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Phase II Study of Lenalidomide in Combination with Nivolumab In Patients with Relapsed/Refractory Multiple Myeloma

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PROTOCOL SYNOPSIS

Study Title	**Phase II Study of Lenalidomide in Combination with Nivolumab in Patients with Relapsed/Refractory Multiple Myeloma**
Study ID	
Sponsor	American Cancer Society
Primary Objectives	To determine the efficacy of Nivolumab in combination with lenalidomide (Revlimid) in terms of overall response rate in patients with relapse/refractory multiple myeloma (MM)
Primary Endpoint	• To determine the overall response rate (ORR) after 4 cycles and then at 8 and 12 months in responding patients according to the International Myeloma Working Group (IMWG) response criteria in the phase II study.
Secondary Endpoints	• To determine time to progression (TTP) and progression free survival (PFS) • To determine overall survival (OS) • To assess Nivolumab correlative biologic studies to assess immunomonitoring of lymphocytes subsets including T and NK cell, and *ex-vivo* assessment of immune functional activities.
Safety parameters	Infusion related and treatment emergent toxicities per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0
Study Design	Nivolumab will be administered intravenously as a 1-hour infusion, 240 mg every 2 weeks (day 1 and 15) of each 28 day cycle. At the treating physician's discretion, patients will receive pre-medication (Tylenol 650mg or Ibuprofen 800mg or related medication), and an antihistamine (phenergan 25mg or equivalent) before Nivolumab infusion. Lenalidomide will be given at starting dose of 25 mg days 1-21 of a 28 day cycle. Patients will be assessed for response at the end of each cycle according to the IMWG response criteria. Patients will be monitored for safety by assessing toxicities as graded by the NCI CTCAE v4.0. Dose limiting toxicity (DLT) will be defined as one or more of the following toxicities considered to be at least possibly related to one of the study drugs during Cycle 1 • Grade 3 or greater nonhematologic toxicity with the exception of Grade 3 nausea, vomiting and diarrhea that responds to supportive therapy. • Grade 4 thrombocytopenia, or grade 3 thrombocytopenia with bleeding, or any requirement for platelets transfusion • Grade 4 neutropenia persisting for more than 5 days. • Grade 3 or greater febrile neutropenia (temperature ≥ 38.5 °C) • Grade 4 anemia, unexplained by underlying disease Patients that experience a lenalidomide-related hematologic DLT may continue on therapy if the event resolves, the investigator considers it in the best interest of the patient to continue and the patient qualifies for initiation of the next cycle with standard of care lenalidomide dose reduction.

	Discontinuation of treatment due to disease progression will not constitute a DLT. After 4 cycles of therapy or earlier if clinically indicated, response determination will be assessed by the IMWG criteria. At the end of Cycle 4, if a subject has responded (complete or partial response) or has stable disease, dosing with Nivolumab and lenalidomide will continue for a minimum of 8 additional cycles or until disease progression or withdrawal. If disease progression is observed at the end of Cycle 4 evaluation, all study therapy will be discontinued. Confirmation of progression of disease will be done according to the IMWG criteria. Following the 30-day post-treatment follow-up assessment, additional evaluations will occur once per month (unless subject discontinued due to progression) until the earliest of the following events: disease progression, the time of initiation of new therapy, death or study completion. Study completion is defined as 30 days after the last subject remaining on study medication discontinues study medication. An independent Data Monitoring Committee will continue oversight of this trial. Treatment will continue until Progression of disease, death, unacceptable toxicity or patient or treating physician decision to discontinue therapy.
Dosing Regimen	Nivolumab will be given at a dose of 240 mg every 2 wks (Day 1 and 15) of a 28-day cycle. Lenalidomide will be given at starting dose of 25 mg days 1-21 of a 28 day cycle. Dexamethasone can be added after 2 cycles if stable disease.
Planned Sample size	18 patients will be recruited
Duration of Study Period	Patient will continue study treatment at the treating physician's discretion. Patients achieving at least a stable disease can continue treatment until progression of disease, death, unacceptable toxicity, or patient decision. Overall response will be assessed after 4, 8, and 12 cycles. The total study enrollment period is expected to be up to 12-18 months.
Eligibility	**Inclusion criteria** • Patients must be at least 18 years of age with evidence of progression, relapse or refractory disease from last line of therapy as defined by IMWG criteria and measurable disease as defined by any of the following: o Serum M-protein ≥0.5 g/dl (≥10 g/l) o Urine monoclonal protein ≥ 200 mg/24h o Involved FLC level ≥ 10mg/dl (≥ 100mg/l) and an abnormal serum free light chain ratio (<0.26, or >1.65)

Measurable biopsy proven plasmacytoma (should be measured within 28 days of initial investigational agent dosing)

- Patients must have exhausted all available therapies known to provide clinical benefit and has progressed, relapsed or is refractory to last line of treatment.
- Patients must have had at least 4 prior lines of therapy.
- Patient may be enrolled at any time from last line of therapy
- Patients must have ANC > 1000/μL; Platelets ≥75,000/μL, if plasma cell percentage on bone marrow biopsy aspirate or core is > 30%, platelet eligibility requirement will be adjusted to 60,000/ul.
- Patients must have adequate hepatic function as evidenced by: total bilirubin ≤ 1.5 mg/dL, alkaline phosphatase ≤ 3X the ULN, AST/ALT ≤ 2X the ULN
- Patients must have adequate renal function as evidenced by serum creatinine ≤ 2mg/dL or calculated creatinine clearance of ≥ 40ml/min within 14 days of registration using MDRD formula.
- Patient must be able to swallow capsule or tablet.
- Patients must provide informed consent.
- Patients must have a left ventricular ejection fraction ≥ 30%, no uncontrolled arrhythmias or New York Heart Association class III-IV heart failure.
- Patients must have a Karnofsky performance status ≥ 70.
- A negative pregnancy test will be required for all women of child bearing potential. Breast feeding is not permitted.
- Fertility requirements
  - Female patients with child bearing potential must have a negative pregnancy test at least 7 days before starting treatment drugs.
  - Male patients must agree to use an adequate method of contraception for the duration of the study and for 7 months afterwards.
  - Female patients must be either post-menopausal, free from menses ≥2 yrs, surgically sterilized, willing to use two adequate barrier methods of contraception to prevent pregnancy, or agree to abstain from sexual activity starting from screening and for 5 months afterwards.
  - Female patients of child bearing potential must agree to comply with the fertility and pregnancy test requirements dictated by the Rev-Assist program.

Exclusion Criteria

- Patients with peripheral neuropathy > CTCAE grade 2
- Patients receiving concurrent corticosteroids at the time protocol therapy is initiated other than for physiologic maintenance treatment.
- History of allergic reaction (including erythema nodosum) to lenalidomide
- Concurrent use of complementary or alternative medicines that would confound the interpretation of toxicities and antitumor activity of the study drugs.
- Patients with contraindication to thromboprophylaxis
- Unacceptable cardiac risk factors defined by any of the following criteria: Patients with congenital long QT syndrome, any history of ventricular fibrillation

	or torsade de pointes, bradycardia defined as HR< 50 bpm, Left ventricular ejection fraction < 30% • Patients who have received targeted or investigational agents within 2 weeks or within 5 half-lives of the agent and active metabolites (whichever is longer) and who have not recovered from side effects of those therapies. • Patients who have undergone major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from the side-effects of surgery • Patients with known positivity for human immunodeficiency virus (HIV), or hepatitis C. Baseline testing for HIV and hepatitis C is not required • Patients with a history of another primary malignancy that is currently clinically significant or currently requires active intervention, other than non-melanoma skin cancer and carcinoma in situ of the cervix should not be enrolled. Patients are not considered to have a "currently active" malignancy if they have completed therapy for a prior malignancy, are disease free from a prior malignancy for ≥ 5 yrs and are considered by their physician to be less than 30% risk of relapse. • Patients with active (untreated or relapsed) CNS metastasis of the patient's myeloma. • Patients with a history of gastrointestinal surgery or other procedure that might, in the opinion of the investigator(s), interfere with the absorption or swallowing of the study drugs. • Patients with any significant history of non-compliance to medical regimens or unwilling or unable to comply with the instructions given to them by the study staff. • Any other medical condition, including mental illness or substance abuse, deemed by the investigator(s) to likely interfere with the patient's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results.

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1 BACKGROUND AND RATIONALE

1.1 Multiple Myeloma

Multiple myeloma (MM) is the second most common hematological malignancy with approximately 22,000 new cases diagnosed each year in the United States. MM is associated with profound and widespread disarray of both the adaptive and innate arms of the immune system[1] specifically including: loss of effector T cell function[2,3], defective maturation and function of antigen presenting cells,[4,5] increased levels of regulatory T cells (Treg),[6] humoral immune deficiency, as well as natural killer (NK) cell immunity.[7,8] . This immunosuppressive milieu, in turn, is crucial to promoting disease progression as both T cell[8] and NK cell[9] mediated tumor-specific immune responses have been demonstrated in early MM; however, these effects are lost in the inexorable progression of the disease.[9,10] Moreover, most standard treatment options (including chemotherapy, radiation, and high-dose corticosteroids) offer only modest benefit, and also contribute to further immune suppression. Due to both disease-related and treatment-related immune compromise, infection remains the most common cause of death for pts with MM.[11] Until recently, little has been known regarding the mechanisms by which immune dysfunction and immunoevasion occur.

1.2 NK cells and MM

NK cells CD56(+),CD3(-) are large granular lymphocytes that comprise a key cellular compartment of the innate immune system, and have been shown to exert anti-tumor activity against the malignant plasma cell clone in MM[12-14]. In fact, both lenalidomide and bortezomib have been shown to confer anti-MM efficacy, in part, through recovery or enhancement of the NK cell versus MM effect[15,16]. However, as the disease progresses, the NK cell versus MM effect is attenuated through a number of established mechanisms including reduced NK cell activity and increased levels of soluble interleukin-2 receptors and impaired NK cell function by inhibitory effect of M-component[6,7,17.]

1.3 Lenalidomide (Revlimid)

Lenalidomide (Revlimid®), a thalidomide analogue, is an immunomodulatory agent with antiangiogenic properties. It's mechanism of action remains to be fully characterized. Lenalidomide inhibited the secretion of pro-inflammatory cytokines and increased the secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells. Of cell lines tested, lenalidomide was effective in inhibiting growth of Namalwa cells (a human B cell lymphoma cell line with a deletion of one chromosome 5) but was much less effective in inhibiting growth of KG-1 cells (human myeloblastic cell line, also with a deletion of one chromosome 5) and other cell lines without chromosome 5 deletions. Lenalidomide inhibited the expression of cyclooxygenase-2 (COX-2) but not COX-1 in vitro. Lenalidomide) is indicated for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. lenalidomide in combination with dexamethasone is indicated for the treatment of newly diagnosed multiple myeloma patients and those who have received at least one prior therapy.

1.3.1 Clinical Experience in Relapsed Multiple Myeloma

A multicenter, open-label, randomized phase 2 study evaluated 2 doses of lenalidomide for relapsed, refractory multiple myeloma patients. Seventy patients were randomized to receive oral lenalidomide either 30 mg once-daily or 15 mg twice-daily for 21 days of every 28-day cycle. Patients with progressive or stable disease after 2 cycles received dexamethasone. Analysis showed an increased grade 3/4 myelosuppression in patients receiving 15 mg twice daily as compared to those receiving

30mg daily (41% versus 13%, P= .03). Responses were evaluated according to European Group for Blood and Marrow Transplantation (EBMT) criteria. Overall response rate (complete, partial, or minor) to lenalidomide alone was 25% (24% for once daily and 29% for twice-daily lenalidomide). Median overall survival (OS) in the 30-mg once-daily and twice-daily groups was 28 and 27 months, respectively. Median progression free survival was 7.7 months on once-daily versus 3.9 months on twice-daily lenalidomide (P = 0.2). Dexamethasone was added in 68 patients and 29% responded. Time to first occurrence of clinically significant grade 3 / 4 myelosuppression was shorter in the twice daily group (1.8 vs 5.5 months, P = .05). Significant peripheral neuropathy and deep vein thrombosis each occurred in only 3%. Lenalidomide was active and well tolerated in relapsed, refractory myeloma, with the 30-mg once-daily regimen providing the basis for future studies as monotherapy and with dexamethasone[18].

In a safety and efficacy study of single agent lenalidomide in relapsed and refractory multiple myeloma patients, lenalidomide 30 mg (days 1-21 of 28 day cycle) was given to 222 patients who had relapsed or progressed after 1 or more prior therapies[19]. Sixty-seven percent of patients had had three or more prior therapies, and 45% had had one or more autologous stem cell transplants. Eighty and 43% of patients had had thalidomide and bortezomib based therapies respectively. The median dose of lenalidomide was 25 mg (5-30mg) and the median duration of treatment was 4.2 months (0.06-38). The overall response rate (complete and partial) was 26% with 2% complete response[19].

Two phase III trials comparing lenalidomide + dexamethasone to single agent dexamethasone in patients with relapsed and/or refractory multiple myeloma were published[20,21]. Patients who had received 1-3 prior therapies, and progressing on their last therapy were randomized to receive lenalidomide, 25 mg daily on days 1-21, placebo on days 22-28 plus dexamethasone, 40 mg, d 1-4, 9-12, 17-20, every 28 day cycle, or placebo daily for 28 days plus dexamethasone, 40 mg, d 1-4, 9-12, 17-20, every 28 days. The responses reported are summarized in **Table 1-1** while the incidence of DVT and pulmonary embolism are summarized in **Table 1-2**. Anemia, thrombocytopenia, neutropenia, fatigue, neuropathy, and constipation were also observed more often in lenalidomide + dexamethasone group compared to dexamethasone only group, however these events were generally manageable.

Table 1-1.

Response Rates in Phase III Trials of Relapse refractory MM

	Weber et al (NEJM 2007)			Dimopoulos et al (NEJM 2007)		
	Lenalidomide + Dexa (n=177)	Dexa Alone (n=176)	*P* Value	Lenalidomide + Dexa (n=176)	Dexa Alone (n=175)	*P* Value
Overall Response Rate (%)	108 (61)	35 (20)	<0.001	106 (60.2)	42 (24)	<0.001
Complete Response	14.1%	0.6%	<0.001	15.9%	3.4%	<0.001
Median TTP (mo.)	11.1	4.7	<0.001	11.3	4.7	<0.001
Median OS (mo.)	29.6	20.2	<0.001	Not Reached	20.6	0.03

Table 1-2

DVT & PE Risks in Phase III Trials of Relapse refractory MM

	Weber et al		Dimopoulos et al	
	Lenalidomide + Dexamethasone	Dexamethasone Alone	Lenalidomide + Dexamethasone	Dexamethasone Alone
Deep Vein Thrombosis (%)	11.9	3.4	4.0	3.5
Pulmonary Embolism (%)	3.4	0.6	4.4	1.2

The dexamethasone used in the above two studies is considered high dose. A phase III study compared lenalidomide plus high-dose dexamethasone (doses and schedule as described above) to lenalidomide (dose and regimen as above) plus low-dose dexamethasone (40 mg given on days 1, 8, 15, 22 of 28 day cycle) in newly diagnosed multiple myeloma patients. Overall survival at 1 year was 96% for the low-dose dexamethasone compared to 87% for the high-dose dexamethasone (P=0.0002). As a result, the trial was stopped and patients on the high-dose therapy were crossed over to the low-dose therapy[22]. Subsequently most therapies involving dexamethasone, uses low-dose.

1.4 Nivolumab

Nivolumab (BMS-936558, ONO-4538, or MDX1106, trade name Opdivo; Bristol-Myers Squibb, Princeton, NJ, USA) is the first-in-human immunoglobulin G4 (IgG4) PD-1 immune checkpoint inhibitor antibody that disrupts the interaction of the, PD-1 receptor with its ligands PD-L1 and PD-L2, thereby inhibiting the cellular immune response [23-25]. Nivolumab binds PD-1 with high affinity (KD=2.6 nmol/L by Scatchard analysis to polyclonally activated human T cells), blocks its interactions with both PD-L1 and PD-L2, and stimulates memory response to tumor antigen-specific T cell proliferation[26,27]. Nivolumab has been approved by the US Food and Drug Administration (FDA) for the treatment of melanoma, renal cell carcinoma, squamous cell and metastatic non-small cell lung cancer[28,29].

1.4.1 Nivolumab: Clinical studies in Hematologic Malignancy

A phase 1 study of patients with relapsed or refractory hematologic cancers were treated with nivolumab at a dose of 1 mg per kilogram of body weight, with escalation of the dose to 3 mg per kilogram[30]. Since the maximum tolerated dose was not reached, a dose of 3 mg per kilogram was chosen for the expansion cohorts that included the 23 HL patients. Patients with relapsed or refractory HL received nivolumab at a dose of 3 mg per kilogram at week 1, week 4, and then every 2 weeks until disease progression or complete response or for a maximum of 2 years. Drug-related adverse events of any grade and of grade 3 occurred in 78% and 22% of patients, respectively (Table). No grade 4 or 5 drug-related adverse events were reported. Two patients (9%) had infusion interruptions that were due to grade 1 hypersensitivity reactions. An objective response was reported in 20 patients (87%), including 17% with a complete response and 70% with a partial response; the remaining 3 patients (13%) had stable disease. The rate of progression-free survival at 24 weeks was 86%; 11 patients were continuing to participate in the study. Reasons for discontinuation included stem-cell transplantation (in 6 patients), disease progression (in 4 patients), and drug toxicity (in 2 patients) [30].

1.4.2 Toxicity of Nivolumab in Hematologic Malignancies

Adverse Events of 23 Hodgkins Lymphoma Patients

Adverse Events(AE)	Any grade (%)	Grade 3 (%)
Any adverse event	18(78)	5(22)
Rash	5(22)	0
Decreased platelet	4(17)	0
Fatigue	3(13)	0
Pyrexia	3(13)	0
Diarrhea	3(13)	0
Nausea	3(13)	0
Cough	2(9)	0
Hypothyroidism	2(9)	0
Decreased lymphocyte count	2(9)	1(4)
hypophosphatemia	2(9)	0
Hypercalcemia	2(9)	0
Increased Lipase level	2(9)	1(4)
Stomatitis	2(9)	1(4)
Drug-related SAE		
Myelodysplastic syndrome	1(4)	1(4)
Lymph node pain	1(4)	0
Pancreatitis	1(4)	1(4)

A phase I open-label dose escalation evaluated 81 patients with non-hodgkins lymphoma (31), T-cell lymphomas (23) and multiple Myeloma (27) with relapsed or refractory disease[31]. Patients were treated with nivolumab 1 or 3 mg/kg administered as a 1-h infusion at weeks 1 and 4 and then every 2 weeks for up to 2 years. Because the maximum tolerated dose of nivolumab was not reached at the highest protocol specified dose, patients in the cohort expansion were treated with nivolumab 3 mg/kg. Seventy-nine (96%) patients experienced at least one AE. Drug-related AEs of any grade were reported in 53 (65%) patients (Table). Fifteen (18%) patients had grade 3 drug related AEs, two had grade 4 AEs, and one had a grade 5 AE. Three patients (4%) had hypersensitivity or infusion reaction). The majority of response was stable disease in 17(63%) patients and 1(4%) complete response[31].

Drug-Related Adverse Events

Adverse Events(AE)	Any grade (%)	Grade ≥3 (%)
By tumor type		
B-cell NHL(n=31)*	22(71)	8(26)
T-Cell (n=23)	17(74)	5(22)
Multiple Myeloma(n=27)	14(52)	5(19)
Any adverse event in ≥5%		
Fatigue	14(17)	0
pneumonitis	9(11)	3(4)
Decreased appetite	7(9)	0
Pruritus	7(9)	0
Rash	7(9)	1(1)
Diarrhea	6(7)	0
Pyrexia	6(7)	0
Hypocalcemia	5(6)	0
Blood creatine phosphokinase increase	3(4)	1(1)
Lipase increase	3(4)	1(1)
Mucosal inflammation	3(4)	1(1)

Stomatitis	2(2)	1(1)
Diplopia	1(1)	1(1)
Pneumonia	1(1)	1(1)
Pulmonary embolism	1(1)	1(1)
Rash pustular	1(1)	1(1)
Sepsis	1(1)	1(1)
ARDS^	1(1)	1(1)
Hematologic		
Anemia	5(6)	3(4)
Leukopenia	4(5)	3(4)
Lymphopenia	3(4)	1(1)
Neutropenia	3(4)	1(1)
Eosinophilia	1(1)	1(1)
Lymphocyte decrease	1(1)	1(1)
Select AEs		
Skin(pruritis, rash)	15(18)	1(1)
Pulmonary(pneumonitis)	9(11)	3(4)
Gastrointestinal(diarrhea, enteritis)	6(7)	0
Hypersensitivity(hypersensitivity, infusion reaction)	3(4)	0
Hepatic(ALT or AST increase)	2(2)	0
Renal(blood creatinine increase)	2(2)	0

*One grade 5 event was observed (pneumonitis/ARDS).
^ Event was grade 5

1.4.3 Nivolumab and lenalidomide in multiple myeloma

Lenalidomide (Revlimid ®, Celgene) exerts efficacy in part through enhancement of the NK cell versus MM effect an effect likely mediated through T cell production of interleukin (IL)-2 in response to the drug[15,32]. Numbers of both T cells and NK cells are increased in patients receiving IMID therapy[33]. NK cell killing is also enhanced including antibody-dependent cellular cytotoxicity (ADCC) and natural NK cell cytotoxicity[33,34]. These events correlate with clinical responses to IMID therapy in patients[33]. Preclinical studies support the combination of PD-1/PD-L1 antibodies with immunomodulatory (IMID) agents such as lenalidomide[35]. Nivolumab, as a single-agent, has established safety and tolerability in patients with previously treated myeloma with disease stabilization observed in many patients[31]. One abstract suggests that the efficacy of nivolumab may be enhanced in the clinical setting in combination with IMIDs[36]. The combination of lenalidomide with another antibody that interacts with PD-1 (CT-011; MDV9300) in relapsed and refractory MM showed an ORR 61.5%[37]. lenalidomide/dexamethasone with another PD-1 blocking antibody (pembrolizumab) demonstrated an ORR of 50% in relapsed/refractory myeloma[38].

1.5 Study rationale

Two phase III studies have shown improved overall response rate (ORR), time to progression (TTP) or progression free survival (PFS), and overall survival (OS) in relapsed MM patients treated with lenalidomide (25mg days 1-21 q 28 days) and high dose dexamethasone (40mg days 1-4, 9-12 and 17-20) as compared to dexamethasone alone[20,21]. Using low dose dexamethasone (40mg days 1, 8, 15, 22) with lenalidomide showed superior OS as compared to high dose dexamethasone with lenalidomide mainly due to much reduced toxicity[39]. The response to the combination was shown even in patients with prior thalidomide use[40], however, response is better if used earlier than later[41]. While lenalidomide as a single agent has also shown some response in relapse MM patients, short of a randomized study, its effectiveness seems to be less than the combination with dexamethasone[19].

While the ORR, median PFS and median OS for relapsed MM patients have improved with agents like lenalidomide many patients still relapse. Hence newer agents to augment current ones are urgently needed.

Myeloma cells express PD-L1 and effector lymphocytes express PD-1 in myeloma. Preclinical studies support the combination of PD-1/PD-L1 antibodies with immunomodulatory (IMID) agents such as lenalidomide[35]. Nivolumab, as a single-agent, has established safety and tolerability in patients with previously treated MM with disease stabilization observed in many patients[31]. In addition to the studies outlined previously, studies of lenalidomide / dexamethasone with nivolumab are recruiting in high-risk smoldering myeloma (NCT02903381), in relapsed/refractory MM (NCT01592370, NCT02726581). Studies of nivolumab with pomalidomide/dexamethasone in relapse and refractory MM (NCT03023527), and lenalidomide and nivolumab in lymphoma (NCT03015896) and are in process

We seek to determine the response in relapse/refractory multiple myeloma patients using nivolumab in combination with lenalidomide. Because decreased NK cell activity and enhancement may be seen with steroids[42] (although less so at low doses), patients will receive nivolumab plus lenalidomide with an option to add low-dose dexamethasone after 2 cycles if stable disease.

2 STUDY OVERVIEW AND OBJECTIVE

2.1 Study Overview

This is phase II Sargent one-stage, three-outcome design with the primary endpoint of overall response rate after 4 cycles by the IMWG criteria. Secondary endpoints include assessment of overall response rate after 8 and 12 cycles of therapy, progression-free survival, time to progression, immunomonitoring of lymphocyte subsets, including T and NK cell subsets, and *ex vivo* immune functional assays. Dexamethasone 40 mg orally weekly may be added if only stable disease after 2 cycles. Dexamethasone can be reduced to 20 mg based on tolerability or if patient is 70 years or older.

2.2 Primary Objective

To determine the efficacy of Nivolumab in combination with lenalidomide (Revlimid) in terms of overall response rate in patients with relapse/refractory multiple myeloma (MM)

2.3 Primary Endpoints

To determine the overall response rate (ORR) after 4 cycles and then at 8 and 12 months in responding patients according to the International Myeloma Working Group (IMWG) response criteria in the phase II study

2.4 Secondary Endpoints

- To determine time to progression (TTP) and progression free survival (PFS)
- To determine overall survival (OS)
- To assess Nivolumab correlative biologic studies to assess immunomonitoring of lymphocytes subsets including T and NK cell, and *ex-vivo* assessment of immune functional activities.

2.5 Safety Parameters

Infusion related and treatment emergent toxicities per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0

3 ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

- Patients must be at least 18 years of age with evidence of progression, relapse or refractory disease from last line of therapy as defined by IMWG criteria. A line of therapy is defined as one or more cycles of a planned treatment program which may be one therapy or a sequence of treatments. A new line of therapy begins when a planned course of therapy is modified due to disease progression, relapse or toxicity or when a planned period of observation off therapy. Measurable disease as defined by any of the following:
    - Serum M-protein ≥0.5 g/dl (≥10 g/l)
    - Urine monoclonal protein ≥ 200 mg/24h
    - Involved FLC level ≥ 10mg/dl (≥ 100mg/l) and an abnormal serum free light chain ratio (<0.26, or >1.65)
    - Measurable biopsy proven plasmacytoma (should be measured within 28 days of initial investigational agent dosing)
- Patients must have exhausted all available therapies known to provide clinical benefit and has progressed, relapsed or is refractory to last line of treatment.
- Patients must have had at least 4 prior lines of therapy.
- Patient may be enrolled at any time from last line of therapy.
- Patients must have ANC > 1000/μL; Platelets ≥75,000/μL, if plasma cell percentage on bone marrow biopsy aspirate or core is > 30%, platelet eligibility requirement will be adjusted to 60,000/ul.
- Patients must have adequate hepatic function as evidenced by: total bilirubin $\leq$ 1.5 mg/dL, alkaline phosphatase $\leq$ 3X the ULN, AST/ALT $\leq$ 2X the ULN
- Patients must have adequate renal function as evidenced by serum creatinine $\leq$ 2mg/dL or calculated creatinine clearance of ≥ 40ml/min within 14 days of registration using MDRD formula.
- Patient must be able to swallow capsule or tablet.
- Patients must provide informed consent.
- Patients must have a left ventricular ejection fraction ≥ 30%, no uncontrolled arrhythmias or New York Heart Association class III-IV heart failure.
- Patients must have a Karnofsky performance status $\geq$ 70.
- A negative pregnancy test will be required for all women of child bearing potential. Breast feeding is not permitted.
- Fertility requirements
    - Female patients with child bearing potential must have a negative pregnancy test at least 7 days before starting treatment drugs.
    - Male patients must agree to use an adequate method of contraception for the duration of the study and for 7 months afterwards.
    - Female patients must be either posy-menopausal, free from menses ≥2 yrs, surgically sterilized, willing to use two adequate barrier methods of contraception to prevent pregnancy, or agree to abstain from sexual activity starting from screening and for 5 months afterwards.

- Female patients of child bearing potential must agree to comply with the fertility and pregnancy test requirements dictated by the Rev-Assist program.\

3.2 Exclusion Criteria

- Patients with peripheral neuropathy > CTCAE grade 2
- Patients receiving concurrent corticosteroids at the time protocol therapy is initiated other than for physiologic maintenance treatment.
- History of allergic reaction (including erythema nodosum) to lenalidomide
- Concurrent use of complementary or alternative medicines that would confound the interpretation of toxicities and antitumor activity of the study drugs.
- Patients with contraindication to thromboprophylaxis.
- Unacceptable cardiac risk factors defined by any of the following criteria: Patients with congenital long QT syndrome, any history of ventricular fibrillation or torsade de pointes, bradycardia defined as HR< 50 bpm, Left ventricular ejection fraction < 30%
- Patients who have received targeted or investigational agents within 2 weeks or within 5 half-lives of the agent and active metabolites (whichever is longer) and who have not recovered from side effects of those therapies.
- Patients who have undergone major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from the side-effects of surgery.
- Patients with known positivity for human immunodeficiency virus (HIV), or hepatitis C. Baseline testing for HIV and hepatitis C is not required
- Patients with a history of another primary malignancy that is currently clinically significant or currently requires active intervention, other than non- melanoma skin cancer and carcinoma in situ of the cervix should not be enrolled. Patients are not considered to have a “currently active” malignancy if they have completed therapy for a prior malignancy, are disease free from a prior malignancy for ≥ 5 yrs and are considered by their physician to be less than 30% risk of relapse.
- Patients with active (untreated or relapsed) CNS metastasis of the patient’s myeloma.
- Patients with a history of gastrointestinal surgery or other procedure that might, in the opinion of the investigator(s), interfere with the absorption or swallowing of the study drugs.
- Patients with any significant history of non-compliance to medical regimens or unwilling or unable to comply with the instructions given to them by the study staff.
- Any other medical condition, including mental illness or substance abuse, deemed by the investigator(s) to likely interfere with the patient’s ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for the study.

4 SUBJECT REGISTRATION PROCEDURES

For subsite patients, sites must send the signed consent form, documentation of the consent process, and the Screening Form (refer to Supplemental Forms Document) within 2 business days of initial consent.

Patients will be registered after meeting all entry requirements and signing of the informed consent document.

OSU patients will be registered by the OSU research coordinator, as per CTO standard practice. Subsite patients will have eligibility verified and will be entered on study centrally at The Ohio State University by the Multi-Center Trial Program (MCTP). All subsites must email the MCTP to verify slot availabilities prior to consenting patients. Once a patient signs consent, the signed consent document and documentation of the consenting process must be faxed or securely emailed to the MCTP. The required forms, including Eligibility Criteria Checklist and Registration Form, can be found in the Supplemental Forms Document.

To register a subsite patient, the following documents must be completed by the subsite research team and faxed or securely e-mailed to the MCTP:

- Copy of all baseline tests required per the protocol calendar. Tests must be within the specified window.
- Signed Patient Consent Form, if not previously sent
- Signed Patient HIPAA Authorization Form (if separate), if not previously sent
- Consent Documentation Note, if not previously sent
- Completed & Signed Eligibility Checklist (refer to Supplemental Forms Document)
- Registration Form (refer to Supplemental Forms Document)
- Source documents verifying every inclusion & exclusion criteria

Upon receipt of registration documents, the MCTP will send an email confirming receipt. If confirmation of receipt is not received within 1 hour of submission, please contact the MCTP by phone and/or pager to confirm receipt.

Upon receipt of all required registration documents and upon verification the subsite patient meets all eligibility criteria, the MCTP will:

- Assign the patient a study sequence ID, if not already provided at time of consent
- Register the patient on the study
- Fax and/or e-mail the subsite the completed Registration Form with the assigned study sequence ID and registration date as confirmation of patient registration

Following registration, patients should begin protocol treatment within 3 business days. Issues that would cause treatment delays should be discussed with the Principal Investigator and MCTP as soon as possible. If a patient does not receive protocol therapy following registration, the PI and MCTP must be notified immediately within 1 business day.

Each participating institution will order study agents directly. Agents may be ordered by a participating site only after the required regulatory documents, including the initial IRB approval for the site, have been forwarded to the MCTP and all other study-specific requirements have been met (as outlined during site activation).

5 STUDY DESIGN AND DURATION

5.1 Study Design

This is a non-randomized open-label phase II study for patients with relapsed and refractory multiple myeloma. Given the established 3 mg/kg dose in hematologic malignancies, nivolumab will be given at a flat dose of 240 mg every 2 wks (Day 1 and 15) of a 28-day cycle. Lenalidomide will be given at

starting dose of 25 mg days 1-21 of a 28 day cycle. Dexamethasone can be added after 2 cycles if stable disease. Patients will be assessed for response at the end of each cycle according to the IMWG response criteria.

5.2 Definition of Dose Limiting Toxicity

Patients will be monitored for safety by assessing toxicities as graded by the NCI CTCAE v4.0. Dose limiting toxicity (DLT) will be defined as one or more of the following toxicities considered to be at least possibly related to one of the study drugs during Cycle 1

- Grade 3 or greater nonhematologic toxicity with the exception of Grade 3 nausea, vomiting and diarrhea that responds to supportive therapy.
- Grade 4 thrombocytopenia, or grade 3 thrombocytopenia with bleeding, or any requirement for platelets transfusion
- Grade 4 neutropenia persisting for more than 5 days.
- Grade 3 or greater febrile neutropenia (temperature ≥ 38.5 °C)
- Grade 4 anemia, unexplained by underlying disease

Patients that experience a lenalidomide-related hematologic DLT may continue on therapy if the event resolves, the investigator considers it in the best interest of the patient to continue and the patient qualifies for initiation of the next cycle with standard of care lenalidomide dose reduction.

Discontinuation of treatment due to disease progression will not constitute a DLT.

After 4 cycles of therapy or earlier if clinically indicated, response determination will be assessed by the IMWG criteria. At the end of Cycle 4, if a subject has responded (complete or partial response) or has stable disease, dosing with Nivolumab and lenalidomide will continue for a minimum of 8 additional cycles or until withdrawal.

If disease progression is observed at the end of Cycle 4 evaluation, all study therapy will be discontinued. Confirmation of progression of disease will be done according to the IMWG criteria.

Following the 30-day post-treatment follow-up assessment, additional evaluations will occur once per month (unless subject discontinued due to progression) until the earliest of the following events: disease progression, the time of initiation of new therapy, death or study completion.

Study completion is defined as 30 days after the last subject remaining on study medication discontinues study medication.

An independent Data Monitoring Committee will continue oversight of this trial.

Treatment will continue until Progression of disease, death, unacceptable toxicity or patient or treating physician decision to discontinue therapy.

5.3 Duration of Treatment

Patient can continue study treatment at the treating physician's discretion. Patients achieving at least a stable disease can continue treatment until one of the following is reached:

- Progression of disease
- Death
- Unacceptable toxicity

- Patient decision
- Treatment delay greater than 4 weeks.

Overall response will be assessed after 4, 8, and 12 cycles. If disease progression is observed at the end of Cycle 4 evaluation, all study therapy will be discontinued. In addition, study therapy will be discontinued at the time of disease progression as noted above.

For subjects who withdraw consent, there must be clear documentation of whether the subject withdraws consents to treatment only (i.e. agrees to follow-up) or withdraws consent to treatment and follow-up.

Following the 30-day post-treatment follow-up assessment, additional evaluations will occur once per month (unless subject discontinued due to progression) until the earliest of the following events:

- Disease progression,
- The time of initiation of new therapy,
- Death.

5.3.1 Early Stopping Rules

The study may be suspended or terminated prematurely with sufficient concern for excessive toxicity. Frequency, nature, and severity of adverse events will be reviewed by the PI and study team and compared to what is known about lenalidomide and nivolumab from other sources, including published literature, scientific meetings and discussion with Bristol Myers Squibb to determine if the trial should be terminated before completion. If n=3 subjects experience an infection of grade 3 and higher or an adverse event of grade 3 or greater which is determined to be immune-mediated,and possibly, probably or definitely related to nivolumab and/or lenalidomide, the study will be suspended to allow assessment of whether to continue further enrollment or terminate the trial. If any subject dies while getting treatment, enrollment will be halted to determine relationship to study drugs. Enrollment will resume if determined not to be related to study drugs. If determined to be related to study drugs, the study will be suspended to allow assessment of whether to continue further enrollment or terminate the trial. If N=3 dies and determined to be related to study drugs, the study will be terminated.

5.4 Study Accrual

Eighteen patients will be accrued.

5.5 Duration of Study Period

The total study enrollment period is expected to be 12-18 months.

6 TREATMENT PLAN AND PROCEDURES

Nivolumab will be administered intravenously as a 1-hour infusion, 240 mg every 2 weeks (day 1 and 15) of each 28 day cycle. The Nivolumab infusion scheduling window is +/- 3 days. Lenalidomide will be given at starting dose of 25 mg days 1-21 of a 28 day cycle. Lenalidomide may be consumed at any time during a dosing day – there is no hourly window.

Dexamethasone 40 mg orally weekly may be added if only stable disease after 2 cycles according to the IMWG response criteria (section 13-0). Dexamethasone can be reduced to 20 mg based on

tolerability or if patient is 70 years or older. There is no required dosing order for all three medications.

6.1 Premedication

All patients may receive pre-medication (Tylenol 650mg or Ibuprofen 800mg or related medication), and an antihistamine (diphenhydramine 25mg or equivalent) before Nivolumab infusion at the investigator's discretion. In cases where patients cannot tolerate diphenhydramine hydrochloride, or cases where this medication is not available at the site's pharmacy, an alternative would be to use one of the following as anti-histamine: promethazine at 25mg I.V. administered 20-50 minutes prior to nivolumab dose, chlorpheniramine administered at 10mg I.V 20-50 minutes prior to nivolumab dose, oral chlorpheniramine taken 2 hours prior to nivolumab dose or oral diphenhydramine taken 2 hours prior to nivolumab dose. Anti-histamines given I.V. should be administered as slow IV (NOT as "push"). H2 blockers may be given in addition to H1 at the investigator's discretion but cannot substitute for an H1 anti-histamine. Patients who develop severe infusion reaction requiring intubation will be taken off study.

6.2 Route and Method of Administration

Nivolumab 240 mg will be administered intravenously. The Nivolumab infusion scheduiling window is +/- 3 days. The drug is diluted into a 250mL saline bag and will be administered over one-hour every 2 wks. (day 1 and 15) of a 28 day cycle. Nivolumab is to be administered using a peripheral line or a central device if such has been inserted.

In the event that Grade 3 or higher infusion-related toxicity occurs during infusion, administration of nivolumab should be stopped immediately. Administration of nivolumab could be resumed only after the toxicity has resolved using the slowest rate of infusion (50mL/hr). Once the infusion is resumed, vital signs will be checked every 15 minutes for the first hour, then every 30 minutes till the end of the infusion and then one hour from end of infusion. The window for vital sign collection will be per institutional standard of practice.

The maximal administration rate is approximately 250 mg/hr. The total dose administered and the dosing rate will be documented in the patient's medical records.

To ensure complete delivery of nivolumab, the IV infusion line must be flushed with 0.9% sodium chloride. The following are three recommended methods for flushing the nivolumab IV infusion line:

1) When the nivolumab infusion is complete, add an additional 50mL of 0.9% sodium chloride for injection to the nivolumab infusion bag. Continue the infusion until a volume equal to that of the volume contained in the tubing has been administered.
2) Replace the empty nivolumab infusion bag with a 50mL bag of 0.9% sodium chloride for injection and infuse a volume equal to the volume contained in the tubing. Please note: the flush is not included in the total recommended infusion times.
3) When the nivolumab infusion is complete (IV bag is empty), hang a 50 mL bag of 0.9% sodium chloride for injection and attach it to the primary line port above the pump. Flush the tubing with 30 mL of 0.9% sodium chloride for injection at the same rate as the infusion.

6.3 Nivolumab infusional monitoring

The potential risks that may be related to the administration of monoclonal antibodies in general, adverse events that were possibly related to nivolumab administration in the Phase 1 study, and a few theoretical risks for nivolumab included infusion-related effects.

Vital signs (temperature, blood pressure, pulse rate, respiratory rate) and ECG will be closely monitored prior to, during, and after first drug infusion to avoid general infusion-related toxicity. In the event that severe allergic or hypersensitivity develop, first-line treatment is epinephrine given intramuscularly (0.2 to maximum 0.5 mL aqueous epinephrine 1:1000). Subsequent management of hypersensitivity reactions should follow the institution's protocol. Other known infusion related effects are milder and typically include chills, fever, throat irritation and nausea, which are treated symptomatically. Patients who develop severe infusion reaction requiring intubation will be taken off study.

6.4 Lenalidomide (Revlimid™)

6.4.1 Lenalidomide Administration and Schedule

Lenalidomide will be given orally. The starting dose is 25 mg days 1-21 of a 28 day cycle.
If a dose is missed or vomited up, the dose will not be made up. Lenalidomide doses may be consumed at any time during a dosing day without being considered 'delayed' or 'missed.'

In the event of a dose hold due to toxicity, the patient's treatment will be considered delayed and not missed.

Beginning on day 1 of cycle #2 and on day 1 of every cycle thereafter, while all conditions below have been met, patients will be evaluated for lenalidomide dose reduction.
For patients that:

- Never had a lenalidomide dose reduction due to a toxicity that was probable or definitely related to lenalidomide.
- Maintained platelet count ≥50,000 at all times in the previous cycle
- Minimum ANC ≥1,000 at all times in the previous cycle
- No clinically significant grade 2 or greater non-hematologic toxicities in the previous cycle

If all conditions are met, no dose reduction will occur. If any of the above conditions is not met, the patient's dose for lenalidomide will be reduced by 5 mg.

Per lenalidomide prescribing information, the starting dose of lenalidomide for patients enrolled with creatinine clearance (Clcr) < 50 mL/min will be 10mg days 1-21 of a 28 day cycle.

Dose reductions are not permanent. Lenalidomide may be increased again per treating physician discretion. In the event a patient is dose reduced to 0mg, patient may continue on study, and may still receive Nivolumab as scheduled.

6.4.2 Lenalidomide dose levels

Before each drug dose, the patient will be evaluated for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the NCI Common Terminology Criteria

for Adverse Events (CTCAE), Version 4.0. Dose modifications or delays will be done based on the toxicity experienced during a cycle of therapy or newly encountered on day one of a cycle.

6.5 Dexamethasone

Dexamethasone 40 mg orally weekly (days 1,8,15, 22) may be added if only stable disease after 2 cycles according to the IMWG response criteria (section 13-0). Dexamethasone can be reduced to 20 mg based on tolerability or if patient is 70 years or older.

6.5.1 Table 6.5.1 Adverse events and Dose Adjustment of drugs

Neutropenia	Grade 3 or greater on day 1 of cycle: delay and monitor CBC weekly; if resolves to ≤ grade 2 within 4 weeks, resume lenalidomide with 5mg dose reduction. If grade 3 or greater during a cycle, hold lenalidomide for the remainder of the cycle. Resume with 5mg dose reduction for subsequent cycles. G-CSF or GM-CSF are not to be used to avoid dose reductions but can be used for treatment of febrile neutropenia
Febrile Neutropenia	Hold lenalidomide for the remainder of the cycle. Consider G-CSF administration until there is adequate count recovery ANC≥1000/μL + absence of fever. If neutropenia resolves ≤ grade 2, resume lenalidomide at 5 mg dose reduction for subsequent cycles.
Thrombocytopenia	If grade 3 or greater, hold lenalidomide for the remainder of the cycle and until platelets ≥ 50,000/μL. Then resume lenalidomide at 5 mg dose reduction for subsequent cycles.
Anemia	For grade 3 or greater, hold lenalidomide for the remainder of the cycle and until hemoglobin recovers to ≤ grade 2.
Fatigue (asthenia, malaise) *Lenalidomide or dexamethasone*	For intolerable grade 2 or grade 3-4, hold the protocol therapy thought to be probable or definitely related to the reaction until resolves to ≤ grade 1, then resume protocol therapy with dose reduction of implicated protocol therapy by one dose level (5 mg for lenalidomide and/or 50% for dexamethasone).
Rash *Lenalidomide*	If grade 3 or greater, hold lenalidomide until resolves to ≤ grade 2, then resume protocol therapy. In the instance of intolerable recurrent rash, stop implicated drug but may continue on study.
Renal insufficiency	For patients with calculated or measured GFR <30ml/min, lenalidomide should be held until creatinine returns to baseline. If the calculated or measured GFR falls under 50 ml/min, the dose of lenalidomide will be reduced to 10mg if the patient began therapy with 25mg dosage.
Venous Thromboembolism	All protocol should be held until the patient is adequately anti-coagulated. Patients with recurrent thrombosis despite adequate anti-coagulation should be removed from protocol therapy.

Suspected Pregnancy	Protocol therapy should be held until pregnancy is ruled out. Discontinue all protocol therapy if pregnancy is positive
Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (requiring medical management)	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level
> Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart and decrease one dose level of current dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Acute pancreatitis	Discontinue dexamethasone and do not resume
Edema > Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and decrease dexamethasone dose by 1 dose level; if edema persists despite above measures, decrease dose another dose level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction.
Confusion or mood alteration > Grade 2 (interfering with function +/- interfering with activities of daily living)	Hold dexamethasone until symptoms resolve. Restart with one dose level reduction. If symptoms persist despite above measures, permanently discontinue dexamethasone.
Muscle weakness > Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living)	Decrease dexamethasone dose by one dose level. If weakness persists despite above measures decrease dose by one dose level Discontinue dexamethasone and do not resume if symptoms persist.
Hyperglycemia > Grade 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by one dose level until levels are satisfactory

6.5.2 Table 6.5.2. Dose modifications for nivolumab related immune toxicities and adverse reactions

AE	Grade of Event (CTCAE v4.03)	Dose modifications	Toxicity management
Overall management for immune-related AE		Drug administration modifications of Nivolumab will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03.	It is recommended that management of AEs follow the guidelines presented in this table: • Subjects should be thoroughly evaluated to rule out any

<table>
<tr><td></td><td></td><td>In addition to the criteria for permanent discontinuation of Nivolumab based on CTC grade/severity, permanently discontinue Nivolumab for the following:
• Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing</td><td rowspan="7">alternative etiology (e.g. disease progression, concomitant medications, infections, etc)
• In the absence of a clear alternative etiology, all events should be considered potentially immune related
• Symptomatic and topical therapy should be considered for any low grade events (Grade 1 or 2, unless otherwise specified)
• For persistent (greater than 3-5 days) low grade (Grade 2) or severe (Grade ≥ 3) events promptly start prednisone PO 1-2 mg/kg/day or IV equivalent
• If symptoms recur or worsen during corticosteroid tapering (28 days), increase the corticosteroid dose (e.g. up to 2-4 mg/kg/day or IV equivalent) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (≥ 28 days of taper)
• More potent immunosuppressives such as TNF inhibitors should be considered for events not responding to systemic steroids
• Discontinuation of Nivolumab is not mandated for Grade 3/4 inflammatory reactions attributed to local tumor response (e.g. inflammatory reaction at sides of plasmacytomas). Continuation of study drug in this situation should be based upon a benefit/risk analysis for that subject</td></tr>
<tr><td></td><td>Grade 1</td><td>No dose modification</td></tr>
<tr><td></td><td>Grade 2</td><td>Hold Nivolumab dose until grade 2 resolution to grade 1
• If toxicity worsens then treat as Grade 3 or Grade 4
• If toxicity improves to baseline then resume treatment as seen best by treating physician
• Nivolumab can be resumed once event stabilizes to grade 1 and 5-7 days have passed after completion of steroid taper.
Subjects with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with Nivolumab on the following conditions: 1) the event stabilizes and is controlled, 2) the subject is clinically stable as per investigator or treating physician's clinical judgement, and 3) doses of prednisone are at less than or equal to 10 mg/day or equivalent</td></tr>
<tr><td></td><td>Grade 3</td><td>Depending on the individual toxicity, may permanently discontinue Nivolumab</td></tr>
<tr><td></td><td>Grade 4</td><td>Permanently discontinue Nivolumab</td></tr>
<tr><td></td><td colspan="2">Note: For Grade 3 and above asymptomatic amylase or lipase levels hold Nivolumab and if complete work-up shows no evidence of pancreatitis, may continue or resume Nivolumab</td></tr>
<tr><td>Pneumonitis / ILD</td><td>Any Grade</td><td></td><td>• Monitor subjects for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Subjects should be evaluated</td></tr>
</table>

			with imaging and/or pulmonary functions tests as indicated by treating physician. Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan
	Grade 1	No dose modification required. However, holding Nivolumab dosing as clinically appropriate and during diagnostic work-up for other etiologies	For radiographic changes only: • Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated • Consider pulmonary and infectious disease consult
	Grade 2	• Hold Nivolumab until G2 resolution to ≤ G1 • If toxicity worsens then treat as G3 or G4 • If toxicity improves to baseline then the decision to reinitiate Nivolumab will be based on physician discretion • Nivolumab can be resumed once event stabilizes to grade 1 and 5-7 days have passed after completion of steroid taper.	For Grade 2 (mild to moderate new symptoms): • Monitor symptoms daily and consider hospitalization • Promptly start systemic steroids (e.g. prednisone 1- 2 mg/kg/day or IV equivalent) • Reimaging as clinically indicated • If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisone 2-4 mg/kg/day started • If still no improvement within 3-5 days despite IV methylprednisone, promptly start immunosuppressive therapy such as TNF inhibitors. • Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungal, or anti-PCP treatment • Consider pulmonary and infectious disease consult • Consider as necessary discussing with study physician

	Grade 3 Grade 4	Permanently discontinue Nivolumab	For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life threatening): • Promptly initiate empiric IV methylprednisolone 1 – 4 mg/kg/day or equivalent • Obtain pulmonary and infectious disease consult • Hospitalize the patient • Supportive care including oxygen • If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors • Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungal, or anti-PCP treatment
Diarrhea / enterocolitis	Any grade		• Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus) • Subjects should be thoroughly evaluated to rule out any alternative etiology (e.g. disease progression, other medications, infections including testing for clostridium difficile toxin, etc) • Steroids should be considered in the absence of clear alternative etiology, even for low grade events, in order to prevent potential progression to higher grade event • Use analgesics carefully; they can mask symptoms of perforation and peritonitis

	Grade 1 diarrhea	No dose modification	For grade 1 diarrhea: • Close monitoring for worsening symptoms • Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes, and loperamide
	Grade 2 diarrhea	• Hold Nivolumab until resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or 4 • If toxicity improves to baseline then treat at next scheduled treatment date • Nivolumab can be resumed once event stabilizes to grade 1 and 5-7 days have passed after completion of steroid taper.	For Grade 2 diarrhea: • Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes, and loperamide and/or budesonide • Promptly start prednisone 1 – 2 mg/kg/day or IV equivalent • If event not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, GI consults should be obtained for consideration of further workup such as imaging and/or colonscopy to confirm colitis and rule out perforation, and prompt treatment IV methylprednisolone 2-4 mg/kg/day started • If still no improvement within 3-5 days despite 2-4 mg/kg methylprednisolone, promptly start immunosuppressives such as a TNF inhibitor • Consult study physician if no resolution to ≤ Grade 1 in 3-4 days • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment
	Grade 3 or 4 diarrhea	Permanently discontinue Nivolumab	For Grade 3 or 4 diarrhea: • Promptly initiate empiric IV methylprednisolone 1 – 4 mg/kg/day or equivalent • Monitor stool frequency and volume and maintain hydration • Urgent GI consult and imaging and/or colonoscopy as appropriate

			• If still no improvement within 3-5 days of IV methylprednisolone 2-4 mg/kg/day or equivalent, promptly start further immunosuppressives • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment
Hepatitis (elevated LFTs)	Any Grade		• Monitor and evaluate liver function test: AST, ALT, ALP, and total bilirubin • Evaluate for alternative etiologies (e.g. viral hepatitis, disease progression, concomitant medications)
	Grade 1	No dose modification, if it worsens, treat as Grade 2 event	For Grade 1 AST or ALT and/or total bilirubin elevation • Continue LFT monitoring per protocol
	Grade 2	Hold Nivolumab until Grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or 4 • If improves to baseline then treat at next scheduled treatment date • Nivolumab can be resumed once event stabilizes to grade 1 and 5-7 days have passed after completion of steroid taper.	For Grade 2 AST or ALT and/or total bilirubin elevation • Regular and frequent checking of LFTs (every 1-2 days) until elevations of these are improving or resolved • If no resolution to ≤ grade 1 in 1-2 days, discuss with study physician • If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2 mg/kg/day or IV equivalent • If still no improvement within 3-5 days despite 1-2 mg/kg/day of prednisone or equivalent, consider additional workup and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started • If still no improvement within 3-5 days despite 2-4 mg/kg/day methylprednisolone, promptly start other immunosuppressives (mycophenolate mofetil)

			• Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment
	Grade 3	For elevations in transaminases ≤ 8 x ULN, or elevations in bilirubin ≤ 5 x ULN: • Hold Nivolumab until resolution to ≤ grade 1 or baseline • Resume Nivolumab if elevations downgrade to ≤ grade 1 or baseline within 14 days • For elevations in transaminases > 8 x ULN or elevations in bilirubin > 5 x ULN, discontinue Nivolumab	For Grade 3 or 4 AST or ALT and/or total bilirubin elevation: • Promptly initiate empiric IV methylprednisolone at 1-4 mg/kg/day or equivalent • If still no improvement within 3-5 days despite 1-4 mg/kg/day methylprednisolone IV or equivalent promptly start immunosuppressive treatment (mycophenolate mofetil) • Hepatology consult, abdominal workup, and imaging as appropriate • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment
	Grade 4	Permanently discontinue Nivolumab	
Nephritis / renal dysfunction	Any grade		• Consult with nephrologist • Monitor for signs and symptoms that may be related to changes in renal function (e.g. UA, elevated BUN and Cr, decreased CrCl, electrolyte imbalance, decrease in urine output, proteinuria, etc) • Subjects should be thoroughly evaluated to rule out any alternative etiology (i.e. disease progression, infections, etc) • Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2), in order to prevent potential progression to higher grade event
	Grade 1	No dose modification	For Grade 1 elevated creatinine: • Monitor serum creatinine weekly and any accompanying symptom • If creatinine returns to baseline, resume its regular

			monitoring per study protocol • If it worsens, depending on the severity, treat as Grade 2 or Grade 3/4 • Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc.
	Grade 2	Hold Nivolumab until resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade ¾ • If toxicity improves to baseline then resume treatment • Nivolumab can be resumed once event stabilizes to grade 1 and 5-7 days have passed after completion of steroid taper.	For Grade 2 elevated creatinine: • Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc. • Carefully monitor serum creatinine every 2-3 days and as clinically warranted • Consult nephrologist and consider renal biopsy if clinically indicated • If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2 mg/kg/day or IV equivalent • If event if not response within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4 mg/kg/day started. • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment • When event returns to baseline, resume Nivolumab and routine serum creatinine monitoring per study protocol
	Grade 3 or 4	Permanently discontinue Nivolumab	• Carefully monitor serum creatinine on a daily basis • Consult nephrologist and consider renal biopsy if clinically indicated • Promptly start prednisone 1-2 mg/kg/day or IV equivalent

			• If event if not response within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4 mg/kg/day started. • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment
Rash	Any Grade		• Monitor for signs and symptoms of dermatitis (rash and pruritis) • If there is any bullous formation, the study physician should be contacted and Nivolumab discontinued
	Grade 1	No dose modification	For Grade 1: • Consider symptomatic treatment including oral antipruritics (e.g. diphenhydramine or hydroxyzine) and topical therapy (e.g. urea cream)
	Grade 2	For persistent (> 1-2 weeks) Grade 2 events, hold Nivolumab until resolution to ≤ Grade 1 or baseline • If toxicity worsens then treat as Grade 3 • If toxicity improves then resume Nivolumab treatment. • Nivolumab can be resumed once event stabilizes to grade 1 and 5-7 days have passed after completion of steroid taper.	For Grade 2: • Obtain dermatology consult • Consider symptomatic treatment including oral antipruritics (e.g. diphenhydramine or hydroxyzine) and topical therapy (e.g. urea cream) • Consider moderate strength topical steroid • If no improvement of rash/skin lesions occurs within 3-5 days) or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, discuss with study physician and promptly start systemic steroids with prednisone 1-2 mg/kg/day or IV equivalent

			• Consider skin biopsy if persistent for > 1-2 weeks or recurs
	Grade 3	• Hold Nivolumab until resolution to ≤ Grade 1 or baseline • If temporarily holding Nivolumab does not provide improvement of the Grade 3 skin rash to Grade 1 or baseline within 30 days, then permanently discontinue Nivolumab	For Grade 3 or 4: • Consult dermatology • Promptly initiate empiric IV methylprednisolone 1-4 mg/kg/day • Consider hospitalization • Monitor extent of rash (Rule of Nines) • Consider skin biopsy (preferably > 1) as clinically feasible • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment • Discuss with study physician
	Grade 4	Permanently discontinue Nivolumab	
Endocrinopathy	Any Grade		• Consult endocrinologist • Monitor subjects for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behaviour changes, changes mental status, vertigo, abdominal pain, unusual bowel habits, hypotension, and weakness • Subjects should be thoroughly evaluated to rule out any alternative etiology (e.g. disease progression including CNS involvement and infections) • Monitor and evaluate thyroid function tests: TSH, free T_3 and T_4, and other relevant endocrine labs depending on the suspected endocrinopathy • If a subject experiences an AE that is thought to be possibly of autoimmune nature (e.g. thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing

	Grade 1	No dose modification	For Grade 1 (including those with asymptomatic TSH elevation): • Monitor subject with appropriate endocrine function tests • If TSH < 0.5x LLN, or TSH > 2X ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider endocrinology consult
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism, hold Nivolumab dose until subject is clinically stable • If toxicity worsens then treat as Grade 3 or 4 If toxicity improves to baseline then resume treatment Nivolumab can be resumed once event stabilizes to grade 1 and 5-7 days have passed after completion of steroid taper. . Subjects with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with Nivolumab on the following conditions: 1) the event stabilizes and is controlled, 2) the subject is clinically stable as per Investigator or treating physician's clinical judgement, and 3) doses of prednisone are at less than or equal to 10 mg/day or equivalent	For Grade 2 (including those with symptomatic endocrinopathy): • Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids • Initiate hormone replacement as needed for management • Evaluate endocrine function, and as clinically indicated, consider pituitary scan • For subjects with abnormal endocrine workup, except for those with isolated hypothyroidism, consider short-term, corticosteroids (e.g. 1-2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g. levothyroxine, hydrocortisone, or sex hormones) • Once improving, gradually taper steroid over $\geq$ 28 days and consider prophylactic antibiotics, antifungals, and anti PCP treatment • For subjects with normal endocrine workup (lab or MRI scans), repeat labs/MRI as clinically indicated
	Grade 3 or 4	• For Grade 3 or 4 endocrinopathy other than hypothyroidism, hold Nivolumab until	For Grade 3 or 4: • Consult endocrinologist • Isolated hypothyroidism may be treated with replacement

		endocrinopathy symptom(s) are controlled • Resume Nivolumab if controlled • Nivolumab can be resumed once event stabilizes to grade 1 and 5-7 days have passed after completion of steroid taper.	therapy without treatment interruption and without corticosteroids • Promptly initiate empiric IV methylprednisolone 1-2 mg/kg/day or equivalent • Administer hormone replacement therapy as necessary • For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate IV corticosteroids with mineralcorticoid activity • Once improving, gradually taper immunsuppressive steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungals, and anti-PCP treatment • Discuss with study physician
Immune-mediated neurotoxicity	Any Grade		• Subjects should be evaluated to rule out any alternative etiology (e.g. disease progression, infections, metabolic syndrome, and medications, etc) • Monitor subject for general symptoms (headache, nausea, vertigo, behavior change, or weakness) • Consider appropriate diagnostic testing (e.g. electromyogram and nerve conduction investigations) • Symptomatic treatment with neurological consult as appropriate
	Grade 1	No dose modifications	See “Any Grade” recommendations
	Grade 2	• For acute motor neuropathies or neurotoxicity, hold Nivolumab until resolution to ≤ grade 1 • For sensory neuropathy/neuropathic pain, consider holding Nivolumab until resolution to ≤ grade 1	• Discuss with the study physician • Obtain a neurology consult • Sensory neuropathy/neuropathic pain may be managed by appropriate medications (gabapentin, duloxetine, etc)

		• If toxicity worsens then treat as Grade 3 or 4 • If toxicity improves to baseline then resume treatment • Nivolumab can be resumed once event stabilizes to grade 1 and 5-7 days have passed after completion of steroid taper. •	• Promptly start systemic steroids prednisone 1-2 mg/kg/day or IV equivalent • In no improvement within 3-5 days despite 1-2 mg/kg/day prednisone or IV equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (e.g. IVIG)
	Grade 3	• Hold Nivolumab until resolution to ≤ grade 1 • Permanently discontinue Nivolumab if Grade 3 irAE does not resolve to ≤ grade 1 within 30 days	For Grade 3 or 4: • Discuss with study physician • Obtain neurology consult • Consider hospitalization • Promptly initiate empiric IV methylprednisolone 1-2 mg/kg/day or equivalent • If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g. IVIG) • Once stable, gradually taper steroids ≥ 4 weeks
	Grade 4	• Permanently discontinue Nivolumab	
Infusion-related reactions	Any Grade		• Management per institutional standard at the discretion of the investigator • Monitor subjects for signs and symptoms of infusion-related reactions (e.g. fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, skin rashes, etc) and anaphylaxis (e.g. generalized urticarial, angioedema, wheezing, hypotension, tachycardia, etc)
	Grade 1	The infusion rate of Nivolumab may be decreased by 50% or temporarily interrupted until resolution of the event	For Grade 1 or 2: • Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator • Consider premedication per institutional standard prior to subsequent doses
	Grade 2	The infusion rate of Nivolumab may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be	

		given at 50% of the initial infusion rate	
	Grade 3 or 4	The administration of Nivolumab should be stopped immediately. Administration of Nivolumab could be resumed only after the toxicity has resolved using the slowest rate of infusion (50mL/hr). Once the infusion is resumed, vital signs will be checked every 15 minutes for the first hour, then every 30 minutes till the end of the infusion, and then one hour from end of infusion. The window for vital sign collection will be per institutional standard of care.	For Grade 3 or 4: • Manage severe infusion-related reactions per institutional standards including IV glucocorticoid, IV diphenhydramine, and IM epinephrine for bronchospasm/edema.
Non-immune mediated reactions	Any grade	Note: dose modifications are not required for adverse events not deemed to be related to study treatment (ie. events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant	Treat according to institutional standard
	Grade 1	No dose adjustment	
	Grade 2	Hold study drug/study regimen until resolution to Grade $\leq$ 1 or baseline	
	Grade 3	Hold study drug/regimen until resolution to Grade $\leq$ 1 or baseline For AEs that downgrade to Grade $\leq$ 2 within 7 days or resolve to Grade $\leq$ 1 or baseline within 14 days, resume study drug/study regimen	
	Grade 4	Discontinue study drug/study regimen (Note for Grade 4 labs, decision to discontinue would be based on accompanying clinical signs/symptoms and as per Investigator's clinical judgement and in consultation with sponsor)	

6.6 **Supportive Care**

Patients will receive full supportive care while on this study. This includes blood product support, antibiotic treatment and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as anti-diarrheal, analgesics, anti-emetics received from the first administration of study drugs until 30 days after the final dose are to be recorded in the medical record.

All patients may receive prophylaxis with either an H-2 blocker or proton pump inhibitor while on study medications if needed or if dexamethasone is added. Suggested medications included ranitidine 150 mg oral twice daily or omeprazole 20 mg oral daily or equivalent.

Patients may receive bisphosphonates at physician's discretion.

Patients may receive local radiation for pain control.

6.6.1 Thromboprophylaxis

Lenalidomide increases the risk of thrombotic events in patients who are at high risk or with a history of thrombosis, in particular when combined with other drugs known to cause thrombosis. When lenalidomide is combined with other agents such as steroids (e.g. dexamethasone, prednisone), anthracyclines (doxil, adriamycin) and erythropoietin, the risk of thrombosis is increased.
It is required that patients receive 81-325 mg of aspirin (enteric-coated is preferred) as thromboprophylaxis, equivalent or more intensive anticoagulation strategies with low molecular weight heparins or full-dose warfarin are permitted.

6.6.2 Growth factors

Prophylactic use of growth factors is not recommended.

6.7 Requirements at the beginning of each cycle

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

- The ANC is ≥ 1,000/μL;
- The platelet count is ≥ 50,000/μL;
- Any lenalidomide-related allergic reaction/hypersensitivity or sinus bradycardia/ other cardiac arrhythmia adverse event that may have occurred has resolved to ≤ grade 1 severity;
- Any other lenalidomide-related adverse event that may have occurred has resolved to ≤ grade 2 severity.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of therapy will not be initiated until the toxicity has resolved as described above. Patients unable to initiate a new cycle of therapy within 4 weeks due to treatment related toxicity will be removed from study.

- If lenalidomide dosing was held during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle.
- If lenalidomide dosing was omitted for the remainder of the previous cycle or if the new cycle is delayed due to lenalidomide related toxicity newly encountered on the scheduled Day 1, then the new cycle will be started with a one-level dose reduction of lenalidomide.

6.8 Patient Withdrawal

A patient should be removed from the study whenever it is necessary to safeguard his/her welfare. Occurrence of a significant adverse event or laboratory abnormalities unexpected for these patients may also necessitate discontinuation from the study. Additional reasons for removing a patient from the study are:

- Patients who participate in another investigational drug trial.
- The occurrence of unacceptable toxicity indicating the need for cessation of treatment. Patients may continue with correlative studies.
- Patient has progressive disease while receiving treatment.
- The physician feels it is in the best interest of the patient to stop treatment and the physician may determine whether to continue with correlative studies.
- Patients who express a desire to withdraw from the study (the patient has the right to withdraw for any reason without prejudice).
- Non-compliance by the patient with protocol requirements.
- Patient is lost to follow-up. If a patient does not return for scheduled visits, every effort should be made to re-establish contact. In any circumstance, every effort should be made to document patient outcome, if possible.
- Patient becomes pregnant.
- Any other reasons deemed by the principal investigator and treating physician.
- Termination of the study.

The reason for any patient withdrawal from the study should be recorded on the case report form (CRF) and the occurrence should be reported to the OSU principal investigator by email. These patients who withdraw from the study in the phase II portion of the trial will not be replaced. When a patient is removed from the study, he/she will receive treatment according to the standard of care (SOC) in the medical center and will be followed-up according to the study schedule whenever possible.

The investigator should complete all end of treatment procedures when a patient withdraws from treatment. A patient who is removed from the study by the investigator due to an adverse event (AE) or serious adverse event (SAE) will be followed until resolution of the toxicity to Grade 1 or baseline. All the tests that are required to assess the patient condition will be made as frequent as necessary until the AE or SAE has been resolved. Samples that have already been obtained will be processed.

A patient who withdraws consent before starting the study will not be followed.

A patient who is removed from the study by the investigator since he/she did not keep the appointments will be hard to follow given the circumstances. The extreme situation of this occurrence is a patient who is defined as “lost to follow-up”. Attempts to follow up on the subject will be made as long as the consent has not been withdrawn by the subject. Samples that have already been obtained will be processed.

A patient who initiated another treatment not allowed in the protocol is to be removed from the study by the investigator. Follow up will be only for safety per above. Attempts to continue the follow up of the patient by monthly phone calls or other means will be made to collect information on the patient's survival. Samples that have already been obtained will be processed.

For patients who withdraw consent, there must be clear documentation of whether the subject withdraws consents to treatment only (i.e. agrees to follow-up) or withdraws consent to treatment and follow-up.

6.9 Schedule of Tests and Observations

6.9.1 Screening

All screening tests must be performed within 4 weeks prior to starting protocol-based therapy with the exception of obtaining informed consent, which should be conducted within the timeframe outlined in local policy (if applicable).

6.9.2 Evaluation during treatment

Clinical examination, ECOG/WHO PS, vital signs, toxicity assessment and documentation of concomitant medications will be performed at each outpatient visit. Toxicity will be assessed according to the NCI CTCAE

6.9.3 Post-treatment Follow-up

After the end of study treatment (whatever the reason for discontinuation), the patient will be followed for at least 30 days, during which time all procedures for the reporting of SAEs will be followed.
All patients who discontinue the trial secondary to an adverse event thought to be related to protocol therapy (probably, possible, or definite) should be followed until resolution, stabilization, return to a baseline condition, or death. Overall and progression free survival will be determined through clinic visits or phone interviews with clinical research staff.

6.9.4 Sample collection for immunologic correlative studies

All patients enrolled on this trial will have samples procured for all proposed laboratory correlative studies as summarized below. With each cycle, approximately 30-mL of blood will be collected and sent to Don Benson's lab for processing. Upon receipt, each sample will be recorded and coded with a unique sample number to keep patient identification confidential. PBMCs and plasma (and/or serum) will be aliquoted and cryopreserved. The vials of viably frozen cells for all time points for each patient will be thawed at the same time whenever possible to avoid inter-experimental variability.

6.9.5 Schedule for correlative studies

Laboratory correlative studies will be obtained at screening, days 1 and 15 of the cycles and off study. Off-study correlates should be obtained at the time the patient is removed from protocol for any reason. In addition, continued T-cell correlate will be done at 1, 3, and 6 months after removal from study. Specimens obtained include BM aspirate (10-15 ml in green-top tubes using heparinized syringe) and peripheral blood (Three-10 ml green top tubes, 2 for cells and 1 for plasma).

6.9.6 Study Calendar Schedule of Events

Investigations	Screening	C1D1[a]	C1D15[a]	C2D1[a]	C2D15[a]	CxD1[a]	CxD15[a]	C12D1[a]	Off study[b]
History, physical examination, concomitant medication review	X	X		X		X		X	X
Informed written consent	X								
Confirmation of disease relapse and prior treatment	X								
Skeletal survey (CT or MRI as clinically indicated)[c]	X								X
MUGA or ECHO	X								
β-hCG[d]	X								
Toxicity evaluation	X	X		X		X	X		X
CBC / differential / platelets[e]	X	X	X	X	X	X	X[f]		X[f]
PTT, INR, TSH[e]	X								
BMP, glucose, magnesium[e]	X	X		X		X	X		
LFTs	X	X		X		X	X		
Beta 2 microglobulin[g]	X								X
12-lead ECG[h]	X								
Serum monoclonal protein assessments[i]	X	X[i]		X[i]		X[i]			X[i]
24hr urine for creatinine clearance	X								
24hr urine monoclonal protein and immunofixation[j]	X	X[j]		X[j]		X[j]	X		X[j]
BM biopsy, unilateral[k]	X						X[k]		X[k]
nivolumab Given		X	X	X	X	X	X	X	

Prescribe lenalidomide via RevAssist[l]	X								
Dexamethasone[m]	X								
Pregnancy test[n]	X								
Correlative studies, peripheral blood[o]		X[o]	X	X	X	X	X	X	X
Correlative studies, bone marrow aspirate[q]	X					X[q]			X
Monitoring[p]	X								

a. Time points in the preceding table have a +/- 4 day window to accommodate weekends, holidays, and for patient convenience.
b. Off study correlates will be done. In addition, continued T-cell correlate will be done at 1,3,and 6 months after removal from study
c. Skeletal survey will be done at baseline and may be done at evidence of progression of disease. CT scan will be done to document size of plasmacytoma if this is the only measurable disease.
d. Female patients of childbearing potential (FCBP, defined in section 8.5) must have a negative pregnancy test (β-hCG) as required by the RevAssist program.
e. CBC d/p will be monitored biweekly in cycles 1 to 4, then monthly thereafter. Chemistry tests, including electrolytes, glucose and serum creatinine, should be performed every 2 weeks during the first 2 months of therapy and once a month thereafter. Serum electrolyte monitoring should include potassium, magnesium and calcium. PTT, INR and TSH will be checked every 2 months.
f. Starting C5D1, CBC will be done monthly on D1 of each cycle.
g. Beta 2 microglobulin will be done after every 2 cycles and at evidence of progression of disease.
h. Baseline and periodic ECGs should be performed during treatment as indicated in the flow chart. In patients who have ECG abnormalities, ECGs should be performed more routinely as clinically indicated. ECGs post-baseline should be performed as indicated
i. Myeloma monoclonal protein assessments (Serum protein electrophoresis & immunofixation, immunoglobulin levels, serum free light chain assay) will be performed on day 1 of each cycle as well as off study.
j. 24hr urine monoclonal protein assessment (Urine protein electrophoresis & immunofixation) will be performed at screening and as required for response assessment.
k. Unilateral bone marrow (BM) biopsy will be done at baseline and at end of 4th cycle and evidence of progression for patients with non-secretory multiple myeloma
l. Lenalidomide must be prescribed through and in compliance with Celgene's RevAssist® program. Prescriptions must be filled within 7 days. Any unused lenalidomide should be returned to the patient for disposition in accordance with the RevAssist® program.
m. Dexamethasone will be started on cycle 3 only if stable disease after 2 cycles.
n. Lenalidomide and dexamethasone will start on day 1 of each cycle. Patients will do not need to be in clinic to initiate this as all patients would have been exposed to both. Lenalidomide will be ordered for the next cycle. A pregnancy test (urine or B-HCG) will also be ordered at this time and must be negative prior to starting treatment.
o. Laboratory correlative studies will be obtained. This will be collected through C5D1, at the off study visit, and at 1, 3, and 6 months post off-study. Off-study correlates should be obtained at the time the patient is removed from protocol for any reason.
p. Vital signs (temperature, blood pressure, pulse rate, respiratory rate) and ECG will be closely monitored prior to, during, and after first drug infusion to avoid general infusion-related reactions. Routine vital signs with subsequent infusions, unless indicated otherwise.
q. Correlative studies for the bone marrow aspirate will be done at screening, cycle 5 day 1, and at the off study visit.

7 STATISTICAL CONSIDERATIONS

7.1 Overview of study design

This is a phase 2 trial to explore the combination of lenalidomide (without dexamethasone) and nivolumab in relapsed/refractory MM. We hypothesize that the direct anti-myeloma effect of lenalidomide in conjunction with the potential, combinatorial effect on favorable immune modulation with lenalidomide and nivolumab without deleterious effects of corticosteroid administration may improve outcomes.

7.1.1 Statistical Rationale

The purpose of the clinical trial per se is to reject the combination of lenalidomide and nivolumab from further clinical development if the therapy is insufficiently active. The trial is designed as a Sargent one-stage, three-outcome design[43] with the following assumptions: the inactivity cut off of the combination is 26% (the previously published, single-agent, objective response rate of lenalidomide in relapsed MM) and the activity cut off is 60% (the previously published, objective response rate of lenalidomide in combination with dexamethasone in the setting of relapsed MM). The type 1 (alpha) and type 2 (beta) error rates are both set to 5%, the probability of correctly rejecting an ineffective treatment is set to 80%. Under these assumptions, the three-outcome design specifies treatment of n=18 pts in this phase II trial. If n=7 or fewer show response to treatment, the combination will be declared ineffective. If n=10 or more pts show objective response, the treatment will be declared effective. If n=8 or 9 pts show response, the trial will be deemed inconclusive and additional pts may be enrolled.

The proportion of responses (partial and complete) will be calculated out of all eligible patients who receive any treatment in that disease group who are included in the phase II assessment. Assuming the number of responses is binomially distributed, 95% binomial confidence intervals will also be calculated for the estimate of the proportion of responses. All adverse events will be summarized by the NCI CTCAE v. 4 criteria, and tabulated across all patients who received any treatment with a focus on severe (grade 3+) adverse events and toxicities (i.e. those deemed at least possibly related to study treatment). In addition, we will summarize the proportion of patients who received dexamethasone after being stable disease but without response after 2 cycles of therapy. We will descriptively summarize how many of these patients were converted to response after the addition of dexamethasone. Since the addition of dexamethasone is part of the overall treatment regimen that is dependent on treatment outcome at a certain time point, we will not make other adjustments to the study design to evaluate these patients separately outside of this descriptive summarization of whether or not they received the dexamethasone. We will evaluate other clinical outcomes such as progression-free survival and overall survival using the methods of Kaplan-Meier, although these analyses will be exploratory and primarily to help describe the cohort itself.

Correlative analyses will also be done, including analysis of markers of the immunogenicity of nivolumab. In particular, we will evaluate biological and cellular markers in patients treated with nivolumab, measure PD-L1 expression on MM cells, percentage increase in NK cell activity, migration, immune complex formation, and cytotoxicity. Other markers such as plasma cell IHC baseline expression to characterize immunologic markers of MM cells that are responsive to nivolumab such as TNF-alpha, IFN-gamma, CD4, CD8, and granzyme B will be evaluated in addition to markers of MM cells responsive to lenalidomide (Sparc, IRF-4). Changes in these markers before and after therapy will be explored using graphical analyses as well as summarized quantitatively. We will also explore how changes in these correlative markers may differ based on whether or not the patient achieved a response or not; to accomplish this, we will utilize different plotting characters and colors for successes

vs. not in the graphical analyses to help identify potential patterns, and summarize the changes quantitatively between successes vs. not. Given the total sample size available, we expect that these analyses will be exploratory at best, but will provide important insights into mechanisms of action and vital preliminary data for future studies and hypothesis generation.

7.2 Safety Endpoints

We will describe the safety profile of treatment by the recording of adverse events experienced by patients in the trial and by the monitoring of clinical laboratory values. The safety analysis will be performed on the safety population, as defined below. Adverse events will be described using the NCI CTCAE V 4.0 criteria.

Laboratory assessments will also be described according to the NCI CTCAE criteria, with separate descriptions for grade 3 or 4 laboratory abnormalities. Clinically significant laboratory abnormalities will be described as well.

7.3 Clinical outcome definitions

Time to progression: TTP will be defined as the time from start of treatment until the date he or she has progression or dies. Any subject who has received study treatment but has neither progressed nor died will be censored on the date of his or her last tumor assessment. A subject who has not received study treatment and who has neither progressed nor died will be censored on the day he or she was enrolled.

Progression Free Survival: PFS will be defined as the time from study entry until disease progression or death at trial closure for the per protocol population. Patients who withdraw from the trial prior to disease progression and who are either lost to follow-up, die or who begin alternative treatments prior to progression, will have their data censored as of the date considered to be lost to follow-up, date of death, or the first day of alternative therapy.

Time to Response: A subject's time to response is defined as the time from first dose of study therapy until measurement criteria are first met for [VG]PR or CR or SD (whichever status is recorded first). Time to response is computed only for subjects whose best response is [VG] PR or CR.

Duration of Overall Response: The duration of overall response will be computed for subjects whose best response is either [VG] PR or CR or SD. It will be measured from the time measurement criteria are first met for complete response or partial response (whichever status is recorded first) until the first date of progressive disease or death. Subjects who neither progress nor die will be censored on the date of their last tumor assessment.

Overall Survival: A subject's survival time will be defined as the time from start of treatment to the date of his or her death. If the subject has not died, survival will be censored on last date the subject was known to be alive.

Response Rate: The tumor response rate will be defined as the total number of subjects whose best response is PR or VGPR or CR or SD, divided by the number of per protocol patients.

7.4 Prior and concomitant treatment

The type (brand name and active ingredient) and duration of administration of all medications taken at the time of the inclusion or during the study will be recorded on the Case Report Form (CRF). Dosage, route of administration, and indication will also be specified.

7.5 Prohibited treatments

The use of concomitant chemotherapy, radiotherapy, biological therapy (including cytokines, however erythropoietin is allowed), and steroid therapy (inhaled, oral or topical steroids for treating mild to moderate asthma, allergies or ocular inflammations, typically at ≤500ug/day of fluticasone or equivalent are allowed), is prohibited as long as the patient is on the study and must have been stopped at least 2 weeks prior to first dose administration. Radiation for palliation of pain is acceptable. Participation in any clinical study involving any medications or treatments, whether approved or investigational, is prohibited.

8 Correlative studies-

To assess nivolumab correlative biologic studies to assess immunomonitoring of lymphocytes subsets including T and NK cells and ex-vivo assessment of immune functional activities. If possible, similar studies will be conducted on the bone marrow aspirates as well.

8.1 Instructions for subsites handling correlative samples

Subsites are requested to procure correlative samples at specified time points. Peripheral blood mononuclear cells (PBMC) and bone marrow samples are to be ficolled and cryopreserved in freezing media aliquots with subject number and cycle/day of collection marked. These may be batched shipped quarterly, Monday - Thursday. The address to which to send samples is:

Benson Laboratory
898 Biomedical Research Tower
460 W 12th Ave Columbus OH 43210

8.2 Correlative laboratory investigations

We will conduct extensive immunomonitoring of T and NK cell subsets at baseline and upon completion of each 28-d cycle of therapy. We will focus our analyses principally on the absolute and relative percentage of CD8(+) T cells and CD4(+) T cell subsets including: CD4(+)C45RO(+)CD62L(-)CCR7(-) effector/memory T cells, CD4(+)CD62L(-)CD127(+) peripheral memory T cells, and CD4(+)CD25^{bright}FOXP3(+),CD127$^{low/absent}$ regulatory T cells. We will study Th1/Th2/Th17 polarization in T cells (by expression of CD3, CD4, CD193, CD293, CXCR3, CCR4, and CD45).

8.3 T-cell specific correlative science

Immunologic assessments will be performed prior to each cycle of therapy, and at 1, 3, and 6 months following the last cycle of therapy. At each time point, PBMC will be isolated from peripheral blood by ficoll density centrifugation and cryopreserved. Following completion of the study, PBMC will be thawed and 1 x 10^6 PBMC will be cultured with lysate generated by freeze thaw cycle of 1 x10^5 unselected MM cells. As a control, PBMC will be cultured with tetanus toxoid (10 ug/ml) or media alone. Following 5 days of coculture, expression of IFN-γ by CD4(+) and CD8(+) populations will be determined by intracellular FACS analysis. Cells will be restimulated with tumor lysate for 6 h and cultured overnight with 1 ug/ml GolgiStop. The cells will be stained with CD4 or CD8 antibodies conjugated to FITC and permeabilized with Cytofix/Cytoperm plus^{TM}. Cells will be stained with PE-conjugated anti-human IFN-γ, fixed in 2% paraformaldehyde and analyzed by flow cytometry. The effect of therapy on levels of circulating tumor reactive T cells will be determined by quantifying IFN- γ expressing CD4(+) and

CD8(+) T cells. The impact of nivolumab and Len on tumor reactive T cells will be determined by comparing the pre-treatment levels with the peak level observed following therapy. The cytolytic capacity of tumor reactive lymphocytes will be determined by measuring expression of granzyme B and perforin in CD8(+) T cells following *ex vivo* exposure to autologous tumor lysate. The presence of naïve, memory effector, and central memory cells in the tumor reactive population will be determined by multichannel FACS analysis. The percentage of activated effector cells will be elucidated by quantifying the percentage of CD4(+)CD25(+) CD69(+) cells. Tregs will be quantified by assessing expression of FOXP3 for the CD4(+)CD25(+)CD127$^{low/absent}$ population. When cell yields allow, we will assess the capacity of T cells to lyse autologous tumor cells in a standard chromium release assay. We will also examine the effect of nivolumab and Len on immunologic responses against previously identified tumor antigens. XBP-1, OFD-1, SOX2, MUC1, and CD138 have been identified as MM associated antigens. In HLA-A2.1 patients, we will quantify the number of CD8(+) T cells binding tetramer constructed from these antigens (as cell yields allow) at serial time points in the circulation. The persistence of tetramer(+) cells in the circulation will be determined. Functional characteristics of the tetramer positive population will be determined by measuring IFN-γ, granzyme B, IL-4, and IL-10 expression in the tetramer(+) cells by intracellular FACS staining.

8.4 NK-cell specific correlative science

We will quantitate CD56^{bright} and CD56^{dim} NK cell subsets in PBMC and other markers of NK cell maturity (proportion of NK cells expressing CD16 and CD117) and developing intermediates in peripheral blood. We will also perform immunophenotyping of NK cell subsets for expression of trafficking antigens (in particular CXCR4 which we have shown to be modulated by nivolumab on NK cells) and markers of activation (CD158, CD69) and degranulation (LAMP-1, LAMP-3, CD107a, CD107b, CD159, and CD314) which may be influenced by nivolumab and Len. Notably, our group has optimized an “immunome” flow cytometry-based profiling technique to allow these characterizations from a very modest amount of pt PBMC to minimize volume of blood collected for correlative science studies. Finally, we will perform *ex vivo* functional assays against MM cell line targets and purified, autologous MM tumor samples obtained at baseline and after each cycle of therapy including trafficking, immune complex and cytotoxicity assays as described by our group previously.[44] We will also attempt to verify our preclinical finding regarding down modulation of PD-L1 on MM tumor cells by Len by comparing PD-L1 expression on pt MM tumor cells at baseline and after one cycle of therapy. We will purify CD138 (+) MM cells from bone marrow aspirates of pts obtained at baseline and after 4 cycles of treatment and assess PD-L1 expression by flow cytometry.

8.5 CD14(+) monocyte specific, correlative science

We will evaluate the expression of PD-L1 and PD-L2 on CD14 (+) monocytes at baseline and after treatment with nivolumab after each cycle of therapy. We will specifically study the induction of these antigens on CD14 (+) cells as a consequence of nivolumab administration. We will attempt to correlate the expression PD-L1 on CD14 (+) cells with clinical activity determined by response rate and progression-free survival if allowable by sample size power. Otherwise, we will limit these analyses to hypothesis-generating, descriptive evaluation.

9 Investigational drugs

9.1 Nivolumab

Nivolumab (humanized monoclonal antibody) for parenteral administration is supplied as a 10 mg/mL clear solution and is preservative-free. Each vial consists of 100 mg in 10 ml solutions.

Label of the Drug: The container label and the immediate outer carton label of the investigational product to be used in the clinical study will contain the following information: product name and strength, lot number, protocol number, vial number, manufacturer's name and address, recommended storage conditions, and an investigational caution statement.

Storage of the Drug: Vials of nivolumab injection must be stored at 2ºC to 8ºC (36ºF to 46ºF) and protected from light and freezing.

Preparation of Nivolumab for Administration: The solution will be prepared by a pharmacist, the Investigator, or a study nurse. Appropriate aseptic techniques should be used. Each vial contains **approximately** 100 mg/10 ml nivolumab. The bag will be identified with the patient number. Parenteral solutions should be inspected visually for particulates and discoloration prior to administration. Once the infusion is prepared, it should be administered within 24 hours. If Not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C, 36°F to 46°F) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (20ºC to 25ºC, 68ºF to 77ºF) and room light. The maximum 8-hour period under room temperature and room light conditions includes the product administration period.

Method of Administration: nivolumab will be administered intravenously on day 1 and 15 of each 28 day cycle. The drug is diluted into a 250mL saline bag and will be administered over one-hour. In the event that Grade 3 or higher toxicity occurs during infusion, administration of nivolumab should be stopped immediately. Administration of nivolumab could be resumed only after the toxicity has resolved using the slowest rate of infusion (50mL/hr). Vital signs will be measured prior to infusion and every 15 minutes for the first hour, then every 30 minutes for an additional hour, and then once an hour until the end of infusion. The window for vital signs will be per institutional standard of practice.

9.2 LENALIDOMIDE (Revlimid™)

Lenalidomide (REVLIMID®), a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic properties. The chemical name is 3-(4-amino-1-oxo 1, 3-dihydro -2*H*-isoindol-2-yl) piperidine-2, 6-dione. Lenalidomide has been studied extensively in myeloma and it is approved for use in newly diagnosed and in relapsed MM.

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

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

Pregnancy: Due to its structural similarities to thalidomide, a known human teratogen, lenalidomide is contraindicated in pregnant women and women capable of becoming pregnant. When there is no alternative, females of childbearing potential may be treated with lenalidomide provided adequate precautions are taken to avoid pregnancy. Females must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control, including at least one

highly effective method (e.g., IUD, hormonal contraception, tubal ligation, or partner's vasectomy) and one additional effective method (e.g., latex condom, diaphragm, or cervical cap), beginning 4 weeks prior to initiating treatment with REVLIMID® (lenalidomide), during therapy with REVLIMID® (lenalidomide), during therapy delay, and continuing for 4 weeks following discontinuation of REVLIMID® (lenalidomide) therapy. If hormonal or IUD contraception is medically contraindicated, two other effective or highly effective methods may be used.

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

10 PATIENT SAFETY

10.1 Monitoring of Adverse Events

Significant adverse events should be identified and recorded. Seriousness, expectedness, and causality will be assessed using the definitions that follow. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting.

10.2 Definitions of Adverse Events and Causality

An **Adverse Event (AE)** is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. For marketed products in the U.S., a **Serious Adverse Event (SAE)** is any untoward medical occurrence that at any dose:

- Results in death (if the patient's death is suspected as being a direct outcome of the adverse event)
- Is life-threatening (the patient was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the product would result in the patient's death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect (i.e., exposure to a medical product prior to conception or during pregnancy resulted in an adverse outcome in a child)
- Requires intervention to prevent permanent impairment or damage
- Overdosage (regardless of adverse outcome) of any study medication. An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important.
- Pregnancy
- Potential drug-induced liver injury(DILI): as defined by: 1:ALT or AST elevation > 3 times upper limit of normal (ULN) **AND 2:** Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase **AND 3:** No other immediately apparent possible causes of AST/ALT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

- Is an important medical event, defined as a medical event(s) that may not be immediately life threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require medical or surgical intervention to prevent one of the other serious outcomes listed in the definition above. Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm, or blood dyscrasias or convulsions that do not result in hospitalization.

The SAE reporting period begins following the subject's written consent to participate in the study through 100 days of discontinuation of dosing. AEs should be followed to resolution or stabilization, and reported as SAEs if they become serious. This also applies to patients experiencing AEs that cause interruption or discontinuation of investigational product, or those experiencing AEs that are present at the end of their participation in the study. Such patients should receive post-treatment follow-up as appropriate. If an ongoing AE changes in its severity or in its perceived relationship to study drug, a new AE entry for the event should be completed.

Additionally, any serious adverse event considered by an investigator to be possibly, probably, or definitely related to the investigational product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the IRB (only as required per local policy) and Bristol-Myers Squibb (BMS) designated pharmacovigilance representative.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Note: The term "life-threatening" in the definition of "Serious Adverse Event" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

An **Unexpected Adverse Event** is not listed in the current US Package Insert may be mentioned in the package insert, but differs from the event because of greater severity or specificity.

Causality is a determination of whether there is a reasonable possibility that the drug may have caused or contributed to an adverse event. It includes assessing temporal relationships dechallenge/rechallenge information, association (or lack of association) with underlying diseases, and the presence (or absence) or a lack of one or more likely causes.

The Investigator must attempt to determine if an adverse event is in some way related to the use of the study drug. This relationship should be described as follows:

Unlikely: The event is clearly due to causes distinct from the use of the study drug, such as a documented pre-existing condition, the effect of a concomitant medication, a new condition which, based on the pathophysiology of the condition, and the pharmacology of the study drug, would be unlikely related to the use of the study drug.

Possible: The event follows a reasonable temporal sequence from administration of the study drug or the event follows a known response pattern to the study drug *BUT* the event could have been produced by an intercurrent medical condition which, based on the pathophysiology of the condition,

and the pharmacology of the study drug, would be unlikely related to the use of the study drug or the event could be the effect of a concomitant medication

Probable: The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug AND the event cannot have been reasonably explained by an intercurrent medical condition *or* the event cannot be the effect of a concomitant medication

Definite: The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug and based on the known pharmacology of the study drug, the event is clearly related to the effect of the study drug

Unknown: Based on the evidence available, causality cannot be ascribed

10.3 Serious Adverse Events

When the principal investigator has determined that a Serious Adverse Event has occurred, the principal investigator is responsible for providing all Serious Adverse Events to BMS within 24 hours of this determination and to the IRB as per local policy. This applies to initial and follow-up information.

Follow-up Reports:

- The Investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow up the outcome of any Serious Adverse Event and complete follow-up forms as necessary. The patient must be followed up until recovery, stabilization or return to baseline. This may mean that follow-up will continue after the patient has completed the trial and that additional investigations may be necessary.
- Any reportable Serious Adverse Events brought to the attention of the Investigator at any time after cessation of the trial and considered by him/her to be reasonably associated with medication administered during the period should also be submitted to the IRB (as required per local policy) and to BMS (worldwide.safety@BMC.com; Fax: 609-818-3804).
- As with the initial submission to the IRB, the principal investigator is also responsible for providing all follow-ups of Serious Adverse Events to the IRB (as required per local policy) and to BMS, using CIOMs or Medwatch form FDA 3500AA.

10.3.1 Subsite/External Participating Site SAE Reporting Requirement.

NOTE: External participating sites are not permitted to report directly to the OSU IRB or FDA. All external site SAEs are to be reported to the OSU Principal Investigator and Multi-Center Trial Program (MCTP). The MCTP will facilitate submission of external site SAEs to the OSU IRB and FDA.

All serious adverse events (SAEs) and other adverse events must be recorded on case report forms. In addition, all SAEs must be reported to the OSU Principal Investigator and MCTP within 24 hours of knowledge of the event using the FDA MedWatch 3500A mandatory reporting form and the “SAE Submission Form” cover sheet (refer to the Supplemental Forms Document).

Copies of de-identified source documentation pertaining to the SAE must be submitted to OSU. If a patient is permanently withdrawn from the study because of a SAE, this information must be included in the initial or follow-up SAE report form.

All SAEs must be submitted to the local IRB per local IRB and institutional policy.

Upon request of additional data or information that is deemed necessary must be reported to OSU as soon as possible but no later than 5 calendar days.

10.4 Reporting of Adverse Event Information Following Study Completion

Collection of safety information following the end of investigational product administration is important in assisting in the identification of possible delayed toxicities or withdrawal effects. All SAEs must be collected following the subject's written consent to participate in the study through 100 days of discontinuation of dosing and must be reported to BMS Worldwide Safety.

10.5 Pregnancy Statement and Use in Nursing Women

All women of childbearing potential MUST have a negative pregnancy test as required by the RevAssist program. If the pregnancy test is positive, the patient must not receive any investigational product and must not be enrolled in the study.
If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).
The investigator must immediately notify Worldwide Safety @BMS of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form [provided upon request from BMS] any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

Definition of Childbearing Potential: For the purposes of this study, a female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time during the preceding 24 consecutive months).

Thalidomide, an analog of lenalidomide causes fetal harm and birth defects when administered to a pregnant woman. There are, however no adequate and well-controlled studies of lenalidomide in pregnant women. In New Zealand white rabbits at 10 and 20 mg/kg/day, lenalidomide was maternally toxic (reduced body weight gain and feed consumption; at 20 mg/kg/day, weight loss and one abortion). Developmental toxicity at 10 and 20 mg/kg/day included reduced fetal body weights and increased post implantation losses and fetal variations (morbidity/purple-discolored skin, undeveloped intermediate lung lobe, irregular nasal-frontal suture, and delayed metacarpal ossification)[45]. The maternal and developmental no observed adverse effect levels (NOAELs) was 3mg/kg/day.

If the drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

During the course of the trial, all patients of childbearing potential should be instructed to contact the treating physician immediately if they suspect they might have conceived a child. In addition, a missed or late menstrual period should be reported to the treating physician. If a female patient or the treating physician suspects that the female patient may be pregnant prior to administration of study drugs, the study drugs must be withheld until the results of a pregnancy test are available. If pregnancy is confirmed the patient must not receive study medications and must be withdrawn from the study. Throughout the entire pregnancy, additional contact should be made with the patient, and in some cases with the healthcare provider, to identify spontaneous abortions and elective terminations, as well as any medical reasons for elective termination. In addition, the study investigator should include perinatal and neonatal outcome. Infants should be followed for a minimum of 4 weeks.

If a male patient is suspected of having fathered a child while on study drugs, the pregnant female partner must be notified and counseled regarding the risk to the fetus. In addition, the treating physician must follow the course of the pregnancy, including prenatal and neonatal outcome. Infants should be followed for a minimum of eight weeks.

Upon live-birth delivery, the minimum information that should be collected includes date of birth, length of pregnancy, sex of infant, major and minor anomalies identified at birth. Outcomes can be obtained via mailed questionnaires, maternal interviews, medical record abstraction, or a combination of these methods. All serious adverse event reports relating to the pregnancy, including spontaneous abortion, elective abortion and congenital anomalies, should be forwarded to the FDA & BMS. (See Safety reporting section).

It is not known whether lenalidomide or nivolumab is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from lenalidomide, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

10.6 Data Safety Monitoring Plan

The data and safety monitoring plan will involve the continuous evaluation of safety, data quality and data timeliness. Investigators will conduct continuous review of data and patient safety at their regular Disease Group meetings (at least monthly) and the discussion will be documented in minutes. For each dose level, the Principal Investigator, study coordinator, and statistician, in consultation with treating physicians as appropriate will review all toxicities at a given dose level to inform the model for dose level adjustments. The Principal Investigator of the trial will review toxicities and responses of the trial where applicable at these disease center meetings and determine if the risk/benefit ratio of the trial changes. Frequency and severity of adverse events will be reviewed by the Principal Investigator and compared to what is known about the agent/device from other sources; including published literature, scientific meetings and discussions with sponsors, to determine if the trial should be terminated before completion. Serious adverse events will be reviewed by the OSUCCC Data and Safety Monitoring Committee (DSMC). The Principal Investigator will also submit progress reports that will be reviewed by the committee per the DSMC plan. All reportable SAEs will be reported to the IRB of record as per the policies of the IRB.

Mandatory safety and trial review teleconferences will be scheduled and moderated by the Multi-Center Trial Program (MCTP). All sites involved in the study are expected to have a representative present for every call to review and discuss patients on study and other applicable agenda items. Meeting minutes will be used to document each teleconference. The minutes will be stored in the MCTP protocol files. Teleconferences must minimally be held monthly and may be held more frequently, as needed. For studies closed to accrual with patients expected to remain on long-term

treatment and/or follow-up, teleconferences may be extended to occur every two months or quarterly. Decreasing frequency of teleconferences requires OSU PI and MCTP approval.

10.7 Data Submission

The study will be managed per the Multi-Center Trial Program (MCTP) policies. Subsite data must be submitted to the MCTP as outlined in the protocol-specific monitoring plan. The protocol-specific monitoring plan will be provided by the MCTP to external participating sites prior to site activation. Data will be submitted using case report forms and the Data Submission Form cover sheet (refer to Supplemental Forms Document) supplied by the MCTP. Access to the OSU OnCore database may be provided to external participating sites for direct electronic data entry. All data submitted must be accompanied by supporting source documents, where applicable and as outlined in the protocol-specific monitoring plan.

10.8 Auditing

As the study sponsor, The Ohio State University Comprehensive Cancer Center (OSUCCC) will audit each site as per OSU policies. Audits will be performed by the OSUCCC Clinical Research Audit Team. For sites with an auditing mechanism in place that are able to share documentation of their auditing standards and processes followed, an agreement may be requested for the site to perform local auditing and provide formal audit reports to the OSUCCC Multi-Center Trial Program (MCTP) and the Quality Assurance Oversight Committee.

10.9 Study Termination

The investigator may discontinue the trial at any time. Reasons for early trial discontinuation may include, but are not limited to, unacceptable toxicity of study treatment, a request to discontinue the trial from a regulatory authority or an IRB, or poor enrollment.

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12 Appendix: ECOG/KPS Scale

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

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13 Appendix. IMWG Response Criteria

Serum and urine M-protein estimates will be performed every 4 weeks; except for assessment of CR, patients with measurable disease restricted to the SPEP (or UPEP) will need to be followed only by SPEP (or UPEP). Responses will be assessed according to the criteria of the International Myeloma Working Group [46], and characterized as follows:

Response Category	Response Criteria[a]
SCR	CR as defined below plus • Normal FLC ration and • Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c]
CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤ 5% plasma cells in bone marrow[b]
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level < 100 mg per 24 hours
PR	≥ 50% reduction of serum M-Protein and reduction in 24 hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours If the serum and urine M-protein are unmeasurable[d] a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are unmeasurable, and the serum free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein provided baseline bone marrow plasma cell percentage was ≥ 30% In addition to the above, if present at baseline a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
SD[e]	Not meeting criteria for CR, VGPR, PR, or progressive disease
Relapse Category[f]	**Relapse Criteria**
Progressive disease	**Requires only one of the following**: Increase of ≥ 25% from baseline in: • Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dl)[g] • Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 hours) • In patients without measurable serum and urine M-protein levels the difference between involved and

	uninvolved FLC levels, the absolute increase must be > 10 mg/dl. • Bone marrow plasma cell percentage, the absolute % must be ≥ 10%[h]. • Definite development of new bone lesions or soft tissue plasmacytomas increase in the size of existing bone lesions or soft tissue plasmacytomas. • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder.
Clinical relapse (Not used for TTP or PFS)	**Clinical relapse requires one or more of**: • Development of new soft tissue plasmacytoma or bone lesions • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion • Hypercalcemia (> 11.5 mg/dl [2.65 mmol/l]) • Decrease in hemoglobin of ≥ 2 g/dl (1.25 mmol/l) • Rise in serum creatinine by 2 mg/dl or more (177 μmol/l or more)
Relapse from CR [i]	**Any one or more of the following:** • Reappearance of serum or urine M-protein by immunofixation or electrophoresis • Development of ≥ 5% plasma cells in the bone marrow[j] • Appearance of any other sign or progression

a. All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response criteria.
b. Confirmation with repeat biopsy not necessary.
c. Presence/absence of clonal cells is based upon the κ/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ration reflecting presence of an abnormal clone is κ/λ of > 4:1 or < 1:2.
d. Applicable only to patients who have 'measurable' disease defined by at least one of the following three measurements: Serum M-protein ≥ 1 g/dl, Urine M-protein ≥ 200 mg/24hour, Serum FLC assay involved FLC level ≥ 10 mg/dl provided serum FLC ration is abnormal.
e. Not recommended for use as an indicator of response; stability of disease is best described by providing the time too progression estimates).
f. All relapse categories require two consecutive assessments made at anytime before classification as relapse or disease progression and/or the institution of any new therapy.

g. For progressive disease, serum M-component increases of ≥ 1 gm/dl are sufficient to define relapse if starting M-component is ≥ 5 g/dl.
h. Relapse from CR has the 5% cutoff versus 10% for other categories or relapse.
i. To only be used if the end point studied is disease free survival. For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.
j. Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.

14 Appendix. NYHA Cardiac Disease

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

15 Appendix. FACT/GOG-Neurotoxicity

By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days</u>.

ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
I have numbness or tingling in my hands……	0	1	2	3	4
I have numbness or tingling in my feet……	0	1	2	3	4
I feel discomfort in my hands…….	0	1	2	3	4
I feel discomfort in my feet……	0	1	2	3	4
I have joint pain or muscle cramps……	0	1	2	3	4
I feel weak all over……	0	1	2	3	4
I have trouble hearing……	0	1	2	3	4
I get a ringing or buzzing in my ears……	0	1	2	3	4
I have trouble buttoning buttons……	0	1	2	3	4
I have trouble feeling the shape of small objects when they are in my hand……	0	1	2	3	4
I have trouble walking……	0	1	2	3	4

Sources: Cella DF, Tulsky DS, Gray G, Sarafian B, Lloyd S, Linn E, et al. The functional assessment of cancer therapy (FACT) scale: development and validation of the general measure. *J Clin Oncol* 1993;11(3):570-79.

16 Appendix. Ethical and regulatory

16.1 Ethical Principles

The study should be conducted according to the principles outlined by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments; the International Conference on Harmonization Guidelines for Good Clinical Practice; and FDA regulations regarding the conduct of clinical trials and the protection of human subjects.

16.2 Protocol Compliance and Protocol Revisions

The study must be conducted as described in this approved protocol. All revisions to the protocol must be provided to BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB of an Amendment, except where necessary to eliminate an immediate hazard(s) to study patients. Documentation of approval signed by the chairperson or designee of the IRB(s) must be sent to BMS. If the revision is an administrative letter, the investigator(s) must inform the IRB.

16.3 Informed consent, Data Safety and Monitoring

It is the responsibility of the investigator to obtain written informed consent from a patient or a patient's legal representative before any study related procedures are performed. The Investigator will provide an informed consent in compliance with ICH GCP and U.S. FDA guidelines (21 CFR 50). The informed consent document must clearly describe the potential risks and benefits of the trial, and each prospective participant must be given adequate time to discuss the trial with the Investigator or site staff and to decide whether or not to participate. The informed consent must be approved by the IRB prior to being presented to a potential patient. One copy of the patient's signed, dated and witnessed written consent will be kept in the patient's medical record and one copy will be given to the patient or the patient's legal representative.

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations. Investigators must enter study data into a secure data collection system that will be accessible to only parties involved in the trial. The Investigator will permit study-related monitoring visits and audits by BMS or its representatives, IRB, providing direct access to the facilities where the study took place, to source documents, and to all other study documents.

16.4 Institutional Review Board (IRB) Approval

The Investigator must obtain the approval of the protocol, the informed consent document and any other material used to inform the patient about the nature of the trial from the local IRB in the form of a written letter. On the approval letter, which must be signed by the chairperson of the IRB or the chairperson's designee, the following items should be clearly stated: trial title, protocol number and version, study-related documents (protocol, informed consent material, advertisement when applicable), IRB review date, and IRB decision. The trial should not start until a copy of this written approval has been received by the Investigator.

If the investigator is a member of the IRB, the Investigator may participate in any discussion of the study, but may not participate in the final vote deciding whether to approve the study.

Annually, or more often if stipulated by the IRB, and at the completion or termination of the study, the Investigator will report the progress of the trial to the IRB and BMS. (see contact information in section "Serious Adverse Events")

16.5 Additional Responsibilities of the Investigator

The investigator(s) agrees to perform the study in accordance with ICH Good Clinical Practice and FDA regulations. The Investigator is required to ensure compliance with respect to the investigational drug schedule, visit schedule and procedures required by the protocol.

The investigator should be able to recruit the required number of suitable patients and should have sufficient time to properly conduct and complete the trial. The Investigator should have available an adequate number of qualified staff and adequate facilities for the duration of the trial, and should ensure that all persons assisting with the trial are adequately informed about the protocol, the protocol-defined procedures, protocol therapy and trial related duties and functions..

The Investigator should be responsible for all trial-related medical decisions. During and following a patient's participation in a trial, the investigator should ensure that adequate medical care is provided to a patient for any adverse events related to the trial.

16.6 Use and Completion of Case Report Forms (CRFs)

It is the responsibility of the Investigator to monitor the preparation and accurate use of CRFs to record all observations and other data pertinent to the clinical investigation. All CRFs should be completed in their entirety to ensure accurate interpretation of data.

Should a correction be made, the information to be modified must not be overwritten. The corrected information will be transcribed next to the previous value, initialed and dated by the authorized person.

16.7 Confidentiality

It is the responsibility of the investigator to ensure that the confidentiality of all patients participating in the trial and all of their medical information is maintained. Case report forms must never contain the name of a trial patient. All case report forms and any identifying information must be kept in a secure location with access limited to the study staff directly participating in the trial. Personal medical information may be reviewed by a representative of BMS, of the IRB, or of regulatory authorities in the course of auditing the trial. Every reasonable effort will be made to maintain such information as confidential.

17 Appendix. REV-ASSIST GUIDELINES

As of 11-Sep-2008,

Initial prescription process (for all patients unless otherwise noted)

1. For females of childbearing potential, obtain two negative pregnancy tests sensitive to at least 50 mIU/mL even if continuous abstinence is the chosen method of birth control. One test must be obtained within 10–14 days and one test within 24 hours prior to writing an initial prescription of REVLIMID® (lenalidomid
2. Obtain a baseline Complete Blood Count
3. Provide mandatory counseling: no drug sharing, no blood or sperm donation, and appropriate contraceptic
4. Complete, print, and sign REVLIMID® Patient-Physician Agreement Form
   - **Males (adults and children)**
   - **Females of childbearing potential include females who have not undergone a natural menopause** for at least 24 consecutive months
   - **Females not of childbearing potential include females who have been postmenopausal natu** for at least 24 consecutive months, or had a hysterectomy, or a bilateral oophorectomy
5. Fax completed and signed REVLIMID® Patient-Physician Agreement Form to 1-888-432-9325
6. Instruct patient to complete phone survey by calling 1-888-423-5436 prior to prescriber obtaining an authorization number
   - **All males:** REVLIMID® Patient-Physician Agreement Form is considered the initial phone survey
   - **All females:** Complete the appropriate phone survey
7. Complete a prescriber phone survey for all patients by calling 1-888-423-5436 and obtain a new authorization number for each prescription
   - You will need to enter the following information:
     - Prescriber's DEA number or Social Security number
     - Patient's Social Security number
     - Date and result of patient's pregnancy test(s) (if applicable); valid only for 7 days
     - Daily dose
     - Total number of days supplied (cannot exceed 28 days)
8. Provide the authorization number on the prescription; authorization number and prescription are valid for 7 days for females of childbearing potential and 14 days for all other patients
9. Healthcare provider contacts a RevAssist® contract pharmacy to fill the prescription
10. RevAssist® contract pharmacy contacts patient for counseling and dispenses REVLIMID® with the FDA-approved MEDICATION GUIDE and educational material

Subsequent REVLIMID® prescriptions (for all patients unless otherwise noted)

1. For females of childbearing potential, obtain scheduled pregnancy tests weekly during the first 4 weeks of use; then pregnancy testing should be repeated every 4 weeks in females with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks
2. Obtain Complete Blood Counts as necessary
3. Provide mandatory counseling: no drug sharing, no blood or sperm donation, and appropriate contraception
4. Instruct patient to complete surveys **as scheduled**, prior to prescriber obtaining an authorization number and filling prescription
   - Monthly:
     - **Males (adults and children)**
     - **Females of childbearing potential (adults and children), female children not of childbearing potential**
   - Every 6 months:
     - **Adult females not of childbearing potential (who have been postmenopausal naturally for at least 24 consecutive months, or had a hysterectomy, or a bilateral oophorectomy)**
5. Complete a prescriber phone survey for all patients by calling 1-888-423-5436 and obtain a new authorization number for each prescription
   - You will need to enter the following information:
     - Prescriber's DEA number or Social Security number
     - Patient's Social Security number
     - Date and result of patient's last pregnancy test (if applicable); valid only for 7 days
     - Daily dose
     - Total number of days supplied (cannot exceed 28 days)
6. Provide the authorization number on the new prescription; authorization number and prescription are valid for 7 days for females of childbearing potential and 14 days for all other patients
7. Healthcare provider contacts RevAssist® contract pharmacy to fill the prescription
8. RevAssist® contract pharmacy contacts patients for counseling and dispenses REVLIMID® with the FDA-approved MEDICATION GUIDE

18 Appendix: Instructions for sample collection, storage and shipment

The total amount of whole blood withdrawn for the laboratory tests will depend on the visit number. Whole blood should be divided and processed as follows:

ANY REMAINING SERUM THAT IS NOT USED IN ANY OF THE TESTS SHOULD BE DISCARDED AS REQUIRED BY THE CENTER'S RELEVANT POLICIES.