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Phase I/II Study of Lenalidomide in Combination with Monoclonal Antibody MDV9300 (CT-011) in Patients with Relapsed/Refractory Multiple Myeloma

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PROTOCOL SYNOPSIS

Study Title	Phase I/II Study of Lenalidomide in Combination with Monoclonal Antibody MDV9300 (CT-011) in Patients with Relapsed/Refractory Multiple Myeloma
Study ID	OSU-13128
Sponsor	Yvonne Efebera, MD (Investigator Sponsor)
IND#	120501
Funding Entity	American Cancer Society
Primary Objectives	To determine the maximum tolerated dose (MTD), safety and efficacy of CT-011 in combination with lenalidomide (Revlimid) and assess efficacy in terms of overall response rate in patients with relapse/refractory multiple myeloma (MM)
Primary Endpoint	• To determine MTD of CT-011 in combination with lenalidomide in the phase I study. The MTD of CT-011 combined with lenalidomide will be defined as the highest dose combination of CT-011 and lenalidomide at which ≤ 1of 6 patients at that dose level has dose-limiting toxicity. • 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) • To determine overall survival (OS) • To assess pharmacokinetics and pharmacodynamics of CT-011 in combination with lenalidomide • To assess CT-011 immunogenicity and 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	**For the phase I portion** We will conduct a standard 3+3 design over 4 dose levels of 1.5, 3, 3, and 6 mg/kg of CT-011 given intravenously every 4 weeks and lenalidomide given at 15,15, 25, and 25 mg orally daily on days 1-21 of a 28-day cycle. CT-011 will be administered intravenously on day 3 of each 28 day cycle. The drug is diluted into a 250mL saline bag which in the FIRST infusion is administered in a step-wise manner: 50ml/hr for 30min; 100ml/hr for 30min; 150ml/hr for 30 min and 200ml/hr till the end (another ~30min) for an approximate time of 2hrs. If no infusion related AEs occurs the first time, subsequent administrations are at 200mL/hr which will deliver the drug over approximately 1:15hrs. All patients will receive pre-medication (Tylenol 650mg or Ibuprofen 800mg or related medication), and an antihistamine (phenergan 25mg or equivalent) before CT-011 infusion. 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 non-hematologic 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. However, the DLT will count towards establishment of maximally tolerated dose (MTD). A cohort will be expanded if 1 of 3 pts experiences a DLT. If 2 of 6 pts on a cohort experience a DLT, then MTD will be determined as the dose level immediately below that in which 2 of 6 pts experience a DLT. The Phase II portion of the trial will commence upon completion of the Phase I portion. In the event that a MTD is not established, safety and tolerability data collected in the Phase I portion of the study will guide decisions on dosing of CT-011 in the phase II trial. The maximum tolerated dose level (MTD) combination is defined as the dose level at which no more than one of six patients experiences a DLT as defined above. Any dose level that has two or more DLTs reported is considered to exceed the MTD and not be a tolerable dose level. Dose escalation will be determined based on the occurrence of DLTs observed in the first cycle of therapy. For the purposes of dose determination, DLTs will be counted by patient, i.e., a patient who experiences more than one DLT will be counted only once. Discontinuation of treatment due to disease progression will not constitute a DLT. In the phase I portion of this trial, if a patient goes off treatment before completing cycle one for reasons other than toxicity or DLT, they will be replaced at that dose level to fully evaluate the tolerability of this regimen at that dose level. 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 CT-011 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. **For the Phase II portion** Upon completion of the cohorts in phase I, the phase II portion of the study will commence utilizing the planned target doses (or MTDs determined) with CT-011 in combination with lenalidomide and dexamethasone During the phase II portion of this trial, we will not evaluate patients for DLTs as was done in the phase I portion; however, we will use the DLT criteria to identify potential toxicity and tolerability concerns occurring at any cycle to initiate further evaluation to ensure safety of patients. 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	Dosing cohorts for the phase I study: We will conduct a standard 3+3 design over 4 dose levels of 1.5, 3, 3, and 6 mg/kg of CT-011 given intravenously every 4 weeks (28 days) on day 3, and lenalidomide given at 15, 15, 25, and 25 mg orally daily on days 1-21 of a 28-day cycle. The study drug CT-011 and lenalidomide can move independently of one another as described in the Table below. Dexamethasone 40 mg orally weekly may be added if only stable disease after 3 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. A minimum of 3 patients to a cohort with at least one week break between cohorts. **CT-011** **Lenalidomide** If a DLT occurs in 2 or more patients during the first cycle, we will consider this

	CT-011- mg/kg day 3
Cohort -1	1.5
Cohort -2	1.5
Cohort 1	1.5
Cohort 2	3
Cohort 3	3
Cohort 4	6

	Lenalidomide- mg Days 1-21
Cohort -1	10
Cohort -2	5
Cohort 1	15
Cohort 2	15
Cohort 3	25
Cohort 4	25

	dose level to exceed the MTD and therefore be deemed intolerable for this patient population. If a DLT occurs in 1 of 3 patients during this time, an additional 3 patients will be enrolled and evaluated for DLT before dose escalation can proceed. If no other patient in the cohort has a DLT, escalation to the next cohort may proceed 1 week later from the last included patient on the current cohort. If a second patient in a cohort has a DLT, MTD determination will then be conducted by one of the following schemes: • If ≥ 2 of 3 patients in cohort 1 exhibit a DLT at the dose of 1.5 mg/kg CT-011 in combination with lenalidomide 15 mg, 3 more patients will be enrolled at a de-escalated dose level cohort. This de-escalation cohort (Cohort -1) will use the same dose of CT-011 (1.5 mg/kg) in combination with 10 mg lenalidomide. If no further DLTs are observed, we will consider dose escalation of the CT-011 with this lower dose of lenalidomide such that the dose escalation of CT-011 to 3 mg/kg with lenalidomide 10 mg will proceed in the next cohort. However, if ≥2 patients experience DLT with CT-011 1.5 mg/kg and lenalidomide 10 mg, then we will further de-escalate lenalidomide to 5 mg and enroll 3 more patients on CT-011 1.5 mg/kg combined with lenalidomide 5 mg. The same criteria for MTD will be used for these de-escalation dose level cohorts. • If ≥ 2 patients in cohort 2 exhibit a DLT at the dose of 3 mg/kg CT-011 in combination with lenalidomide 15 mg, we will explore tolerability of an intermediate dose level of lenalidomide, where 3 patients will be enrolled and treated with 3 mg/kg of CT-011 in combination with 10 mg lenalidomide. The dose escalation of CT-011 to 6 mg/kg with lenalidomide 10 mg will proceed in the next cohort if no more than one DLT is observed in the 3 mg/kg CT-011+10mg lenalidomide cohort. • If ≥ 2 patients in cohort 3 exhibit a DLT at the dose of 3 mg/kg CT-011 in combination with lenalidomide 25 mg, 3 more patients will be enrolled at the 3 mg dose of CT-011 in combination with 15 mg lenalidomide. If there is < 1 DLT with CT011 3mg/kg and lenalidomide 15 mg, this will be defined as the MTD. If there are 2 or more DLT, then 3 additional patients will be enrolled at the CT-011 3mg/kg and lenalidomide 10 mg, which will become the MTD. • If ≥ 2 patients in cohort 4 exhibit a DLT at the dose of 6 mg/kg CT-011 in combination with lenalidomide 25 mg, 3 more patients will be enrolled at the 6 mg dose of CT-011 in combination with 15 mg lenalidomide. If there is < 1 DLT with CT011 6mg/kg and lenalidomide 15 mg, this will be defined as the MTD. If there are 2 or more DLT, then 3 additional patients will be enrolled at the CT-011 6mg/kg and lenalidomide 10 mg, which will become the MTD. Once the MTD has been established or determined, an additional 18 subjects will be treated at the MTD in the phase II.
Planned Sample size	For the phase I portion: a minimum of 12 and a maximum of 30 patients will be recruited. For the phase II portion: a maximum of 23 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 12-24 months.

Eligibility	**Inclusion criteria**
	
	• Patients must be at least 18 years of age with evidence of relapse or refractory disease 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)
	  o Measurable biopsy proven plasmacytoma (should be measured within 28 days of registration to study)
	• Patients must have had at least 2 prior lines of therapy.
	• Patients must not have had progression of disease on lenalidomide 25 mg. Stable disease on lenalidomide is permitted.
	• 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
	  o Female patients with child bearing potential must have a negative pregnancy test at least 7 days before starting treatment drugs.
	  o Male patients must agree to use an adequate method of contraception for the duration of the study and for 90 days afterwards.
	  o 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 90 days afterwards.
	  o 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 other than for physiologic maintenance treatment. Patients should otherwise discontinue corticosteroids prior to registration to study.
- 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 prior to registration 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 registration to study 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.

Contents

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. Natural Killer cells and MM

Natural Killer cells (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[13-15]. 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[16, 17]. 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[6,7,18.]

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[32].

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[33]. 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[33].

Two phase III trials comparing lenalidomide + dexamethasone to single agent dexamethasone in patients with relapsed and/or refractory multiple myeloma were published[34,35]. 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 + Dexamathasone	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[36]. Subsequently most therapies involving dexamethasone, uses low-dose.

1.4 MDV9300 (CT-011)

MDV9300 (Medivation, Inc., previously CT-AcTibody or BAT) is a novel IgG1 humanized monoclonal antibody (mAb) that modulates the immune system, with previously demonstrated anti-tumor efficacy in experimental models of both solid and liquid tumors[25,29,30,37-39].

1.4.1 CT-011 Preclinical Studies

The efficacy of CT-011 and its murine version mCT-011 (formerly BAT) was studied in experimental tumor models of leukemia, lymphoma, melanoma, lung, colon, fibrosarcoma, and breast cancers[37, 39, 41, 43-46]. Treatment with the antibody resulted in an immune response against murine and human tumors, and inhibited tumor growth, extended the survival of tumor-bearing mice, and generated tumor-specific protection against tumor re-challenge. Specifically for BCL1 leukemia/lymphoma model, mCT-011 treatment resulted in the reduction of peripheral blasts and blood leukocytosis and in the enhancement of survival of tumor-bearing mice[43]. CT-011 was shown to best operate when administered 10-14 days post tumor inoculation, suggesting it may be relevant for the treatment of active disease. The activity of the antibody was suggested to be associated also with processes of lymphopoiesis as the administration of mCT-011 to athymic mice and to athymic mice engrafted with human colon carcinoma resulted in induced lymphopoiesis exhibited in the increase in the number of CD3 CD4 and CD8 T cells as well of CD56 positive NK cells[47]. In MM, CT-011 was shown to enhance ex-vivo T cell responses to autologous dendritic/myeloma fusion vaccine for multiple myeloma[48]. CT-011 also enhanced human NK-cell function against autologous primary MM cells through effects on NK-cell trafficking, immune complex formation with MM cells, and cytotoxicity specifically toward MM tumor cells but not normal cells[12]. CT-011 alone or the combination with lenalidomide was shown to statistically significantly increase cytotoxicity against MM tumor cell targets when compared to control ($p=0.02$)[49].

1.4.2 CT-011 Clinical Studies

A Phase 1, open-label, dose-escalation study was conducted in 17 hematological malignancy patients[50]: eight acute myeloid leukemia (AML) patients, four non-Hodgkin's lymphoma (NHL)

patients, three chronic lymphocytic leukemia (CLL) patients, one Hodgkin's disease (HD) patient, and one multiple myeloma (MM) patient. The purpose of the study was to evaluate the safety, pharmacokinetics, clinical response, and maximum tolerated dose (MTD) of CT-011 (0.2, 0.6, 1.5, 3.0, and 6.0 mg/kg). Most patients had failed several lines of conventional chemotherapy and radiotherapy as well as allogeneic (n=6) or autologous (n=3) stem cell transplantation prior to their enrollment to the study. Eleven of the patients were females and six were males, with an average age of 61 (20–77) years. Sixteen were Caucasian and one Middle-Eastern. In this study, CT-011 was found to have an acceptable safety profile at all dose levels, and was overall well tolerated with no observed serious/unexpected treatment-related adverse events and no observed infusion-related responses. The most common adverse event was diarrhea, which was detected in one low-dose patient (0.2 mg/kg) and one patient treated at the 3 mg/kg dose level. No single dose MTD could be established in this study. Apparent clinical responses were observed in six of the patients 12 months after treatment with CT-011: one complete remission (NHL - follicular lymphoma), four stable disease (HD, 2 CLL, and MM), and one minimal response (AML: platelet-transfusion-independency for 11 months post treatment). Transient elevations in the percentage of peripheral blood CD4+ lymphocytes were observed at 24 hours post CT-011 treatment in 15 of the patients.

A phase II study of CT-011 in combination with rituximab in patients with relapsed follicular lymphoma has been completed. CT-011 given to patients with diffuse large B-Cell lymphoma following autologous stem cell transplant showed increases in specific CD4+ effector/memory T-lymphocytes[51]. The study has been completed and results and analysis of progression free survival are forthcoming.

The pharmacokinetics of CT-011 was found to be proportionally correlated with the dose with a median t1/2 ranging between 270 hrs. and 410 hrs. No gender-related or disease-related differences in the pharmacokinetics of CT-011 were found. The median t1/2 for the six patients evaluated for apparent beneficial clinical responses was higher than that of the rest of the patients.

1.4.3 Toxicity of CT-011

Adverse Events Reported during Phase 1 Human Study

Adverse Events	Number of patients	Relationship to treatment
Diarrhea[1]	2	none
Rash[2]	1	none
Pain	1	none
Back pain	1	none
Shortness of breath	1	none
Weakness	1	possible
Flushing	1	possible
Blurred vision	1	none
Pressure wound	1	none
Urine infection	1	none

1. One of the patients had diarrhea at the time of enrollment
2. The patient was enrolled with rash

Adverse Events reported in the study in DLBCL patients after transplant:

Data presented as number of patients with a given AE (number of events are shown in parentheses). Events noted ONLY as Grade 1-2, are shown at ≥10% of total number of events.

Event	**Number of patients (Number of events)**					
	Severity Grade					
	All grades	1	2	3	4	5

Event	Number of patients (Number of events)					
	Severity Grade					
	All grades	1	2	3	4	5
Any AE	69(613)	65(392)	49(145)	30(60)	9(14)	1[a] (1)
Neutropenia	19(25)	3(3)	7(7)	9(10)	5(5)	-
Fatigue	18(21)	16(19)	2(2)	-	-	-
Upper respiratory tract infection	14(15)	9(10)	5(5)	-	-	-
Diarrhea	12(19)	10(14)	4(5)	-	-	-
Cough	12(14)	11(13)	1(1)	-	-	-
Thrombocytopenia	10(15)	5(6)	-	4(5)	2(4)	-
Hyperglycemia	9(12)	8(10)	2 (2)	-	-	-
Leukopenia	9(12)	6(8)	3 (3)	1(1)	-	-
Pyrexia	9(11)	3(3)	4(6)	2(2)	-	-
Anemia	7(8)	2(3)	2(2)	3(3)	-	-
Neurtophil count decreased	7(7)	1(1)	3(3)	3(3)	-	-
Hypotension	7(9)	3(5)	3(3)	1(1)	-	-
APTT prolonged	6(7)	3(4)	2(2)	1(1)	-	-
Headache	6(8)	5(7)	-	1(1)	-	-
Herpes zoster	5(5)	1(1)	3(3)	1(1)	-	1(1)[a]
Lymphopenia	5(5)	1(1)	3(3)	1(1)	-	-
Platelet count decreased	5(5)	4(4)	-	1(1)	-	-
Vomiting	4(6)	2(2)	2(2)	1(2)	-	-
Urinary tract infection	4(4)	1(1)	2(2)	1(1)	-	-
Renal failure	3(3)	1(1)	-	2(2)	-	-
Hypertension	3(3)	-	2(2)	1(1)	-	-
DVT	3(3)	1(1)	1(1)	1(1)	-	-
Pain	3(3)	2(2)	-	1(1)	-	-
Fall	3(3)	1(1)	1(1)	1(1)	-	-
Lobar pneumonia	2(2)	1(1)	-	1(1)	-	-
Hypophosphatemia	2(3)	-	2(2)	1(1)	-	-
Bone pain	2(2)	-	1(1)	1(1)	-	-
Head injury	1(1)	-	-	-	1(1)	-
Accident	1(1)	-	-	-	1(1)	-
Myelodysplastic syndrome	1(1)	-	-	-	1(1)[b]	-
Intracranial hemorrhage	1(1)	-	-	-	1(1)	-
Subarachnoid hemorrhage	1(1)	-	-	-	1(1)	-
Pneumothorax	1(1)	-	-	-	1(1)	-
Cardiac arrest	1(1)	-	-	1(1)	-	-
Duodenal ulcer	1(1)	-	-	1(1)	-	-
GI hemorrhage	1(1)	-	-	1(1)	-	-
General physical health decline	1(1)	-	-	1(1)	-	-
Clostridium difficile colitis	1(1)	-	-	1(1)	-	-
Vascular injury	1(1)	-	-	1(1)	-	-
Pelvic fracture	1(1)	-	-	1(1)	-	-
Hyperhidrosis	1(1)	-	-	1(1)	-	-
Cholecystectomy	1(1)	-	-	1(1)	-	-
Blood Phosphorus decreased	1(1)	-	-	1(1)	-	-
Glioma	1(1)	-	-	1(1)	-	-
Tachypnea	1(1)	-	-	1(1)	-	-
COPD	1(1)	-	-	1(1)	-	-
ARDS	1(1)	-	-	1(1)	-	-

Event	Number of patients (Number of events)					
	Severity Grade					
	All grades	1	2	3	4	5
Facial bone fracture	1(1)	-	-	1(1)	-	-
Myositis	1(1)	-	-	1(1)	-	-
Rhabdomyolysis	1(1)	-	-	1(1)	-	-
Hemoglobin decreased	9(9)	6(6)	3(3)	-	-	-
Nausea	8(9)	7(8)	1(1)	-	-	-
Sinusitis	6(9)	2(2)	4(7)	-	-	-
Insomnia	7(7)	7(7)	-	-	-	-
Rash	6(7)	6(7)	-	-	-	-

[a]One patient developed fatal disseminated zoster infection during the follow-up period 10 months after last dose of pidilizumab. This was considered unrelated to study drug.
[b]One patient with pre-existing leukopenia and thrombocytopenia developed myelodysplasia 13 months following the last dose of pidilizumab. This was considered unrelated to study drug.

Adverse events reported in the study in patient with follicular lymphoma observed in at least 3 patients regardless of attribution

Adverse Event	Number of Patients (Percentage of Patients)			
	Severity Grade			
	All	1	2	3/4/5
Fatigue	15 (50%)	13 (43%)	2 (7%)	0
Anemia	14 (47%)	14 (47%)	0	0
Leukopenia	11 (37%)	11 (37%)	0	0
Thrombocytopenia	10 (34%)	8 (27%)	2 (7%)	0
Respiratory Infection	6 (20%)	1 (3%)	5 (17%)	0
Neutropenia	6 (20%)	5 (17%)	1 (3%)	0
Dyspnea	6 (20%)	6 (20%)	0	0
Pain	5 (17%)	3 (10%)	2 (7%)	0
Nausea	5 (17%)	5 (17%)	0	0
Edema	4 (13%)	3 (10%)	1 (3%)	0
Sweating	4 (13%)	4 (13%)	0	0
Neuropathy	4 (13%)	4 (13%)	0	0
Cough	4 (13%)	4 (13%)	0	0
Hypotension	3 (10%)	2 (7%)	1 (3%)	0
Pruritus	3 (10%)	3 (10%)	0	0
Diarrhea	3 (10%)	3 (10%)	0	0
Anorexia	3 (10%)	3 (10%)	0	0

Infusion related Events:

Infusion related actions were not reported as such in study in patients with DLBCL following autologous stem cell transplantation. However, there were several adverse events that were noted on the days when CT-011 was administered that were regarded as possibly or probably related to CT-011 by the investigators. These included the following:

Adverse event	Grade	Number of patients	Action taken
Hypotension	1 (3 subjects) 2 (1 subject)	4	None (2 subjects) Dosing temporary interrupted (2 subjects)
Fatigue	1	3	None

Adverse event	Grade	Number of patients	Action taken
Pain	1	2	None
Nausea	1	2	None
Arthralgia	1	1	None
Cough	1	1	None
Drowsiness	1	1	None
Facial flushing	1	1	None
Hot flashes	1	1	None
Hypoxia	2	1	None
Pruritius	1	1	None

Two infusion reactions have been reported in study in patients with colorectal cancer, both at the FOLFOX plus CT-011 arm. In one patient “infusion related reaction/hypersensitivity” was noted after 4 dosages of CT-011 (approximately 3 months from study start) that was assessed by the investigator to be a grade 2 oxaliplatin related toxicity (unrelated to CT-011) manifested by shortness of breath and flushing. Further treatment in the study was discontinued. The second patient experienced an “infusion allergic reaction” after 4 dosages of CT-011 (approximately 3 months from study start) that was assessed by the investigator to be a grade 1 5FU and oxaliplatin related toxicity (unrelated to CT-011). In addition, there has been one case of Grade 2 hypersensitivity possibly related to CT-011 that occurred on the day of CT-011 infusion in the study but not defined as an infusion related. Two additional hypersensitivity events (Grade 1 and 3) had occurred previously in the same patient on days other than those of CT-011 administration and also defined as possibly related to CT-011.

Eight subjects that participated in a study in patients with metastatic melanoma experienced infusion reactions manifested in the following symptoms:

Adverse event	Grade	Number of patients[1]	Dose (mg/kg)	Action taken
Urticaria	3 (1 subject) 1 (1 subject)	2	6.0	Patient with Grade 1 event: Dose interrupted; Patient with Grade 3 event: Dose interrupted, concomitant medication given and dose reduced to 1.5mg/kg.
Hypotension	2	1	6.0	Dose interrupted
Hypertension	2	2	6.0	Dose interrupted
Rigors	2	1	6.0	Dose interrupted (event accompanying hypertension)
Facial flushing	1	1	6.0	None
Injection site reaction	1	1	6.0	None
Burning at iv site	1	1	1.5	None

(1) Hypertension and rigors occurred in the same patient

Autoimmune Toxicity
Three serious adverse events with potentially immunological etiology have been noted in a study in patients with metastatic melanoma and include Grade 3 arthritis, Grade 3 pneumonitis and Grade 4 hepatitis.

1.4.4 CT-011 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[16, 52]. Numbers of both T cells and NK cells are increased in patients receiving IMID therapy[53]. NK cell killing is also enhanced including antibody-dependent cellular cytotoxicity (ADCC) and natural NK cell cytotoxicity[53, 54]. These events correlate with clinical responses to IMID therapy in patients[53]. In our study, CT-011 alone, and with lenalidomide, exerts effects on the NK cell cytoskeleton and increased migration of NK cells towards MM targets mediated via the CXCR4 / stromal-derived factor-1α (SDF-1α) pathway. Pretreatment of NK cells with CT-011 with or without lenalidomide enhanced immune complex formation between NK cells and MM tumor targets and also augmented NK cell activation and cytotoxicity against MM, as well. The combination of CT-011 and lenalidomide synergistically enhanced NK cell interferon-gamma production against RPMI-8226, a lenalidomide-resistant multiple myeloma cell line, and enhanced NK cell target acquisition of primary multiple myeloma tumor cells.

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[34,35]. 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[36]. The response to the combination was shown even in patients with prior thalidomide use[55], however, response is better if used earlier than later[56]. 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[33]. 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.

We sought to determine the response in relapse/refractory multiple myeloma patients using CT-011 in combination with lenalidomide. Because decreased NK cell activity and enhancement may be seen with steroids[57] (although less so at low doses), patients will receive CT-011 plus lenalidomide with an option to add low-dose dexamethasone after 3 cycles if stable disease.

2 STUDY OVERVIEW AND OBJECTIVE

2.1 Study Overview

This is a single-arm, open label, phase I/II study of CT-011 in combination with lenalidomide in adult (age 18 years and older) patients with relapsed MM. A 4-cohort, dose-escalation, phase I portion will

be completed with the primary endpoint to determine safety and tolerability, seeking maximally tolerated doses (MTDs) of each agent in combination in a standard 3+3 design over 4 dose levels of 1.5, 3, 3, and 6 mg/kg of CT-011 given intravenously every 4 weeks (every 28 days), and lenalidomide given at 15, 15, 25, and 25 mg orally daily on days 1-21 of a 28-day cycle. A minimum of 12 and a maximum of 30 patients will be recruited for the phase I portion of the study. Upon identification of the MTD for the dose level combination of CT-011 and lenalidomide, the phase II portion of the study will commence accruing an additional 23 patients to assess 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, pharmacokinetic and pharmacodynamics data, immunomonitoring of lymphocyte subsets, including T and NK cell subsets, and *ex vivo* immune functional assays. For both phases, Dexamethasone 40 mg orally weekly may be added if only stable disease after 3 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 maximum tolerated dose (MTD), safety and efficacy of CT-011 in combination with lenalidomide (Revlimid) and assess efficacy in terms of overall response rate in patients with relapse/refractory multiple myeloma (MM)

2.3 Primary Endpoints

- To determine MTD of CT-011 in combination with lenalidomide in the phase I study. The MTD of CT-011 combined with lenalidomide will be defined as the highest dose combination of CT-011 and lenalidomide at which ≤ 1of 6 patients at that dose level has dose-limiting toxicity.
- 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).
- To determine overall survival (OS).
- To assess pharmacokinetics and pharmacodynamics of CT-011 in combination with lenalidomide.
- To assess CT-011 immunogenicity and 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 NCI CTCAE v.4

3 ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

- Patients must be at least 18 years of age with evidence of relapse or refractory disease as defined by IMWG criteria and 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 registration to study)

- Patients must have had at least 2 prior line of therapy.
- Patients must not have had progression of disease on lenalidomide 25 mg. Stable disease on lenalidomide is permitted.
- 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 within 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 90 days after study therapy discontinuation.
  - 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 continuing through 90 days after study therapy discontinuation.
  - 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 for reason(s) other than for physiologic maintenance treatment. Patients should otherwise discontinue corticosteroids prior to registration to study.
- 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 prior to registration 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 registration to study 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 STUDY DESIGN AND DURATION

4.1 Study Design

This is a non-randomized open-label phase I/II study for patients with relapsed and refractory multiple myeloma. For the phase I part, we will conduct a standard 3+3 design over 4 main dose levels cohorts evaluating 1.5, 3, 3, and 6 mg/kg of CT-011 given intravenously every 4 weeks (every 28 days) on day 3, and lenalidomide given at 15, 15, 25, and 25 mg orally daily on days 1-21 of a 28-day cycle, to determine the maximum tolerated dose. The phase II will commence once the MTD is determined, and this dose level combination for CT-011 and lenalidomide will be used for the phase II portion of this trial. Patients will be assessed for response at the end of cycle 4 or sooner if necessary according to the IMWG response criteria.

4.2 Definition of Dose Limiting Toxicity

For the phase I portion, patients will be monitored for safety by assessing toxicities as graded by the NCI CTCAE v4.0. The maximum tolerated dose (MTD) or 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 non-hematologic 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

4.3 Dose Escalation/De-escalation

If a DLT occurs in 2 or more patients on a dose level during the first cycle, the MTD will be exceeded and we will consider this dose level to be intolerable. If a DLT occurs in 1 of 3 patients during this time, an additional 3 patients will be enrolled at that dose level cohort and evaluated for DLT before dose escalation can proceed. If no other patient in the cohort has a DLT, escalation to the next cohort may proceed 1 week later from the last included patient on the current cohort. If a second patient in a cohort has a DLT, MTD determination will then be conducted by one of the following schemes:

- If ≥ 2 of 3 patients in cohort 1 exhibit a DLT at the dose of 1.5 mg/kg CT-011 in combination with lenalidomide 15 mg, 3 more patients will be enrolled at a de-escalated dose level cohort. This de-escalation cohort (Cohort -1) will use the same dose of CT-011 (1.5 mg/kg) in combination with 10 mg lenalidomide. If no further DLTs are observed, we will consider dose escalation of the CT-011 with this lower dose of lenalidomide such that the dose escalation of CT-011 to 3 mg/kg with lenalidomide 10 mg will proceed in the next cohort. However, if ≥2 patients experience DLT with CT-011 1.5 mg/kg and lenalidomide 10 mg, then we will further de-escalate lenalidomide to 5 mg and enroll 3 more patients on CT-011 1.5 mg/kg combined with lenalidomide 5 mg. The same criteria for MTD will be used for these de-escalation dose level cohorts.

- If ≥ 2 patients in cohort 2 exhibit a DLT at the dose of 3 mg/kg CT-011 in combination with lenalidomide 15 mg, we will explore tolerability of an intermediate dose level of lenalidomide, where 3 patients will be enrolled and treated with 3 mg/kg of CT-011 in combination with 10 mg lenalidomide. The dose escalation of CT-011 to 6 mg/kg with lenalidomide 10 mg will proceed in the next cohort if no more than one DLT is observed in the 3 mg/kg CT-011+10mg lenalidomide cohort.

- If ≥ 2 patients in cohort 3 exhibit a DLT at the dose of 3 mg/kg CT-011 in combination with lenalidomide 25 mg, 3 more patients will be enrolled at the 3 mg dose of CT-011 in combination with 15 mg lenalidomide. If there is < 1 DLT with CT011 3mg/kg and lenalidomide 15 mg, this will be defined as the MTD. If there are 2 or more DLT, then 3 additional patients will be enrolled at the CT-011 3mg/kg and lenalidomide 10 mg, which will become the MTD.

- If ≥ 2 patients in cohort 4 exhibit a DLT at the dose of 6 mg/kg CT-011 in combination with lenalidomide 25 mg, 3 more patients will be enrolled at the 6 mg dose of CT-011 in combination with 15 mg lenalidomide. If there is < 1 DLT with CT011 6mg/kg and lenalidomide 15 mg, this will be defined as the MTD. If there are 2 or more DLT, then 3 additional patients will be enrolled at the CT-011 6mg/kg and lenalidomide 10 mg, which will become the MTD

To determine dose escalation, we will focus on the number of patients who experience dose limiting toxicity; i.e. a patient who experiences more than one DLT will be counted only once.

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

In the Phase 1 portion of the study, subjects who withdraw or prematurely discontinue treatment before completing the first treatment cycle for reasons other than toxicity and DLT will be replaced.

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 CT-011, lenalidomide and dexamethasone(if initiated after cycle 1-2) will continue for a minimum of 8 additional cycles or until withdrawal.

For the Phase II portion
Upon determination of the MTD in the phase I portion of this trial, the phase II portion of the study will commence enrollment at the MTD determined in the phase I portion with CT-011 in combination with lenalidomide. In the event that a MTD is not established, safety and tolerability data collected in the Phase I portion of the study will guide decisions on dosing of CT-011 in the phase II trial. Dexamethasone 40 mg orally weekly may be added if only stable disease after 3 cycles according to the IMWG criteria (section13). Dexamethasone can be reduced to 20 mg based on tolerability or if patient is 70 years or older.

During the phase II portion of this trial, we will not evaluate patients for DLTs as was done in the phase I portion; however, we will use the DLT criteria to identify potential toxicity and tolerability concerns occurring at any cycle to initiate further evaluation to ensure safety of patients. An independent Data and Safety Monitoring Committee will continue oversight of this trial. See Appendix E for details.

4.4 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. Otherwise patient can continue treatment until one of the above endpoints is reached.

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.

4.5 Study Accrual

For the phase I portion, a minimum of 12 and a maximum of 30 patients will be recruited. Once the MTD has been established, an additional 23 subjects will be treated at the MTD in the phase II.

4.6 Duration of Study Period

The total study enrollment period is expected to be up to 24 months.

5 TREATMENT PLAN AND PROCEDURES

For the Phase I portion, this is a standard 3+3 design over 4 dose levels of 1.5, 3, 3, and 6 mg/kg of CT-011 given intravenously every 4 weeks (every 28 days) on day 3, and lenalidomide given at 15, 15, 25, and 25 mg orally daily on days 1-21 of a 28-day cycle. The study drug CT-011 and lenalidomide can be escalated or de-escalated independently of one another as described in the Table below. Twelve to 30 patients will be recruited in the phase I portion of the trial. The phase II portion will utilize the 6 patients treated at the MTD in the phase I portion and an additional 23 patients will be accrued. Dexamethasone 40 mg orally weekly may be added if only stable disease after 3 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.

5.1 CT-011

5.1.1 Schedule

Table 5-1: Treatment Regimen During Phase I Study: 28 day Cycle

	CT-011- mg/kg day 3
Cohort -1	1.5
Cohort -2	1.5
Cohort 1	1.5
Cohort 2	3
Cohort 3	3
Cohort 4	6

	Lenalidomide- mg Days 1-21
Cohort -1	10
Cohort -2	5
Cohort 1	15
Cohort 2	15
Cohort 3	25
Cohort 4	25

CT-011 is an investigational agent supplied by Medivation, Inc., It is supplied for this protocol for clinical trial use only and it is not commercially available.

5.1.2 Premedication

All patients will receive pain relief medication (Tylenol 650mg or Ibuprofen 800mg or related medication), and an antihistamine (H1 blocker; 25-50mg diphenhydramine hydrochloride administered I.V.). 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 CT-011 dose, chlorpheniramine administered at 10mg I.V 20-50 minutes prior to CT-011 dose, oral chlorpheniramine taken 2 hours prior to CT-011 dose or oral diphenhydramine taken 2 hours prior to CT-011 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.

5.1.3 Route and Method of Administration

CT-011 will be administered intravenously on day 3 of a 28 day cycle.
CT-011 is to be administered intravenously using a peripheral line or a central device if such has been inserted. Patients will be dosed on a mg/kg basis.

The first time CT-011 is to be administered intravenously at a dose of 1.5/3.0/6.0mg/kg delivered over approximately 2 hours as follows:

1. Initial rate of infusion is 50 mL/hr for 30 minutes; If no symptoms related to infusion appear:
2. Increased rate to 100 mL/hr; for 30 minutes; If no symptoms appear:
3. Increased rate to 150 mL/hr for 30 minutes; If no symptoms appear:
4. Increase rate to 200 mL/hr for 30 minutes;

In the event that Grade 3 or higher infusion-related toxicity occurs during infusion, administration of CT-011 should be stopped immediately. Administration of CT-011 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.

If no drug related or infusion related adverse events occur during the first administration, further CT-011 administrations could be delivered over approximately 1:15 hours at a rate of 200mL/hr. Subsequent administrations should be made as scheduled in the absence of Grade 3 or higher adverse events or disease progression.

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 CT-011, the IV infusion line must be flushed with 0.9% sodium chloride. The following are two recommended methods for flushing the CT-011 IV infusion line:

1) When the CT-011 infusion is complete, add an additional 50mL of 0.9% sodium chloride for

injection to the CT-01 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 CT-011 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.

5.1.4 CT-011 Infusional monitoring

The potential risks that may be related to the administration of monoclonal antibodies in general, adverse events that were possibly related to CT-011 administration in the Phase 1 study, and a few theoretical risks for CT-011 included infusion-related effects. Infusion related effects have not been observed in the Phase I clinical study with CT-011.

Vital signs (temperature, blood pressure, pulse rate, respiratory rate) and ECG will be closely monitored prior to, during, and after 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.

5.1.5 CT-011 Dose Adjustments

The phase I study showed that CT-011 was well tolerated with no treatment related toxicity at all dose level[50]. Specifically no hematologic toxicity was seen. No dose adjustments or modifications will be made with CT-011 except If DLT was seen with CT-011 at 3 mg/kg in combination with lenalidomide 5 mg, then CT-011 will be reduced to 1.5 mg/kg with lenalidomide 5 mg, which will be the DLT. If adverse events occur that require holding CT-011, the dose will remain the same once treatment resumes. If CT-011 is held for more than 4 weeks, then patient will be taken off study.

5.2 Lenalidomide (Revlimid™)

5.2.1 Lenalidomide Administration and Schedule

Lenalidomide will be given orally. Schedule as shown in table 5.1
The first dose level starts at 15 mg days 1-21 of a 28 day cycle.
If a dose is missed or vomited up, the dose will not be made up.

Beginning by day 1 of cycle #2 and on day 1 of every cycle thereafter, while all six conditions below have been met, patients will be evaluated for lenalidomide dose escalation.
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
- Not yet reached the maximum daily dose of 25 mg of lenalidomide
- Are willing to undergo dose escalation of lenalidomide.
- Serum Creatinine maintained at ≤ 2mg/dL as in initial eligibility

Then the patient's dose for lenalidomide will be increased by 5 mg per cycle for days 1-21 of a 28 day cycle. If any of the criteria are not met, then no lenalidomide dose escalations will occur during this cycle.

5.2.2 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.

5.3 Dexamethasone

Dexamethasone 40 mg orally weekly (days 1,8,15, 22) may be added if only stable disease after 3 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.

5.3.1 Table 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 dexamethsone).
Rash *Lenalidomide*	If grade 3 or greater, hold lenalidomideuntil 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
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

5.3.2 Lenalidomide dose levels

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.

5.4 Dexamethasone

Dexamethasone 40 mg orally weekly (days 1,8,15, 22) may be added if only stable disease after 3 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.

5.5 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 will receive prophylaxis with either an H-2 blocker or proton pump inhibitor while on study medications. 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.

5.5.1 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.

5.5.2 Growth factors

Prophylactic use of growth factors is not recommended.

5.6 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 by 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.

5.7 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
- Patients' non-compliance with the protocol that can negatively affect the treatment effect
- Patients who express a desire to withdraw from the study (the patient has the right to withdraw for any reason without prejudice)
- Evidence of progressive disease would require withdrawal of the patient from the study.
- Any other reasons deemed by the principal investigator and treating physician.
- Patients who must discontinue use of either CT-011 or lenalidomide

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 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.
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 up.

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.

5.8 Schedule of Tests and Observations

5.8.1 Screening

Medical history & clinical examination, ECOG/WHO PS, vital signs, concomitant medications, date of diagnosis, previous treatment, and appropriate assessment of inclusion and exclusion criteria will be performed within 4 weeks prior to starting protocol-based therapy.

5.8.2 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

5.8.3 Post-treatment Follow-up

After the end of study treatment (whatever the reason for discontinuation), the patient will be followed for 6 months. Adverse events will be followed for at least 30 days, during which time all procedures for the reporting of SAEs will be followed.

a. 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. Follow up data should be submitted at 1 month after protocol therapy discontinuation and then every 3 months until progression or death, whichever occurs first.

5.8.4 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.

5.8.5 Schedule for correlative studies

Laboratory correlative studies will be obtained at screening, days 3, 4, 6, 10 and 17 of cycle 1, days 3 of subsequent 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).

5.8.6 Schedule of Events[a]

Investigations	Screening	C1D3	C1D4	C1D6	C1D10	C1D17	C2D3	C3D3	C5D3	CxD3	End of Tx[b]	Follow Up[p]
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	X										
Toxicity evaluation	X	X					X	X		X	X	X
CBC / differential / platelets[e]	X	X					X	X	X	X[f]	X	
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			X	
12-lead ECG[h]	X							X				
Serum monoclonal protein assessments[i]	X	X[i]					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[j]	X[j]	
BM biopsy, unilateral[k]	X								X[k]		X[k]	
CT-011 Given		X					X	X	X	X		
Prescribe lenalidomide via RevAssist[l]	X											
T-cell, NK-cell, and CD14 Correlative studies[m]	X	X	X	X	X	X	X	X	X	X	X	X

CT-011 PK[n]		X	X	X	X	X	X					
ADA (immunogenicity)[o]	X											

a. With the exception of PK samples, all othertime points 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. Lenalidomide and dexamethasone will start on day 1 of each cycle. Patients 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 serum ß-HCG) will also be ordered at this time. Patients must have a negative ß-HCG result prior to starting lenalidomide on day 1 of each cycle.
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. CBC/d/p should also be checked on day 17 of a cycle where lenalidomide's dose has been escalated.
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 electropheresis & immunofixation, immunoglobulin levels, serum free light chain assay) will be performed on day 3 of each cycle (when patients come in for CT-011 infusion) as well as off study.
j. 24hr urine monoclonal protein assessment (Urine protein electropheresis & 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. T-cell, NK-cell, and CD14 correlates will be collected prior to CT-011 dosing on C1D3, C1D4, C1D6, C1D10, C1D17 and then on Day 3 of all subsequent cycles. T-cell correlates only will also be collected at 1, 3, and 6 months after discontinuation of protocol therapy.
n. Samples for CT-011 PK determination will be collected in cycle 1 prior to CT-011 infusion, immediately at the end of the infusion, 1 hour after end of infusion, approximately 24(C1D4), 72(C1D6), 168 (C1D10)) & 336 (C1D17)) hrs– and just prior to next (cycle 2) infusion. Off-study correlates should be obtained at the time the patient is removed from protocol for any reason.
o. We will assess for immunogenicity at baseline and monthly starting 1 month after dose level 3 (3 mg/kg) is started. This will be done within 30 minutes of CT-011 infusion. This will be done by Medivation Inc. (see Appendix G)
p. Adverse events 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. Follow up data should be submitted at 1 month after protocol therapy discontinuation and then every 3 months until progression or death, whichever occurs first.

6.0 STATISTICAL CONSIDERATIONS

6.1 Overview of study design

This is a phase I/II clinical trial designed to first determine the MTD of the combination of CT-011 + lenalidomide in relapsed/refractory MM patients and then to assess the associated efficacy of this regimen in this patient population through evaluation of the overall response rate. The phase I portion follows the standard cohorts-of-3 phase I clinical trial design, and the phase II portion will utilize a one-stage three outcome phase II design (Sargent et al, 2001).

6.1.1 Phase I portion

In the phase I portion, we will assess the MTD using a standard cohorts-of-3 phase I trial design, where the MTD is defined as the dose level at which no more than one of 6 patients experiences a dose-limiting toxicity (DLT). The dose escalation rules follow the standard design, where cohorts of 3 are accrued to a dose level and evaluated for DLT before making a decision to dose escalate or not. If in the first 3 patients on a dose level there are no DLTs observed, the next cohort of 3 can be accrued to the next dose level. If one DLT of the first 3 patients at a dose level experiences DLT, then 3 additional patients will be accrued to that dose level to ensure it is tolerable and does not exceed the MTD. Any dose that has two or more patients with DLTs has exceeded the MTD and is deemed to have unacceptable toxicity. If the first dose level proves to have unacceptable toxicity (i.e. 2+ DLTs), then 3-6 patients will be accrued to the de-escalation dose level (dose level -1). For this portion of the trial, we expect a minimum of 12 patients (worst case scenario of 2+ DLTs on dose level cohorts 1, -1, and -2) and a maximum of 30 patients (e.g. 6 at each of the 4 dose levels and an intermediate dose level). Adverse events and toxicities will be summarized using the NCI CTCAE version 4 and based on severity and perceived attribution to study treatment; these outcomes will be assessed and tabulated by dose level.

6.1.2 Phase II portion

Previous studies of lenalidomide alone in a similarly defined relapsed/refractory MM patient population has shown an overall response rate of 25%, which also included the addition of dexamethasone after 2 cycles to non-responding stable disease patients. We will consider this regimen promising if the true overall response rate is 50% or greater when lenalidomide is combined upfront with CT-011. Therefore, we will test the null hypothesis that the true overall response rate (ORR) is at most 25% (reflecting a combination regimen ORR that would not be of interest) versus our alternative hypothesis that the true ORR in patients treated with this combination regimen is at least 50%.

Decision Rule: The largest response rate where this treatment regimen would be considered ineffective in this population is 25%, and the smallest response rate that would warrant subsequent studies with this proposed regimen in this patient population is 50%. The following Three-Outcome phase II study design is a modification of the standard one-stage phase II design and uses a maximum of 29 evaluable patients to test the null hypothesis that the true response rate is at most 25%. Since we will include the 6 patients treated at the MTD from the phase I portion of the trial, this will require accruing an additional 23 evaluable patients for this phase of the study. Based on this study design, there are three possible outcomes:

- "Not promising": This regimen will be classified as not promising with respect to the response rate in this patient population if at most 9 patients have any response after 4 cycles of therapy out of the total 29 evaluable patients.
- "Promising": This regimen will be classified as promising with respect to increasing the response rate in this patient population if at least 12 patients have an observed response to treatment after 4 cycles of therapy out of the total 29 evaluable patients. Subsequent larger confirmatory studies may be warranted.
- "Inconclusive": The results of this study will be classified as inconclusive with respect to this regimen demonstrating an improved response rate if only 10 or 11 of the 29 total evaluable patients have a response after 4 cycles of therapy. In this case, other factors such as progression-free survival, toxicity, and correlative outcomes will be used in addition to the response data to make the final determination as to whether or not this treatment is considered promising and worthy of further study in this patient population.

In this type of three-outcome phase II design with an uncertainty region, the associated errors are not the same as in the standard phase II study designs. In this study, the type I and type II error rates are constrained at 4% and 3%, respectively; The other parameters included in this type of design are eta (the probability of determining that a regimen is not worth pursuing further when it truly is not effective) and pi (the probability of determining that a regimen is promising when it truly is). Under this design, eta=0.83 and pi=0.87.

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 CT-011. In particular, we will evaluate biological and cellular markers in patients treated with CT-011, 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 CT-011 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.

6.2 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.

6.3 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.

6.4 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.

6.5 Prohibited treatments

The use of concomitant chemotherapy, 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 4 weeks prior to first dose administration. Concomitant radiotherapy during treatment for palliation of pain may be permissible with prior approval of study PI. Radiotherapy should be directed to a localized area (involved field radiotherapy) and cannot exceed 25Gy. Radiotherapy to more than one localized area at a time is not allowed. Participation in any clinical study involving any medications or treatments, whether approved or investigational, is prohibited.

7.0 REGISTRATION PROCEDURES

7.1 Registration Guidelines

Eligible patients will be entered on study centrally at The Ohio State University. OSU patients will be registered by the OSU Clinical Research Coordinator/Specialist. Subsite patients will be registered by the OSU Subsite Coordinator.

Following registration, patients should begin protocol treatment within 72 hours. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration may be canceled, pending approval by the Principal Investigator who will determine whether the patient will be replaced. Patients that do not receive any protocol therapy will not be evaluable for toxicity or response

7.2 Assignment of Study Numbers

Each patient enrolled in the study will be registered in the OSU database. Each patient enrolled will be assigned a sequential study identifier by the study team.

7.3 Study Records

Study data will be collected in standardized case report forms (CRF). The investigator or designate will record all patient information, including patient identification, disease stage, previous treatment, as well as information concerning drug administration, results of laboratory tests, toxicity and efficacy data.

A specific form will be used for recording and reporting serious adverse events as defined in section 10.

7.4 Selection Procedures

All eligible patients must be registered. This must be done before the start of treatment. On receipt of all the necessary baseline information, a clinical research coordinator will assess whether the patient is eligible or not.

7.5 Subsite Patient Registration

Subsite patients will have eligibility verified and will be centrally registered at The Ohio State University by the OSU Subsite Coordinator. Subsites should call or email the OSU Subsite Coordinator to verify enrollment availability prior to consenting patients.

Following registration, patients should begin protocol treatment within 72 hours. Issues that may cause treatment delays should be discussed with the OSU Principal Investigator and OSU Subsite Coordinator as soon as possible. The OSU Subsite Coordinator must be notified immediately if a patient does not receive protocol therapy.

Only patients deemed eligible by the subsite research team should be submitted for eligibility verification and registration by the OSU Subsite Coordinator.

To request subsite patient registration, the documents below must be completed by the subsite research team and faxed to the OSU Subsite Coordinator. The OSU secure email system may be used. Contact the OSU Subsite Coordinator for more information.

Required documents for registration (refer to Supplemental Forms Document):

- Enrollment Form
- Signed Eligibility Checklis
- Source documents verifying every inclusion & exclusion criteria
- Required screening items as listed in the Protocol Calendar. Screening tests must be within the specified window.
- Signed informed consent document (and HIPAA form, if separate)
- Documentation of consent process
- Emails and other signed and dated documents used as source documentation

The OSU Subsite Coordinator will confirm receipt of the registration documents with the subsite contact listed on the Enrollment Form (refer to Supplemental Forms Document). If confirmation is not received within 2 hours, it is strongly recommended that the subsite call the OSU Subsite Coordinator to confirm registration documents were received.

Registration requests will be processed as soon as possible and no later than 1 business day after receipt of the registration documents, pending there is no additional information needed to complete eligibility verification. Registration will occur upon OSU confirmation that the patient meets eligibility criteria.

The Subsite Coordinator will securely email the subsite contact listed on the Enrollment Form (refer to Supplemental Forms Document) with the registration confirmation and the patient's assigned study number.

8.0 Correlative studies

The focus of our correlative studies will be to study the immunogenicity of CT-011 through peripheral blood studies in the following general areas:

- To assess pharmacokinetics (PK) and pharmacodynamics of CT-011 in combination with lenalidomide.
- To assess CT-011 immunogenicity and correlative biologic studies to assess immunomonitoring of lymphocytes subsets including T and NK cells and ex-vivo assessment of immune functional activities.

8.1 PK and correlative laboratory investigations

Samples for CT-011 PK determination will be collected with cycle 1 prior to CT-011 infusion, immediately at the end of the infusion, 1 hour after end of infusion, approximately 24(C1D4), 72(C1D6), 168 (C1D10) & 336 (C1D17) hrs– and just prior to cycle 2 CT-011 administration. CT-011 blood levels will be assessed with a specific ELISA technique previously validated and derived concentrations will be used to calculate PK parameters. We will compare these results with PK data obtained in the single agent phase I study previously completed to assess for any effects of co-administration of len on CT-011 PK.
We will also assess for immunogenicity at baseline and monthly starting 1 month after dose level 3 (3 mg/kg) is started. This will be done by Medivation Inc. (see Appendix G)

We will also 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).

8.2 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-□, 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-□ expressing CD4(+) and CD8(+) T cells. The impact of CT-011 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 CT-011 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.

8.3 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. Preliminary data from another group suggest that CT-011 upregulates activation markers on NK cells in an *in vitro* system.[58] 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 CT-011 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 CT-011 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.[59] 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 one cycle of treatment and assess PD-L1 expression by flow cytometry.

8.4 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 CT-011 after each cycle of therapy. We will specifically study the induction of these antigens on CD14(+) cells as a consequence of CT-011 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.

9.0 Investigational drugs

9.1 CT-011

CT-011 (humanized monoclonal antibody) for parenteral administration is supplied as a 20 mg/mL clear solution in phosphate buffer saline and is preservative-free. The drug product is packaged in depyrogenated clear 6-mL glass vials (type 1 neutral glass) sealed with Tefloncoated gray chlorobutyl rubber stoppers and sealed with aluminum seals. Each vial consists of 5.25 mL of approximately 20 mg/mL CT-011.

Label Of The Drug: The container label and the immediate outer carton label of the marketed 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: The vials of CT-011 MUST be kept frozen as per US Pharmacopoeia, between -13ºF to 5ºF until use. Prior to planned infusion, the CT-011 drug product vial(s) must be thawed at room temperature for approximately 1 hour. Once thawed, the drug product should be diluted immediately into an infusion bag and administered to the patient as soon as possible. It is important to note that the thawed vials of CT-011 drug product can be held refrigerated at 2ºC to 8ºC (35ºF to 46ºF) for no longer than 7 days, though it is advised to use the thawed drug product immediately. The thawed drug product vials must not be frozen again. The infusion bag containing

CT-011 can be stored at room temperature for no longer than 2 hours prior to the initiation of infusion, though it is advised to administer drug product immediately. CT-011 vials or infusion bags that are not stored as described above (e.g. at longer periods of time or at higher temperatures) must not be used and must be discarded according to the Center's policy for handling of unused drugs and only after drug accountability monitoring has been performed.

Preparation of CT-011 For Administration: The solution will be prepared by a pharmacist, the Investigator, or a study nurse. Appropriate aseptic techniques should be used. Prior to infusion the vial(s) must be thawed at room temperature for approximately 1 hour; the vial(s) should be swirled gently to make sure that the solution is clear, colorless, and transparent**. DO NOT SHAKE!** Effort must be made so that once thawed; the drug will be diluted immediately into an infusion bag and administered to the patient as soon as possible (see Section 8.3 for drug product storage conditions). Each vial contains **approximately** 20 mg/mL CT-011. While most lots will be provided at this concentration, note that current specifications allow for a concentration range of 19mg/ml to 21mg/ml. Determine the total amount of CT-011 required based on the drug handling sheet provided keeping in mind that maximal total dose allowed is 600mg per patient

The appropriate amount of CT-011 solution should be withdrawn from the vial(s) and added to an infusion bag containing 250 mL of 0.9% sodium chloride solution, USP. The bag will be identified with the patient number. The bag should then be gently inverted to mix the solution in order to avoid foaming. Parenteral solutions should be inspected visually for particulates and discoloration prior to administration. Once the infusion is prepared, it should be administered immediately.

Method of Administration: CT-011 will be administered intravenously on day 3 of each 28 day cycle. The drug is diluted into a 250mL saline bag which in the FIRST infusion is administered in a step-wise manner: 50ml/hr for 30min; 100ml/hr for 30min; 150ml/hr for 30 min and 200ml/hr till the end (another ~30min) for an approximate time of 2hrs. If no infusion related AEs occurs the first time, subsequent administrations are at 200mL/hr which will deliver the drug over approximately 1:15hrs. In the event that Grade 3 or higher toxicity occurs during infusion, administration of CT-011 should be stopped immediately. Administration of CT-011 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.

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.

10.0 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

- 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 once study drug treatment is initiated to within 30 days following cessation of treatment. 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 within 24 hrs of the site becoming aware of the event to the IRB and ProductLife Ltd using the forms provided by Medivation Inc. for this purpose.

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 Subsite SAE Reporting Requirements

NOTE: Subsite institutions are NOT permitted to report directly to the FDA or The Ohio State University Office of Responsible Research Practices. All reports must be sent to the OSU Principal Investigator and Subsite Coordinator for submission to the FDA and ORRP.

Subsites must report SAEs to their IRB of record as per their institutional and IRB policies.

Subsites must report all SAEs to the lead Principal Investigator and the OSU Subsite Coordinator within 24 hours of knowledge of the event. SAEs are to be reported on MedWatch 3500A form and submitted with the SAE Submission Form (refer to Supplemental Forms Document). All SAEs and unanticipated problems involving risk to subjects or others will be reported by the OSU Subsite Coordinator following institutional and FDA guidelines. In addition, all serious adverse events (SAEs) are reported by the OSU Subsite Coordinator to The Ohio State University Office of Responsible Research Practices, Medivation Inc. via ProductLife Ltd and to the Food and Drug Administration (FDA) if applicable and within the timeframes outlined in the below table. Subsite institutions are NOT permitted to directly report to The Ohio State University Office of Responsible Research Practices, Medivation Inc., ProductLife Ltd or FDA. All AE/SAEs will be reported to the DSMC at the quarterly DSMC review meetings; however, the investigator determines corrective action is necessary, and “ad hoc” DSMC meeting will be called.

Fatal adverse events related to treatment which are unexpected must be reported within 24 hours of the Investigators first awareness of the event to the OSU Principal Investigator, OSU Subsite Coordinator and Medivation Inc. via ProductLife Ltd. The OSU Subsite Coordinator will immediately report to The Ohio State University Office of Responsible Research Practices and the DSMC. Fatalities not related to the study drug/device must be reported within 5 days.

10.4 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 ProductLife LTD by fax [0 800 022 4815] within 24 hrs of the site becoming aware of the event and to the IRB within respective required guidelines. If fax is not available, the form may be scanned and emailed to safety@productlife-group.com. 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 and to Medivation Inc via ProductLife Ltd.
- 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 and to Medivation Inc, designated pharmacovigilance representative, ProductLife Ltd, using the forms provided by Medivation Inc. for this purpose.

10.5 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 which occur within 30 days of discontinuation of dosing or completion of the patient's participation in the study if the last scheduled visit occurs at a later time.

10.6 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.

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 postimplantation losses and fetal variations (morbidity/purple-discolored skin, undeveloped intermediate lung lobe, irregular nasal-frontal suture, and delayed metacarpal ossification)[60]. 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 & Medivation Inc. (See Safety reporting section).

It is not known whether lenalidomide or CT-011 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.

10.7 Patient Withdrawal and Study Termination

A patient should be withdrawn from the trial treatment if, in the opinion of the investigator, it is medically necessary, or if it is the wish of the patient. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible.

Patients should be removed from therapy if any of the following occurs:

- 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.
- Patient refusal to continue with therapy.
- 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.
- Termination of the study.

If a patient withdraws from protocol therapy, it should be clearly documented with additional notation of whether the patient has agreed to complete follow up as outlined in the protocol. Subsite

institutions must notify the OSU Subsite Coordinator as soon as possible if the patient withdraws from protocol therapy and must provide the documentation of the reason and whether the patient will complete follow up.

The reason and date of discontinuation are to be documented in the patient's medical record and in the CRF.

The investigator should complete all end of treatment procedures when a patient withdraws from treatment. All patients who discontinue the trial secondary to an adverse event should be followed until resolution, stabilization or return to a baseline condition.

Patients who fail to complete treatment for reasons other than adverse event or unacceptable toxicity may be replaced. All patients who receive one dose of study treatment should be included in any safety analysis.

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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Appendix A: 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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Appendix B: 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 [61], 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.

Appendix C: 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.

Appendix D: 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.

Appendix E: Ethical and regulatory

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.

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 Medivation Inc. 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 Medivation Inc. If the revision is an administrative letter, the investigator(s) must inform the IRB.

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 Medivation Inc. or its representatives, IRB, providing direct access to the facilities where the study took place, to source documents, and to all other study documents.

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

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 the minutes. The PI 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 PI and compared to what is known about the agent/device

from other sources; including published literature, scientific meetings and discussions with the sponsors, to determine if the trial should be terminated before completion. Serious adverse events and responses will also be reviewed by the OSUCCC Data and Safety Monitoring Committee (DSMC). The PI will also submit a progress report quarterly that will be reviewed by the committee per the DSMC plan. All reportable Serious Adverse Events (SAE) will also be reported to the IRB of record as per the policies of the IRB.

Subsite institutions are expected to perform internal data and safety monitory and must submit the findings to the OSU Subsite Coordinator. Likewise, the OSU Data and Safety Monitoring reports will be distributed to the subsite institutions participating in this study.

Monthly safety and trial review teleconferences will be scheduled and moderated by the Multi-Institution Program. All sites involved in the study are expected to have a representative present every month to review and discuss patients on study and other applicable agenda items. Meeting minutes will be used to document each monthly teleconference. The minutes will be stored in the Multi-Institution Program protocol files.

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 Medivation Inc. (see contact information in section "Serious Adverse Events")

All subsite consents must be sent to the OSU Subsite Coordinator for review and approval prior to submission to the local IRB. In addition, all subsite IRB approval letters for amendments and annual renewals must be sent to the OSU Subsite Coordinator in a timely manner.

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.

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.
All subsite data is to be submitted within 2 weeks of completion of each cycle of therapy. Refer to the Data Submission Form in the Supplemental Forms Document for submission information.

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 Medivation Inc., 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.

The investigator is required to retain, in a confidential manner, sufficient information on each participant (specifically, full name; current address; and social security number), so the participant may be contacted by the FDA or the Ohio State University, should the need arise.

Appendix F: 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 contracepti
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

Appendix G: 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:

A. Immunogenicity

3.0mL of whole blood should be transferred to a tube without anticoagulant for the generation of serum for the performance of immunogenicity evaluation (serum will be generated as per the standard Center's procedure). Approximately 1.5 mL serum will be collected per patient per sampling time and will be divided into separate test tubes that will be clearly labeled with the following information: test type (IMM), patient study identification number, visit number, date and time of blood withdrawal.

4 tubes, each containing 200 µL serum will be stored at -80°C pending shipment instructions by Medivation Inc. or a designated laboratory. A -20°C freezer could serve as an alternative in the event that the center does not have access to a -80°C freezer. In such an instance, shipment of of serum samples will be made within 30 days from date of serum collection.

The kits containing tubes, packaging material, shipment forms will be provided by Medivation Inc. Each kit contains all the material that is needed to collect the samples for one visit. The packaging material and shipment forms will be provided by the courier company.

B. Pharmacokinetics

3.0 mL of whole blood should be transferred to a tube without anticoagulant for the generation of serum for the performance of immunogenicity evaluation (serum will be generated as per the standard Center's procedure). Approximately 0.6 mL serum will be collected per patient per sampling time and will be divided into separate test tubes that will be clearly labeled with the following information: test type (PK), patient study identification number, visit number, date and time of blood withdrawal.

4 tubes, each containing 200 µL serum will be stored at -80°C pending shipment instructions by Medivation Inc. A -20°C freezer could serve as an alternative in the event that the center does not have access to a -80°C freezer. In such an instance, shipment of serum samples to the testing lab will be made within 30 days from date of serum collection.

The kits containing tubes, packaging material, shipment forms will be provided by Medivation Inc. Each kit contains all the material that is needed to collect the samples for one visit. The packaging material and shipment forms will be provided by the courier company.

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