

Mayo Clinic Cancer Center

Phase 2 Trial of Pembrolizumab, Lenalidomide and Dexamethasone for Initial Therapy of Newly Diagnosed Multiple Myeloma Eligible for Stem Cell Transplantation

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Drug Availability

Commercial Agents: Lenalidomide, Dexamethasone

Drug Company Supplied: Pembrolizumab

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Protocol Resources

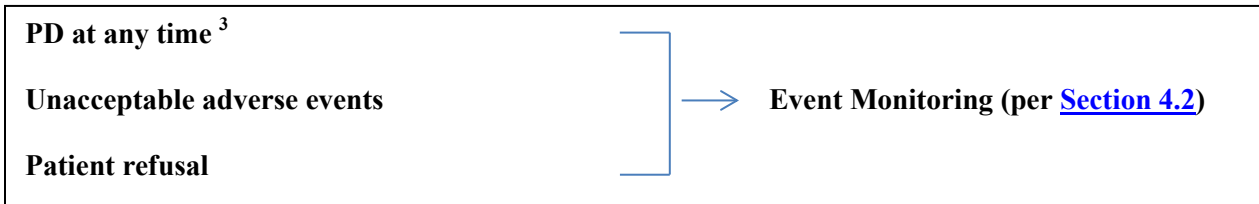
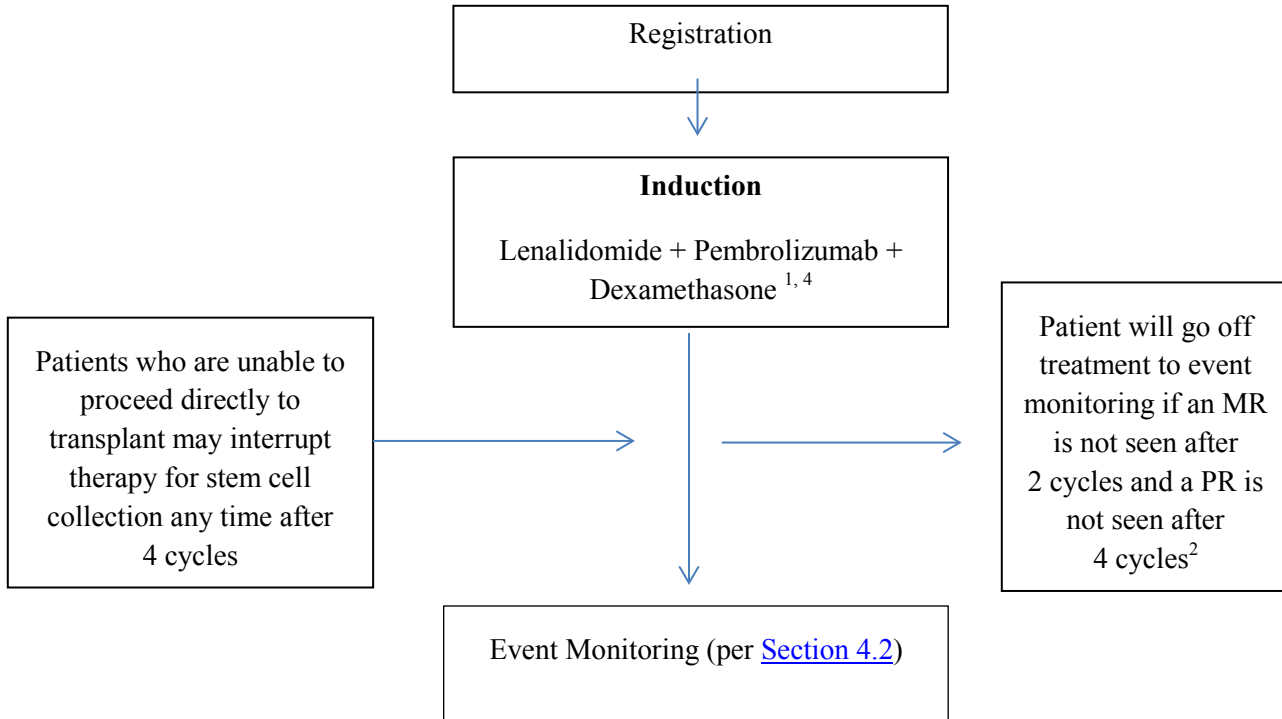
Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	██████████ Quality Assurance Specialist Phone: ██████████ E-mail: ██████████
Drug administration, infusion pumps, nursing guidelines	██████████ Phone: ██████████ E-mail: ██████████
Forms completion and submission	██████████ Phone: ██████████ Email ██████████
Protocol document, consent form, regulatory issues	██████████ Research Protocol Specialist Phone: ██████████ Email: ██████████
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*No waivers of eligibility per NCI

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Schema



If a patient is deemed ineligible or a cancel, please refer to [Section 13](#) for follow-up information.

¹Cycle length during Induction = 28 days

²Confirmation of MR or PR is not required.

³Progressive disease should be confirmed. However, treatment may be discontinued for progressive disease that is unconfirmed per physician discretion. In this case, an objective status of PD should be entered on the measurement form and progressive disease should be reported on the event monitoring form.

⁴Patients may receive stem cell transplant (SCT) at physician discretion at any time after 4 cycles. If patient goes to SCT, they will go to Survival and Disease Status Follow-Up/ Event Monitoring per Section 4.2 and the transplant should be recorded on the event monitoring form.

Generic name: Pembrolizumab Brand name(s): Keytruda® Mayo Abbreviation: MK-3475 Availability: Provided by Merck	Generic name: Lenalidomide Brand name(s): Revlimid® Mayo Abbreviation: LEN Availability: Revlimid REMS™ program	Generic name: Dexamethasone Brand name(s): Decadron® Mayo Abbreviation: DXM Availability: Commercial
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1.0 Background

1.1 Multiple Myeloma:

Multiple myeloma is a malignancy of the differentiated plasma cells, that affect the older patient with a median age at onset of 65-70 years and a slight male predominance. Nearly 20,000 patients with myeloma are diagnosed in the United States each year, and despite considerable improvements in therapy, the disease remains incurable and uniformly fatal with a median overall survival of around 8 years. Recent improvements in therapies have significantly improved the survival outcomes, but given the inevitable relapses seen in these patients, new approaches to therapy are clearly needed. The highly effective drug combinations currently used are beset with a degree of toxicity that precludes long-term therapy and also can affect quality of life metrics. Finally, some of these regimens require IV or subcutaneous administration, which can require frequent clinic visits for patients. The highly effective multi-drug regimens currently in use typically include a proteasome inhibitor, either bortezomib given IV or SQ or carfilzomib given IV.

1.2 Lenalidomide:

Lenalidomide has significant activity in the setting of multiple myeloma; both in relapsed and in newly diagnosed disease. Initial phase I/II study of lenalidomide in relapsed myeloma determined the ideal dose to be 25 mg once daily given for 3 of 4 weeks.¹ The initial trial in the relapsed disease also demonstrated increased activity in combination with pulsed doses of dexamethasone. These findings led to the initial trials of the combination in newly diagnosed disease as well as randomized trials of the combination in relapsed myeloma.² In the phase III trials of lenalidomide and dexamethasone, the combination was demonstrated to be superior to dexamethasone in terms of response rates and progression free and overall survival.³ The initial phase II study of lenalidomide and dexamethasone in newly diagnosed myeloma, conducted at the Mayo Clinic, also employed the combination of lenalidomide and pulsed dose dexamethasone (40 mg daily on four days on four days off schedule) for the first four cycles followed by 40 mg weekly for the subsequent cycles. The phase II study demonstrated significant response rates and long term follow up demonstrated sustained responses and 1-year survival rates of over 90%. The subsequent phase III trial in the ECOG (E4A03) compared the same dosing strategy to one that employed a lower dose of dexamethasone (40 mg weekly) right from the start of therapy.³ The results of the trial demonstrated a superior overall survival for the lower dose dexamethasone arm.

Two large, multicenter, randomized, placebo-controlled phase III pivotal trials MM-009 (n = 353) conducted in North America, and MM-010 (n = 351) in Europe, Australia and Israel; which collectively included 704 patients assessed the efficacy and safety of lenalidomide plus dexamethasone versus dexamethasone alone in patients with relapsed/refractory multiple myeloma (RRMM).^{4,5} Patients were randomized to receive either oral lenalidomide 25 mg per day or placebo for three weeks along with 40 mg oral dexamethasone for four days starting 1, 9 and 17 day of each 28-day cycle (for 4 cycles) until disease progression. After four cycles, dexamethasone (40 mg/day) was limited to days 1-4 only. The results of both studies were similar and the pooled analysis showed that treatment with lenalidomide plus dexamethasone significantly improved overall response (OR: 60.6 vs 21.9%, P<0.001), complete response rate (CR: 15.0 vs 2.0%, P<0.001), time to progression (TTP: median of 13.4 vs 4.6 months, P<0.001) and duration of response (DOR: median of 15.8 months vs 7 months, P<0.001) compared with dexamethasone-placebo. Even at a median follow-up of 48 months for surviving patients, a significant benefit in overall survival (median of 38.0 vs 31.6 months, P=0.045) was retained. Thus the data confirmed the significant response and survival benefit with lenalidomide and dexamethasone and this led to approval of lenalidomide in combination with dexamethasone for

the treatment of MM in patients who have received at least one earlier therapy by the US FDA in June 2006 followed by European Medicines Agency in June 2007.

Sub-analysis of MM-09 and MM-10 by Harousseau et al revealed that half of the patients who initially had a partial response achieved a complete or very good partial response with further treatment. (Harousseau, Dimopoulos et al. 2010) The probability of achieving a complete or very good partial response with continued lenalidomide treatment decreased with delayed achievement of a partial response (by cycle 4 versus later); however, it still remained clinically significant. The quality of response also showed a positive prognostic impact with an extended follow-up of 48 months, as patients who achieved a CR/VGPR as their best response had significantly longer median response duration, time-to-progression, and overall survival than in those with a partial response (24.0 versus 8.3 months, $P<0.001$; 27.7 versus 12.0 months, $P<0.001$; not reached versus 44.2 months, $P=0.021$, respectively) and this was regardless of when the CR/VGPR was achieved. Another sub-analysis of the same studies determined that continued lenalidomide treatment until disease progression after achievement of \geq PR is associated with a significant survival advantage when controlling for patient characteristics. A Dutch study showed that treatment with Len-Dex is highly effective and feasible in heavily pretreated multiple myeloma patients by analyzing the clinical data of more than 100 patients who had been on a median of 3 previous lines of therapy, including thalidomide in most. With a median of 7 cycles of treatment, an overall response rate of 69%, including complete response in 6% was achieved and this was not influenced by previous thalidomide and/or bortezomib treatment. Using the recommended prophylaxis, incidence of venous thrombotic events was low (5%) but grade \geq 3 myelosuppression occurred in more than a third (37%).

Lenalidomide has significant activity in the setting of multiple myeloma; both in relapsed and in newly diagnosed disease. Initial phase 1/2 study of lenalidomide in relapsed myeloma determined the ideal dose to be 25 mg once daily given for 3 of 4 weeks. The initial trial in the relapsed disease also demonstrated increased activity in combination with pulsed doses of dexamethasone. These findings led to the initial trials of the combination in newly diagnosed disease as well as randomized trials of the combination in relapsed myeloma. In the phase III trials of lenalidomide and dexamethasone, the combination was demonstrated to be superior to dexamethasone in terms of response rates and progression free and overall survival. The initial phase II study of lenalidomide and dexamethasone in newly diagnosed myeloma, conducted at the Mayo Clinic, also employed the combination of lenalidomide and pulsed dose dexamethasone (40 mg daily on four days on four days off schedule) for the first four cycles followed by 40 mg weekly for the subsequent cycles. The phase II study demonstrated significant response rates and long term follow up demonstrated sustained responses and 1-year survival rates of over 90%. The subsequent phase III trial in the ECOG (E4A03) compared the same dosing strategy to one that employed a lower dose of dexamethasone (40 mg weekly) right from the start of therapy. The overall (complete plus partial) response to therapy after four cycles was higher with high-dose dexamethasone than with low-dose, 169 (79%) of 214 patients on high-dose dexamethasone had an overall response (complete or partial) compared with 142 (68.3%) of 208 on low-dose ($p=0.008$). Despite this, the trial demonstrated a superior overall survival for the lower dose dexamethasone arm. 90 (42%) patients achieved complete response or very good partial response in the high-dose dexamethasone group in the first four cycles of therapy compared with 49 (24%) patients in the low-dose treatment group ($p<0.0001$). Long term follow up of patients receiving lenalidomide and dexamethasone induction followed by autologous stem cell transplantation demonstrated 86% overall survival at 4 years, in a single institution study, underscoring the utility of this regimen as a well-tolerated and effective initial therapy.

Lenalidomide and dexamethasone was studied in a large phase 3 trial, where 1623 patients were randomized to lenalidomide and dexamethasone in 28-day cycles until disease progression (535

patients), to the same combination for 72 weeks (18 cycles; 541 patients), or to MPT for 72 weeks (547 patients). Response rates were higher with continuous lenalidomide–dexamethasone (75%) and with 18 cycles of lenalidomide–dexamethasone (73%) than with MPT (62%; $P < 0.001$ for both comparisons). Rates of very good partial response or better were also higher with continuous lenalidomide–dexamethasone (44%) or 18 cycles of lenalidomide–dexamethasone (43%) than with MPT (28%), as were rates of complete response (15%, 14%, and 9%, respectively). The median progression-free survival was 25.5 months with continuous lenalidomide–dexamethasone, 20.7 months with 18 cycles of lenalidomide–dexamethasone, and 21.2 months with MPT (hazard ratio for the risk of progression or death, 0.72 for continuous lenalidomide–dexamethasone vs. MPT and 0.70 for continuous lenalidomide–dexamethasone vs. 18 cycles of lenalidomide–dexamethasone; $P < 0.001$ for both comparisons). Overall survival at 4 years was 59% with continuous lenalidomide–dexamethasone, 56% with 18 cycles of lenalidomide–dexamethasone, and 51% with MPT. As compared with MPT, continuous lenalidomide–dexamethasone was associated with fewer hematologic and neurologic toxic events, a moderate increase in infections, and fewer second primary hematologic cancers.

1.3 Pembrolizumab

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an Ig superfamily member related to CD28 and CTLA-4, which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 ζ , PKC θ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-

cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

1.4 Rationale for the current trial:

Currently, there is considerable amount of work being done to enhance this regimen. Combining a proteasome inhibitor with lenalidomide clearly enhances the efficacy, but also increases the toxicity and can be an issue in the older patient. Recent trials are evaluating monoclonal antibodies in combination with lenalidomide, to capitalize on the immunomodulatory effects of lenalidomide, specifically the NK cell and T-cell enhancing activity. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occur in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth. In the setting of myeloma, B-cell responses are altered to a state of functional hypogammaglobulinemia, leading to an increased risk for infections. T-cell-mediated immunity is also severely impaired in MM with T-helper (Th)1/Th2 imbalance leading to immune dysfunction. Several studies have shown that PD-L1 is absent from normal plasma cells, whereas it is expressed on myeloma cell lines and primary myeloma tumor cells from patients with MM. It has been demonstrated that PD-1 expression is upregulated on T cells isolated from patients with MM, suggesting that this pathway is of importance in mediating the immunosuppressive state in this patient population. Benson et al. have shown that NK cells from MM patients express PD-1 and suggested that PD-1/PD-L1 interactions undermine the immunological control of MM by NK cells. They have also demonstrated that the application of an anti-PD-1 monoclonal antibody enhances the cytolytic activity of NK cells against autologous, primary MM cells. It was observed that lenalidomide was capable of downregulating the expression of PD-L1 on the malignant plasma cells from MM patients and that its *in vitro* application resulted in an enhancement of the myeloma-targeting activity of the anti-PD-1 antibody. Preliminary results from an ongoing phase 1 trial of lenalidomide, dexamethasone, and pembrolizumab have demonstrated evidence of activity with one complete response and two VGPR in patients with relapsed disease. Given these findings, it is rational to evaluate the combination of pembrolizumab in combination with lenalidomide and dexamethasone in newly diagnosed myeloma, which allows for early intervention and maximal benefit from such an immunological approach.

2.0 Goals

2.1 Primary

To determine the VGPR or better response rate (\geq VGPR) after 4 cycles of Pembrolizumab added to standard doses of lenalidomide and dexamethasone, when used as initial therapy in patients with previously untreated symptomatic MM in patients, who are considered eligible for stem cell transplantation.

2.2 Secondary

2.21. To determine the \geq partial response (PR) rate after 4 cycles of treatment with Pembrolizumab added to standard doses of lenalidomide and dexamethasone.

2.22 To determine the \geq VGPR response rate at any time during treatment with Pembrolizumab added to standard doses of lenalidomide and dexamethasone.

2.23 To determine the progression free survival and overall survival among patients with previously untreated symptomatic MM following treatment with the combination of pembrolizumab, lenalidomide and dexamethasone.

2.24 To determine the toxicities associated with pembrolizumab added to standard doses of lenalidomide and dexamethasone in patients with previously untreated symptomatic MM.

2.25 To determine the success rate of stem cell collection following initial therapy with the combination of pembrolizumab, lenalidomide and dexamethasone in patients with newly diagnosed MM.

2.3 Correlative Research (IRB#521-93)

2.31 PDL-1 expression on myeloma cells and non-tumor cell compartments from the bone marrow will be assessed at baseline

2.32 Measures of T-cell activation / exhaustion will be assessed at baseline and after Cycle 1, Cycle 2, Cycle 3, and Cycle 4.

2.33 NK cell function and numbers will be evaluated at baseline and after Cycle 1, Cycle 2, Cycle 3, and Cycle 4.

3.0 Patient Eligibility

3.1 Inclusion Criteria

- 3.11 Diagnosis and previously untreated active multiple myeloma by IMWG diagnostic criteria for multiple myeloma
- 3.12 Age ≥ 18 years.
- 3.13 The following laboratory values obtained ≤ 14 days prior to registration.
- Calculated creatinine clearance (using Cockcroft-Gault equation below)* ≥ 30 mL/min
 - Absolute neutrophil count (ANC) $\geq 1000/\text{mm}^3$
 - Platelet count $\geq 75000/\text{mm}^3$
 - Hemoglobin ≥ 8.0 g/dL
 - Total bilirubin $\leq 1.5 \times \text{ULN}$
 - ALT and AST $\leq 3 \times \text{ULN}$

*Cockcroft-Gault Equation:

$$\text{Creatinine clearance for males} = \frac{(140 - \text{age})(\text{actual body weight in kg})}{(72)(\text{serum creatinine in mg/dL})}$$

$$\text{Creatinine clearance for females} = \frac{(140 - \text{age})(\text{actual body weight in kg})(0.85)}{(72)(\text{serum creatinine in mg/dL})}$$

- 3.14 Prior therapy for the treatment of solitary plasmacytoma is permitted, but >7 days should have elapsed from the last day of radiation.
NOTE: Prior therapy with clarithromycin, DHEA, anakinra, pamidronate or zoledronic acid is permitted. Any additional agents not listed must be approved by the Principal Investigator.
- 3.15 Measurable disease of multiple myeloma as defined by at least ONE of the following:
- Serum monoclonal protein ≥ 1.0 g/dL (see [Section 11.1](#) for definition)
 - >200 mg of monoclonal protein in the urine on 24 hour electrophoresis
 - Serum immunoglobulin free light chain ≥ 10 mg/dL AND abnormal serum immunoglobulin kappa to lambda free light chain ratio.
- 3.16 ECOG performance status (PS) 0 or 1 (See [Appendix I](#))
- 3.17 Provide written informed consent.
- 3.18 Negative pregnancy test done ≤ 7 days prior to registration, for women of childbearing potential only.
- 3.19a Willing to follow strict birth control measures as suggested by the study.
- 3.19a1 Female patients: If they are of childbearing potential, must agree to one of the following:
- Practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug, AND must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR

- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)
- 3.19a2 Male patients: even if surgically sterilized (i.e., status post-vasectomy), must agree to one of the following:
- Agree to practice effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug, OR
 - Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
 - Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)
- 3.19b Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).
- 3.19c Willing to provide consent to IRB#521-93 and provide research tissue and blood specimens.
- 3.2 Exclusion Criteria
- 3.21 MGUS or smoldering myeloma.
- 3.22 Prior cytotoxic chemotherapy or corticosteroids for the treatment of multiple myeloma.
NOTE: Prior corticosteroid use for the treatment of non-malignant disorders is permitted
- 3.23 Diagnosed or treated for another malignancy ≤ 2 years before study enrollment or previously diagnosed with another malignancy and have any evidence of residual disease.
NOTE: Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.
- 3.24 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:
- Pregnant women
 - Nursing women
 - Men or women of childbearing potential who are unwilling to employ adequate contraception
- 3.25 Other co-morbidity which would interfere with patient's ability to participate in trial, e.g. uncontrolled infection, uncompensated heart or lung disease.
- 3.26 Other concurrent chemotherapy or any ancillary therapy considered investigational.
NOTE: Bisphosphonates are considered to be supportive care rather than therapy, and are thus allowed while on protocol treatment.
- 3.27 Peripheral neuropathy \geq Grade 3 on clinical examination or Grade 2 with pain during the screening period.

- 3.28 Major surgery ≤ 14 days prior to study registration.
- 3.29a Radiotherapy ≤ 14 days prior to registration.
NOTE: If the involved field is small, 7 days will be considered a sufficient interval between treatment and administration of study drugs
- 3.29b Participation in any other clinical trials with other investigational agents not included in this trial, ≤ 21 days prior to registration
- 3.29c Active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs).
NOTE: Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
- 3.29d Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
- 3.29e Active infection requiring systemic therapy.
- 3.29f History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
- 3.29g Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
- 3.29h Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
- 3.29i Received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
- 3.29j Known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
- 3.29k Known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
- 3.29l Received a live vaccine ≤ 30 days of planned start of study therapy.

4.0 Test Schedule

4.1 Schedule of assessments

Tests and Procedures	Screening		Active Treatment ¹						
	≤30 days	≤14 days	Cycles 1-3 to be repeated beyond 3 cycles						
			Cycle 1		Cycle 2		Cycle 3		End of Induction treatment
			Weekly (For first 2 cycles)	Cycle 1, Day 1, Pre-treatment ¹⁰	Pembrolizumab infusion Cycle 1, Day 22, Pre-treatment ¹¹	Cycle 2, Day 1, Pre-treatment	Pembrolizumab infusion Cycle 2, Day 15, Pre-treatment ¹¹	Cycle 3, Day 1, Pre-treatment	
Complete medical history	X								
Adverse Event monitoring		X		X		X		X	X
Physical exam, including weight, vital signs		X		X		X		X	X
Height		X							
Performance status (ECOG scale)		X		X		X		X	X
CBC with diff (includes hemoglobin, ANC, WBC with complete differential, platelets)		X	X	X	X	X	X	X	X
Prothrombin time (PT)	X								
Chemistry group to include sodium, potassium, glucose, alkaline phosphatase; Total and Direct bilirubin; SGOT (AST); SGPT (ALT); serum creatinine, calcium		X	X	X	X	X	X	X	X
LDH, Beta ₂ -microglobulin, Plasma cell assessment	X								
sTSH	X			Every 6 months while on treatment					
Electrophoresis of serum and urine (SPEP/UPEP)		X		X ⁹		X ⁹		X ⁹	X ⁹
Affected Immunoglobulin ²		X		X		X		X	X
Immunofixation serum and urine	X			X ³		X ³		X ³	X ³
Immunoglobulin free light chain		X		X ⁴		X ⁴		X ⁴	X ⁴
X-ray skeletal survey or low dose whole body CT	X								
Bone marrow aspirate and biopsy, myeloma FISH, plasma cell proliferation, and flow cytometry	X			X ⁵		X ⁵		X ⁵	X ⁵

	Screening		Active Treatment ¹							
	≤30 days	≤14 days	Cycles 1-3 to be repeated beyond 3 cycles							
			Cycle 1		Cycle 2		Cycle 3		End of Induction treatment	
			Weekly (For first 2 cycles)	Cycle 1, Day 1, Pre-treatment ¹⁰	Pembrolizumab infusion Cycle 1, Day 22, Pre-treatment ¹¹	Cycle 2, Day 1, Pre-treatment	Pembrolizumab infusion Cycle 2, Day 15, Pre-treatment ¹¹	Cycle 3, Day 1, Pre-treatment		Pembrolizumab infusion Cycle 3, Day 8, Pre-treatment ¹¹
Tests and Procedures										
Research bone marrow ^R (IRB 521-93)	X			X ⁵		X ⁵		X ⁵		X ⁵
Research blood sample ^R (IRB 521-93)	X			X ⁶		X ⁶		X ⁶		
Chest x-ray	X									
Serum pregnancy test		X ⁷								
Patient Medication Diary (Appendix II) ⁸ .				X		X		X		X

Cycle length during induction = 28 days

- 1) All scheduled visits will have a window of ± 4 days, except pembrolizumab infusion days which will have a window of ± 1 day
- 2) Affected immunoglobulin refers to the baseline M-protein type, that is, IgG, IgA, or IgD. Not applicable if patient “non-secretory” or if patient has no heavy chain, i.e. light chain myeloma.
- 3) Immunofixation (IF) needed only in the absence of M-spike to document CR or sCR.
- 4) FLC is required only if used to assess disease response during active phase
- 5) At the end of 4 cycles and to document CR at any time point.
- 6) End of each cycle for first 4 cycles, and then at time of disease progression.
- 7) For women of childbearing potential only. Must be done ≤ 7 days prior to registration
- 8) The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution.
- 9) Urine Electrophoresis required after baseline only if used to assess disease response
- 10) Does not need to be repeated at Cycle 1 Day 1. Baseline values can be used for Cycle 1.
- 11) If pembrolizumab is discontinued, the patient may continue treatment with the remaining drugs and these visits do not apply.
- R) Research funded (see Section 19.0). Will be charged to study and not to patient’s account.

4.2 Event Monitoring/Survival Follow-up

	Event Monitoring Phase ¹				
	q. 3 months until PD	At PD	After PD q. 6 months	Death	New Primary
Event Monitoring	X	X	X	X	At each occurrence

1. If a patient is still alive 3 years after registration, no further follow-up is required.

5.0 Grouping Factor: None

6.0 Registration Procedures

6.1 Registration Procedures

6.11 To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the remote registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at [REDACTED] between the hours of 8 a.m. and 5:00 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page [REDACTED] detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office [REDACTED]. If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to “Instructions for Remote Registration” in Section “Finding/Displaying Information about A Registered Subject.”

6.12 Correlative Research:
A mandatory correlative research component is part of this study (under IRB#521-93), the patient will be automatically registered onto this component (see Sections 3.19c and 14.0).

6.13 Prior to accepting the registration, registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form

- Existence of a signed authorization for use and disclosure of protected health information

- 6.14 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office

██████████ If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

- 6.15 At the time of registration, the following will be recorded:
- Patient has/has not given permission to store and use his/her sample(s) for future research of Multiple Myeloma at Mayo.
 - Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.
 - Patient has/has not given permission for MCCC to give his/her sample(s) to researchers at other institutions.
- 6.16 Treatment on this protocol must commence at Mayo Clinic under the supervision of a medical oncologist/hematologist.
- 6.17 Treatment cannot begin prior to registration and must begin ≤ 14 days after registration.
- 6.18 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.
- 6.19 All required baseline symptoms (see Section 10.8) must be documented and graded.

6.2 Trial rules:

The clinical trial will be conducted in compliance with regulations (21 CFR 312, 50, and 56), guidelines for Good Clinical Practice (ICH Guidance E6), and in accordance with general ethical principles outlined in the Declaration of Helsinki; informed consent will be obtained from all participating patients; the protocol and any amendments will be subject to approval by the designated IRB prior to implementation, in accordance with 21 CFR 56.103(a); and subject records will be stored in a secure location and subject confidentiality will be maintained. The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

7.0 Protocol Treatment

7.1 Treatment Schedule

Cycle length: 28 days.

Agent	Route	Dose	Day	Retreatment
Lenalidomide	PO	25 mg*	1-21	Every 28 days
Pembrolizumab	IV	200mg	Every 21 days	Every 21 days
Dexamethasone	PO	40 mg	1, 8, 15, 22	Every 28 days

* If the patient has renal insufficiency, lenalidomide dose modifications should be made according to the following criteria:

CrCl >50 mL/min: No adjustment

CrCl 30-50 mL/min: 10 mg/day

CrCl <30 mL/min (no dialysis): 15 mg every 48 hours

CrCl <30 mL/min (dialysis): 5 mg daily (after HD (hemodialysis) on HD days)

7.2 Lack of Response

Patients will go off treatment to event monitoring if an MR is not seen after 2 cycles and a PR is not seen after 4 cycles. Confirmation of MR or PR is not required.

7.3 Patient return to Mayo Clinic

For this protocol, the patient must return to the consenting institution (Mayo Clinic) for evaluation every 21 days on the days of infusion while receiving pembrolizumab. (If pembrolizumab has been discontinued these visits are not required.) In addition, the patient must return every 28 days on Day 1 of each cycle while receiving any study treatment. Treatment by a local medical doctor (LMD) is not allowed.

7.4 Stem cell collection and transplant

Patients are allowed to collect stem cells and proceed to transplant any time after 4 cycles of initial therapy. If patient goes to transplant, they will go directly to event monitoring per Section 4.2 and the transplant should be reported on the event monitoring form. In the case that patients are unable to go to transplant due to other reasons, they can continue on study. In those cases, therapy may be interrupted for up to 4 weeks for the purpose of stem cell collection. Stem cells can be collected using standard institutional protocols. Any delay beyond 4 weeks should be discussed with the study PI prior to reinitiating protocol therapy.

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table for the first **two** cycles, until individual treatment tolerance can be ascertained. Individual drugs can be dose reduced as per the table below depending on the adverse event attribution. Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

ALERT: ADR reporting may be required for some adverse events (See Section 10)

8.1 Dose Levels for each drug in the combination

	Pembrolizumab (Every 21 days)	Lenalidomide (Days 1-21)	Dexamethasone (Days 1, 8, 15, 22)
Starting dose	200 mg	25 mg	40 mg
-1		15 mg	20 mg
-2		10 mg	12 mg
-3		5 mg	4 mg
-4		Discontinue	Discontinue

Note: If pembrolizumab is discontinued, the patient may continue treatment with the remaining drugs. If lenalidomide is discontinued, patient will go to event monitoring.

8.11 Instruction for initiation of a new cycle of therapy

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

- The ANC is $\geq 1000/\mu\text{L}$
- The platelet count is $\geq 50,000/\mu\text{L}$
- Any other non-hematologic drug-related adverse event that may have occurred has resolved to \leq Grade 1 or baseline severity.

If these conditions are not met on Day 1 of a new cycle, dosing should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria have been met. If the patient continues to fail to meet the above-cited criteria, delay therapy and continue to re-evaluate.

If any drug dosing was halted 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 any drug dosing was omitted for the remainder of the previous cycle or if the new cycle is held due to known hematologic toxicity newly encountered on the scheduled Day 1, then the new cycle will be started with a one-level dose reduction. If a new cycle of therapy cannot be restarted within 4 weeks of the scheduled Day 1 due to non-resolution of drug related toxicities, the patient will be removed from protocol therapy and will go to event monitoring.

8.2 Dose modifications for pembrolizumab based on adverse events during a cycle

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←

CTCAE System/Organ/Class (SOC)	Adverse Event	Omit Pembrolizumab for Grade	Timing for Restarting Pembrolizumab	Pembrolizumab Discontinuation
Gastrointestinal disorders	Diarrhea or Colitis	2-3	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
		4	Permanently discontinue pembrolizumab	Permanently discontinue pembrolizumab
Investigations	AST, or ALT, or Blood bilirubin	2	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose.
		3-4	Permanently discontinue pembrolizumab	Permanently discontinue pembrolizumab
Metabolism and nutrition disorders	Glucose intolerance (Type 1 diabetes mellitus [if new onset]) or Hyperglycemia	T1DM or 3-4	Omit pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when patients are clinically and metabolically stable.
Endocrine disorders	Endocrine disorders – Other, specify: Hypophysitis	2-4	AE resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Endocrine disorders	Hyperthyroidism	3	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
		4	Permanently discontinue pembrolizumab	Permanently discontinue pembrolizumab

CTCAE System/Organ/Class (SOC)	Adverse Event	Omit Pembrolizumab for Grade	Timing for Restarting Pembrolizumab	Pembrolizumab Discontinuation
Endocrine disorders	Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
General disorders and administration site conditions	Infusion related reaction	2 ^a	AE resolves to Grade 0-1	Permanently discontinue pembrolizumab if AE develops despite adequate premedication
		3-4	Permanently discontinue pembrolizumab	Permanently discontinue pembrolizumab
Respiratory, thoracic and mediastinal disorders	Pneumonitis	2	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
		3-4	Permanently discontinue pembrolizumab	Permanently discontinue pembrolizumab
Renal and urinary disorders	Acute kidney injury or Chronic kidney disease (e.g. Renal failure or Nephritis)	2	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
		3-4	Permanently discontinue pembrolizumab	Permanently discontinue pembrolizumab
	All Other Drug-Related Adverse Events ^b	3 or severe	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
		4	Permanently discontinue pembrolizumab	Permanently discontinue pembrolizumab

Note: Permanently discontinue for any severe or Grade 3 (Grade 2 for pneumonitis) drug-related AE that recurs, or any lifethreatening event.

a If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose (Section 9.9f).

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

* Located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

** Use the following to describe actions in the Action column:

- Omit = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time
- Hold/Delay = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs
- Discontinue = The specified drug(s) are totally stopped

8.3 Dose modifications for lenalidomide based on adverse events during a cycle

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION** Days 2-14 of cycle	ACTION** Day ≥15 of cycle
Blood and lymphatic system disorders	Febrile neutropenia associated with fever (temperature ≥38.5°C)	Lenalidomide	Omit lenalidomide dose. Follow CBC weekly. If neutropenia has resolved to ≤Grade 2 prior to Day 35, restart lenalidomide at next lower dose level and continue the cycle through Day 35. If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the lenalidomide dose maintained	Omit lenalidomide for remainder of cycle. See Section 8.11 for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level. If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the lenalidomide dose maintained for the next cycle at the investigator's discretion.
Investigations	Platelet count decreased ≥Grade 3 (platelet count <50,000/mm ³)	Lenalidomide	Omit lenalidomide dose Follow CBC weekly Hold anticoagulation until platelets >50,000 If thrombocytopenia resolves to ≤Grade 2 prior to Day 35, restart lenalidomide at next lower dose level and continue the cycle through Day 35	Omit lenalidomide for remainder of cycle See Section 8.11 , Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level
Skin and subcutaneous tissue disorders	Rash maculo papular Grade 2 or 3.	Lenalidomide	Omit lenalidomide dose Follow weekly If the event resolves to ≤Grade 1 prior to Day 35, restart lenalidomide at next lower dose level and continue the cycle through Day 35	Omit lenalidomide for remainder of cycle See Section 8.11 , Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level
	Any rash Grade 4	Lenalidomide	Discontinue lenalidomide	Discontinue lenalidomide

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION** Days 2-14 of cycle	ACTION** Day \geq15 of cycle
Nervous System Disorders	Peripheral sensory neuropathy Grade 3	Lenalidomide	Omit lenalidomide dose Follow at least weekly If the event resolves to \leq Grade 1 prior to Day 35, restart lenalidomide at next lower dose level and continue the cycle through Day 35	Omit lenalidomide for the remainder of the cycle. See Section 8.11 Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level
	Peripheral sensory neuropathy Grade 4	Lenalidomide	Discontinue lenalidomide	Discontinue lenalidomide
Immune system disorders	Allergic reaction Grade 2-3	Lenalidomide	Omit dose Follow at least weekly If the toxicity resolves to \leq Grade 1 prior to Day 35 restart at next lower dose level and continue the cycle until Day 35	Omit lenalidomide for the remainder of the cycle If the adverse event resolves to \leq Grade 1, reduce dose 1 level in next cycle If adverse event recurs, discontinue therapy
	Grade 4	Lenalidomide	Discontinue lenalidomide	Discontinue lenalidomide
Vascular disorders	Thromboembolic event \geq Grade 3	Lenalidomide	Omit dose and start anticoagulation; restart at investigator's discretion (maintain dose level)	Omit lenalidomide for remainder of cycle and start anticoagulation. Maintain dose level in next cycle
Kidney and Urinary System	Renal Insufficiency	Lenalidomide	CrCl $>$ 50 mL/min: No adjustment CrCl 30-50 mL/min: 10 mg/day CrCl $<$ 30 mL/min (no dialysis): 15 mg every 48 hours CrCl $<$ 30 mL/min (dialysis): 5 mg daily (after HD (hemodialysis) on HD days)	

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION** Days 2-14 of cycle	ACTION** Day \geq 15 of cycle
Endocrine disorders	Hyperthyroidism or Hypothyroidism \geq Grade 2	Lenalidomide	Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level	Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. See Section 8.11 , Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level
Other non-hematologic adverse event	Other non-hematologic toxicity \geq Grade 3	Lenalidomide	Omit lenalidomide dose Follow at least weekly If AE resolves to \leq Grade 2 prior to Day 35, restart lenalidomide at next lower dose level and continue the cycle through Day 35	Omit lenalidomide for remainder of cycle See Section 8.11 , Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level.

* Located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

** Use the following to describe actions in the Action column:

- Omit = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time
- Hold/Delay = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs
- Discontinue = The specified drug(s) are totally stopped

8.4 Dose modifications for dexamethasone based on adverse events during a cycle

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Gastrointestinal disorders	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (Symptomatic; altered GI function; medical intervention indicated; limiting instrumental ADL)	Dexamethasone	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
	Dyspepsia, gastric or duodenal ulcer, gastritis ≥Grade 3 (Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling)	Dexamethasone	Omit dexamethasone until symptoms adequately controlled. Restart one dose level below along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
	Pancreatitis ≥Grade 3 (Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support))	Dexamethasone	Discontinue dexamethasone and do not resume.
General disorders and administration site conditions	Edema ≥Grade 3 (limiting function and unresponsive to therapy or anasarca)	Dexamethasone	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.
Psychiatric disorders	Confusion or Mood alteration ≥Grade 2 (Severe disorientation; limiting self-care ADL)	Dexamethasone	Omit dexamethasone until symptoms resolve. Restart with one dose level reduction. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Musculoskeletal and connective tissue disorders	Muscle weakness ≥Grade 2 Weakness limiting self care ADL; disabling	Dexamethasone	Decrease dexamethasone dose by one dose level; if weakness persists despite above measures decrease dose by one additional dose level. Discontinue dexamethasone and do not resume if symptoms continue to persist.

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Metabolism and nutrition disorders	Hyperglycemia \geq Grade 3 (>250 - 500 mg/dL; >13.9 - 27.8 mmol/L); hospitalization indicated	Dexamethasone	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by one dose level at a time until levels are satisfactory.

* Located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

** Use the following to describe actions in the Action column:

- Omit = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time
- Hold/Delay = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs
- Discontinue = The specified drug(s) are totally stopped

NOTE: Adverse events requiring a dose-reduction step for any or all drugs beyond the three dose-reduction steps (levels -1, -2 and -3) will be at the discretion of the Principal Investigator, if the decision is made for the patient to be kept on study. These dose reductions must be clearly recorded in reported clinical data.

9.0 Ancillary Treatment/Supportive Care

9.1 Full Supportive Care

Patients should 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 antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.2 Thromboprophylaxis

All patients should receive aspirin 325 mg daily for thromboprophylaxis. For patients considered high risk for thrombosis, therapeutic anticoagulation with warfarin or low molecular weight heparin should be used

9.3 Steroid use

Patients may continue on low level/stable steroid doses for replacement or inhalation therapy.

9.4 Medications not permitted

The following medications are not permitted during the trial:

- Any other investigational treatment
- Any other systemic anti-neoplastic therapy including, but not limited to, immunotherapy, hormonal therapy or monoclonal antibody therapy
- Any external beam radiotherapy

9.5 Use of growth factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the Journal of Clinical Oncology, Vol 24, No 18 (June 20), 2006: pp. 2932-2947.

9.6 Bisphosphonates

Patients may receive concurrent treatment with a bisphosphonate.

9.7 Pneumonitis:

For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.

Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

9.8 Diarrhea/Colitis

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

- All subjects who experience diarrhea/colitis should be advised to drink liberal **quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and**

electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.

- For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

9.9a Type 1 diabetes mellitus

If new onset, including diabetic ketoacidosis [DKA] or \geq Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)

- For **T1DM** or **Grade 3-4** Hyperglycemia
- Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
- Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

9.9b Hypophysitis:

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

9.9c Hyperthyroidism or Hypothyroidism:

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

- **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
 - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy
 - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care
- **Grade 3-4** hyperthyroidism
 - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

9.9d Hepatic:

- For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
 - Treat with IV or oral corticosteroids
- For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

9.9e Renal Failure or Nephritis:

- For **Grade 2** events, treat with corticosteroids.
- For **Grade 3-4** events, treat with systemic corticosteroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

9.9f Management of Infusion Reactions:

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 9.9e1 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 9.9e1 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
<u>Grade 1</u> Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator	None
<u>Grade 2</u> Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	<p>Stop Infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics</p> <p>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.</p> <p>Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.</p>	<p>Subject may be premedicated 1.5h (\pm 30 minutes) prior to infusion of pembrolizumab (MK-3475) with:</p> <p>Diphenhydramine 50 mg po (or equivalent dose of antihistamine)</p> <p>Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic)</p>

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
<p><u>Grades 3 or 4</u></p> <p>Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)</p> <p>Grade 4: Life-threatening; pressor or ventilatory support indicated</p>	<p>Stop Infusion.</p> <p>Additional appropriate medical therapy may include but is not limited to:</p> <ul style="list-style-type: none"> IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine <p>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated.</p> <p>Subject is permanently discontinued from further trial treatment administration.</p>	<p>No subsequent dosing</p>
<p>Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.</p>		

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP

web:(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.5). With this information, determine whether the event must be reported as an expedited report (see Section 10.4). Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.4. All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

10.12 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT). Grade is an essential element of the Guidelines and, in general, relates to **severity** for the purposes of regulatory reporting to NCI.

NOTE: A severe AE, as defined by the above grading scale, is **NOT** the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

- The determination of whether an AE is expected is based on agent-specific information provided in Section 15.0 of the protocol and the study specific consent form.
- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of the protocol and the study specific consent form.

NOTE: “Unexpected adverse experiences” means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).

Probable - The adverse event *is likely related* to the agent(s).

Possible - The adverse event *may be related* to the agent(s).

Unlikely - The adverse event *is doubtfully related* to the agent(s).

Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.31 **AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME Arm**

NOTE: When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the entire combination (arm) is then considered an investigational intervention for reporting-

Routine Reporting

- Routine AE reporting for Phase 1 and Phase 2 clinical studies using an investigational agent /intervention in combination with a commercial agent is stated in the protocol. See Section 10.6.
- Routine AE reporting for Phase 3 clinical studies using an investigational agent/intervention and a commercial agent in combination must be reported as defined by the general guidelines provided by sponsors, Groups, Cancer Centers, or Principal Investigators. See Section 10.6.

Expedited Reporting

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for investigational agents/interventions in Section 10.4, and where indicated, an expedited report must be submitted.
- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report. Refer to Section 10.4 for specific AE reporting requirements or exceptions.
- Commercial agent expedited reports must be submitted to the FDA via MedWatch.
- An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity, expedited reporting is required. The clinical investigator must determine severity.

10.4 Expedited Reporting Requirements for IND/IDE Agents

10.41 Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention^{1,2}

<p>FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312) NOTE: Investigators MUST immediately report to the sponsor ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64) An adverse event is considered serious if it results in ANY of the following outcomes:</p> <ol style="list-style-type: none"> 1) Death 2) A life-threatening adverse event 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for \geq 24 hours 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions 5) A congenital anomaly/birth defect 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6 				
<p>ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported within the timeframes detailed in the table below.</p>				
Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization \geq 4 hrs	7 Calendar Days			24-Hour 3 Calendar Days
Not resulting in Hospitalization \geq 24 hrs	Not required		7 Calendar Days	
<p>NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in section 10.6 of the protocol. Expedited AE reporting timelines are defined as:</p> <ul style="list-style-type: none"> o “24-Hour; 3 Calendar Days” - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report. o “7 Calendar Days” - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE. 				
<p>¹Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows: Expedited 24-hour notification followed by complete report within 3 calendar days for:</p> <ul style="list-style-type: none"> • All Grade 4, and Grade 5 AEs <p>Expedited 7 calendar day reports for:</p> <ul style="list-style-type: none"> • Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization • Grade 3 adverse events 				
<p>² For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above applies after this reporting period.</p>				
<p>Effective Date: May 5, 2011</p>				

10.42 Additional instructions:

Mayo Clinic Cancer Center (MCCC) Institutions: Attach copies of MedWatch 3500A to Mayo Clinic Cancer Center SAE Reporting Form: <http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56> which will automatically be emailed to the MCCC Regulatory Affairs Unit (RAU) Risk Information Specialist at cancercrosafetyin@mayo.edu, who will determine and complete IRB reporting. The RAU will submit to the MCCC SAE Coordinator and the MCCC IND Coordinator.

10.5 Adverse event reporting requirements for Merck

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets.

10.51 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥ 5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with (“results from”) the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck’s product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology “accidental or intentional overdose without adverse effect.”

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; [REDACTED]).

10.52 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; [REDACTED]).

10.53 Immediate Reporting of Adverse Events to Merck

Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Merck's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is another important medical event

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck.

10.54 SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: [REDACTED]

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; [REDACTED]) at the time of submission to FDA.

All subjects with serious adverse events must be followed up for outcome.

10.55 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; [REDACTED])

Events of clinical interest for this trial include:

1. An overdose of Merck product, as defined above - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline

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

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

10.56 Additional adverse events:

A separate guidance document has been provided entitled “Event of Clinical Interest Guidance Document” (previously entitled, “Event of Clinical Interest and Immune-Related Adverse Event Guidance Document”). This document can be found in Appendix 4 and provides guidance regarding identification, evaluation and management of ECIs and irAEs.

ECIs (both non-serious and serious adverse events) identified in this guidance document from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; [REDACTED]), regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

10.6 Special Situations for Expedited Reporting

Exceptions to Expedited Reporting: EXPECTED Serious Adverse Events¹

An expedited report may not be required for specific Grade 1, 2, 3 and 4 Serious Adverse Events. Any protocol specific reporting procedures **MUST BE SPECIFIED BELOW** and will **supersede** the standard Expedited Adverse Event Reporting Requirements (see footnote 1):

CTCAE System/Organ/Class (SOC)	Adverse event/Symptoms	CTCAE Grade at which the event will not be expeditedly reported
General disorders and administrations site conditions	Fatigue	≤Grade 3
Gastrointestinal	Vomiting	≤Grade 3
	Nausea	≤Grade 3
	Diarrhea	≤Grade 3
Investigations	Neutrophil count decreased	≤Grade 4
	White blood cell count decreased	≤Grade 4

CTCAE System/Organ/Class (SOC)	Adverse event/Symptoms	CTCAE Grade at which the event will not be expeditedly reported
	Lymphocyte count decreased	≤Grade 4
	Platelet count decreased	≤Grade 4
Blood and lymphatic system disorders	Anemia	≤Grade 4

¹ These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

10.7 Other Required Reporting

10.71 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital abnormalities or birth defects, must be reported immediately if they occur at any time following treatment with an agent under an IND/IDE since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).

10.72 Death

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life. Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as **Grade 5 “Neoplasms benign, malignant and unspecified (incl cysts and polyps) – Other (Progressive Disease)”** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

- Any death occurring **within 30 days** of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.
- Any death occurring greater than 30 days after the last does of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.

10.73 Secondary Malignancy

- A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND/IDE be reported. Three options are available to describe the event:
 - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
 - Myelodysplastic syndrome (MDS)
 - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.74 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.75 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug.

Suggested Pregnancy Reporting Form:

- Pregnancy Report Form

Use form available from the CTEP protocol development page:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf

Mayo Clinic Cancer Center (MCCC) Institutions: Provide copies, along with the UPIRTSO cover sheet, by email to the MCCC Regulatory Affairs Unit (RAU) Risk Information Specialist at [REDACTED], who will determine and complete IRB reporting. The RAU will submit to the MCCC SAE Coordinator and the MCCC IND Coordinator to determine if FDA submission is needed.

Non Mayo Clinic institutions: Submit forms via email to Mayo Clinic Cancer Center CRO [REDACTED]. The CRO will submit to the MCCC SAE Coordinator and to the MCCC IND Coordinator.

10.8 Required Routine Reporting

Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:

SYSTEM ORGAN CLASS	Adverse event/Symptoms	Baseline	Each evaluation
Investigations	Creatinine increased	X	X
	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
	White Blood cell decreased (WBC)	X	X
General disorders and administration site conditions	Fatigue	X	X
Gastrointestinal Disorders	Nausea	X	X
	Vomiting	X	X
	Baseline # of Stools	X	
	Diarrhea		X
	Constipation		X
Infections and infestations	Sepsis	X	X
Blood and lymphatic system disorders	Anemia	X	X
	Febrile neutropenia	X	X
Skin and subcutaneous tissue disorders	Rash, maculopapular	X	X

- 10.81 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.5:
- 10.811 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.
 - 10.812 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.
 - 10.813 Grade 5 AEs (Deaths)
 - 10.8131 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.
 - 10.8132 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.
- 10.83 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation

The International Myeloma Working Group (IMWG) uniform response criteria (Rajkumar et al, 2011) will be used to assess response to therapy.

11.1 Terms and definitions

- **M-protein:** synonyms include M-spike, monoclonal protein and myeloma protein, paraprotein, M-component.

Serum M-protein level is quantitated using densitometry on SPEP except in cases where the SPEP is felt to be unreliable.

- M-proteins migrating in the β -region (usually IgA M-proteins)
- Cases in which the M-spike is so large and narrow on agarose (some specimens >4 g/dL) that they underestimate the actual immunoglobulin level (by greater than 1500 mg/dL) due to technical staining properties of the agarose gel.
- Cases in which there are multiple peaks of same monoclonal protein (aggregates or dimers)

If SPEP is not available or felt to be unreliable (above examples) for routine M-protein quantitation, then quantitative immunoglobulin levels derived from nephelometry or turbidometry can be accepted, with the exception that quantitative IgG may not be used. However, this must be explicitly reported at baseline, and only nephelometry can be used for that patient to assess response. SPEP derived M-spike values and quantitative nephelometric immunoglobulin values cannot be used interchangeably.

Urine M-protein measurement is estimated using 24-h UPEP only. Random or 24 h urine tests measuring kappa and lambda light chain levels are not reliable and are not recommended.

FLC estimation is currently carried out using the serum FLC assay (Freelite, The Binding Site Limited, UK). Patients with kappa/lambda FLC ratio <0.26 are defined as having monoclonal lambda FLC and those with ratios >1.65 as having a monoclonal kappa FLC. The monoclonal light chain isotype is considered the involved FLC isotype, and the opposite light chain type as the uninvolved FLC type.

- **Response terms:** The following response terms will be used: stringent Complete Response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), Minimal Response (MR), stable disease (SD), and progressive disease (PD).

In addition, for each response category, there will be an “unconfirmed” response category, which will be for internal use, for the purpose of guiding decision making and test ordering. These designations will be applied at the time of the first measurement at which the quantitative aspect of the response category has been satisfied without the confirmation step having been satisfied. The designation “u” will precede the standard abbreviations, and will include usCR, uCR, uVGPR, uPR, uMR, uPD.

- **Measurable disease:** Patients who have a measurable serum or urine M-protein.
 - Serum M-protein ≥ 1 g/dl
NOTE: Quantitative IgG may not be used for defining measurable disease
 - Urine M-protein ≥ 200 mg/24 h
 - Serum FLC assay: Involved FLC level ≥ 10 mg/dl provided serum FLC ratio is abnormal

- Bone marrow plasma cells $\geq 30\%$

The serum free light chain (FLC) assay is of particular use in monitoring response to therapy in patients who have oligo-secretory or non-secretory disease and **should be used in assessing response only if the baseline serum and/or urine M proteins are not “measurable” as above, and the baseline level of the involved FLC is “measurable.”** When using this assay, it is important to note that the FLC levels vary considerably with changes in renal function and in patients with renal insufficiency, the levels of both the kappa and lambda may remain elevated, but the ratio normalizes with achievement of CR. Thus, both the level of the involved and the uninvolved FLC isotype (i.e., the involved/uninvolved ratio or involved-uninvolved difference) should be considered in assessing response. *Patients included on the study on the basis of FLC alone (i.e., no measurable serum/urine m-spike) should be the only ones who are evaluated using FLC response criteria. The others should follow usual criteria and ignore FLC results with the exception of defining stringent complete response.*

- **Evaluable disease:** Patients who do not have a “measurable” serum M-spike, serum free light chain, or urine M-spike.
- **Oligosecretory myeloma:** Patient with multiple myeloma who has NEVER had “measurable” serum M-spike or urine M-spike, but has had a detectable monoclonal protein in his/her serum and/or urine and/or measurable serum free light chain.
- **Non-secretory myeloma:** Patient with multiple myeloma who has NEVER had a detectable monoclonal protein in his/her serum and/or urine.

11.2 Clarification of test indications

Listed below are the minimal required tests required to assess response based on the characteristics of their disease at on study.

Table 11.21: Tests Required to Assess Response (Must Be Done at Each Disease Measurement Visit Except as Indicated^{1,2})

On Study Baseline Value	SPEP ⁴	24 hr UPEP ²	Ig FLC	BM Bx
Serum monoclonal protein ≥ 1 g/dl, and urine M-spike ≥ 200 mg/24 hrs	X	X		
Serum monoclonal protein ≥ 1 g/dl, but urine M-spike < 200 mg/24 hrs	X			
Serum monoclonal protein < 1 g/dl, and urine M-spike ≥ 200 mg/24 hrs		X		
Serum monoclonal protein < 1 g/dl, urine M-spike < 200 mg/24 hrs, but involved Ig FLC is ≥ 10 mg/dL			X	
Serum monoclonal protein < 1 g/dl, urine M-spike < 200 mg/24 hrs, involved Ig FLC is < 10 mg/dL, bone marrow $\geq 30\%$ plasma cells				X ³

¹ **SPEP, UPEP, Immunofixation studies of both serum and urine, and Bone marrow biopsy** are required to document CR regardless of registration values, and in addition **FLC measurement and bone marrow immunophenotyping** is required to document sCR. SPEP and UPEP are required to document VGPR regardless of registration values.

² For serum measurable patients, 24 hour urine does not need to be confirmed (i.e. repeated after documented response) for any response category.

³ At a minimum, a bone marrow biopsy should be repeated every 3 months until documented response. Bone marrow biopsy results do not need to be repeated after documented response.

⁴ If serum monoclonal protein is being followed by quantitative immunoglobulin levels derived from nephelometry or turbidometry, quantitative immunoglobulins are required. SPEP is only required to document CR or VGPR.

11.3 Confirmed response

In order to be classified as a hematologic response, confirmation of serum monoclonal protein, serum immunoglobulin free light chain (when primary determinant of response) and urine monoclonal protein (when primary determinant of response) results must be made by verification on two consecutive determinations.

- Bone marrow aspirate and biopsy are **only** required to document CR or sCR, except for patients with evaluable disease **only**, where a bone marrow is required to document all response categories including progression. However, a second confirmatory bone marrow is **not** required to confirm response in any case.
- Radiographic studies are not required to satisfy these response requirements, however, if radiographic studies were performed there should be no evidence of progressive or new bone lesions.

Appropriate tests required to document and confirm response are listed in Table 11.21.

11.4 Bone progression

Caution must be exercised to avoid rating progression on the basis of variation of radiologic technique alone. Compression fracture does not exclude continued response and may not indicate progression. When progression is based on skeletal disease alone, it should be discussed with the Study Chair before removing the patient from the study.

11.5 Response and Progression

Criteria for response and progression are listed in Table 11.51. Progressive disease for all patients as defined in Table 11.51.

Table 11.51

CATEGORY	RESPONSE CATEGORY ^a
Stringent Complete Response (sCR) ^b	<ul style="list-style-type: none"> • CR as defined <i>plus</i> • Normal FLC ratio <i>and</i> • Absence of clonal PCs by immunohistochemistry or 2- to 4-color flow cytometryⁱ
Complete Response (CR) ^b	<ul style="list-style-type: none"> • Negative immunofixation of serum and urine^c <i>and</i> • Disappearance of any soft tissue plasmacytoma <i>and</i> • ≤5% PCs in Bone Marrow <i>and</i> • If the only measurable disease is FLC, a normal FLC ratio^d
Very Good Partial Response (VGPR)	<ul style="list-style-type: none"> • Serum and urine M-component detectable by immunofixation but not on electrophoresis^c <i>or</i> • ≥90% reduction in serum m-component and urine m-component <100 mg/24 h^c • If the only measurable disease is FLC, a ≥90% reduction in the difference between involved and involved FLC levels

CATEGORY	RESPONSE CATEGORY ^a
Partial Response (PR)	<ul style="list-style-type: none"> • If present at baseline, $\geq 50\%$ reduction of serum M-protein and reduction in 24-hour urinary M-protein or to < 200 mg/24hrs • If the only measurable disease is FLC, a $\geq 50\%$ reduction in the difference between involved and involved FLC levels • If the only measurable disease is BM, a $\geq 50\%$ reduction in BM PC's (provided the baseline PC's was $\geq 30\%$) • If present at baseline, $\geq 50\%$ reduction in the size of soft tissue plasmacytomas
Minor Response (MR)	<ul style="list-style-type: none"> • If present at baseline, $\geq 25\%$ but $< 49\%$ reduction of serum M protein <i>and</i> reduction in 24-hour urine M-protein by 50-89% which still exceeds 200mg/24 hours ^c <i>and</i> • If present at baseline, 25-49% reduction in the size of soft tissue plasmacytoma <i>and</i> • No increase in the size or number of lytic bone lesions (development of compression fracture does not exclude response)
Progressive Disease (PD) ^{b, h}	<p>Increase of 25% from lowest value in any of the following ^{f, g}:</p> <ul style="list-style-type: none"> • Serum M-component (absolute increase must be ≥ 0.5 mg/dL) AND/OR • Urine M-component (absolute increase must be ≥ 200 mg/24 hrs) AND/OR • If the only measurable disease is FLC, the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL) AND/OR • If the only measurable disease is BM, bone marrow PC percentage (absolute increase must be $> 10\%$) ^e <p>Or any one or more of the following:</p> <ul style="list-style-type: none"> • Development of new bone lesion or soft tissue plasmacytoma or definite increase in the size of existing bone lesions or soft tissue plasmacytoma • Development of hypercalcemia (corrected serum calcium > 11.5mg/dL) that can be attributed solely to the PC proliferative disorder
Stable Disease (SD)	Not meeting criteria for sCR, CR, VGPR, PR, MR or PD

^a All response categories require two consecutive assessments (sCR, CR, VGPR, PR, MR, PD) made at anytime before the institution of any new therapy; sCR, CR, VGPR, PR, MR and SD 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 requirements. Bone marrow assessments need not be confirmed. Each category, except for stable disease, will have a working subcategory of “unconfirmed” [prefix ‘u’] to designate first time point at which response category MAY have been achieved if confirmed.

^b CR patient will need to progress at the same level as VGPR and PR patients to be considered a PD. A positive immunofixation alone is not sufficient.

^c If more than one M protein spikes meet the criteria for measurable disease at baseline, then both need to be followed for response. Otherwise, only follow the measurable M protein spike for response.

^d In patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26-1.65 in addition to the CR criteria listed above.

^e Bone marrow criteria for PD are only to be used in patients without measurable disease by M protein and by FLC.

^f A "25% increase" refers to M protein, FLC and bone marrow results and does not refer to bone lesions, soft tissue plasmacytoma or hypercalcemia. The lowest value does not need to be a confirmed value. If the lowest serum M-component is ≥ 5 g/dL, an increase in serum M-component of ≥ 1 g/dL is sufficient to define disease progression.

^g In the case where a value is felt to be a spurious result per physician discretion (for example, a possible lab error), that value will not be considered when determining the lowest value.

^h Progressive disease should be confirmed. However, treatment may be discontinued for progressive disease that is unconfirmed per physician discretion. In this case, an objective status of PD should be entered on the measurement form and progressive disease should be reported on the event monitoring form.

ⁱ Presence/absence of clonal cells is based upon the k/l ratio. An abnormal k/l ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/l of 4:1 or 1:2.

12.0 Descriptive Factors

- 12.1 Parameters followed for hematologic response (pick one): serum monoclonal protein ≥ 1 g/dL and urine M-spike ≥ 200 mg/24 hours vs. serum monoclonal protein ≥ 1 g/dL only vs. urine M-spike ≥ 200 mg/24 hours only vs. serum immunoglobulin free light chain ≥ 10 mg/dL.

NOTE: Distinguish between SPEP measurement versus quantitative IgA measurement for serum monoclonal protein.

13.0 Treatment/Follow-up Decision at Evaluation of Patient

13.1 Categories of response

Patients who are sCR, CR, VGPR, PR, MR, or (or usCR, uCR, uVGPR, uPR, uMR) will continue treatment per protocol. Patients will go off treatment to event monitoring if an MR is not seen after 2 cycles and a PR is not seen after 4 cycles. Confirmation of MR or PR is not required.

13.2 Patients who receive transplant

Patients who receive a transplant will go to event monitoring per Section 18.0. The transplant should be reported on the event monitoring form.

13.3 Progressive disease or alternate therapy

Patients who develop progressive disease or start alternate therapy will go to the event-monitoring phase per Section 18.0.

13.4 Off protocol for reasons other than PD

Patients who go off protocol treatment for reasons other than PD will go to the event-monitoring phase per Section 18.0.

13.5 Discontinuation for unacceptable AEs

Patients who discontinue therapy for an unacceptable adverse event(s) will be followed until resolution or stabilization of the AE(s).

13.6 Criteria for Patient Withdrawal from Study Treatment

Patients may be withdrawn from the study for the following reasons:

- Progressive multiple myeloma
- Patient refuses further treatment on the trial
- Patient develops an intercurrent illness that precludes further participation, or requires a prohibited concomitant treatment
- The Investigator withdraws the patient in the patient's best interests
- Patient is lost to follow-up (defined as the inability to contact the patient on 3 separate occasions)
- Administrative reasons (e.g., the patient is transferred to hospice care)
- An adverse event, which in the opinion of the Investigator, precludes further trial participation

All attempts should be made to complete the End of Study procedures if a patient withdraws from the trial early.

13.7 Criteria for Study Discontinuation

The study may be temporarily or permanently discontinued at any site and at any time. Reasons for study discontinuation may include, but are not limited to, the following:

- Safety concerns
- Poor enrollment
- Non-compliance with the protocol, Good Clinical Practice guidances or other regulatory requirements by the Investigator(s)
- Request to discontinue the trial by a regulatory or health authority or an IRB
- Manufacturing difficulties/concerns

All Investigators and the requisite regulatory authorities will be notified if the study is suspended or terminated for safety reasons. In the case of such termination, the Investigator will notify the IRB.

13.8 Patient Ineligible

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.9a Patient major violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

13.9b Patient cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be collected for IRB #521-93 :

Correlative Study (Section for more information)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Baseline	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycles ≥5	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
						End of cycle	End of cycle	End of cycle	End of cycle			
PDL1 expression (14.41)	Mandatory	Marrow	ACD (yellow)	6 ml per tube (3)	X				X	Any subsequent marrow	No	Kool-pak
Immune markers (14.42)	Mandatory	Blood	ACD (yellow)	6 mL (4)	X	X	X	X	X	At progression	No	Kool-pak

14.2 Collection and Processing:

14.21 Samples are to be shipped the same day as they are collected. No processing is required at the sites.

14.3 Shipping and Handling

14.31 Kits

14.311 Kits will be used for this study. Kits will contain supplies and instructions for collection, processing and shipping specimens

14.312 Participating sites may obtain kits by emailing: [REDACTED] Email requests should include address, contact information and number of kits being requested.

14.313 Kits will be sent via FedEx Ground at no additional cost to participating sites. Allow 3-4 business days to receive kits.

14.32 Shipping

Bone marrow and blood samples can be shipped with Kool Pak the same day they are collected (Monday-Thursday). They should be shipped priority overnight taking care to avoid Friday collection and shipping.

If unavoidable, Friday shipping with Saturday delivery can be arranged contacting the laboratory **in advance**.

Please notify Mayo Clinic by email [REDACTED] or phone [REDACTED] to notify laboratory when specimens are being shipped.

[REDACTED]

14.4 Background and Methodology

14.41 PDL1 expression

PDL1 expression will be measured on the myeloma cells in the bone marrow (CD138, 38 positive) by using flow cytometry. The expression will also be determined on other cell types in the bone marrow.

14.42 Measures of immune activation

The “global” impact of therapy on immune cell subsets will be ascertained by immunophenotypic analysis of PBMCs for subsets of T, B, NK cells, monocytes and dendritic cells (DC) and their activation status using commercially available monoclonal antibodies directed at the following antigens: CD3, CD4, CD8, CD11c, CD14, C16, CD19, CD20, CD25, CD45RA/RO, CD56, CD69, CD63L, CD80, CD83, CD86, CD123, DR. The flow cytometric analysis will also be performed on the bone marrow samples.

Activation of DC and subsequent modulation of the immune response caused by treatment with lenalidomide may directly or indirectly alter the cytokines present in plasma. The BioRad human 27-plex cytokine panel will be used for the measurements of plasma concentrations of IL-1 β , IL-1 α , IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12(p70), IL-13, IL-15, IL-17, basic FGF, eotaxin, G-CSF, GM-CSF, IFN- γ , IP-10, MCP-1, MIP-1 α , MIP-1 β , [REDACTED] PDGF, RANTES, TNF- α , and VEGF.

14.43 Samples for future studies

An aliquot of CD138 sorted MM cells and CD138 negative cells will be stored for future studies. An aliquot of peripheral blood plasma as well as white blood cells (WBC) will be stored for potential studies in future.

15.0 Drug Information

15.1 Pembrolizumab (MK-3475, SCH 900475, Keytruda®)

15.11 **Background:** Pembrolizumab is a potent humanized IgG4 monoclonal antibody with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical *in vitro* data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1.

15.12 **Formulation:**

Pembrolizumab (MK-3475) Solution for Infusion is a sterile, non-pyrogenic aqueous solution supplied in single-use Type I glass vial containing 100 mg/4 mL of pembrolizumab (MK-3475). The product is preservative-free solution which is essentially free of extraneous particulates. s available as a liquid 25 mg/mL, 100 mg/vial.

15.13 **Preparation and storage:**

Vials should be stored in the refrigerator at temperatures between 2-8°C.

Drug concentrate is further diluted with normal saline (or 5% dextrose) in the concentration range of 1 to 10 mg/m in IV containers made of polyvinyl chloride (PVC) or non-PVC material. Reconstituted vials should be immediately used to prepare the infusion solution in the IV bag and the infusion solution should be immediately administered. Diluted pembrolizumab solutions may be stored at room temperature for a cumulative period of up to 4 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion. In addition, IV bags can be stored at 2-8 °C for up to a cumulative time of 20 hours.

15.14 **Administration:**

Pembrolizumab is administered by intravenous infusion over 30 minutes via a 0.22 micron in-line filter. The final infusion volume must be between 1 and 10 mg/mL. Maximum rate of infusion should not exceed 6.7 mL/minute through a peripheral or indwelling catheter. Flush the line with 0.9% NaCL following the completion of the infusion.

15.15 **Pharmacokinetic information:**

- a) Absorption – Steady-state is predicted to be achieved after ~18 weeks of repeated dosing, with ~2.2-fold accumulation in exposure during administration Q3W relative to exposure observed following single dose administration. The majority (~81%) of this accumulation has occurred by the fourth dose. In the dose range studied for efficacy (2 to 10 mg/kg), pembrolizumab exposure increases in a dose-proportional manner, with clearance being independent of time or pembrolizumab concentration.
- b) Distribution – Pembrolizumab has a limited volume of distribution.
- c) Excretion – The systemic clearance of pembrolizumab is ~0.22 L/day and the terminal elimination half-life ($t_{1/2}$) is estimated to be ~26 days.
- d) Metabolism - Pembrolizumab is catabolized by general protein degradation processes; typical small molecule metabolic pathways (eg, cytochrome P450 enzymes, glucuronosyltransferases) do not contribute to its clearance.

15.16 **Potential Drug Interactions:** There are no known significant drug interactions.

15.17 **Known potential toxicities:**

Common known potential toxicities, > 10%:

Dermatologic: Pruritus, skin rash
 Gastrointestinal: diarrhea
 Neuromuscular & skeletal: arthralgia, back pain
 Respiratory: Cough

Less common known potential toxicities, 1% - 10%:

Infusion related reactions
 Dermatologic: vitiligo, severe skin reactions
 Endocrine & metabolic: Hypothyroidism, hyperthyroidism, hyponatremia
 Gastrointestinal: Colitis, abdominal pain
 Respiratory: Pneumonitis

Rare known potential toxicities, <1% (Limited to important or life-threatening):

Secondary adrenocortical insufficiency (immune-mediated), hepatitis (including autoimmune hepatitis), hypophysitis, nephritis, Guillain-Barre syndrome (immune-mediated), myositis (immune-mediated), pancreatitis (immune-mediated), uveitis (immune-mediated), and Type 1 diabetes mellitus.

Stevens-Johnson syndrome, Toxic Epidermal Necrolysis, and Immune-mediated myocarditis

Two important potential risks have been identified, although the data available thus far for these events does not provide sufficient evidence of a causal relationship to pembrolizumab. The two important potential risks are: a) myasthenic syndrome, and b) an increased risk of severe complications (such as early severe graft versus host disease and venoocclusive disease) of allogeneic transplant in patients with hematologic malignancies who have previously been treated with PD-1 inhibitors. The Sponsor continues to monitor and collect data on these potential risks in order to further characterize their potential relationship to Pembrolizumab.

15.18 **Drug procurement:** Pembrolizumab will be provided free of charge to study participants by Merck.

15.19 **Nursing Guidelines:**

- 15.191 Pembrolizumab side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening. Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids.
- 15.192 Diarrhea can be seen however is less common than that seen with anti-CTLA-4 agents. However it can be severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.
- 15.193 Rash/pruiritis/dermatitis is seen. Patients should report any rash to the study team. Treat per [Section 9.0](#) and monitor for effectiveness.

- 15.194 Monitor LFT's closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.
 - 15.195 Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.
 - 15.196 Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysitis, and adrenal insufficiency) are seen with this agent. Patients may present only with the vague sense of fatigue and "not feeling well". Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.
 - 15.197 Patients who are started on steroid therapy for any side effects of pembrolizumab toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.
 - 15.198 Fatigue is common and may or may not be associated with immune related side effects. Assess patient's fatigue level prior to each cycle of therapy and report any *changes to the study team*.
 - 15.199a Patients should avoid receiving live vaccines within 30 days of study drug administration or per other study guidelines.
 - 15.199b Patients who have undergone an allogenic bone marrow transplant, have an increased risk of severe complications including early GVHD, and venoocclusive disease, if they have previously been treated with Pembrolizumab.
- 15.2 Lenalidomide (Revlimid®, CC-5013, CDC-501)
- 15.21 **Background:** Lenalidomide has a wide range of effects, including the inhibition of hematopoietic tumor cell proliferation, the enhancement of T cells and natural killer (NK) cell activity, the modulation of stem cell differentiation, the inhibition of angiogenesis, and the inhibition of inflammation.
 - 15.22 **Formulation:** For clinical study, lenalidomide is provided as 1.25-, 2.5-, 5-, 10-, 15-, 20-, and 25-mg capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The lenalidomide capsules are supplied in push-through blister foil or tamper-evident, child-resistant, opaque, high-density polyethylene (HDPE) containers with HDPE caps.
 - 15.23 **Preparation and storage:** Lenalidomide should be stored at room temperature, between 59 and 86°F (15-30°C). Store drug away from direct sunlight.

15.24 **Administration:** Capsules are administered by mouth daily with water. Patients should not break, chew or open the capsules.

15.25 **Pharmacokinetic information:**

a) Absorption – Lenalidomide is rapidly absorbed following oral administration to healthy subjects, with maximum plasma concentrations occurring between 0.5 and 1.5 hours post-dose. Co administration with a high-fat and high-calorie meal in healthy subjects reduced the extent of absorption, resulting in an approximately 20% decrease in AUC and 50% decrease in C_{max} in plasma.

In the pivotal MM and MDS registration trials where the efficacy and safety were established for lenalidomide, the drug was administered without regard to food intake. Thus, lenalidomide can be administered with or without food.

Multiple dosing (up to 100 mg BID) did not cause marked drug accumulation. In plasma, the relative exposures of the S- and R-enantiomers of lenalidomide are approximately 55% and 45% respectively.

b) Distribution – In vitro (14C)-lenalidomide binding to plasma proteins was low, with mean plasma protein binding at 22.7% and 29.2% in multiple myeloma subjects and healthy volunteers, respectively. In a multiple dose study in healthy subjects administered 25 mg/day for 4 days, a small amount of lenalidomide (<0.01% of the dose) was detected in semen. Three days after stopping the drug, the amount of drug in semen was undetectable.

c) Metabolism – Results from in vitro metabolism studies showed that lenalidomide was neither metabolized by nor inhibited or induced the CYP pathway. In healthy subjects, lenalidomide undergoes limited metabolism and the parent compound is the predominant circulating component.

d) Excretion – Approximately 65% to 85% of lenalidomide is eliminated unchanged through urinary excretion in subjects with normal renal function. The half-life of elimination is approximately 3 to 4 hours at the clinically relevant doses (5 to 50 mg/day). Steady-state levels are achieved within 4 days.

Analyses in subjects with impaired renal function indicate that as renal function decreases, the total drug clearance decreases proportionally resulting in an increase in AUC. The t_{1/2} of lenalidomide was longer by approximately 6 to 12 hours in subjects with moderate or worse RI.

15.26 **Potential Drug Interactions:**

Results from human in vitro metabolism studies indicated that lenalidomide is not metabolized by CYP enzymes, suggesting that administration of lenalidomide with drugs that inhibit CYP enzymes is not likely to result in metabolic drug interactions. Lenalidomide did not inhibit or induce marker enzyme activities for human CYP1A2, 2C9, 2C19, 2D6, 2E1, or 3A4 in vitro. In cultured human hepatocytes, lenalidomide did not induce the catalytic activities of CYP1A2, 2B6, 2C9, 2C19, or 3A4/5. Results from in vitro studies showed that lenalidomide is not a substrate of human MRP1, MRP2, or MRP3 efflux transporters. Results from in vitro studies also demonstrated that lenalidomide is not a substrate of human OAT1, OAT3, OATP1B1 (OATP2), nor OCT1. Lenalidomide is a weak substrate of P-glycoprotein, but does not inhibit P-glycoprotein. Therefore, clinically relevant drug-drug interactions are unlikely between lenalidomide and P-glycoprotein substrates or inhibitors.

Co-administration of multiple doses of 10 mg of lenalidomide had no effect on the single dose pharmacokinetics of R- and S-warfarin. Co-administration of

single 25-mg dose warfarin had no effect on the pharmacokinetics of lenalidomide. However, it is not known whether there is an interaction during clinical use.

Concomitant administration with lenalidomide 10 mg/day increased the plasma exposure of digoxin (0.5 mg, single dose) by 14%. It is not known whether the effect will be different in the therapeutic situation (higher lenalidomide doses and concomitant treatment with dexamethasone).

15.27 **Known potential toxicities:**

Pregnancy Warning: Lenalidomide is structurally related to thalidomide, a known human teratogen. Therefore, in an effort to prevent to the greatest extent possible any chance of fetal exposure, lenalidomide is available through a controlled distribution program, specifically a pregnancy prevention program called Revlimid REMS. It is contraindicated in women who are or may become pregnant. Female subjects of childbearing potential are required to submit to regular pregnancy testing, and to agree to use effective forms of birth control as outlined in study protocols. Male subjects, even those who have had a vasectomy, must agree to use a condom during sexual contact with a pregnant woman or a woman who can become pregnant.

Very Common AEs (≥10%): anemia, febrile neutropenia, leukopenia, neutropenia, thrombocytopenia, cataracts, blurred vision, abdominal pain, constipation, diarrhea, dyspepsia, nausea, vomiting, asthenia, chills, edema including peripheral, fatigue, pyrexia, abnormal liver function tests, bacterial, viral and fungal infections (including opportunistic infections), bronchitis, nasopharyngitis, sinusitis, pneumonia, rhinitis, upper respiratory tract infection, urinary tract infection weight decreased, decreased appetite, hyperglycemia, hypocalcemia, hypokalemia, arthralgia, back pain, bone pain, muscle spasms, musculoskeletal pain, myalgia, pain in extremity, dizziness, dysgeusia, headache, hypoesthesia, neuropathy peripheral, neuropathy, tremor, depression, insomnia, renal failure, cough, dyspnea, epistaxis, pharyngitis, pulmonary embolism, dry skin, pruritus, rash, and deep vein thrombosis.

Common (≥1% and <10%): granulocytopenia, hemolytic anemia, lymphopenia, pancytopenia, acute myocardial infarction, atrial fibrillation, cardiac failure, congestive heart failure, myocardial ischemia, tachycardia, vertigo, upper abdominal pain, dry mouth, toothache, chest pain, fall, cholestasis, bacteremia, cellulitis, erysipelas, gastroenteritis, herpes simplex, herpes zoster, influenza, lower respiratory infection, respiratory infection, sepsis, contusion, alanine aminotransferase increased, c-reactive protein increased, gamma-glutamyltransferase increased, dehydration, diabetes mellitus, gout, hypercalcemia, hyperuricemia, hypophosphatemia, hypomagnesemia, hyponatremia, iron overload, muscular weakness, acute myeloid leukemia, basal cell carcinoma, Myelodysplastic syndrome, squamous cell carcinoma of skin, T-cell type acute leukemia, tumor flare, tumor lysis syndrome, cerebrovascular accident, lethargy, paresthesia, peripheral sensory neuropathy, syncope, mood altered, renal failure, respiratory distress, erythema, hyperhidrosis, night sweats, hematoma, hypertension, hypotension, peripheral ischemia, thrombosis, and vasculitis.

Uncommon, limited to important or life-threatening (<1%): hypersensitivity, Graft vs. Host Disease, viral reactivation (such as hepatitis B virus or herpes zoster), DRESS.

The following additional adverse reactions have been reported in Celgene-sponsored clinical studies and are considered by the company to be possibly related to the administration of lenalidomide: granulocytopenia, cataract, vision blurred, abdominal pain upper, dry mouth, gastrointestinal motility disorder, toothache, fall, herpes simplex, influenza, rhinitis, hyperuricemia, hypophosphatemia, iron overload, musculoskeletal pain, dysgeusia, headache, paresthesia, dry skin, hyperhidrosis, and pruritus.

Please refer to the Investigator Brochure for a more comprehensive list of treatment-emergent adverse events.

15.28 **Drug procurement and accountability:**

As a requirement of the REMS program, access to Lenalidomide is restricted. Lenalidomide is approved for marketing only under a FDA approved, restricted distribution program called REVLIMID REMS (www.REVLIMIDREMS.com) formerly known as the RevAssist program. Physicians, pharmacies, and patients must be registered; a maximum 28-day supply may be dispensed; a new prescription is required each time it is filled; pregnancy testing is required for females of childbearing potential.

Drug will be shipped directly to the patient through Revlimid REMS Program. Any unused lenalidomide should be returned for disposition in accordance with the REVLIMID REMS™ program.

15.29 **Nursing Guidelines**

15.291 The most common side effects are neutropenia and thrombocytopenia.

15.292 Due to the highly teratogenic potential of the closely related thalidomide, it is highly recommended that all women of childbearing age group and all men use effective contraception during therapy. All staff who are pregnant or who can become pregnant should not handle this drug outside of its original packaging.

15.293 Instruct patient to report any rash immediately to the study team.

15.294 Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened.

15.295 If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.

15.296 Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

15.3 **Dexamethasone for Oral Administration (DXM)**

15.31 **Background:** Dexamethasone is an adrenal corticosteroid compound. Dexamethasone decreases inflammation by suppression of neutrophil migration, decreased production of inflammatory mediators, and reversal of increased capillary permeability; suppresses normal immune response. Dexamethasone's mechanism of antiemetic activity is unknown.

15.32 **Formulation:** Commercially available for oral administration as:
Tablets [scored]: 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, and 6 mg.

Solution, oral: 0.5 mg/mL (500 mL).

Solution, oral concentrate: Dexamethasone Intensol: 1 mg/mL (30 mL).

- 15.33 **Preparation, storage, and stability:** Refer to package insert for complete preparation and dispensing instructions. Store oral tablets at room temperature between 20°C to 25°C (60°F to 77°F). Protect from moisture. Dispense in a well-closed, light-resistant container as defined in the USP/NF. Store oral liquid at room temperature, do not freeze. Do not use if solution contains a precipitate. Refer to commercial package for drug expiration date.
- 15.34 **Administration:** Refer to the treatment section for specific administration instructions. May be taken with meals to decrease GI upset.
- 15.35 **Pharmacokinetic information:**
Onset of action: Prompt
Duration of metabolic effect: 72 hours
Metabolism: Hepatic
Half-life elimination: Normal renal function: 1.8-3.5 hours; **Biological half-life:** 36-54 hours
Time to peak, serum: Oral: 1-2 hours
Excretion: Urine and feces
- 15.36 **Potential Drug Interactions:**
Cytochrome P450 Effect: Substrate of CYP3A4 (major); **Induces** CYP2A6 (weak), 2B6 (weak), 2C8 (weak), 2C9 (weak), 3A4 (strong)
Increased Effect/Toxicity: Aprepitant, azole antifungals, calcium channel blockers, cyclosporine, estrogens, and macrolides may increase the serum levels of corticosteroids. Corticosteroids may increase the hypokalemic effects of amphotericin B or potassium-wasting diuretics (loop or thiazide); monitor. Refer to the package insert for a listing of other drugs.
Decreased Effect: Antacids and bile acid sequestrants may reduce the absorption of corticosteroids; may reduce the absorption of corticosteroids; separate administration by 2 hours. Aminoglutethimide, barbiturates, and CYP3A4 inducers may reduce the serum levels/effects of dexamethasone and dexamethasone may decrease the levels/effects of other CYP3A4 substrates. Serum concentrations of isoniazid may be decreased by corticosteroids. Corticosteroids may lead to a reduction in warfarin effect. Corticosteroids may suppress the response to vaccinations.
Ethanol/Nutrition/Herb Interactions:
Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).
Food: Dexamethasone interferes with calcium absorption. Limit caffeine.
Herb/Nutraceutical: Avoid cat's claw (*Uncaria tomentosa*), echinacea (have immunostimulant properties)
- 15.37 **Known potential adverse events:** Consult the package insert for the most current and complete information.
Common known potential toxicities, frequency not defined:
Fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, exacerbation of infection, exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer, dermatologic disturbances,

convulsions, vertigo and headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some patients have experienced itching and other allergic, anaphylactic or hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia and arthralgia.

- 15.38 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.
- 15.39 Nursing Guidelines:
- 15.391 Monitor patient regularly for hypertension, CHF and other evidence of fluid retention.
 - 15.392 Advise patient of possible mood or behavioral changes, i.e., depression, euphoria, insomnia, even psychosis. Instruct patient to report any suspected changes to healthcare team.
 - 15.393 Assess for symptoms of gastric ulcer, heartburn, or gastritis. Suggest antacids. Instruct patient to report symptoms to healthcare team if unable to control.
 - 15.394 Evaluate signs of infection, particularly local candidal infections and treat appropriately.
 - 15.395 Monitor blood glucose frequently.
 - 15.396 Instruct patient to report frequent, unrelenting headaches or visual changes to healthcare team.
 - 15.397 Advise patient that easy bruising is a side effect.

16.0 Statistical Considerations and Methodology

16.1 Overview

This is a phase II study of a novel regimen of pembrolizumab with lenalidomide and dexamethasone for initial treatment of newly diagnosed multiple myeloma patients requiring therapy. This study is designed to assess the VGPR or better response rate associated with therapy with pembrolizumab added to standard doses of lenalidomide and dexamethasone, in patients with previously untreated multiple myeloma using a single stage phase II study design with an interim analysis.

- 16.11 **Endpoint:** The primary endpoint of the trial is the rate of complete or very good partial response after 4 cycles of induction treatment. A success will be defined as an sCR, CR, or VGPR noted as the objective status on two consecutive evaluations. Response will be evaluated using the first 4 cycles of induction therapy. Throughout Section 16.0, sCR, CR, or VGPR will be considered synonymous with “success” in the phase II portion, unless specified otherwise.
- 16.12 **Sample Size:** The single-stage study design with an interim analysis to be used is fully described below. A minimum of 13 and a maximum of 37 evaluable patients will be accrued in the phase II study unless undue toxicity is encountered. We anticipate accruing an additional 4 patients to account for ineligibility, cancellation, major treatment violation, or other reasons for a maximum of 41 patients.
- 16.13 **Accrual Rate and Study Duration:** The anticipated accrual rate is 2-3 evaluable multiple myeloma patients per month. At this rate, it will likely take about 1.5 years to enroll the patients. The maximum total study duration is expected to be approximately 2 years, or until the last patient accrued has been observed for at least 6 months.

16.2 Statistical Design:

16.21 Decision Rule:

A combination of lenalidomide plus dexamethasone, an oral regimen, is the mainstay therapy for newly diagnosed multiple myeloma. In a large multi-center study, 208 patients were evaluated for response to treatment with lenalidomide plus low dose dexamethasone.⁶ Forty-nine patients (24%) achieved a complete or very good partial response. An increase in the rate of complete plus very good partial response with the addition of pembrolizumab to lenalidomide plus dexamethasone would be of interest.

The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 25%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 45%. The following one-stage design with an interim analysis is based on a Simon optimum design¹³ and requires 37 evaluable patients to test the null hypothesis that the true success proportion in this patient population is at most 25%.

- 16.211 **Interim Analysis:** Enter 13 evaluable patients into the study. If 3 or fewer successes are observed in the first 13 evaluable patients, we will consider this regimen ineffective in this patient population and terminate this study. Otherwise, if the number of successes is at least 4, we will continue accrual.

- 16.212 Final Decision Rule: Enter an additional 24 evaluable patients into the study. If 12 or fewer successes are observed in the first 37 evaluable patients, we will consider this regimen ineffective in this patient population. Otherwise, if the number of successes is at least 13, this will be considered evidence of promising activity and the treatment may be recommended for further testing in subsequent studies.
- 16.213 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process. Analyses involving over accrued patients are discussed in Section 16.34.
- 16.214 NOTE: We will not suspend accrual at the interim analysis to allow the first 13 patients to become evaluable, unless undue toxicity is observed. Given the limited overall sample size and the inclusion of an adverse events stopping rule, we feel it is ethical to not halt accrual for the interim analysis. However, if accrual is extremely rapid, we may temporarily suspend accrual in order to obtain safety data on these patients before re-opening accrual to further patients
- 16.22 Power and Significance Level: Assuming that the number of successes is binomially distributed, the significance level is .09, i.e. there is a 9% chance of finding the drug to be effective when it truly is not. The probability of declaring that this regimen warrants further study (i.e. statistical power) and the probability of stopping after the interim analysis under various success proportions can be tabulated as a function of the true success proportion as shown in the following table.

If the true success proportion is..	0.25	0.30	0.35	0.40	0.45
Then the probability of declaring that the regimen warrants further study is...	0.092	0.256	0.485	0.703	0.856
And the probability of stopping after the interim analysis is ...	0.584	0.421	0.278	0.169	0.093

- 16.23 Other considerations: Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.3 Analysis Plan

16.31 Primary Outcome Analyses:

- 16.311 Definition: The primary endpoint in the phase II portion of this trial is the proportion of complete plus very good partial responses after 4 cycles of induction treatment. A success is defined as an sCR, CR, or VGPR noted as the objective status on two consecutive evaluations. Response will be evaluated using the first 4 cycles of induction therapy. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response, with the exception of patients who are determined to be a major violation.
- 16.312 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients.

Confidence intervals for the true success proportion will be calculated according to the approach of Duffy and Santner (Duffy D 1987).

16.32 Secondary Outcome Analyses

- 16.321 The \geq PR response rate after 4 cycles of induction treatment with pembrolizumab added to lenalidomide and dexamethasone will be estimated by the number of patients who achieve a PR, VGPR, CR, or sCR after 4 cycles divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for the true success rate will be calculated.
- 16.322 The \geq VGPR response rate at any time during treatment with pembrolizumab added to lenalidomide and dexamethasone will be estimated by the number of patients who achieve a VGPR, CR, or sCR at any time divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for the true success rate will be calculated.
- 16.323 Survival time is defined as the time from registration to death due to any cause. The distribution of survival time will be estimated using the method of Kaplan-Meier⁷.
- 16.324 Progression-free survival is defined as the time from registration to the earliest date of documentation of disease progression or death due to any cause. Patients who receive subsequent treatment for myeloma before disease progression will be censored on the date of their last disease assessment prior to initiation of the subsequent treatment. Transplant will not be considered subsequent treatment. The distribution of progression-free survival will be estimated using the method of Kaplan-Meier
- 16.325 Adverse Events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.
- 16.326 The success rate of stem cell collection following initial therapy with the combination of pembrolizumab, lenalidomide and dexamethasone in patients with newly diagnosed MM will be estimated by the number of patients with a successful stem cell collection divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for the true success rate will be calculated.

16.33 Correlative Analyses (IRB#521-93)

- 16.331 PDL-1 expression on myeloma cells and non-tumor cell compartments from the bone marrow will be assessed at baseline. Each measure will be summarized descriptively by median, min, max and interquartile range.
- 16.332 Markers of T-cell activation and exhaustion will be summarized descriptively by median, min, max, and interquartile range at each time point. Patterns over time will be summarized by absolute difference or relative change. Changes across time will be assessed using paired

analyses, including Wilcoxon signed rank tests. Jitplots will be used to visually examine differences between groups for continuous factors.

16.333 NK cell function and numbers will be summarized descriptively by median, min, max, and interquartile range at each time point. Patterns over time will be summarized by absolute difference or relative change. Changes across time will be assessed using paired analyses, including Wilcoxon signed rank tests. Jitplots will be used to visually examine differences between groups for continuous factors.

16.34 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final endpoint estimates and confidence intervals.

16.4 Data & Safety Monitoring:

16.41 The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.42 Adverse Event Stopping Rules: The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as “possible,” “probable,” or “definite”) that satisfy one of the following:

- if 5 or more patients in the first 15 treated patients experience a Grade 4 or higher non-hematologic adverse event at least possibly related to treatment.
- if after the first 15 patients have been treated, 40% of all patients experience a Grade 4 or higher non-hematologic adverse event at least possibly related to treatment.

We note that we will review grade 4 and 5 adverse events deemed “unrelated” or “unlikely to be related”, to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.5 Results Reporting on ClinicalTrials.gov:

At study activation, this study will have been registered within the “ClinicalTrials.gov” website. The Primary and Secondary Endpoints along with other required information for this study will be reported on www.ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 2 years after the study opens to accrual. The definition of “Primary Endpoint Completion Date” (PECD) for this study is at the time the last patient registered has been followed for at least 6 months.

16.6 Inclusion of Women and Minorities

- 16.61 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.
- 16.62 There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.
- 16.63 The geographical region served by MCCC has a population which includes approximately 3% minorities. Based on prior MCCC studies involving similar disease sites, we expect about 3-5% of patients will be classified as minorities by race and about 33% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Estimates by Gender/Ethnicity/Race

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	0	1	0	1
Not Hispanic or Latino	14	26	0	40
Ethnic Category: Total of all subjects*	14	27	0	41
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	0	0	0	0
Black or African American	1	1	0	2
Native Hawaiian or other Pacific Islander	0	0	0	0
White	13	26	0	39
Racial Category: Total of all subjects*	14	27	0	41

Ethnic Categories: **Hispanic or Latino** – a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term “Spanish origin” can also be used in addition to “Hispanic or Latino.”

Not Hispanic or Latino.

Racial Categories: **American Indian or Alaskan Native** – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.”

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens: None

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Data submission instructions for this study can be found in the Case Report Form packet.

18.2 Event monitoring

See [Section 4.2](#) and data submission table in the case report form packet for the event monitoring schedule.

18.3 CRF completion

This study will use Medidata Rave® for remote data capture (rdc) of all study data.

18.4 Responsibilities

Each site coordinator will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.5 Supporting documentation

This study requires supporting documentation for diagnosis prior to study entry as well as for evidence of response to study therapy and progression after study therapy. Supporting documentation for diagnosis will include either a pathology report or a laboratory report demonstrating multiple myeloma (including SPEP, UPEP, FLC, Serum and Urine Immunofixation, Bone Marrow Biopsy and Aspirate, X-ray skeletal, Plasma Cell Proliferation and Assessment and FISH. These reports should be submitted within 14 days of registration.

For progression of disease prior to study entry, supporting documentation includes the evidence needed to determine the patient's progression prior to enrollment. These documents should be submitted within 14 days of registration.

For response to treatment, supporting documentation may include SPEP, UPEP, FLC, Serum and Urine Immunofixation, Bone Marrow Biopsy and aspirate, and X-ray skeletal survey/low dose whole body CT.

For patients who progress after study therapy supporting documentation may include any of the following: SPEP, UPEP, FLC, serum and urine immunofixation, bone marrow biopsy and aspirate, and X-ray skeletal survey.

Submit reports to:



18.6 Labelling of materials

Each site coordinator will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.7 Incomplete materials

Any materials deemed incomplete by the MCCC Operations Office will be considered “not received” and will not be edited or otherwise processed until the missing information is received. A list of the missing documents will be made available to the appropriate site coordinator.

18.8 Overdue lists

A list of overdue materials and forms for study patients will be generated monthly. The listings will be sorted by location and will include the patient study registration number. The appropriate site coordinator will be responsible to obtain the overdue material.

18.9 Corrections forms

If a correction is necessary the QAS will query the site. The query will be sent to the appropriate site coordinator who will make the correction and return the query and documentation of correction back to the QAS.

19.0 Budget

19.1 Costs charged to patient: routine clinical care, study drugs lenalidomide and dexamethasone

19.2 Tests to be research funded: study drug pembrolizumab

19.3 Other budget concerns: None

20.0 References

1. Richardson P, Jagannath S, Schlossman R, et al. A Multi-center, Randomized, Phase 2 Study to Evaluate the Efficacy and Safety of 2 CDC-5013 Dose Regimens When Used Alone or in Combination with Dexamethasone (Dex) for the Treatment of Relapsed or Refractory Multiple Myeloma (MM). *Blood*. 2003;102:235a.
2. Lacy M, Gertz M, Dispenzieri A, et al. Lenalidomide Plus Dexamethasone (Rev/Dex) in Newly Diagnosed Myeloma: Response to Therapy, Time to Progression, and Survival. *Blood*. 2006;108(11):798-.
3. Rajkumar SV, Jacobus S, Callander N, et al. Phase III trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed multiple myeloma (E4A03): a trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol 2007 ASCO Annual Meeting Abstracts 2007*;25 (18S):LBA8025.
4. Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med*. 2007;357(21):2133-2142.
5. Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med*. 2007;357(21):2123-2132.
6. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. *Lancet Oncol*. 2010;11(1):29-37.
7. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457-481.

Appendix I ECOG Performance Status

ECOG PERFORMANCE STATUS*	
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

*As published in Am. J. Clin. Oncol.:

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

From http://www.ecog.org/general/perf_stat.html

Appendix II Patient Medication Diary

Name _____ Mayo Clinic No. _____

Please complete this diary on a daily basis. On the days that you do not take any study drug, please write in "0". If you forget to take your daily dose, please write in "0", but remember to take your prescribed dose at the next regularly scheduled time.

Swallow pills whole, with water, and do not to break, chew, crush or open the pills.

Dexamethasone must be taken with food.

Week of: _____

Study Drug	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Lenalidomide							
Dexamethasone							

Week of: _____

Study Drug	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Lenalidomide							
Dexamethasone							

Week of: _____

Study Drug	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
Lenalidomide							
Dexamethasone							

Week of: _____

Study Drug	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Lenalidomide							
Dexamethasone							

Patient Signature: _____

Health or medical complaints during this time:

Other medications or supplements taken during this time:

Name of medication or supplement	How much did you take? (example: Two 500mg pills)	When did you take it (examples: Every day Or Day 19 and Day 20)

Use a separate sheet of paper if more space is needed.

<p>My next scheduled visit is: _____</p> <p>If you have any questions, please call: _____</p> <p>Bring <i>all</i> bottles and any unused study medication along with this diary when you return for your next appointment.</p>

Number of pills returned Discrepancy Yes ___/No ___	Study Coordinator Use Only Number of vials returned: Verified by _____	Date _____
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