide
     - weekly for the first 28 days
     - if you have regular menstrual periods: every 28 days after the first month
     - if you have irregular menstrual periods: every 14 days after the first month
     - if you miss your period or have unusual menstrual bleeding
     - 28 days after the last dose of lenalidomide (14 and 28 days after the last dose if menstrual periods are irregular)
   - **Stop taking lenalidomide if you become pregnant while taking lenalidomide**
     - If you suspect you are pregnant at any time during the study, you must stop lenalidomide immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to Celgene Corporation.
   - **Do not breastfeed while taking lenalidomide and for at least 28 days after the last dose of lenalidomide**

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

If you are a female not able to become pregnant:

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

If you are a male:

A small amount of lenalidomide is found in human semen. The risk to an unborn baby in females whose male partner is receiving lenalidomide is unknown at this time.

- Male subjects (including those who have had a vasectomy) must practice complete abstinence or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
  - While you are taking lenalidomide
  - During breaks (dose interruptions) of lenalidomide
  - For at least 28 days after the last dose of lenalidomide
- **Male subjects should not donate sperm or semen** while taking lenalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of lenalidomide.
- **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation. Your partner should call their healthcare provider immediately if they become pregnant.**

2. **All subjects:**

- **Do not share lenalidomide with other people. It must be kept out of the reach of children and should never be given to any other person.**
- **Do not donate blood** while you take lenalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of lenalidomide.
- **Do not break, chew, or open lenalidomide capsules at any point.**
- You will get no more than a 28-day supply of lenalidomide at one time.
- Return unused lenalidomide capsules to your study doctor.

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