CLINICAL STUDY PROTOCOL

Pilot single arm, single center, open label trial of pembrolizumab in patients with intermediate and high risk smoldering multiple myeloma

Principal Investigator: Elisabet E Manasanch, MD, MHSc
UT MD Anderson Cancer Center
Department of Lymphoma and Myeloma
1515 Holcombe Blvd, Unit 429
Phone: 713-745-8092
Fax: 713-563-5067
Email: eemanasanch@mdanderson.org

Collaborators: Robert Orlowski M.D. Ph.D., UT MD Anderson Cancer Center
Jatin Shah, M.D., UT MD Anderson Cancer Center
Donna Weber M.D., UT MD Anderson Cancer Center
Sheeba Thomas M.D., UT MD Anderson Cancer Center
Hans Lee, M.D. UT MD Anderson Cancer Center
Francesco Turturro, M.D., UT MD Anderson Cancer Center
Sattva Neelapu M.D., UT MD Anderson Cancer Center*
Pei Lin, M.D. UT MD Anderson Cancer Center*
Lei Feng Ph.D., Biostatistics, UT MD Anderson*
Eric Davis M.D., UT MD Anderson Cancer Center*
Michael Andreeff M.D., Ph.D., UT MD Anderson Cancer Center*

Research Contact: Research nurse: Victoria Waterfield*, VWaterfield@mdanderson.org
Data manager: Maureen Daily, MEDaily@mdanderson.org and Claudia Morales*, CMMorales@mdanderson.org*

**Not making clinical decisions*

Investigational Agents:

Drug Name:	Pembrolizumab
IND Number:	126,511
Sponsor:	MD Anderson
Manufacturer:	Merck

CONTENTS

1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab in SMM
Trial Phase	Pilot study
Clinical Indication	Intermediate and high-risk smoldering multiple myeloma
Trial Type	Pilot study, single center, single arm
Type of control	No control
Route of administration	intravenous
Trial Blinding	unblinded
Treatment Groups	One treatment group with pembrolizumab
Number of trial subjects	16
Estimated enrollment period	6 months to one year
Estimated duration of trial	18 months for response rate data after 8 cycles of treatment and 42 months for PFS data at 30 months after study entry
Duration of Participation	8 cycles of initial treatment In patients who show a continued response (≥ minor response) after 8 cycles of treatment, treatment can be continued for up to 1 year In patients who show a continued response ((≥ minor response) after 8 cycles of treatment, but who choose to stop treatment after 8 cycles of therapy and then experience progressive disease within 6 months of treatment stop, treatment can be restarted and continued for up to an additional 16 cycles to a maximum of 24 cycles.

2.0 TRIAL DESIGN

2.1 Trial Design

This will be an open label, single center, single arm, pilot trial based on the established dose from the phase 1 trial.

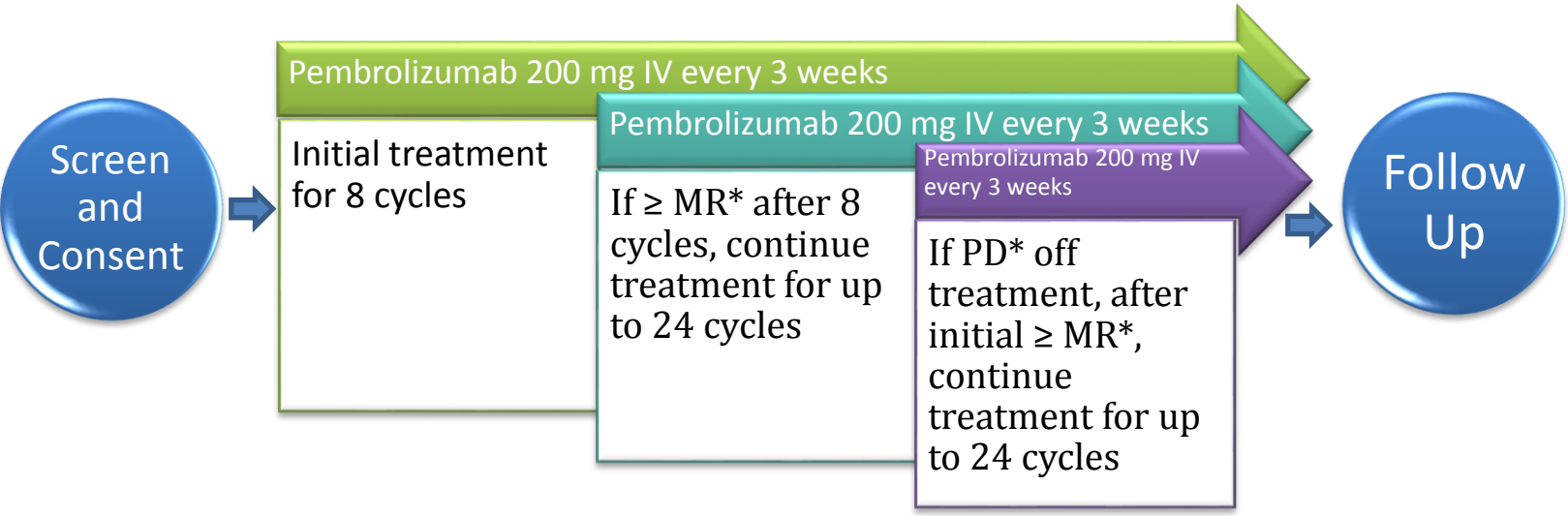
Pembrolizumab 200 mg will be administered as a single agent intravenous infusion every 3 weeks (one cycle=21 days) for up to 24 cycles.

Disease evaluation will be done at baseline and at each cycle. Patients will continue with therapy until they have progressive disease or intolerable side effects for 8 cycles initially, with an option to continue therapy beyond 8 cycles if there is continued clinical benefit without serious adverse events.

In patients who show a continued response (≥ minor response) after 8 cycles, treatment can be continued for an additional 16 cycles to a maximum of 24 cycles.

In patients who show a continued response ((≥ minor response) after 8 cycles, but who choose to stop treatment after 8 cycles of therapy and then experience progressive disease within 6 months of treatment stop, treatment can be restarted for an additional 16 cycles to a maximum of 24 cycles.

2.2 Trial Diagram



*MR=minor response, PD=progressive disease

3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objective & Hypothesis

(1) **Objective:** ORR (partial response [PR]or better) after 8 cycles of treatment per IMWG criteria for multiple myeloma (MM)[1]

Hypothesis: In this pilot, exploratory trial, we hypothesize that pembrolizumab in intermediate and high-risk smoldering multiple myeloma (SMM) will have a target response rate after 8 cycles of treatment of at least 25%. A response rate of 5% or lower will be considered a failure and this new regimen will be rejected.

3.2 Secondary Objectives & Hypotheses

(1) **Objective**: TTP (time to progression to multiple myeloma) at 30 months from study entry

(2)**Objective**: Duration of response

(3)**Objective**: Safety and tolerability

(4)**Objective**: Clinical benefit rate (minor response [MR] or better) after 8 cycles of treatment per modified IMWG criteria for MM

(5)**Objective**: Overall survival

3.3 Exploratory Objectives

1. **Objective:** Rate of MRD negativity at complete remission (CR). MRD assessment will be based on bone marrow aspirates. We will use flow cytometry as well as next generation sequencing of the VDJ segment.

2. **Objective:** Molecular profiling (including whole exome sequencing and gene expression profiling) and cellular (including flow cytometry) profiling at baseline and/or at progression using bone marrow aspirate samples and peripheral blood.

3. **Objective:** Immunophenotypic characterization of dendritic, T-, B-, NK- and NKT-cells, and inhibitory/activation markers on tumor cells at baseline and at completion of 8 cycles of therapy in bone marrow aspirate samples and/or peripheral blood.

4. **Objective:** Evaluation of changes in PD-L1 and PD-1 expression at baseline/end of 8 cycles of treatment and correlate with clinical response.

4.0 BACKGROUND & RATIONALE

4.1 Background and Rationale

Multiple myeloma (MM) is a plasma cell malignancy that is preceded by monoclonal gammopathy of unknown significance (MGUS) and smoldering multiple myeloma (SMM)[2,3]. Although treatment outcomes over the past decade have improved dramatically, there is still no established curative therapy[4,5]. There is consistent evidence to support the fact that deeper responses correlate with better progression-free survival (PFS) and some studies report better overall survival (OS) as well[6,7].

Although current guidelines still recommend watchful waiting for asymptomatic (also known as smoldering) myeloma patients (i.e. SMM), during the past decade, several smaller clinical trials have been developed to test the hypothesis that early treatment is beneficial. In 2013, a small randomized clinical trial using lenalidomide and dexamethasone for 9 cycles followed by 24 months of maintenance (versus observation) found a 21% complete response (CR) rate and 79% overall response rate (ORR) after completion of 9 cycles of lenalidomide and dexamethasone therapy. Patients on the treatment arm had a significantly better PFS and OS[8,9]. This trial provided proof of concept that early intervention in high risk SMM is feasible and may impact the disease/outcome.

Pembrolizumab is a highly selective, humanized monoclonal IgG4-kappa isotype antibody against programmed death receptor-1 (PD-1) on antigen-stimulated T cells. It blocks the PD-1 interaction with PD-1 ligand (PD-L1) and PD-2 ligand (PD-L2) on tumor cells, thereby releasing PD-1 pathway-mediated inhibition of the immune system and allowing for anti-tumor immune responses. Pembrolizumab received accelerated approval status by the Food and Drug Administration (FDA) in 2014 given as an intravenous infusion of 2 mg/kg every 3 weeks[10]. It is indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. Approval was based on tumor response rate and durability of response observed in a

multicenter, open-label, randomized (1:1) early phase clinical trial of 173 patients with unresectable or metastatic melanoma[11]. Patients were treated in two cohorts of pembrolizumab 2 mg/kg (n=8) and 10 mg/kg (n=84) intravenously every 3 weeks until disease progression or unacceptable toxicity. Efficacy endpoints were overall response rate (ORR) assessed by Response Evaluation Criteria in Solid Tumors (RECIST v1.1) by independent central review. The ORR was 26% in both cohorts (p=0.96). Median duration of response was not reached in either dose group at time of study publication (range >6 weeks to >37 weeks). The safety profiles were similar between the two dosing cohorts. Drug-related adverse events (AE) occurred in 82% of patients in either dose group. However, drug-related grade 3 or 4 AE occurred in only 12% of patients. The only drug-related grade 3 to 4 AE that occurred in more than one patient was fatigue (3%). The most common drug-related AE of all grades were fatigue, pruritus and rash. Grade 3 or 4 immune-mediated AE occurred in 1.7% of patients: autoimmune hepatitis, maculopapular rash and pancreatitis. Other special interest grade 3 or 4 drug-related AEs occurred in 6% of patients: autoimmune hepatitis, diarrhea, hypophysitis, maculopapular rash, pancreatitis, rash and pneumonitis. These were generally manageable with treatment interruption and corticosteroid treatment. Only 2.3% of patients discontinued treatment because of AE that were immune related or of special interest.

Most MM cells express PD-L1 which might represent a mechanism of tumor immune evasion[12]. By blocking the interactions between PD-L1/PD-L2 and PD-1, pembrolizumab may be able to reactivate immune surveillance leading to improved anti-tumor activity. Several clinical trials (NCT01953692, NCT02036502, NCT02289222 and NCT02331368) (www.clinicaltrials.gov) are currently ongoing either in the post-transplant or relapsed/refractory setting, with pembrolizumab single agent or in combination with lenalidomide and pomalidomide.

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475.

4.1.1 Pharmaceutical and Therapeutic Background

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 CD3ζ, PKCθ 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.

4.1.2 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for Preclinical and Clinical data.

4.1.3 Rationale for the Trial and Selected Subject Population

There is currently an unmet need in the treatment of intermediate and high risk SMM patients in clinical trials. Based on available data, SMM patients with intermediate or high-risk have at least a 50% risk of progression to symptomatic multiple myeloma at 5 years after diagnosis[13-15]. Given the favorable toxicity profile of pembrolizumab and potential ability to harness the relatively intact immune system of SMM when compared to patients with MM, we believe pembrolizumab might have activity as a single agent in SMM. Advantages of pembrolizumab compared to previous regimens studied in the SMM setting (including lenalidomide /dexamethasone or carfilzomib/lenalidomide/dexamethasone) include: 1) ability to delay treatment with lenalidomide and other novel anti-myeloma therapies until after progression with pembrolizumab, 2) avoidance of dexamethasone, and its side effects, in treatment of asymptomatic patients, 3) avoidance of need for early collection of stem cells, and minimizing stem cell toxicity with prolonged exposure to lenalidomide; 4) evaluation of immunotherapy in a population that might be very sensitive to this approach while at the same time having tolerable toxicities; 5) harness intact immune function in SMM to maximize relative activity/benefit of immunotherapy with pembrolizumab in earlier lines of therapy.

We are proposing to conduct a single center, open label, pilot study of pembrolizumab for this population.

4.1.4 Rationale for Endpoints

The overall response rate (ORR) of Lenalidomide/Dexamethasone combination in the high risk SMM population has been reported at 79%. Despite this, Lenalidomide/Dexamethasone has a number of limitations in this asymptomatic population (increased risk of thromboembolic events, possibility of stem cell damage, need for early stem cell collection- not currently a standard of care-, numerous side effects of

long term Dexamethasone). Thus, the use of this combination is potentially less attractive than immunotherapy. Lower ORR (25%) with single agent pembrolizumab might also signal the potential for chemoimmunotherapy combinations to achieve improved response in this patient population in the future. Evaluation of myeloma free survival (defined as free of progression to MM by current clinical guidelines), progression free survival and overall survival also are important in evaluating impact of immunotherapy in this patient population.

5.0 METHODOLOGY

5.1 Entry Criteria

Adult patients (age ≥18 years old) with intermediate or high-risk SMM are eligible. Patients need to have clonal bone marrow plasma cells ≥ 10% and/or monoclonal spike in blood of ≥ 3 g/dL and/or monoclonal urine component (Bence jones proteinuria) ≥ 500 mg/24 hours and need to meet subject inclusion criteria and exclusion criteria as per below.

5.1.1 Subject Inclusion Criteria

Patients must have histologically confirmed SMM based on the following criteria:

(A) Mayo clinic criteria (patient must have at least 2 risk factors present) [14]:

1. Bone marrow core biopsy plasma cell involvement by CD138 immunohistochemistry ≥ 10%
2. Monoclonal spike ≥3g/dL
3. Free light chain ratio in serum < 0.125 or > 8.

*2 of 3 risk factors: intermediate risk for progression at a rate of 51% at 5 years
*3 of 3 risk factors: high risk for progression at a rate of 76% at 5 years

OR

(B) PETHEMA criteria (patient must have at least 1 risk factor present)[13]

1. ≥95% abnormal plasma cells/total plasma cells in bone marrow compartment
2. Immunoparesis

*1 of 2 risk factors: intermediate risk for progression at a rate of 46% at 5 years
*2 of 2 risk factors: high risk for progression at a rate of 72% at 5 years

OR

(C) SWOG criteria (patient must have 2 risk factors present or one risk factor if this risk factor if a GEP70 score of > 37.2)[15]

1. Monoclonal spike ≥ 3 g/dL
2. Involved free light chain ≥ 25 mg/dL
3. GEP70 risk score > 37.2

*≥2 risk factors: high risk of progression at a rate of 70% at 2 years

* We would also include patients with 1 risk factor as long as this risk factor is GEP70 risk score > 37.2 since patients with this risk factor have an intermediate risk of progression at a rate of 50% at 2 years.

5.1.1.1 Creatinine clearance ≥ 50 ml/min. CrCl will be calculated by Cockcroft-Gault method. CrCl (calculated) = (140 – Age) x Mass (in kilograms) x [0.85 if Female] / 72 x Serum Creatinine (in mg/dL). If calculated CrCl based on Cockcroft-Gault method is < 50 mL/min, patient will have a 24 hr urine collection to measure CrCl. The measured CrCl must also be ≥ 50 ml/min

5.1.1.2 Age ≥ 18 years.

5.1.1.3 Eastern Cooperative Oncology Group (ECOG) performance status 0-1

5.1.1.4 Absolute neutrophil count (ANC) ≥ 1.0 x 10^9 /L, hemoglobin ≥ 10 g/dL and platelet count ≥ 50 x 10^9/L

5.1.1.5 Adequate hepatic function with bilirubin < 1.5 x the ULN, and AST and ALT < 3.0 x ULN.

5.1.1.6 Subjects must be able to give informed consent

5.1.1.7 Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

5.1.1.8 Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.10.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

5.1.1.9 Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

5.1.2 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject has any of the following:

5.1.2.1 Evidence of myeloma defining events or biomarkers of malignancy due to underlying plasma cell proliferative disorder meeting at least one of the following[16]

1) Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or > 2.75 mmol/L (> 11 mg/dL)
2) Renal Insufficiency: creatinine clearance < 40 ml/min or serum creatinine > 2 mg/dL
3) Anemia: hemoglobin value <10 g/dL or 2 g/dL < normal reference
4) Bone lesions: one or more osteolytic lesions on skeletal radiography, computerized tomography (CT) or 2-deoxy-2[F-18] fluoro-D-glucose positron emission tomography CT (PET-CT).
5) Clonal bone marrow plasma cell percentage ≥ 60%
6) Involved: uninvolved serum free light chain ratio ≥100 measured by Freelite assay (The Binding Site Group, Birmingham, UK)
7) >1 focal lesions on MRI studies (each focal lesion must be 5 mm or more in size), if clinically indicated

5.1.2.2 Prior or concurrent systemic treatment for SMM.

a) Bisphosphonates are permitted.
b) Treatment with corticosteroids is not permitted
c) Radiotherapy is not permitted.
d) Prior treatment for smoldering multiple myeloma with chemotherapy agents approved for the treatment of multiple myeloma is not permitted.

5.1.2.3 Plasma cell leukemia

5.1.2.4 Pregnant or lactating females. Because there is a potential risk for adverse events in nursing infants secondary to treatment of the mother with pembrolizumab, breastfeeding should be discontinued if the mother is treated with pembrolizumab. These potential risks may also apply to other agents used in this study.

5.1.2.5 Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

5.1.2.6 Has a known history of active TB (Bacillus Tuberculosis)

5.1.2.7 Hypersensitivity to pembrolizumab or any of its excipients.

5.1.2.8 Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

5.1.2.9 Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

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

5.1.2.11 Has known history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

5.1.2.12 Has an active infection requiring systemic therapy.

5.1.2.13 Has a 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.

5.1.2.14 Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

5.1.2.15 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.

5.1.2.16 Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

5.1.2.17 Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

5.1.2.18 Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

5.1.2.19 Has received a live vaccine within 30 days of planned start of study therapy.

Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

5.1.2.20 Evidence of interstitial lung disease.

Patients with progressive disease after initial response and who elect to restart treatment after the initial 8 cycles of therapy will need to meet Subject Inclusion Criteria 5.1.1 and exclusion criteria 5.1.2 except points 5.1.2.2 (prior or concurrent systemic treatment for SMM) and 5.1.2.16 (prior treatment with anti-PD-1, anti-PD-L1 or anti-PD-L2 agents) since the patients will have received treatment with anti-PD-1 (pembrolizumab) for SMM. The subject may need additional testing as determined by the Principal Investigator.

5.2 Screening Evaluation

5.2.1 Clinical Evaluation

5.2.1.1 A complete history and physical examination with documentation of disease and assessment of performance status using the ECOG scale must be performed prior to patient registration.

5.2.1.2 The following studies and laboratory tests will be completed 4 weeks prior to study treatment:

1. CBC with differential and reticulocyte count
2. Chemistry (total protein, calcium, glucose, creatinine, sodium, chloride, magnesium, potassium, carbon dioxide, phosphorus) and Hepatic (indirect bilirubin, direct bilirubin, total bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase) panels, amylase, lipase and creatinine clearance (CrCl) calculation
3. Uric acid, LDH, albumin and Beta-2 Microglobulin
4. PT, PTT
5. Thyroid function tests (TSH, T_4)
6. Serum protein electrophoresis (SPEP) and immunofixation to assess for presence and quantity of monoclonal protein (M-protein)
7. 24 hour urine sample for protein electrophoresis (UPEP) and immunofixation to assess for monoclonal protein in the urine (Bence-Jones proteinuria).
8. Serum free light-chain studies, determined using the FreeliteTM assay system
9. Quantitative serum immunoglobulins
10. Viral serologies:
    a. Hepatitis B surface antigen.
    b. Anti-Hepatitis C (HCV) antibody. If positive, will follow with HCV RNA PCR
    c. Human Immunodeficiency Virus (HIV) screening test
11. Serum or urine pregnancy test in women of child-bearing potential.
12. 12-lead EKG
13. Skeletal survey
14. A whole body PET-CT, if clinically indicated
15. MRI of the thoracic and lumbar spine, if clinically indicated

5.3 Baseline Evaluation

Research and clinical laboratory tests to be performed within 4 weeks of study treatment:

5.3.1.1 Bone Marrow

1. Immunophenotyping of aberrant clonal plasma cells by multiparametric flow cytometry. Interphase fluorescence in situ hybridization (FISH)/cytogenetics.
2. Cell sorting and storage
3. Histopathological evaluation on bone marrow aspirate and biopsy
4. Immunoglobulin heavy and/or light chain rearrangement.
5. VDJ sequencing
6. Gene expression profiling
7. Whole exome sequencing
8. Immune, cellular and molecular profiling

5.3.1.2 Peripheral Blood/Urine

1. Peripheral blood and urine samples for storage.

5.4 Biospecimen collection

5.4.1 Correlative Studies

5.4.1.1 Bone Marrow

Sampling Time Points of Bone Marrow correlative studies (see Table 1)

a) Baseline
b) Post cycle 8
c) Post cycle 24 (in patients receiving an additional 16 cycles of therapy only)
d) At progression
e) End of Study

Table 1	Baseline	Post Cycle 8 /end of study	Post Cycle 24 /end of study	Progression of Disease
Pathology/immuno-histochemistry	**X**	**X**	**X**	**X**
Multiparametric Flow Cytometry	**X**	**X**	**X**	**X**
FISH/Cytogenetics	**X**	**X**	**X**	**X**
Gene expression profiling	**X**			**X**
VDJ sequencing	**X**	**X**	**X**	**X**
Immune studies	**X**	**X**	**X**	**X**
Cytometry time of flight (CyTOF)	**X**	**X**	**X**	**X**
Whole exome sequencing	**X**			**X**
Storage	**X**	**X**	**X**	**X**

- Correlative studies associated with bone marrow specimen will be performed and related to clinical outcome if the results of the study indicate a clinical or translational rationale for analyzing the samples. Such studies may include but are not limited to the following:

    - Pathology/Immunohistochemistry: Bone marrow biopsy and aspirate will be sent to the Department of Pathology at MD Anderson Cancer Center. Immunohistochemical staining will be performed. Plasma cell burden will be assessed using immunohistochemistry markers such as CD138, light chains, CD56 etc.

    - Minimal Residual Disease:

        - Flow cytometry: Immunophenotyping of aberrant plasma cells by flow cytometry currently involves, but is not limited to, the use of the following reagents: CD138, CD19, CD45, CD38, and CD56. Characteristic changes in immunophenotypically abnormal plasma cells (CD138 positive) include but are not limited to absent CD19 and CD45, decreased CD38, and increased CD56. These studies will be performed following the Euroflow method.

        - Bone marrow, blood and urine samples, and associated clinical lab data will be sent to Adaptive Biotechnologies (Seattle, Washington) for deep sequencing of the VDJ sequence. Samples and data will be submitted to Adaptive Biotechnologies in an anonymized and de-identified manner.

    - FISH and cytogenetics: Interphase FISH/cytogenetics will be performed on patients enrolled in this protocol under the direction of the Molecular Diagnostics Core Laboratory of the Department of Pathology at MD Anderson Cancer Center

- Gene expression profiling (GEP): CD138+ plasma cells will be purified from bone marrow aspirates harvested at each indicated time point. Bone marrow samples and associated clinical lab data will be sent to Signal Genetics (Little Rock, Arkansas) for gene expression and will be analyzed to identify potential markers of early progression. Changes in selected genes may be confirmed by quantitative PCR if suggested to be related to risk of progression to MM. Samples and data will be submitted to Signal Genetics in an anonymized and de-identified manner.

- Whole exome sequencing will be performed to identify genomic alterations. Bone marrow aspirates will be done at baseline and saved at the Myeloma Tissue Bank. Peripheral blood will be collected at baseline for germ line DNA analysis.

- Characterization of T-cell and dendritic cell numbers in the bone marrow microenvironment that could contribute to immune escape and progression from SMM to symptomatic MM. These will be assessed by multiparametric flow cytometry for the following: Helper (CD4) and cytotoxic (CD8) effector T-cell differentiation subsets (naïve, effector memory, central memory, terminally differentiated, Th1, Tc1, Th2, Tc2, Th17, Tc17, Th22, Tc22), T-cell activation (CD137 (4-1BB), CD134 (OX-40), CD40L, CD69, ICOS) and inhibitory receptors (PD-1, LAG3, TIM3, CD244, CD160, BTLA, CD200R, CTLA4), T cells, NKT cells, and myeloid and plasmacytoid dendritic cells.

- Evaluation of changes in PD-L1 and PD-1 expression at baseline, end of cycle 8 and end of cycle 24 treatment and correlate with clinical response.

5.4.1.2 Research Blood/Serum and Urine

a) At any given time, up to 50 ml of peripheral blood will be collected. The amount of blood collected will be dictated by the number of experiments to be performed, and by the patient's peripheral blood count. Typical time points include: baseline, Cycle 1, Day 2 and Day 15, then Day 1 of every cycle during cycles 2-8, end of Cycle 8, Day 1 of cycles 9-24, end of Cycle 24 and at any time point if the patient has progression of disease.

b) At any given time, approximately 45 mL of urine will be collected into a standard urine collection cup and sent for analysis and storage at each time point. Typical time points include: baseline, Cycle 1Day 2 and Day 15, then Day 1 of every cycle during cycles 2-8, end of Cycle 8, Day 1 of cycles 9-24, end of Cycle 24 and at any time point if the patient has progression of disease.

c) Peripheral blood and/or urine samples from patients will be analyzed for potential serum or urine biomarkers, and correlated to clinical outcomes if the results of the study indicate a clinical or translational rationale for analyzing the samples. Such biomarkers may include but are not limited to:

- Bone marrow, blood and urine samples, and associated clinical lab data will be sent to Adaptive Biotechnologiesfor deep sequencing of the VDJ sequence.

- Immune cell populations including, but not limited to T cells (CD4 and CD8), LGL, and NK cells using flow cytometry.

5.4.1.3 Procedures for genomic sequencing of samples at MD Anderson Cancer Center

a) Sample sharing: In some cases samples may be sent to or received from outside collaborators such as Broad Institute for next-generation sequencing and/or analysis. All samples will be sent under a specific contract or Material Transfer Agreement (MTA). We will protect participant's privacy by coding samples and keeping the master list of identifiers accessible to only key project staff. Data will be kept on secure computers and samples will be kept in freezers in locked laboratories and buildings. Additionally in some other cases, samples may be provided from outside collaborators or institutions for discovery and research purposes. In such cases, the samples should be obtained under IRB-approved protocols at these outside collaborators and institutions to allow them for participation in this protocol and under a specific grant/ contract or Material Transfer Agreement (MTA) with MD Anderson Cancer Center.

b) Internal/External Sequencing may be done here at MD Anderson, in one of the Core labs such as Cancer Genomics Lab, but in some cases samples may be sent to outside collaborators for sequencing and/or analysis such as Broad Institute. Sequencing performed by Broad or any other external collaborator will be conducted under specific contract or Material Transfer Agreement (MTA).

c) Data Sharing/Deposition: Researchers can do more powerful studies when they share with each other the information they get from studying human samples. Next generation sequencing data may be placed in a local M.D. Anderson Institutional Data Repository (IDR), such as the access controlled BigData; where both deposition of and access to data require governance and approval. In some cases, grant requirements may require deposition of large-scale data into the public Genotypes and Phenotypes database (dbGaP) an access controlled database overseen by the National Center for Biotechnology Information (NCBI). In other cases peer reviewed Journals may require data to be shared through a resource such as dbGaP. Data submitted to those repositories will only be shared in a de-identified fashion and without associated clinical data or identifiers. This data will be used only for research purposes, and the data elements collected and analyzed will only be those that are necessary to conduct this research.

d) Database access additional protections: The precedent to publically broadcast sequence data has been set by large consortial projects, such as The Cancer Genome Atlas (TCGA) and the Encyclopedia of DNA Elements (ENCODE), in order to maximize data utility. However, we know there is the potential for privacy risks associated with the release of sequence data to databases and while the risk may be small it could grow in the future as technology advances. To minimize this potential, we will implement good faith efforts to ensure patient confidentiality and reduce patient exposure. The database of Genotypes and Phenotypes and others like it are extremely access restricted. Only authorized researchers may deposit or access the data and either or both efforts require MD Anderson institutional approval. Sequence data will only be broadcast through secure transmission processes. All samples will be de-identified with access to the linking table available

only to the MD Anderson PI and his/her designees. Only non-identifiable data will be deposited to dbGaP i.e., no linking table or access to a linking table will be available. Research records will be kept separate from medical records and patients will not have access to any of the research data.

e) Protected health information (PHI) may be collected from medical records that are related to health and/or disease history including test results, medical procedures, and images (such as X-rays) in addition demographic and environmental factors may be requested. Researchers will use this information to better understand how genes affect health and response to treatment. All samples will be de-identified with access to the linking table available only to the MD Anderson PI and his/her designees.

5.5 Registration Procedures

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

5.6 Monitoring

5.6.1 Study Monitoring

The University of Texas MD Anderson Cancer Center IND Office will monitor the study investigators to assure satisfactory enrollment rate, data recording, and protocol adherence. The site principal investigator and staff are expected to cooperate and provide all relevant study documentation in detail at each site visit on request for review. MD Anderson Cancer Center will monitor and/or audit the other participating sites to assure satisfactory protocol adherence and enrollment.

5.6.1.1 Patients will be observed in the infusion center after administration of cycle 1 Day 1 of therapy at least for 2 hours after receiving the infusion.

5.6.1.2 Routine labs (CBC with differential, chemistry panel and mineral panel, LDH, magnesium, uric acid, phosphate) will be performed on Day 1 of each cycle. Myeloma tests include serum protein electrophoresis, serum immunofixation, 24 hour urine protein electrophoresis and immunofixation, serum free light chains, quantitative immunoglobulins and beta-2 microglobulin will be performed at baseline and Day 1 of each cycle.

5.6.1.3 Patients will have clinic visits with H&P or standard progress notes assessing for toxicity/side effects on Day 1 of cycle 1 and Day 1 of each cycle thereafter.

5.6.1.4 Additional laboratory studies and clinic visits will be performed if clinically indicated.

5.7 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 every 21 days	Experimental

5.7.1 Dose Selection/Modification

5.7.1.1 Dose Selection

Dose selection is based on the current FDA approved dose of pembrolizumab[10].

5.7.1.2 Dose Modification

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment.

Pembrolizumab must be withheld for drug-related serious adverse events grade 4 or higher or intolerable side effects.

Additionally, pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.9 and Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids.

Table 3

Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
			per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism	2-4	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[2]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

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

[2] 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.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

5.7.2 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Study Calendar (Section 7.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Every effort should be made to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

5.8 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.8.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded in the medical record including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included in the medical record.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 8.2.

5.8.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.9 Rescue Medications & Supportive Care

5.9.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below and in greater detail in the ECI guidance document. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 5.7.1.2 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

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

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

    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
    - For **Grade 2 diarrhea/colitis** 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.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

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

- **Hypophysitis**:

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

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

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

- **Hepatic**:

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

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

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

Table 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 4 Infusion Reaction Treatment Guidelines

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

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.10 Diet/Activity/Other Considerations

5.10.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

5.10.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 8.2.2-Reporting of Pregnancy and Lactation to the Sponsor and to Merck. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.10.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours to the Sponsor and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 8.2.2.

5.10.4 Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.11 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 8.1.2 – Other Procedures.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed disease progression
    - Increase in ≥25% from best response and/or lowest measurable value in
        - Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL)
        - Urine M-component and/or (the absolute increase must be ≥ 200 mg/24h)
        - Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved free light chains levels. The absolute increase must be > 10 mg/dl.
        - Bone marrow plasma cell percentage: the absolute % increase must be ≥ 10%
    - Definite development of new bone lesions or soft tissue plasmacytomas
    - Development of hypercalcemia (corrected serum calcium > 1 mg/dL higher than the upper limit of normal or > 11 mg/dL) that can be attributed solely to the plasma cell proliferative disorder
    - Rise in serum creatinine by 2 mg/dl or more and/or creatinine clearance >40 ml/min, that can be attributed solely to the plasma cell proliferative disorder
    - Development of anemia with a hemoglobin 2 g/dl below the lower limit of normal

- Unacceptable adverse experiences as described in Section 5.7.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 7.0 (Study Calendar).After the end of treatment, each subject will be followed for 90 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.0 (study calendar, adverse events/toxicity, footnotes [i, j]). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.12 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

2. Plans to modify or discontinue the development of the study drug

In the event of Merck decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 DATA COLLECTION AND EVALUATION

6.1 Data Collection

Data will be prospectively collected and entered into a clinical trials database. The protocol specific data will be entered into Redcap, the electronic case report form. All data will be kept secure. Personal identifiers will not be used when collecting and storing data. An enrollment log will be maintained in the regulatory binder/file which is the only location of personal identifiers with unique subject identification number. The Investigator or physician designee is responsible for providing source documentation and assigning attribution for all AEs.

When patients enter the long-term follow-up period, the following data will be collected:

- Adverse events related to Pembrolizumab
- Survival status which will be collected by phone or clinic visit
- Additional cancer therapy received

6.1.1 Record Keeping

Complete records must be maintained on each patient; these records will consist of the hospital chart as well as any other outside information obtained from outside laboratories, radiology reports, or physician's records. These records will serve as the primary source material that forms the basis for the research record. All relevant data will also be entered on a computer database from which formal analyses are done. The primary source documentation will include patient eligibility data, patient history, flow sheets (including specialty forms for pathology, radiology, or surgery), an off-study summary sheet, and a final assessment by the treating physician.

6.1.2 Forwarding of Patient Data from Other Institutions

Either due to extenuating medical circumstances or for convenience, some patients may elect to have certain routine laboratory studies or protein marker analyses performed at an outside institution between scheduled interval visits to MD Anderson Cancer Center for this protocol. These results will be forwarded to the study designated data manager who will enter the data into the study database. Additional blood or tissue samples drawn on patients enrolled in this protocol between scheduled visits may be forwarded and entered into the database as well.

6.2 Response Criteria

Response assessments will be performed on Day 1 of each cycle during Cycle 1-24 and at the end of Cycle 24.

6.2.1 Light chain only disease

a) If patient does not have presence of "measurable" serum or urine M-protein (those are negative in electrophoresis), but has either a serum kappa or lambda FREE light chain of 10 mg/dL along with an abnormal kappa to lambda free light chain ratio, patient is considered to have "measurable" disease.

b) The serum free light chain (FLC) assay is of particular use in monitoring response to therapy in patients who have oligo-secretory disease. When using this assay, it is important to note that the FLC levels vary considerably with changes in renal function and do not solely represent monoclonal elevations. 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. The serum FLC assay should be used in assessing response only if the baseline serum and/or urine M proteins are not "measurable" by traditional criteria, and the baseline level of the involved FLC is 10mg/dL and clonal (abnormal ratio). Patients included on the study on the basis of FLC alone (i.e., no measurable serum/urine) should be the only ones who are evaluated using FLC response criteria. The others should follow usual criteria and ignore FLC results.

c) 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.

d) Caution must be exercised to avoid rating progression or relapse on the basis of variation of radiological 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 PI before removing the patient from the study.

6.2.2 Evaluation of response Criteria by modified International Myeloma Working Group Criteria for Multiple Myeloma

a) **Stringent Complete Response (sCR)**
   - Complete Response as defined below plus: Normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence (presence/ absence of clonal cells is based on the kappa/ lambda ratio.

b) Complete Response (CR)
   - Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <= 5% plasma cells in bone marrow

c) Very Good Partial Response (VGPR)
   - Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100mg per 24h. If the serum and urine M-protein are unmeasurable, a ≥ 90% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria.

d) **Partial Response (PR)**
   - ≥ 50% reduction in M protein and reduction in 24-h urinary M-protein by ≥ 90% or to < 200 mg per 24h. If the serum and urine M-protein are unmeasurable, a ≥ 50% difference between involved and uninvolved FLC levels is required in place of the M-protein criteria

e) **Minor Response (MR)**
   - ≥ 25% but ≤ 49% reduction of serum M protein and reduction in 24-hour urine M-protein by 50%-89%. In addition to this, if present at baseline, 25%-49% reduction in the size of soft tissue plasmacytomas is also required. No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)

f) **Stable Disease (SD)**
   - Not meeting criteria for CR, VGPR, PR, MR or progressive disease. All categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

g) Progressive disease (PD)
   - Requires any one or more of the following:
     - Increase of ≥ 25% of best response and/or lowest measurable value in:
     - Serum M-component and/or (absolute increase must be ≥ 0.5 g/dl. The serum M-component increases of ≥ 1gm/dl are sufficient to define

relapse if starting M-component is ≥ 5 gm/dl.
- Urine M-component and/or (the absolute increase must be ≥ 200 mg/24h
- Only in patients without measureable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be >10mg/dl.
- Bone marrow plasma cell percentage: the absolute % must be ≥ 10%
- Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in size of existing bone lesions or soft tissue plasmacytomas
- Development of that can be attributed solely to the plasma cell proliferative disorder

h) **Relapse from CR:**
- Any one or more of the following:
  - Reappearance of serum or urine M-protein by immunofixation or electrophoresis
  - Development of ≥ 5% plasma cells in the bone marrow
  - Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, hypercalcemia)

6.2.3 Duration of first Response
The duration of overall response is measured from the time measurement criteria are met for initial response until the first date that recurrent or progressive disease is objectively documented.

6.2.4 Progression-Free Survival
PFS is defined as time of start of treatment to time of progression to multiple myeloma or death, whichever occurs first.

6.2.5 Time to progression
TTP is defined as time of start of treatment to time of progression to multiple myeloma.

6.2.5.1 Overall Survival
Overall survival is defined as the time of start of treatment to death from any cause.

6.2.6 Overall response rates after 8 and 24 cycles of treatment
Overall response rates (ORR) is PR+VGPR+CR+sCR.

6.2.7 Clinical Benefit Rate after 8 and 24 cycles of treatment
Clinical benefit rate (CBR) is sCR+CR+VGPR+PR+MR.

7.0 STUDY CALENDAR

Study	Pre-Treatment	Initial treatment			Disease progression at any time point [j]	Follow Up[i,j]
		Cycle 1[k]	Cycles 2-24[k]			
		Day 1	Day 1	End of Cycle 8/ end of Cycle 24		
Medical Record Review	X					
H&P	X	X	X	X	X	X
ECOG	X	X	X	X	X	X
Informed Consent	X					
EKG	X					
Routine Labs[a]	X	X	X	X	X	X
24 hour urine for UPEP and IFE [m]	X		X	X	X	X
Viral Studies[b]	X					
Pregnancy Test[c,d,e]	X[c]	X	X[c]			
Myeloma tests[f]	X	X	X	X	X	X
Research Blood/Urine	X		X	X	X	X
Bone Marrow/Aspirate	X[g]			X[h]	X[h]	X[m]
FDG PET-CT	X[m]			X[m]	X[m]	X[m]
Skeletal Survey	X			X	X	X[m]
MRI of the thoracic and lumbar spine	X[m]			X[m]	X[m]	X[m]
Pembrolizumab		X	X			
Adverse Events/Toxicity			X	X	X	X
Concomitant Medications [n]	X				X	

a. Routine tests include CBC with differential, chemistry panel, liver function tests (AST, ALT, ALK and total bilirubin), amylase, lipase, TSH, T4, uric acid, eGFR determination and LDH. PT and PTT will only be performed at baseline. Reticulocyte count will only be performed at baseline.
b. Viral studies include HIV, Hep B surface antigen and Hep C antibody. If Hep C antibody positive, Hep C RNA PCR will be performed

c. Pregnancy tests (urine or serum) for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months)
d. Pregnancy tests (urine or serum) must occur within 10 – 14 days and again within 24 hours prior to prescribing pembrolizumab for Cycle 1
e. FCBP with regular or no menstruation must have a pregnancy test (serum or urine) weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy); at discontinuation of pembrolizumab and at Day 28 post the last dose of pembrolizumab. Females with irregular menstruation must have a pregnancy test (serum or urine) weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of pembrolizumab and at Day 14 and Day 28 post the last dose of pembrolizumab.
f. Myeloma tests include serum protein electrophoresis, serum immunofixation, 24 hour urine electrophoresis and urine immunofixation, serum free light chains, quantitative immunoglobulins, beta-2 microglobulin.
g. Baseline bone marrow aspiration and biopsy will be sent to Department of Pathology, flow cytometry, FISH/cytogenetics, multiple myeloma tissue bank, gene expression profiling, whole exome sequencing, VDJ sequencing and storage.
h. Bone marrow aspirate and biopsy can be performed +/- 21 days of intended cycle day. Bone marrow aspirate and biopsy will be sent to Department of Pathology, flow cytometry, FISH/cytogenetics, gene expression profiling, VDJ sequencing and storage.
i. At minimum, follow-up will be every 6-12 months until progression of disease, institution of alternative therapy, or death. Patients may be followed at more frequent time intervals if clinically indicated, ie following post-therapy toxicity. Patients who have progressive disease while on study will be followed with restaging scans and laboratory tests as clinically indicated. Patients who are taken off treatment will continue to be followed for survival by phone or clinic visit.
j. Variations of +/- 14 days of scheduled visits are permitted.
k. Variations of +/- 3 days of scheduled visits are permitted.
l. Peripheral blood sample only.
m. If clinically indicated
n. All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded in the medical record.

8.0 TRIAL PROCEDURES

8.1.1 Administrative Procedures

8.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB requirements, applicable laws and regulations and Sponsor requirements.

8.1.1.2 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the study calendar and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see the separate ECI guidance document in Appendices (Section 12.0) regarding the identification, evaluation and management of potential irAEs.

8.1.2 Other Procedures

8.1.2.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.2 - Assessing and Recording Adverse Events.

8.1.2.1.1 Survival Follow-up

Once a subject finishes 8 or 24 cycles of treatment with pembrolizumab or experiences confirmed disease progression, the subject moves into the survival follow-up phase and should be seen in clinic as per Section 7.0 Study calendar.

8.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of Merck product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

All adverse events will be recorded in Redcap from the time the consent form is signed through 90 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 8.2.3.1.

8.2.1 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 1000 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; FAX 215 993-1220)

8.2.2 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 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; FAX 215 993-1220)

8.2.3 Immediate Reporting of Adverse Events to the Sponsor and to Merck

8.2.3.1 Serious Adverse Events

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

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

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

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected

or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 90 days after the last study treatment/intervention, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

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

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

Investigator Communication with Supporting Companies:

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

Refer to Table 5 for additional details regarding each of the above criteria.

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.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220

A copy of all reports are submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) 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; FAX 215 993-1220) at the time of submission to FDA.

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

8.2.3.2 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; FAX 215 993-1220)Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 8.2.1 - 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).

1. 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 the appendicesand 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; FAX 215 993-1220), 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.

8.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 5 Evaluating Adverse Events

An investigator, who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Merck product to be discontinued?	
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Merck product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE MERCK PRODUCT, OR IF REEXPOSURE TO THE MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Merck product relationship).**
Yes, there is a reasonable possibility of Merck product relationship.		There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.
No, there is not a reasonable possibility Merck product relationship		Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

8.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB and investigators in accordance with all applicable global laws and regulations.

First stage: The principal investigator will submit a response/toxicity summary to the IND Medical monitor after the first 12 subjects have completed 8 cycles

Second Stage: The principal investigator will submit a response/toxicity summary to the IND Medical monitor after additional 4 subjects have completed 8 cycles

9.0 STATISTICAL ANALYSIS PLAN

The overall response (≥ partial response) after 8 cycles of treatment is the primary endpoint. The trial will be conducted by the Simon's Minimax design and the response rate will be estimated accordingly (Simon, 1989).

It is assumed that Pembrolizumab will have a target response rate after 8 cycles of treatment of 25%. A response rate of 5% or lower is considered a failure and the new regimen will be rejected under this circumstance. When the probability of accepting a "bad" regimen (i.e. response rate≤5%) is 0.05 and the probability of rejecting a "good" regimen (i.e. response rate ≥25%) is 0.20, Simon's Minimax design requires to enter 12 patients in the first stage. If no patient responds to the treatment, the trial will be stopped and the regimen will be declared as ineffective. If there is at least one response observed, 4 more patients will be entered in the study to reach a total of 16 patients. By the end of the study, the new regimen will be rejected if response rate is less than or equal to 2/16 and will be accepted otherwise. The operating characteristics of the trial are given as follows. When the true response rate is 5% the probability of stopping the trial early is 54%. On the other hand, if the true response rate is 0.25, the probability to stop the trial early is 3.2%. The expected sample sizes are 13.8 and 15.9 when the true response rates are 0.05 and 0.25, respectively.

If the number of responses required for moving the trial to the second stage has not been achieved, the patient enrollment will be halted until enough responses observed.

Summary statistics will be provided for continuous variables. Frequency tables will be used to summarize categorical variables. The response rate and its 95% confidence interval will be calculated. The distribution of time-to-event endpoints including progression free survival and overall survival will be estimated using the method of Kaplan and Meier.

Toxicity data will be summarized by frequency tables for all patients. For the efficacy endpoints, intent-to-treat analysis will be applied to the eligible patients. For the toxicity endpoint, per-treated analysis will be performed to include any patient who received the treatment regardless of the eligibility nor the duration or dose of the treatment received.

10.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

10.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by Merck as summarized in Table 6.

Table 6 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

10.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

10.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

10.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

10.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

11.0 ADMINISTRATIVE AND REGULATORY DETAILS

11.1 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

12.0 APPENDICES

12.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. 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 Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

12.2 Events of Clinical Interest Guidance Document

See appendix 1, Pembrolizumab Program, event of clinical interest guidance document version 5.0.

13.0 REFERENCES

1. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. *Leukemia*. 2006;20(9):1467-1473.
2. Landgren O, Kyle RA, Pfeiffer RM, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. *Blood*. 2009;113(22):5412-5417.
3. Weiss BM, Abadie J, Verma P, Howard RS, Kuehl WM. A monoclonal gammopathy precedes multiple myeloma in most patients. *Blood*. 2009;113(22):5418-5422.
4. Kristinsson SY, Landgren O, Dickman PW, Derolf AR, Bjorkholm M. Patterns of survival in multiple myeloma: a population-based study of patients diagnosed in Sweden from 1973 to 2003. *J Clin Oncol*. 2007;25(15):1993-1999.
5. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood*. 2008;111(5):2516-2520.

6. Paiva B, Vidriales MB, Cervero J, et al. Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation. *Blood*. 2008;112(10):4017-4023.
7. van de Velde HJ, Liu X, Chen G, Cakana A, Deraedt W, Bayssas M. Complete response correlates with long-term survival and progression-free survival in high-dose therapy in multiple myeloma. *Haematologica*. 2007;92(10):1399-1406.
8. Mateos MV, Hernandez MT, Giraldo P, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. *N Engl J Med*. 2013;369(5):438-447.
9. Landgren O, Mailankody S, Kwok M, Manasanch Eea. Clinical and correlative pilot study of carfilzomib, lenalidomide and dexamethasone followed by lenalidomide extended dosing (CRd-R) in high risk smoldering multiple myeloma patients. *Blood*. 2013;122:1939.
10. FDA. Pembrolizumab http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm412861.htm; 2014.
11. Robert C, Ribas A, Wolchok JD, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. *Lancet*. 2014;384(9948):1109-1117.
12. Liu J, Hamrouni A, Wolowiec D, et al. Plasma cells from multiple myeloma patients express B7-H1 (PD-L1) and increase expression after stimulation with IFN-{gamma} and TLR ligands via a MyD88-, TRAF6-, and MEK-dependent pathway. *Blood*. 2007;110(1):296-304.
13. Perez-Persona E, Vidriales MB, Mateo G, et al. New criteria to identify risk of progression in monoclonal gammopathy of uncertain significance and smoldering multiple myeloma based on multiparameter flow cytometry analysis of bone marrow plasma cells. *Blood*. 2007;110(7):2586-2592.
14. Dispenzieri A, Kyle RA, Katzmann JA, et al. Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. *Blood*. 2008;111(2):785-789.
15. Dhodapkar MV, Sexton R, Waheed S, et al. Clinical, genomic, and imaging predictors of myeloma progression from asymptomatic monoclonal gammopathies (SWOG S0120). *Blood*. 2014;123(1):78-85.
16. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15(12):e538-548.