MD Anderson IND Sponsor Cover Sheet	
Protocol ID	2012-0947
Protocol Title	A Pilot Study of Lenalidomide Alternating with Ipilimumab Post Allogeneic and Autologous Stem Cell Transplantation
Protocol Phase	Pilot
Protocol Version	26
Version Date	08 August 2022
Protocol PI	Issa F. Khouri, M.D.
Department	Stem Cell Transplantation and Cellular Therapy
IND Sponsor	MD Anderson Cancer Center
IND #	119181

A Pilot Study of Lenalidomide Alternating with Ipilimumab Post Allogeneic and Autologous Stem Cell Transplantation

Institution Study Number: **2012-0947**

Financial Support: Bristol-Myers Squibb

IND Holder: The University of Texas MD Anderson Cancer Center

IND Number: 119181

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Protocol Body

1.0 Objectives

The primary objective of this pilot study will be to assess the safety of lenalidomide in combination with ipilimumab in autologous and allogeneic stem cell transplantation.

Secondary objectives include assessing:
1. Overall response rate
2. Overall survival, progression-free survival
3. Cumulative incidence of acute and chronic GVHD with the competing risk of relapse in allogeneic transplant patients.

2.0 Background

Relapse or progression of malignancy is an important cause of failure after hematopoietic stem cell transplantation. Adoptive immunotherapy can induce clinical responses in several malignancies.[1]

Revlimid (Lenalidomide, LEN or IMiD3) is the leading compound among the immunomodulatory drugs or IMiDs.[2] It was developed as a structural analog of Thalidomide, from which it differs by the addition of an amino group and the removal of one of the carbonyl groups from the phthaloyl ring system. Thanks to these changes, LEN minimizes the toxicity typical of its parental drug, while optimizing therapeutic efficacy. This drug is now considered an emerging compound in hematologic malignancies.

The therapeutic efficacy of LEN is mainly associated with immunomodulatory, antiangiogenic, anti-inflammatory and, to a lesser extent, antineoplastic effects. The drug has indeed been shown to modulate several components of the immune system by restraining pro-inflammatory cytokine production, enhancing NK cell cytotoxicity and regulating T-cell proliferation. *in vitro* studies have demonstrated that LEN induces up to a 50 000-fold decrease in TNF-a, IL-1b, IL-6, and IL-12 production by human peripheral blood mononuclear cells (PBMCs), whereas synthesis of IL-2 and IFN-g was found to be dramatically increased.[2] T-cell proliferation, differentiation, and survival are primed by LEN via the B7-CD28 co-stimulatory pathway. Hayashi et al. have shown that incubation of PBMCs in the presence of LEN leads to an increase up to 1.5 times in NK cell number as compared to control cultures[3]. LEN has also been shown to significantly affect angiogenesis in various cancers, presumably by uncoupling angiogenesis from secretion of VEGF through inhibition of Gab1 and Akt phosphorylation, both proteins being recruited downstream of VEGFR stimulation.

Inadequate co-stimulation of T cells may be one mechanism underlying failure of adoptive immunotherapy. Expression of CTL4 is induced upon T cells upon activation. It competes with co-stimulatory receptor CD28 for the B7 ligands CD80 and CD86 on antigen-presenting cells. Through this and other mechanisms, CTLA4 functions as an important negative regulator of the duration and intensity of antigen-specific T-cell responses.[5] CTLA4 is an important mediator of peripheral self-tolerance and tolerance to tumor antigens. Ipilimumab

is a fully human immunoglobulin G1 (IgG1) monoclonal antibody that antagonizes CTLA4. The rational for using anti-CTL4 is to un-restrain pre-existing anticancer T-cell responses (in this case, induced by LEN) and possibly trigger new responses. This is the reason why this clinical trial with Ipilimumab is so important, especially now that Ipilimumab has been approved by the U.S. Food and Drug Administration for the treatment of metastatic melanoma. The assessment of the potentiating effect of Ipilimumab on the immunomodulatory effects of LEN will open new treatment options for lymphoid and other hematologic malignancies.

Three published studies have established the safety of ipilimumab after allogeneic stem cell transplantation.[5-7] The dose of 3.0 mg/kg iv every 3 to 4 weeks x 4 was not associated with significant toxicity.[5-7] We are proposing the same dose level in this pilot study.

The use of LEN after allogeneic stem cell transplantation has also been studied at MD Anderson using protocol 2007-0871. No patient in that trial died of graft-versus-host disease (GVHD) induced or related to LEN.

3.0 Eligibility

3.1 Inclusion Criteria

a. Age >/= 18 years to </= 80 years.
b. Hematologic or lymphoid malignancy.
c. Autologous patients can be included anytime within 6 months post-transplant, if they had no signs of progression and meet one of the following criteria:[8-9]
    i. Leukemia
    ii. Lymphoma (all types of B and T cell lymphoma)
    iii. Multiple myeloma
d. Allogeneic patients if:
    i. Patients had engrafted donor cells (i.e., > 20% donor T-cell from PB/PCR); and,
    ii. Patients NOT in CR after their allogeneic transplant, and off tacrolimus and/or mycophenolate mofetil for at least 3 to 4 weeks with no signs of GVHD; or,
    iii. Patients had evidence of relapse after their transplant who are off tacrolimus and/or mycophenolate mofetil or other immunosuppressants for GVHD for 3 to 4 weeks with no signs of GVHD (Prednisone doses </= 10 mg are permitted as stated previously).
e. No active infection.
f. ANC >/= 1.5 x 10^9/L; platelets >/= 50 x 10^9/L.
g. Able to adhere to the study visit schedule and other protocol requirements.
h. Performance status: ECOG 2 or less or Karnofsky of at least 60.
i. Cardiac EF >/= 45% by 2D-ECHO within 3 months of study entry (or within 1 month if received chemotherapy within the past 3 months).
j. FEV1, FVC and DLCO >/= 40% within 3 months of study entry (or within 1 month if received chemotherapy within the past 3 months).
k. Serum creatinine </= 1.6 mg/dL and creatinine clearance >/= 30 ml/min. Creatinine clearance will be calculated using the Cockcroft-

Gault equation: Use actual body weight if it is less than or equal to ideal body weight. Use ideal body weight if patient greater than ideal body weight, but is less than or equal to 50% over ideal body weight. Use adjusted body weight if patient is greater than 50% over ideal body weight.

l. Liver function tests (unless related to Gilbert's disease or medications)
   i. SGPT, SGOT less than 2x the upper limit of normal range.
   ii. Direct Bilirubin <1.6
m. Patient or legally authorized representative able to sign informed consent.
n. Females of childbearing potential (FCBP)† must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 - 14 days prior to study entry.

3.2 Exclusion criteria

a. Immunotherapy or chemotherapy with approved or investigational anticancer therapeutics within 4 weeks of first dose.
b. Patients on alemtuzumab within 6 weeks prior to consenting.
c. Active congestive heart failure (NYHA Class III to IV), symptomatic ischemia or conduction abnormalities uncontrolled by conventional interventions. Myocardial infarction within 6 months of study entry.
d. Deep vein thrombosis or pulmonary embolism within 3 months of study entry.
e. Pregnant or breast-feeding females. (Lactating females must agree not to breast-feed while taking lenalidomide).
f. Acute active infection requiring intravenous antibiotics, antiviral (except antiviral directed at hepatitis B), or antifungal agents within 14 days of first dose.
g. Known HIV seropositive, hepatitis C infection, and/or hepatitis B (except for patients with hepatitis B Sag or core antibody receiving and responding to antiviral therapy directed at hepatitis B: these patients are allowed).
h. Patients with other known malignancies within the past three years except:
   i. Adequately treated basal or squamous cell skin cancer.
   ii. Carcinoma in situ of the cervix.
   iii. Prostate cancer with Gleason score < 6 with stable PSA over the past three months.
   iv. Breast cancer in situ with full surgical resection.
i. Significant neuropathy (grades 3 to 4 or grade 2 pain).
j. Known hypersensitivity to thalidomide, lenalidomide or ipilimumab.
k. Active life-threatening autoimmune disease.
l. Active GVHD or recent GVHD and still on > 10 mg prednisone (or equivalent).
m. Prior auto-immune disease.

4.0 Treatment Plan

Eligible patients will receive lenalidomide alternating with ipilimumab for 8 cycles.

Patients who are still receiving or just finished (i.e., within 3 months) the original treatment plan will be re-consented to receive 4 additional cycles (i.e., 8 total cycles).

Lenalidomide will be given daily for 21 days (Cycle 1). One dose of ipilimumab (Cycle 2) will be given within 1-3 days from the last day of lenalidomide, then followed by 4 weeks of rest.
Repeat lenalidomide daily for 21 days (Cycle 3) followed by one dose of ipilimumab (Cycle 4) within 1-3 days from the last dose of lenalidomide. Treatment will be repeated for a total of 8 cycles.

Creatinine Clearance (mL/min)	**Cycles 1, 3, 5, 7**	**Cycles 2, 4, 6, 8**
Greater than 60	Lenalidomide 10 mg PO daily for 21 days	Ipilimumab 3 mg/kg IV x 1 dose (given 1-3 days after lenalidomide, then followed by 4 weeks of rest)
30 to 60	Lenalidomide 5 mg PO daily for 21 days	Ipilimumab 3 mg/kg IV x 1 dose (given 1-3 days after the last dose of lenalidomide)

Creatinine clearance. Use Cockcroft-Gault formula and ideal body weight (IBW) as described above in inclusion criteria (Section 3.1)

If the starting combination of lenalidomide 10 mg/day alternating with ipilimumab 3 mg/kg results in toxicity in the first 3 of 3 patients (as defined in toxicity monitoring rule) then subsequent patients will be started at a lower combination dose of lenalidomide 5 mg/day (or 5 mg every other day for creatinine clearance of 30 to 60 ml/min) and ipilimumab 3 mg/kg.

4.1 Management of Immune-Mediated toxicity from ipilimumab:

There are no dose reductions for Ipilimumab. The only modifications to drug are to pause until improvement or stop.

Signs and Symptoms	Assessment of cause and severity	Procedure for adverse effects	Ipilimumab therapy
Gastrointestinal Colitis, diarrhea, blood in stool and/or abdominal pain	Exclude other causes (disease progressions, GVHD, infection) Measure AE severity using NCI-CTCAE v3.0 (diarrhea/colitis severity grading scale 3)	Mild (grade 1,2): - Symptomatic therapy	Continue therapy
		Mild (grade 2) with longer term symptoms (5-7 days): - Corticosteroid therapy with prednisone 1 mg/kg/day (or equivalent) Symptom improvement: taper drug over 4 weeks	Pause therapy until improvement to ≤ grade 1
		Severe (grade 3,4) or no improvement after 5 days on steroid (grade 2) or relapse after steroid taper : - Methylprednisolone 2 mg/kg/day IV Symptom improvement: taper drug over 4 weeks	STOP
		Severe (grade3,4) and no improvement after 5 to 7 days of steroid or relapse after reducing steroids: - Consider adding other immunosuppressant's (i.e. infliximab 5mg/kg IV or other agents per departmental GVHD standard of care). *Infliximab is contraindicated in bowel perforation or sepsis.*	
Hepatitis Increased liver values (> 2.5x ULN or > 2 x baseline)	Rule out other causes (medication, infection, GVHD) Close control of liver values (assess every 3 days)	Other causes (not believed to be ipilimumab and not from GVHD)	Continue therapy
		Liver values > 2.5 x to 8 x ULN: - Daily LFTs on 3 consecutive days. If no improvement steroid therapy	Pause therapy until LFTs back to normal or ≤ 2.5x ULN
		Liver values > 8 x ULN or total bilirubin > 5 x ULN: - Methylprednisolone 2 mg/kg/day IV. Daily LFTs for 5 days, then every 3 days thereafter. Once LFTs are under control: taper steroid over at least 4 weeks and check LFTs weekly	STOP
		Persistently high LFTs after 3 to 5 days or a new increase in LFTs during steroid reduction: - Consider adding additional immunosuppressant drugs (i.e mycophenolate mofetil 15 mg/kg IV/PO every 8 to 12 hours)	
Dermatitis Skin eruptions and pruritis	Perform skin biopsy to rule out GVHD in allogeneic patients	Grade 1,2: - Topical management (topical corticosteroid and/or topical anti-pruritic)	Continue therapy
		Grade 3 or persistent grade 2: - Corticosteroid therapy with prednisone 1 mg/kg/day (or equivalent) Symptom improvement: taper drug over 4 weeks	Pause
		Grade 4 (i.e. Stevens-Johnson Syndrome, toxic epidermal necrolysis): - Methylprednisonlone 2 mg/kg/day IV Taper over a MINIMUM of 4 weeks	STOP

Signs and Symptoms	Assessment of cause and severity	Procedure for adverse effects	Ipilimumab therapy
Endocrine Headache, vision field disturbance, fatigue, loss of appetite, nausea and vomiting, lethargy, impotence, amenorrhea, fever, coma, inset of heart flutter, hypotension, hypoglycemia, hyponatremia, eosinophilia	If no suspected adrenal insufficiency: 1. TSH, Free T4 and ACTH 2. MRI of the head with hypophysis, possible vision filed testing 3. Endocrine consultation	No abnormal results: - Rule out other causes, - Repeat labs in 1-3 weeks - Frequent follow up	Continue therapy
	Suspected adrenal insufficiency: - Therapy for adrenal insufficiency - Exclude sepsis	Abnormal results: - Short term (7 days) high dose mineral corticoids against inflammation (i.e dexamethasone 4 mg IV or PO every 6 hours) - Hormone substitution therapy against endocrinopathy - Endocrine consult Taper high dose steroid over at least 4 weeks and continue hormone substitution if necessary. Repeat MRI depending on clinical signs *Antimicrobial prophylaxis per departmental standard of care (as applicable to patients with acute GVHD on steroids)*	Grade 2 – Pause and resume upon symptom improvement Grade 3,4 - STOP
Neuropathies Assessment of neuropathy Sensory symptoms constant for ≥ 5 days Motor testing	Rule out inflammatory causes (i.e. infection, metabolic, other drugs) Neurological consult, EMG and nerve conduction studies, comprehensive testing of neurologic syndrome and measurement of baseline values to assess development	Grade 1: - Treat symptoms based on recommendations from Neurology consult - If related to ipilimumab, possible IV steroids for grade 3,4 AEs	Continue therapy
		Grade 2: - Treat symptoms based on recommendations from Neurology consult - If related to ipilimumab, possible IV steroids for grade 3,4 AEs	Pause (if related)
		Grade 3,4 sensory or clinically stable motor: - Treat symptoms based on recommendations from Neurology consult - If related to ipilimumab, possible IV steroids for grade 3,4 AEs	STOP
		Grade 3,4 motor and not clinically stable: - If atypical or progressive, admit to hospital and give IV steroids (methylprednisolone 2 mg/kg/day) - Possible IVIG or other immunosupressants	STOP

In all patients who receive corticosteroids to treat/manage ipilimumab AEs, antimicrobial prophylaxis should be given for prevention of herpes infection, bacterial infection, fungal infection and PCP pneumonia as per departmental standard of care (as applicable to allogeneic patients with acute GVHD on steroids)

4.2 Ipilimumab specific requirement/toxicity management

1. Liver toxicity
   a. Monitor liver function and evaluate for signs of hepatotoxicity prior to each dose (cycles 2, 4, 6, and 8). If hepatotoxicity develops, liver function should be monitored frequently until resolution.
2. Other monitoring
   a. Monitor serum chemistries before each dose
   b. Monitor for signs of hypophysitis, adrenal insufficiency and thyroid disorders
      i. Abdominal pain, fatigue, headache, hypotension, mental status changes, unusual bowel habits
   c. TSH, free T4 and total cortisol level should be checked at baseline, prior to each dose and as clinically indicated
   d. Monitor for signs or symptoms of enterocolitis
   e. Monitor for signs of motor or sensory neuropathy
   f. Monitor for ocular toxicity at baseline then and before each dose

4.3 Lenalidomide specific requirements/toxicity management

1. Females of childbearing potential (FCBP)† must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days prior to and again within 24 hours of the first dose of lenalidomide in Cycles 1, 3, 5, and 7 and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts

taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. See Appendix C: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

a. All study participants must be registered into the mandatory Revlimid REMS™ program, and be willing and able to comply with the requirements of the Revlimid REMS™ program.
b. Prescriptions must be filled within 7 days.

2. Dosing Regimen: Patients will be given a pill diary for Cycles 1, 3, 5, and 7 in order to document self-administration of the lenalidomide.
   a. The drug will be given in the morning at approximately the same time each day for a total of 21 days (which should be consecutive, unless held for toxicities as described in the table below). Only enough lenalidomide for 21-days of therapy will be supplied to the patient.
   b. Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened.
   c. If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.
   d. Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.
   e. Subjects experiencing adverse events may need study treatment modifications
   f. Special Handling Instructions
   g. Females of childbearing potential should not handle or administer lenalidomide unless they are wearing gloves.

NCI CTC Toxicity Grade	Action
Grade 3 neutropenia associated with fever (temperature >/= 38.5° C) or Grade 4 neutropenia (ANC </= 500/mm3, </= 75% of baseline)*.	1) Hold (interrupt dose). 2) Follow CBC weekly until resolution or stabilization 3) If neutropenia has resolved to </= grade 2, implement one dose reduction and continue therapy. 4) If neutropenia is the only toxicity for which a dose reduction is required, GCSF may be used and the lenalidomide dose maintenance.
Thrombocytopenia Grade 4 (platelet count </= 25,000/mm3)*.	1) Hold (interrupt dose). 2) Follow CBC weekly until resolution or stabilization 3) If thrombocytopenia resolves to </= grade 2, implement one dose reduction and continue therapy.
Non-blistering rash Grade 3 Grade 4	1) If grade 3, hold (interrupt) dose. Follow weekly until resolution or stabilization. 2) If the toxicity resolves to </= grade 1, implement one dose reduction and continue therapy. 1) Discontinue lenalidomide study drug.
Desquamating (blistering) rash-any Grade	Discontinue lenalidomide study drug.
Erythema multiforme Grade 3	Discontinue lenalidomide study drug.
Neuropathy Grade 3 Grade 4	1) If grade 3, hold (interrupt) dose. Follow weekly until resolution or stabilization. 2) If the toxicity resolves to </= grade 2, implement one of dose reduction and continue therapy. Discontinue lenalidomide study drug.
Sinus bradycardia/other cardiac arrhythmia Grade 2 >/= Grade 3	1) Hold (interrupt dose). Follow at least weekly until resolution or stabilization. 2) If the toxicity resolves to </= grade 1, implement one dose reduction and continue therapy. Discontinue lenalidomide study drug.
Allergic reaction or hypersensitivity Grade 3 Grade 4	1) Hold (interrupt dose). Follow at least weekly until resolution or stabilization 2) If the toxicity resolves to </= grade 1, implement one dose reduction and continue therapy. Discontinue lenalidomide study drug.

NCI CTC Toxicity Grade	Action
Venous thrombosis/embolism >/= Grade 3	Hold (interrupt) dose and start anticoagulation; restart at investigator's discretion (maintain dose level).
Hepatic or other non-hematologic toxicity assessed as lenalidomide-related >/= Grade 3	1) Hold (interrupt) dose. Follow at least weekly until resolution or stabilization. 2) If the toxicity resolves to </= grade 2, implement one dose reduction and continue therapy.
Tumor flare refractory to oral pain meds and/or antihistamines	Hold dose and differentiate tumor flare from progression. Restart therapy at the investigator's discretion.

4. Treatment and Dose Modification for Tumor Lysis Syndrome for Patients receiving Lenalidomide
   a. All subjects meeting criteria of laboratory TLS or >/= Grade 1 TLS according to the Cairo-Bishop Definition of Tumor Lysis Syndrome (see Appendix D) should receive vigorous intravenous hydration and should be considered for rasburicase therapy as needed to reduce hyperuricemia, until correction of electrolyte abnormalities.
      i. In cases of laboratory TLS and Grade 1 TLS (see Appendix D: Cairo-Bishop Definition of Tumor Lysis Syndrome), lenalidomide will be continued at the same dose without interruption or dose reduction. TLS prophylaxis measures outlined in Lenalidomide Maintenance should be continued or re-instituted.
      ii. Subjects with >/= Grade 2 TLS (see Appendix D: Cairo-Bishop Definition of Tumor Lysis Syndrome) will be managed as follows in addition to intravenous hydration and consideration for rasburicase therapy (above).
         1. Hold (interrupt) treatment.
         2. First episode: restart lenalidomide at the current dose with appropriate TLS prophylaxis after resolution of electrolyte abnormalities to Grade 0
         3. Subsequent episodes: restart lenalidomide with appropriate TLS prophylaxis after resolution of electrolyte abnormalities to Grade 0. At physician discretion, the lenalidomide dose may be restarted at the current dose or lenalidomide may be reduced by 1 dose level.
         4. First or subsequent episodes: subjects should be closely monitored for signs of TLS after resuming treatment. To monitor for TLS, serum chemistry and uric acid tests should be performed at least every week following initiation of lenalidomide for 4 consecutive weeks and on Day 3 or 4 following initiation of lenalidomide.

5. Tumor Flare Reaction (TFR)
   a. Prophylaxis for TFR is not recommended for patients who receive lenalidomide.
      i. Grade 1 TFR may be treated with NSAIDs (i.e. ibuprofen 400-600 mg orally every 4-6 hours as needed).
      ii. TFR >/= Grade 2 may be treated with corticosteroids. Narcotic analgesics may be added as needed for pain control in subjects experiencing >/= Grade 2 tumor flare.

6. Recommended Concomitant Therapy
    a. Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, antihistamines, and allopurinol when appropriate.
    b. Anticoagulation Consideration
        i. Lenalidomide increases the risk of thrombotic events in patients who are at high risk or with a history a thrombosis, in particular when combined with other drugs known to cause thrombosis.
        ii. When lenalidomide is combined with other agents such as steroids (e.g. dexamethasone, prednisone), anthracyclines (Doxil, Adriamycin) and erythropoietin the risk of thrombosis is increased.
        iii. For this study, patients will receive one aspirin (81 mg) a day while on lenalidomide. Low molecular weight heparin may be utilized in patients that are intolerant to aspirin. Coumadin should be used with caution and close monitoring of INR.
        iv. Patients who already have a history of deep-vein thrombosis or pulmonary embolism will receive either coumadin or low-molecular weight heparin while on lenalidomide.
        v. If patients develop thrombosis or embolism while they are receiving aspirin prophylaxis, lenalidomide will be held, patients will be anticoagulated, and once a stable anticoagulation is achieved, patients with be restarted on the same dose of lenalidomide. Patients will then continue to receive either coumadin or low-molecular weight heparin as long as they continue to receive lenalidomide.

7. Prohibited Concomitant Therapy
    a. Concomitant use of sargramostim (GM-CSF), other anti-cancer therapies, including radiation, thalidomide, or other investigational agents is not permitted while subjects are receiving study drug during the treatment phase of the study. Concomitant medications will be documented in the medical record but will not be entered into the case report form.

5.0 Evaluation During Study

1. Serum pregnancy test within 10 to 14 days prior to and again within 24 hours prior to the first dose of lenalidomide for Cycles 1, 3, 5, and 7.
2. Baseline:
    a. Thyroid function tests (TSH and free T4)
    b. Total cortisol level
    c. Standard chemistries including AST, ALT, Direct and Indirect Bilirubin, Alk Phos, LDH,
    Albumin, BUN, serum creatinine, CBC
    d. For multiple myeloma patients only (within 30 days of registration): SPEP and serum IFE, UPEP and urine IFE, immunoglobulins IgA, IgG, IgM, Beta 2 microglobulin, Serum free kappa and lambda light chain assay. Bone marrow aspiration and biopsy. Bone survey.

3. Before Cycle 1 (if baseline tests and/or exam are > 7 days before start of Cycle 1):
   a. Standard chemistries including AST, ALT, Direct and Indirect Bilirubin, Alk Phos, LDH,
      Albumin, BUN, serum creatinine, CBC
   b. Physical examination and toxicity assessment
   c. Creatinine clearance. Use Cockcroft-gault formula and ideal body weight (IBW). Use adjusted body weight if >50% over IBW
4. Before Cycles 3, 5, and 7:
   a. Standard chemistries including AST, ALT, Direct and Indirect Bilirubin, Alk Phos, LDH,
      Albumin, BUN, serum creatinine, CBC
   b. Physical examination and toxicity assessment
   c. Creatinine clearance. Use Cockcroft-gault formula and ideal body weight (IBW). Use adjusted body weight if >50% over IBW
5. Day 14 (+/-2 days) in Cycles 1, 3, 5, and 7: CBC
6. Before Cycles 2, 4, 6, and 8:
   a. Thyroid function tests (TSH and free T4)
   b. Total cortisol level
   c. Standard chemistries including AST, ALT, Direct and Indirect Bilirubin, Alk Phos, LDH, Albumin, BUN, serum creatinine, CBC
   d. Physical examination and toxicity assessment (and GVHD assessment in allos)
   e. Ocular exam to assess for ocular toxicity if clinically indicated.
7. At 1 (+/- 7 days), 3 (+/- 10 days), 6 (+/- 15 days) months, and (+/- 30 days) for months 12, 24, and 36 after last dose of ipilimumab and/or when clinically indicated:
   a. Physical examination and toxicity assessment.
   b. Assessment for toxicity (through 30 days after last dose of study drug)
   c. Assessment for GVHD (in allogeneic patients)
   d. Thyroid function tests (TSH and free T4)
   e. Total cortisol level
   f. Standard chemistries including AST, ALT, Direct and Indirect Bilirubin, Alk Phos, LDH, Albumin, BUN, serum creatinine, CBC
   g. Bone marrow aspiration and biopsy, CT scan, PET/CT scan depending on patient's type of hematologic or lymphoid malignancy
   h. For multiple myeloma patients only: SPEP and serum IFE, UPEP and urine IFE, immunoglobulins IgA, IgG, IgM, Beta 2 microglobulin, Serum free kappa and lambda light chain assay at each visit.
      Bone marrow at 1 month follow-up and as clinically indicated.
      Bone survey (+/- 30 days) for months 12, 24, and 36 after last dose of ipilimumab and/or when clinically indicated.

8. The International Working Group Response Criteria (Appendix I.) will be used.
9. We will use the International Myeloma Working Group (IMWG) uniform response criteria for multiple myeloma patients. All response categories require no known evidence of progressive or new bone lesions.

   International Myeloma Working Group uniform response criteria.
   All response categories require two consecutive assessments made at any time.
   All response categories require no known evidence of progressive or new bone lesions.

Stringent complete response (sCR) (all of the following):
1. CR as defined.
2. Normal free light chain ratio
3. Absence of clonal cells in bone marrow by inmmunohistochemistry or immunofluorescence (defined by absence of abnormal k/l ratio of > 4:1 or <1:2)

Complete response (CR) (all of the following):
1. Negative immunofixation in serum and urine.
2. £ 5% plasma cells in the bone marrow.
3. Disappearance of any soft tissue plasmacytomas.

Note: While healing of pre-existing bone lesions is not required, no new lytic lesions should appear. Further compression fracture of previously known spine lesion will not be considered as progressive disease.

Very good partial response (VGPR) (one of the following):
1. Serum and urine M protein detectable by immunofixation but not by electrophoresis.
2. 90% or greater reduction in serum M protein plus urine M protein level < 100 mg per 4h.

Partial response (PR) (all of the following):
1. Reduction by > 50% in serum monoclonal protein.
2. Reduction of urinary monoclonal protein to < 200 mg/24h or > 90%.

Stable disease:
1. Not meeting criteria for CR, VGPR, PR or PD.

Progressive disease (PD) (any one or more of the following):
1. Increase of ³ 25% from baseline in:
   Serum M protein (absolute increase must be ³ 0.5 g/dL).
   Urine M component (absolute increase must be ³ 200 mg/24h). Only in patients without measurable serum and urine M protein levels.
   Difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL).
   Bone marrow plasma percentage (absolute % must be ³ 10%).
2. Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
3. Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mol/L) that can be solely attributed to the myeloma.

Relapse from CR (any one or more of the following):
1. Reappearance of serum or urine M protein by immunofixation or electrophoresis.
2. Development ³ 5% plasma cells in the bone marrow.
3. Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion or hypercalcemia).

6.0 Background Drug Information

See package inserts for YERVOY® (ipilimumab) in Appendix E. and REVLIMID® (lenalidomide) in Appendix F.

7.0 Statistical Considerations

Overview
The primary objective of this study will be to assess the safety of lenalidomide alternating with ipilimumab in stem cell transplantation. Patients will receive lenalidomide alternating with ipilimumab for 8 cycles (lenalidomide for 21 days, then one dose of ipilimumab, then repeat lenalidomide 4 weeks later, etc.). The starting and highest allowable dose of lenalidomide in this study will be 10 mg/d. Dose reductions to 5 mg may be allowed within patient based on clinical practice. Ipilimumab is fixed at 3 mg/kg. If the starting combination of lenalidomide 10 mg/d and ipilimumab 3 mg/kg results in toxicity, as defined below in the toxicity monitoring rule, in the first 3 of 3 patients, subsequent patients will be started at a lower combination dose of lenalidomide 5 mg/d and ipilimumab 3 mg/kg.

Secondary objectives include assessing overall response rate, overall survival, progression-free survival, and the cumulative incidence of acute and chronic GVHD with the competing risk of relapse in allogeneic transplant patients.

Safety Monitoring
We expect to accrue a total of 40 transplant patients onto two arms: Autologous (N=25) and allogeneic (N=15). All patients will receive lenalidomide alternating with ipilimumab (L+I). Each transplant arm will be monitored separately using monitoring rules for toxicity. The following stopping rules and boundaries were developed using the Multc Lean Desktop application (version 2.1.0) in the Biostatistics department.

The Principal Investigator and assigned Research Nurse will review the enrolled patients monthly while on active treatment to assess adverse events and stopping rules. The Biostatistician will be consulted as necessary. The data monitoring plan will be provided by the MD Anderson IND Office. This office is responsible to monitor the protocol conduct and data entry.

Toxicity monitoring rules: Each transplant arm (either autologous or allogeneic) will be monitored separately for toxicity. If there is a high probability of observing more than a 30% toxicity rate in either arm, that arm will be stopped. Toxicity for this stopping rule will include the following, at any time during active study treatment, which is defined as the first eight cycles plus 30 days following the last dose of study drug:

- Any grade 4 hematological toxicity at least probably related to study drug that does not resolve within 2 weeks
- Any immune-mediated reaction to ipilimumab that requires permanent cessation of the drug

- Any other grade 3-5 organ toxicity at least probably related to study drug
- (Allogeneic arm only) Any acute grade III or higher GVHD.

Bayesian sequential monitoring[7] will be employed to perform interim safety monitoring targeting a toxicity rate of not more than 30%. Patients will be monitored in cohorts of 1.

Autologous Arm

For the autologous arm, accrual will be stopped early if

$$Pr [prob(toxicity) > 0.30 | data] > 0.975$$

That is, if we determine that there is a greater than 97.5% chance that the toxicity rate is greater than 30% in this arm, then accrual will be stopped. We assume a beta (0.6, 1.4) prior distribution for the toxicity rate, which has a mean of 0.3 corresponding to the 30% target toxicity rate. Stopping boundaries corresponding to this probability criterion are to terminate accrual in autologous patients if

If there are this many (or more) patients in the autologous transplant arm with Toxicity	**Stop the arm if this many patients in the arm**
3	3
4	4-5
5	5-7
6	6-9
7	7-11
8	8-13
9	9-16
10	10-18
11	11-21
12	12-23
13	13-24
14	ALWAYS STOP

Patients must complete at least two cycles of treatment or have toxicity to be included in the rule. Patients who complete at least two cycles but drop out without experiencing toxicity will be included but not counted as toxicities. If accrual onto this arm is stopped, the study will continue enrolling patients to the allogeneic transplant arm.

The rule will reset at lenalidomide 5 mg if the first 3 of 3 patients at the combination 10 mg lenalidomide dose experience toxicity. If the rule resets after the first three patients, we will continue to enroll up to 25 patients in the autologous arm at the lower combination dose using lenalidomide 5 mg. The Biostatistical collaborator will be consulted as necessary.

The operating characteristics of this rule are shown below.

Table 1. Operating Characteristics for Toxicity Stopping Rule in Autologous Arm

		Achieved Sample Size Percentiles		
If the true toxicity rate is...	**Early Stopping Probability**	**25th**	**50th**	**75th**
0.1	0.0014	25	25	25
0.2	0.0163	25	25	25
0.3	0.0891	25	25	25
0.4	0.3013	18	25	25
0.5	0.6324	7	16	25
0.6	0.8929	5	9	16
0.7	0.9872	3	5	9

Allogeneic Arm

For the allogeneic arm, accrual will be stopped early if

$$\Pr [\text{prob(toxicity)} > 0.30 \mid \text{data}] > 0.95$$

That is, if we determine that there is a greater than 95% chance that the toxicity rate is greater than 30% in this arm, then accrual for this arm will be stopped. We assume a beta (0.6, 1.4) prior distribution for the toxicity rate, which has a mean of 0.3 corresponding to the 30% target toxicity rate. Stopping boundaries corresponding to this probability criterion are to terminate accrual in allogeneic patients if

If there are this many (or more) patients in the allogeneic transplant arm with Toxicity	**Stop the arm if this many patients in this arm**
3	3-4
4	5-6
5	7-9
6	10-11
7	12-13
8	14-15
9	ALWAYS STOP

Patients must complete at least two cycles of treatment or have toxicity to be included in the rule. Patients who complete at least two cycles but drop out without experiencing toxicity will be included but not counted as toxicities. If accrual onto this arm is stopped, the study will continue enrolling patients to autologous arm.

The rule will reset at lenalidomide 5 mg if the first 3 of 3 patients at the combination 10 mg lenalidomide dose experience toxicity. If the rule resets after

the first three patients, we will continue to enroll up to 15 patients in the allogeneic arm at the lower combination dose using lenalidomide 5 mg. The Biostatistical collaborator will be consulted as necessary.

The operating characteristics of this rule are shown below.

Table 2. Operating Characteristics for Toxicity Stopping Rule in Allogeneic Arm

		Achieved Sample Size Percentiles		
If the true toxicity rate is...	**Early Stopping Probability**	**25th**	**50th**	**75th**
0.1	0.0016	15	15	15
0.2	0.0210	15	15	15
0.3	0.0998	15	15	15
0.4	0.2780	14	15	15
0.5	0.5367	7	12	15
0.6	0.7866	3	7	12
0.7	0.9406	3	5	7

Primary Objective

We will estimate the toxicity rate in each arm along with a corresponding 95% credible interval. In addition, toxicity will be summarized by arm, type, and grade.

Secondary Objectives

For secondary objectives, we will estimate response at the end of eight cycles and overall with a 95% confidence interval. We will also estimate specific response types such as humoral and cellular. This data will be used to inform future studies using higher dose combinations. With 15 patients assigned to a transplant arm, if the response rate is 20%, an asymptotic 95% confidence interval will be (0, 0.402). With 25 patients assigned to a transplant arm, if the response rate is 20%, an asymptotic 95% confidence interval will be (0.043, 0.357).

Kaplan-Meier[10] survival curves will be used to estimate overall survival and progression-free survival. We will also assess the rates of acute and chronic GVHD, other organ toxicity, and secondary immune-based diseases such as arthritis, lupus, and thyroid dysfunction. We will use the method of Gooley et al[11] to estimate the cumulative incidence of acute and chronic GVHD with the competing risk of relapse in allogeneic transplant patients. Cox proportional hazards regression analysis will be used to model the association between overall survival and progression-free survival and disease and demographic covariates of interest, including data from the correlative cytokine, immune, and pharmacokinetic studies.

Summary/Cohort Reports

The Principal Investigator is responsible for completing a safety/efficacy summary report, and submitting it to the IND Office Medical Affairs and Safety Group, for review and approval. This should be submitted after the first 3 evaluable patients per cohort, complete 30 days after the last dose of study treatment, and prior to changing dose levels; and every patient per cohort, thereafter.

A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

8.0 Reporting Requirements

8.1 Expected Adverse Events and Grading

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial

The research team will ensure that all adverse events are entered into the study case report form CORe/PDMS. All adverse events entered into the case report form must have a verifiable source document that is maintained in the subject's medical record. PDMS/CORe will be used as the electronic case report form for this protocol.

1. All patients will be registered in CORe
2. The severity of the adverse events (AEs) will be graded according to the Common Terminology Criteria v4.0 (CTCAE)
3. For the purpose of causality:
   a. Known adverse events of lenalidomide and ipilimumab will be reported as **definitely** related.
   b. When the relationship of the adverse event cannot be ruled out with certainty the AE may be considered **probable or possible related**.
   c. Adverse events known to be related to drugs used for supportive treatment will be scored as **unrelated**.
   d. The principal investigator will be final arbiter in determining causality assessment.

8.2 Adverse events considered serious

1. Graft Failure/rejection.
2. Any expected or unexpected event resulting in an irreversible condition and/or leading to death.

8.3 Serious Adverse Event Reporting (SAE)

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

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse

experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- **Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.**

- **Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.**

- **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.**

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

9.0 Criteria for Removal from the Study

9.1 Completion of study. This is defined as three years after the last dose if Ipilimumab.
9.2 Disease progression.
9.3 Intolerable side effects.
9.4 Unable to follow study directions.
9.5 Withdrawal of consent.

10.0 References

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