TITLE: Pilot Study of Pembrolizumab and Single-fraction, Low-dose, Radiation Therapy in Patients with Relapsed or Refractory Multiple Myeloma

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1. PROTOCOL SUMMARY

Abbreviated Title	Pilot Study of Pembrolizumab and Single-fraction, Low-dose, Radiation Therapy in Patients with Relapsed or Refractory Multiple Myeloma
Trial Phase	*Pilot Study*
Clinical Indication	Relapsed or Refractory Multiple Myeloma
Trial Type	Pilot study
Type of control	None
Route of administration	Patients will receive on **day 1**, **cycle 1,** radiotherapy (**8 Gy/1fx**) to an **extra-osseous or osseous myeloma** site followed by pembrolizumab (**200 mg/kg i.v. on day 2 or 3**, then every **3 weeks** +/- 7 days).
Trial Blinding	N/A
Number of trial subjects	24 patients (20 patients minimum, with 4 extra patients to account for loss to follow-up/attrition and/or failure to comply with recommended treatments); 12 patients will be allowed to not have measurable myeloma disease.
Estimated enrollment period	*2 years*
Description of enrollment	Following evaluation by medical oncology and radiation oncology, patients will be enrolled. Baseline assessment prior to enrollment may include bone marrow biopsy, peripheral blood collection, and staging of the patient per standard of care. Baseline serum and urine paraprotein analysis, bone marrow biopsy, PET/CT imaging, routine blood work, and baseline physical exam prior to enrollment. Patient with **measurable myeloma disease** will be screened for tolerability to Pembrolizumab and radiotherapy. Patients will be assessed **at 1st month and every 3 month** for response using the standard International Myeloma Working Group (IMWG) Response Criteria, and will undergo **routine myeloma labs every 6 weeks until progression or as clinically indicated**; **Patients with stable disease or better per IMWG response criteria will continue with maintenance pembrolizumab (200 mg/kg every 3 weeks for 2 yrs)**. Patients that have progressive disease, or relapse after a complete response will be removed from the trial and treated per standard of care at the discretion of the treating physician.
Duration of Intervention	At least 24 months of Pembrolizumab, or until progression.
Duration of Evaluation	3 year (2 yrs for accrual, and at least 1 year follow-up for the last patient accrued on the study)
Estimated duration of trial	3 years (2 years to accrue + 1 years to follow all patients)
Duration of Participation	3 years
Study Center	Emory University. Atlanta, Georgia.

2. TRIAL DESIGN/SCHEMA

1. Trial Overview

Following evaluation by medical oncology and radiation oncology, patients with **measurable myeloma disease** will be enrolled. Baseline assessment prior to enrollment may include bone marrow biopsy, peripheral blood collection, and staging of the patient per standard of care. Baseline serum and urine paraprotein analysis, bone marrow biopsy, PET/CT imaging, skeletal survey, routine blood work, and baseline physical exam prior to enrollment. Patient will be screened for tolerability to Pembrolizumab, and those that are also eligible for radiotherapy will be identified.

Patients will receive on **day 1, cycle 1,** radiotherapy (**8 Gy/1fx**) to an extra-osseous site and/or any osseous bony site, followed by pembrolizumab (**200 mg/kg i.v. on day 2 or 3**). Baseline peripheral blood will be collected for myeloma response as well as for correlative biomarker analysis (timing of blood draws are defined in the flow chart in section 10.0).

Patients will be assessed for safety during routine visits, as well as treatment response using the standard International Myeloma Working Group (IMWG) Response Criteria (see Appendix II for IMWG Criteria) at **1 month** (shortly after completion of cycle 2 of pembrolizumab, anytime between **Day 23-30 +/- 7 days**), and **at least every 3 months +/-14 days** (**or as clinically indicated**). Patients with stable disease or better per IMWG response criteria will continue with maintenance pembrolizumab (**200 mg/kg every 3 weeks for 2 yrs**). Patients that have progressive disease, or relapse after a complete response will be removed from the trial and will be treated per standard of care at the discretion of the treating physician.

Patients will continue to be monitored per standard of care on the trial. Patients will be monitored for known radiation related toxicity, known pembrolizumab toxicity, as well as any unexpected toxicity, per standard of care. PET/CT scans will be done at baseline and every 3 months, per standard of care.

The primary endpoint is to evaluate the **safety and tolerability** of concurrent single/low dose radiotherapy (8 Gy/1fx) in combination with pembrolizumab in relapsed and/or refractory myeloma patients at 3 months (**acute toxicity, primary endpoint**) and at 6 and 12 months (**late toxicity**). The secondary objective is to characterize the effect of radiation in combination with pembrolizumab on systemic response rates using international myeloma working group (IMWG) uniform response criteria for myeloma, to assess baseline changes in PET/CT as a result of combining pembrolizumab and radiotherapy, and to evaluate treatment response at irradiated and un-irradiated sites (i.e. the abscopal effect) using baseline PET/CT. Exploratory analysis would include analyzing Circulating Myeloma Tumor cells and phenotype of T cells as a prognostic and predictive biomarker. Compare blood Myeloma tumor cells with BM tumor cells. We are interested in comparing T cell phenotype after each treatment and using that as a prognostic biomarker. We will also evaluate serum LDH, CRP, ESR, ALC, cytokines and chemokines (such as IL-6, s IL-6R) and other immune related biomarkers, and correlate their expression pre and post treatment and evaluate changes in bone marrow biopsy and peripheral blood for mutational load, mutational signature (whole exome sequencing), transcriptome of the T cells, mutation specific T cells, PD1 and PDL1 expression on MM cells and T cells by flow/IHC, RNA-seq. Other biomarker correlative exploratory analysis (role of exosomes, etc) may also be pursued as ancillary research to this trial;

2. Acute Toxicity and Late Toxicity Assessment:

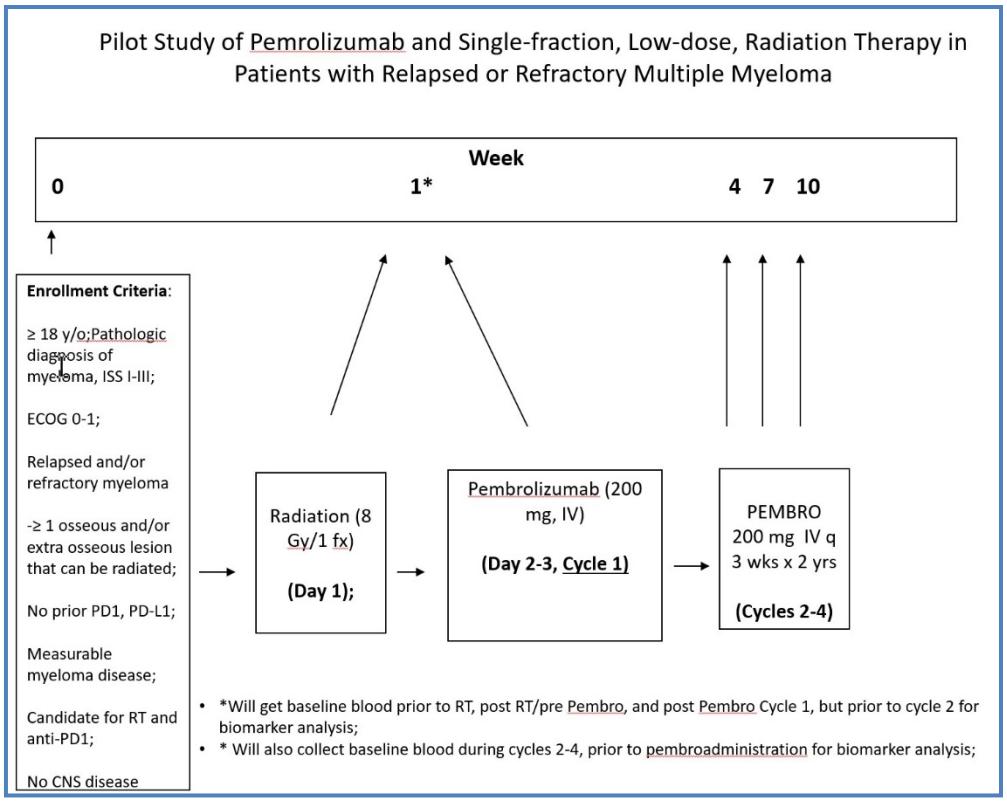
Acute toxicity (i.e, > Grade 2 CTCAE toxicity at **3 months**) associated with radiation therapy at the **radiated site** will be analyzed as the **primary safety endpoint** in this pilot study; Goal would be to see less than 20% > grade 2 toxicity at 3 months within the radiated area.

CTCAE criteria (see Appendix I) will be applied to assess acute toxicity.

Other endpoints that may be analyzed include late toxicity (> Grade 2 CTCAE toxicity at the radiated site at **6 months and 12 months**), systemic response against myeloma burden to localized radiation and pembrolizumab using IMWG uniform criteria, as well as other endpoints (defined in more detail in section 3.0).

3. Trial Schema

Figure 1: Trial Overview



Baseline work-up (per NCCN guideline) within 28 days +/- 14 days prior to enrollment: CBC with Diff, CMP, Calcium, Albumin, Serum Protein analysis, Quantitative Immunoglobulin, Serum Immunofixation (SIFE), 24 hr urine total protein, Urine Immune-Fixation, Serum Free Light Chain, Bone Marrow Biopsy (with IHC, flow, cytogenetics, FISH),

Whole Body PET/CT, Biopsy of Osseous or extra-osseous site (only if clinically indicated); Pregnancy test;

Inclusion Criteria:

1) ≥ 18 years old; ISS stage I-III multiple myeloma that has progressive, relapsed, or refractory disease;

2) Able to give informed consent;

3) ECOG 0-1;

4) Relapsed and/or refractory myeloma; There is no minimum or maximum number of previous therapies that a patient may have received previously before being put on the current trial.

5) ≥ 1 osseous and/or extra-osseous lesion that can be radiated**;**

6) Candidate for pembrolizumab (as determined by physician, and adequate organ function as noted in **Table 1**);

7) Candidate for radiotherapy (as determined by treatment physician); These patients can have symptomatic disease and/or asymptomatic disease. A minimum of one site of radiation is required to any osseous and/or any extra-osseous disease. Radiation to any bony parts of the Head and Neck, Skull, Spine, ribs, and/or extremities are allowed. Radiation to any bony part for documented lytic disease is allowed. Radiation to any soft tissue plasmacytoma (including osseous and extra-osseous plasmacytoma) is allowed. The only exclusion criteria for radiation, is CNS metastases (see exclusion criteria # 16);

8) Measurable myeloma disease **(urine protein > 200 mg in 24 hr urine collection, serum free light chain ratio> 100 with an abnormal k/l ratio, serum M protein > 0.5 g/dl) ; 12 of the 24 patients do not have to have measurable disease;**

9) Negative urine pregnancy test within 2 weeks for female subjects;

Female subjects 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.

a. 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. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
b. 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.

c. Abstinence is acceptable, if this is the usual life style and preferred contraception for the patient.

Exclusion Criteria:

1) Previous anti-PD1 or anti-PD-L1;

2) Solitary plasmacytoma;

3) Smoldering (asymptomatic) multiple myeloma;

4) Currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment;

5) Has a diagnosis of immunodeficiency;

6) Known history of active TB (Bacillus Tuberculosis);

7) Hypersensitivity to Pembrolizumab or any of its recipients;

8) 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);

9) 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);

10) Known history of, or any evidence of active, non-infectious pneumonitis;

11) Active infection requiring systemic therapy;

12) 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.

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

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

15) 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.

16) Patients requiring radiation for CNS diseases are excluded (CNS defined as brain soft tissue/intra parenchymal metastases within the gray and white matter of the brain and/or for CSF disseminated disease, including leptomeningeal carcinomatous disease).

17) Has a history of Allogeneic Stem Cell Transplantation.

Follow-up:

Radiation Oncology: at **4 week** post radiation and **every 3 months** (per standard of care, and as clinically indicated);

Medical Oncology: **every 3 weeks**, or as clinically indicated per standard of care for administration of pembrolizumab, and to monitor for any potential side effects from pembrolizumab;

Labs to be done during these visits:

Prior to cycle 2 of Pembrolizumab: Myeloma labs (CBC with diff, CMP, Calcium, Quantitative Immunoglobulin, M-Protein (Serum and Urine), Serum Free Light Chain);

Prior to Cycle 4 and every 6 weeks after that (until progression or as/clinically indicated): Myeloma labs (CBC with diff, CMP, Calcium, Quantitative Immunoglobulin, M-Protein (serum and Urine), Serum Free Light Chain);

Imaging: PET/CT will be done every 3 months;

Bone Marrow Biopsy: one biopsy at 6 months (if clinically indicated);

Table 1 - Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥75,000 / mcL (rare exception for ≥ 50K per PI*)
Hemoglobin	≥7.5 g/dL or ≥5.6 mmol/L and allow transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

*In rare exceptions, where medical interest of patient to get on the trial supercedes the platelet cutoff, the PI can make an exception to allow a lab value lower than 75K. PI can allow for lab value up to 50K. * 50K cutoff is a lab value that used by several other myeloma protocols at Emory, especially for relapsed/refractory myeloma patients. The maximum number of patients that can be allowed this exception on the protocol is no more than 3. Transfusion is allowed to help increase platelets.

3. OBJECTIVES, ENDPOINTS & HYPOTHESES

1. Primary Objective, Endpoint, & Hypothesis

Primary Objective

To evaluate the safety of concurrent single/low dose radiotherapy (**8 Gy/1fx**) in combination with Pembrolizumab in relapsed or refractory myeloma patients; **Once 10 patients are enrolled, we will stop trial for 3 months to assess for acute toxicity, and then resume the trial.**

Primary Endpoint

CTCAE > grade 2 toxicity at the specific irradiated **organ site at 3 months** (the Dose Limiting Toxicity);

Primary Hypothesis

The primary hypothesis of this pilot study is that the use of concomitant Pembrolizumab and radiation therapy in multiple myeloma patients will be well tolerated and safe.

Alternative Hypothesis

It is possible that concurrent use of radiotherapy and Pembrolizumab in relapsed/refractory myeloma may increase CTCAE > grade 2 toxicity within the radiated site at 3 months.

2. Secondary Objective(s), Endpoint(s) & Hypothesis (es)

Secondary Objectives

To characterize late toxicity (CTCAE > grade 2 toxicity at **6 and 12 months**) and the effect of radiation in combination with Pembrolizumab on systemic response rates using international myeloma working group (IMWG) uniform response criteria for multiple myeloma at **6 months and 12 months;**

To assess changes in PET/CT as a result of combining Pembrolizumab and radiotherapy at **6 months and 12 months**;

Secondary Endpoints

a. 1. Number of patients achieving any response (from baseline) per IMWG response criteria at **6 months and 12 months**;

b. 2. Overall survival time at **6 months and 12 months**;

c. 3. Overall response based on baseline changes on PET/CT at **6 months and 12 months;**

d. 4. Difference in pre and post treatment serum immune biomarkers;

Secondary Endpoint Definitions

a. Response is defined per IMWG criteria, and will be calculated at **6 months and 12 months;**
b. Overall survival will be defined as time from first treatment on cycle 1, day 1 to the earlier of date of death and/or last follow up at **6 months and 12 months.**
c. Overall response will be defined using IMWG uniform response criteria.
d. Several serum biomarkers will be analyzed.

Secondary Hypotheses

The secondary hypothesis is that low dose/single fraction (8Gy/1fx) will synergize with Pembrolizumab for a more effective anti-myeloma response per IMWG, via the radiation induced abscopal response.

4. BACKGROUND & RATIONALE

26,850 new myeloma cases with 11,240 deaths were expected in 2015. While outcomes have improved with the introduction of new agents, patients continue to relapse after effective therapy, and ultimately develop refractory disease. Treatment of relapsed myeloma include bortezomib, lenalidomide, dexamethasone, carfilzomib, pomalidomide, panobinostat, monoclonal antibodies and/or some combination of these. The role of pembrolizumab within myeloma, an anti PD-1 immune checkpoint inhibitor, is currently under investigation. The role of radiotherapy for relapsed myeloma is typically limited to palliation of bony pain and/or for prevention of significant neurological effects or end organ damage due to progression of extra-osseous manifestation of relapsed myeloma. **However, whether radiation therapy may enhance PD-1 inhibitor responses within myeloma is unknown**. **We believe that PD1 inhibitor in combination with radiotherapy may improve systemic responses.**

We have demonstrated that radiation therapy can augment the immune response via the radiation induced "**abscopal effect**". We utilized a human equivalent syngeneic mouse model implanted with B16 melanoma cells on both flanks of a mouse; using a 10 Gy single dose of radiation, we observed significant delay of the radiated site, as well as the remote non-radiated tumor site (**Fig. 1A).** This action at a distance implies that immune mechanisms are responsible. To validate this, we quantified the different immune cells that are responsible for the "**abscopal effect**" (**Fig. 1B,1C & 1D**). For many years, mouse xenograft models have dominated in cancer drug development fields. Due to its immunedeficiency, these models are not suitable to address immune response in cancer treatment. Our novel syngeneic mouse models provide us reliable platform for immunotherapy studies. Our results are provocative given that post-irradiation increases PD-1 expression on T cells, and combining radiation with anti-PD1 antibody therapy demonstrates synergy[1].

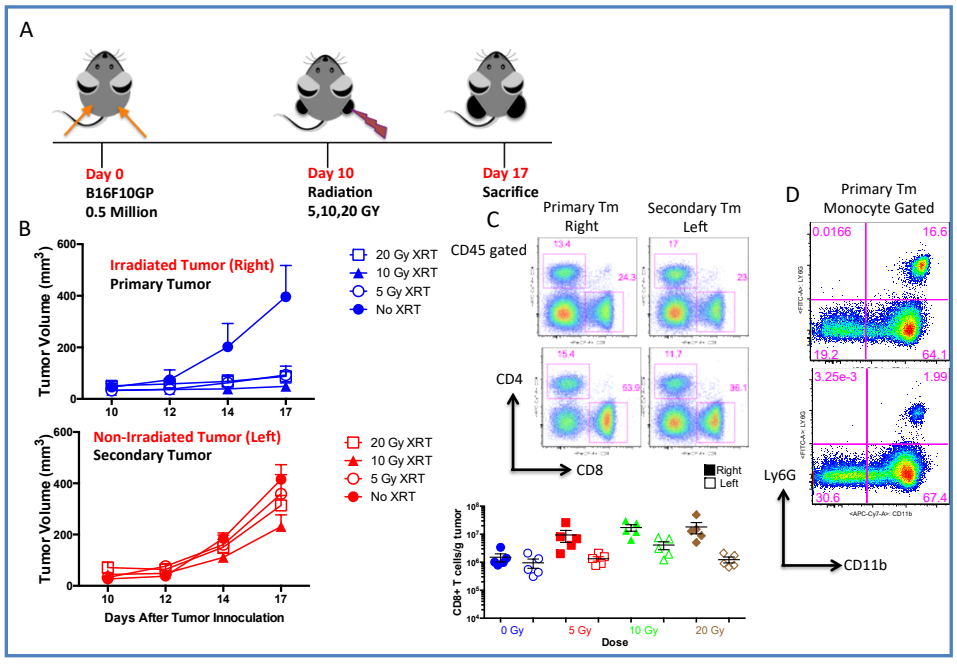


Figure 1. Mouse model of abscopal effect. **A**. 0.5x10^6 B16F10gp melanoma cells were injected subcutaneously

in the left and right flanks. Ten days post implantation, mice were irradiated with different radiation doses (right) flank, and tumors measured every other day. The mice were sacrificed at day 17. **B**. Tumor growth kinetics in mice with Irradiated tumor (blue) or un-Irradiated tumor (Red), demonstrating a decreased tumor volume with Irradiation in primary as well as secondary tumor **C**. Expansion of CD8 and CD4 T cells was found in irradiated side of tumor (left column) after radiation therapy, suggesting that radiation influences immune cell phenotypes within tumor microenvironment. **D.** Radiated decreased myeloid suppressor cells. All the Ly6G+ cells were Ly6C+ characteristic MDSCs.

Several reports have suggested that radiotherapy in combination with emerging immunotherapy agents such as PD-1, PD-L1[1], CTLA-4 inhibitors[2] as well as other immunotherapy agents (FLT-3 ligand[3], 4-1 BB [4,5]etc) may increase the efficacy of these agents. Sharabi et al.[6] and Dovedi et al.[7] together demonstrate that radiation therapy increases the T cell repertoire and antigen presentation to T cells; furthermore, adding radiation to PD-1 blockade in mice models demonstrate significant improvement in systemic response and local control.[8] Trials using some of these agents (PD-1 and others, in combination with radiotherapy) are ongoing, while others are in the planning stages for a wide variety of malignancies.

Clinically, the combination of the PD-1 inhibitor, pembrolizumab in combination with revlamid (Rd) produced responses in 76% of the 17 heavily pretreated patients with relapsed or refractory multiple myeloma in the KEYNOTE-023 study (San Miguel J, Mateos MV, Shah JJ, et al. 57th American Society of Hematology Annual Meeting; Orlando, Florida; December 5-8, 2015. Abstract 505). Similar impressive results were seen with pembrolizumab in combination with pomalidomide and dexamethasone. Overall response rates of 60% among double refractory patients were seen with this safe combination.

While future therapies for multiple myeloma may combine PD-1 inhibitors as part of their medical oncology designs, it is also possible that some of these patients may also receive local radiotherapy (for palliation and/or prophylaxis) as part of their standard of care treatments. Thus, we propose to evaluate the safety and efficacy of pembrolizumab in combination with radiotherapy. *Our pilot study will provide insights for future clinical trial designs and help guide future clinical management decisions regarding early safety and efficacy of this combination.* Thus, we propose to evaluate the safety and outcomes of this combination in a small cohort of patients.

4.1 The Immune System in Cancer

In 2000, Hanahan and Weinberg published their seminal review describing the 6 biological hallmarks acquired during the development from benign to malignant to metastatic tumors[9]. Eleven years later, they illustrated 2 further important processes that were since realized, including “evading the immune system”[10].

The immune system consists of two main components, innate and adaptive system. In brief, the innate system is a non-specific response to differences between innate and foreign pathogens, while the adaptive system is a more tailored response that induces memory. As part of this adaptive response, macrophages and dendritic cells present foreign antigens to the T cell’s receptors. Further T cell activation is regulated by multiple factors, including both positive (co-stimulatory) and negative (co-inhibitory) surface receptors. Tumors can subvert the related immune recognition in part through increase of co-inhibitory molecule expression; two of these regulatory molecules are cytotoxic T lymphocyte antigen-4 (CTLA-4) and

programmed death 1 (PD-1) receptor.

4.2 Anti-PD-1 in Pre-Clinical Models

Programmed death 1 (PD-1) (or CD279) is part of the CD28 family of proteins, which includes CTLA-4 and ICOS, that regulate T cell activity[21]. PD-1 is a glycoprotein receptor that can be expressed on the surface of T cells, B cells and myeloid cells (monocytes and dendritic cells)[21]. In T cells, PD-1 expression is primarily induced by T cell receptor (TCR) engagement and ligation with PD-L1 and PD-L2, expressed on antigen presenting cells, and induces an inhibitory signal that antagonizes TCR signaling and other important pathways necessary for optimal T cell activation

Interestingly, melanoma, and to a lesser effect NSCLC, expresses abundant PD-1 ligand (PD-L1), whereas T cells of advanced cancer patients notoriously express increased levels of PD-1. The combined effect is that these cancer cells are spared from T-cell-mediated cytotoxicity, and tumor infiltrating lymphocytes are maintained in a dysfunctional state, described as T cell exhaustion. Indeed, PD-1 expression on T cells of patients has been associated with progression to metastatic disease.

Targeting the PD-1 pathway in pre-clinical models has demonstrated promising activity. Utilizing murine cancer cells, anti-PD1 antibody decreased tumor growth and decreased metastatic potential. Uisng B16 cells (a PD-L1 positive cell line) and 4T1 cell line (a PD-L1 negative cell line), the author demonstrated similar efficacy of PD-1 pathway blockade. Prior studies demonstrate that PD-L1 expression varies in response to the microenvironment, including increased expression in response to cell death. Consistent with this model of variable PD-L1 expression over time, several authors have since demonstrated the efficacy of anti-PD-1 antibodies in both PD-L1 positive and negative tumors. We hypothesize that combining radiotherapy (**Fig. 1**) in combination with PD-1 blockade may enhance PD-1 responses in patients.

4.3 Rationale for Pembrolizumab Dose Selection/Regimen/Modification

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

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

This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 200 mg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 200 mg200 mg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 200 mg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 200 mg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 200 mg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

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

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

4.4 Safety and toxicity of Pembrolizumab

Pembrolizumab has been administered to a total of 308 melanoma patients, from 2 prospective clinical trials[11]. The first trial administered pembrolizumab at 3 different doses (2mg/kg q3weeks, 10mg/kg q3weeks, and 10mg/kg q2weeks) for 4 total cycles, followed by continued maintenance therapy until progression. Overall, 79% of patients develop any grade of toxicity. The most common toxicities were fatigue (30%), rash (21%), pruritus (21%), and diarrhea (20%). However, most of these symptoms were low grade, as only 13% developed grade 3- 4 toxicities. Furthermore, grade 3-4 adverse events were dose related: the 10mg/kg,

q2week cohort was 23%, while the q3week cohorts was 4-9%. The grade 3 clinical toxicities documented included rash (2%), pruritus (1%), hypothyroidism (1%), diarrhea (1%), abdominal pain (1%), decreased appetite (1%), elevated AST (1%), and renal failure (1%). In the 2 cases of renal failure, both cases improved with discontinuation of pembrolizumab and initiation of glucocorticoid therapy

In the trial of pembrolizumab in advanced melanoma patients, the toxicity profile was similar to that reported by Hamid et al: 82% developed any grade of toxicity, while 12% developed grade 3-4 toxicities. Most common toxicities were fatigue, pruritus, and rash. Reported grade 3-4 toxicities included fatigue (3%), elevated amylase (<1%), anemia (<1%), autoimmune hepatitis (<1%), confusion (<1%), diarrhea (<1%), dyspnea (<1%), encephalopathy (<1%), hypophysitis (<1%), hypoxia (<1%), muscular weakness (<1%), musculoskeletal pain (<1%), pancreatitis (<1%), peripheral motor neuropathy (<1%), pneumonitis (<1%), rash (<1%), rash maculopapular (<1%). Overall 6 patients (7%) developed adverse events leading to discontinuation of the drug. 3 of these cases (3%) were immune mediated. No drug related grade 5 toxicities were reported. Other side effects that have been discovered include vasculitis and hypothyroiditis (refer to latest investigator brochure accompanying the trial).

In the phase 1 study with 495 NSCLC patients[12], no grade 3 or higher CNS toxicities were noted. Furthermore, the toxicity profile was similar to that identified in the two melanoma studies. Most common grade $\geq$ 3 adverse events were fatigue (0.8%), decreased appetite (1.0%), nausea (0.8%), asthenia (1.0%), dyspnea (3.8%) and pneumonitis (1.8%). 1 patient who developed pneumonitis did die; overall, these findings demonstrate pembrolizumab is well tolerated and has similar toxicity profiles among the two histologies.

Keynote 023 (San Miguel et al. Blood 2015, 126:505), conducted an open phase 1, multi-center, non-randomized, dose escalation trial to evaluate the safety, toxicity, and tolerability of pembrolizumab in combination with lenalidomide and low-dose dexamethasone in patients with relapsed/refractory myeloma. A 2 mg/kg q 2 weeks as well as a fixed 200 mg dose of pembrolizumab doses were used in combination with lenalidomide and dexamethasone in myeloma patients. By July of 2015, 34 patients had been enrolled. No deaths of treatment discontinuation was noted. Most frequent AEs were: thrombocytopenia (47%), neutropenia (41%), fatigue (29%), anemia, hyperglycemia, and muscle spasms (23%). No dose limiting toxicity were noted in the 10 mg-lenalidomide cohort; The MTD/MAD was defined as 200 mg fixed dose; The objective response was 13/17 patients (76%) with 4 patients achieving a very good partial response and 9 patients achieving a partial response; The authors concluded that PD-1 blockade showed promising anti-myeloma activity in heavily pre-treated relapsed/refractory myeloma patients.

5. ADMINSTRATION OF STUDY PHARMACEUTICAL

In 2015, FDA approved Pembrolizumab (Keytruda) for the treatment of advanced melanoma and NSCLC patients; Pembrolizumab is a monoclonal antibody that targets the PD-1 receptor. Programmed death 1 (PD-1) (or CD279) is part of the CD28 family of proteins, which includes CTLA-4 and ICOS, that regulate T cell activity. PD-1 is a glycoprotein receptor that can be expressed on the surface of T cells, B cells and myeloid cells (monocytes and dendritic cells). In T cells, PD-1 expression is primarily induced by T cell receptor (TCR) engagement and ligation with PD-L1 and PD-L2, expressed on antigen presenting cells, and induces an inhibitory signal that antagonizes TCR signaling and other important pathways necessary for optimal T cell activation. Clinical trials with Pembrolizumab in advanced melanoma and NSCLC patients lead to approval by the FDA. Some efficacy in combination with lenalidomide for multiple myeloma has also been recently demonstrated. The recommended dose of Keytruda is 2mg/kg administered as IV infusion over 30 minutes every 3 weeks until disease progression, or unacceptable toxicity. Alternative dosing regimens are also available. The dose used on the Keynote -023 trial was 200 mg.

Dose Selection

Patients will receive pembrolizumab 200 mg IV delivered over a 30-minute period every 3 weeks until 2 years, or until disease progression, and/or unacceptable toxicity at the discretion of the treating physician. Infusions should be given over 30 minutes (not bolus or IV push).

Timing of Pembrolizumab Administration

Trial treatment should be administered on **Day 2 or 3 and then every 3 weeks +/- 7 days** after that as outlined in the Trial Flow Chart;

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. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, 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.

Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

Randomization Allocation

Not applicable

Stratification

Not applicable

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 sponsor-investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the sponsor-investigator and/or the subject's primary physician.

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 on the case report form (CRF) 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 on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and within 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 11.

2. **Prohibited Concomitant Medications**

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

1. Antineoplastic systemic chemotherapy or biological therapy
2. Immunotherapy not specified in this protocol
3. Chemotherapy not specified in this protocol
4. Investigational agents other than pembrolizumab

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.

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.

3. **Administration of Pembrolizumab Beyond Progression**

If the initial **week 6-week 8** myeloma labs show disease progression per IMWG response criteria, patients are allowed to continue treatment until progression is confirmed again at a **subsequent 4-8 week later**, to account for atypical response patterns (especially, if the clinician suspects, that there may still be a benefit to continue for a little bit longer). A physician would be allowed the choice to continue the patients on the current trial or removed from the trial;

If the repeat myeloma labs **beyond the 12 weeks** shows evidence of disease stabilization or objective response (relative to the previous scan that showed PD) as per IMWG response criteria, pembrolizumab may be continued per treatment calendar. However, if the repeat assessment at **12 weeks** per IMWG criteria shows disease progression relative to the previous labs that showed PD, then pembrolizumab should be discontinued;

6. DOSE MODIFICATION, DOSE LIMITING TOXICITIES, AND SUPPORTIVE CARE

Dose modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in **Table 2.**

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in **Table 3**.

Other allowed dose interruption for pembrolizumab

Pembrolizumab maybe interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. 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.

TABLE 2: Dose Modifications and Toxicity Management of irAEs associated with Pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent grade 2	Permanently discontinue		
Diarrhea / colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of enterocolitis (i.e. diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. peritoneal signs and ileus). • Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Subjects with 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.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is

Bilirubin	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	stable
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for subjects with T1DM • Administer anti-hyperglycemic in subjects with hyperglycemia	• Monitor subjects for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or Permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g. levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs (i.e vasculitis, hypothyroidits,etc)	Grade 3, or intolerable/ persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes • Refer to investigator brochure for additional side effects
	Grade 4 or recurrent Grade 3	Permanently discontinue		

NOTES:

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.
2. For subjects with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM)

Table 3: Dose Modification and Toxicity Management Related to Infusion Related Reactions to Pembrolizumab		
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 therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** 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 1 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 study drug treatment**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of _____ with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

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 initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids 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. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

7. DIET/ACTIVITY/OTHER CONSIDERATIONS

Diet

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

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. For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

(1) Postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) Has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) Practice abstinence† from heterosexual activity;

OR

(2) Use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- Intrauterine device (IUD)

- Vasectomy of a female subject's male partner
- Contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- Cervical cap with spermicide (nulliparous women only)
- Contraceptive sponge (nulliparous women only)
- Male condom or female condom (cannot be used together)
- Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

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 subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. **If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.**

Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study treatment. 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.

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.

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 sponsor-investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.
A subject must be discontinued from the trial for any of the following reasons:

8. The subject or legal or legal representative (such as a parent or legal guardian) withdraws consent.
9. Confirmed extra- extra-cranial radiographic disease progression.
10. Unacceptable adverse experiences as described in section 6 and 7.
11. Intercurrent illness that prevents further administration of treatment.
12. Investigator's decision to withdraw the subject.
13. The subject has a confirmed positive serum pregnancy test.
14. Noncompliance with trial treatment or procedure requirements.
15. The subject is lost to follow-up.
16. Completed at least 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, or whichever occurs last;

Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment at the discretion of their treating physician, especially if their disease is clinically stable;

17. Administrative reasons
18. Confirmed radiographic disease progression per RECIST criteria
    1. *Note*: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section *6 and 7.*

The End of Treatment and Follow-up visit procedures are listed in Section 10 (Protocol Flow Chart) and Section 11. After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment). 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.

Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 months with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation.

Clinical Criteria for Early Trial Termination

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

1) Quality or quantity of data recording is inaccurate or incomplete
2) Poor adherence to protocol and regulatory requirements
3) Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4) 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.

8. DELIVERY OF RADIATION THERAPY TREATMENT

Patients will receive on **day 1**, radiotherapy (**8 Gy/1fx**) to an extra-osseous site and/or any bony site containing myeloma deposit, followed by pembrolizumab (**200 mg/kg i.v. on day 3**).

Radiation Simulation and Diagnostic Procedures

All simulation and treatment procedures represent **current institutional practice**, and will be the same for all study participants.

A radiation patient should have some evidence of disease on imaging prior to CT simulation. This can include a lytic lesion in a bony site or an extra-osseous disease. Lytic lesions and/or extra-osseous noted on X-Ray, CT scan, PET/CT, and/or MRI are allowed.

CT Simulation: A CT simulation using appropriate immobilization will be performed for radiation therapy treatment planning purposes several days to the initiation of radiation therapy. This procedure consists of a CT scan performed in the treatment position. It is not for diagnostic purposes and is not itself therapeutic, but the CT image is required for radiation planning and delivery.

Radiation Dose and Tumor Volume Definition

Patients will be treated per institutional standard of care protocol.

The prescribed radiation dose will be **8 Gy in 1 fraction prescribed to the** planning target volume **(PTV)**.

Treatment shall be delivered with megavoltage machines of a minimum energy of 4 MV photons or electron machine containing a minimum energy of 4 MeV. Selection of the appropriate photon energy should be based on optimizing the radiation dose distribution within the target volume and minimizing dose to non-target normal tissue.

The **Gross Tumor Volume (GTV)** will contain the lytic lesion and/or the extra-osseous lesion noted on the simulation CT. Image fusion to adjust the CT simulation based GTV is allowed.

The **Clinical Target Volume (CTV)** will be a **0.5- 2.0 cm margin** around the GTV.

The **Planning Target Volume (PTV)** will be an additional **0.3-1.0 cm margin** around the CTV.

Radiation Treatment Planning

Any radiation treatment planning approach is allowed. For superficial lesions amenable to electron treatments, use of En-Face electron technique is encouraged using appropriate energy

selection ranging from 4 MeV – 20 MeV. For deeper seated tumors, photon therapy should be used with energy range of 4MV – 18 MV, based on appropriate coverage of the PTV. The goals should be to provide adequate coverage, while minimizing hot spots as well as scattered radiation dose to the surrounding structures.

A range of radiation fields are allowed. A single beam, an AP/PA, or multiple beams are allowed. A range of radiation techniques (2D, 3DCRT, IMRT, IMRS) are allowed;

Institutional standard of care protocol will be followed when assessing adequate PTV coverage and dose volume histogram normal tissue limits.

Radiation Toxicity Evaluation

Patients should undergo evaluation for development of acute and chronic radiotherapy toxicity at the time of protocol visits. This should be at done at **1 month+/- 2 weeks** after completing radiotherapy and **every 3 months for at least 1 year**. Toxicity will be graded per CTCAE 4.0 adverse events grading system. If there is a suspicion of a novel or unexpected toxicity of grade 3 or higher severity that is suspected to be related to the combination of pembrolizumab and radiotherapy, the study coordinator should be immediately notified. If possible, a determination should be made whether the toxicity is likely to be the result of immune therapy, radiotherapy, or was exacerbated by the combination. The AE or SAE should be attributed as definite, probable, possible, or unlikely for each.

9. TRIAL FLOW CHART

9.1 Study Flow Chart (Table 4: Trial Flow Chart)

Procedure	Pre- Treatment (within 28 days of starting)	Cycle 1, Day 1 week 1	Cycle 1, Day 2-3	Cycle 2, Day 22	q 3 WK cycles	q6 WK cycles x 2 yr or until progression	q 3 months (Rad Onc)	q 6 months
Initial Screening	X							
Informed Consent	X							
Inclusion/Exclusion	X							
Prior and Concomitant Medication	X							
Full Physical Examination	X			X				
Review of Systems	X			X		X	X	X
Vital Signs	X	X		X		X	X	X
Weight	X	X		X		X	X	X
ECOG Performance Status	X	X		X		X	X	X
HBcAb, HepC Ab	X							
*Bone Marrow Biopsy	X							X (clinical indication)
PET/CT	X						X	
Adverse effects Assessment	X			X	X (Pembro)	X	X	X
Labs								
Baseline Labs *	X							
Myeloma Labs *, LDH, ESR				X		X		
T3, FT4, TSH	X						X	
Pregnancy Test - urine or ser	X						X	
Urinanalysis	X						X	
uric acid, mg, phos, Coags (PTT,	X							
Correlative Biomarkers								
Serum markers (collect	X	X (pre-RT)	X (Pre-PD1)	x (pre-PD1)	X (3,6 mo) (Pre-PD1)			
ExtraOsseous/Osseous Biopsy*	(clinical indication)							
Treatment								
***Pembrolizumab 200 mg IV**			X	X	X			
RT (8 Gy/1fx)		X						
Survival Analysis								X
IMWG Assessment*	x						x	
CTCAE Toxicity*						x	x	

* EOS = end of study (at progression, or when patient stops being treated on the trial)

* Pembrolizumab 200 mg IV q3wk should be given for at least 2 yr and/or until progression.

* Baseline labs = CBC with Diff, CMP, calcium, Albumin, Serum Protein analysis, Quantitative Immunoglobulin, Serum Immunofixation (SIFE), 24 hr urine total protein, Urine Immune-Fixation, Serum Free Light Chain;

*Bone Marrow Biopsy (with IHC, flow, cytogenetics, FISH);

*Whole Body PET/CT every 3 months (as long as insurance approves);

*Biopsy of Osseous or extra-osseous site (if clinically indicated at baseline);

*Myeloma labs: (CBC with diff, CMP, Calcium, Quantitative Immunoglobulin, M-Protein (serum and Urine), Serum Free Light Chain;
* IMWG Assessment = Done at least during 1st month and every 3 months, or as clinically indicated;
*CTCAE Toxicity at the radiated site once at 3 months, 6 months, and 12 months;

9.2 Serum Biomarker Correlates

We plan to monitor the immune responses of the patients enrolled in this clinical trial, by collecting peripheral blood before treatment and during treatment, as outlined above under "serum biomarkers".

When possible, blood collection will be synchronized to pembrolizumab infusion cycles (C). Blood will be collected as outlined in the flow chart;

Samples will be drawn into three 4-8 ml CPT tubes for PBMC and plasma isolation, and one 4.5 ml K3EDTA tube, for whole blood analysis. Tubes will be labeled and logged at Emory's Winship Cancer Institute by a skilled clinical research nurse or phlebotomist. They will be maintained at room temperature until transport to Dr. Ahmed's laboratory. Samples distributed to the Ahmed laboratory will only be identifiable by an assigned donor number, study identifier and a draw date. Samples will be transported in sealed biohazard containers between sites per standard protocol. Whole blood and/or PBMC will be used fresh or will be frozen and banked for future batch analyses. Plasma will be frozen at -80C. Frozen PBMC samples will be stored in liquid nitrogen at the Emory Vaccine center. All assays will be performed as per Ahmed lab standard of practice. Briefly, frequency and absolute cell counts will be determined for the major lymphocyte populations (CD3, CD4, CD8, CD19) and monocytes (CD14) through the use of BD TruCount tubes. Detailed phenotypic analysis will be performed through whole blood staining with the following markers; CD3, CD4, CD8, Foxp3, CD45RA, CCR7, CD28, CD27, CD127, PD-1, Ki-67, Bcl-2, HLA-DR, CD38, ICOS, CD137, Tbet, eomes, Granzyme B, Perforin, CTLA-4, Tim-3, CD14, CD16, CD11c, CD123, PD-L1, CD86. Besides flow cytometry phenotypic analysis, sample collected at early time points after irradiation, will be used for transcriptional profiling. Frozen plasma will be used for monitoring cytokine expression. Stored blood may also be used to analyze exosomes and/or search for other serum biomarker analysis.

When possible, fresh tumor tissue will be collected from biopsy or surgical procedure (biopsy only done, if clinically indicated). Depending on material availability samples will be analyzed by flow cytometry or florescence microscopy with some of the markers listed above.

10. TRIAL PROCEDURES

Trial Procedures

The Trial Flow Chart – Section 9.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points, if deemed clinically necessary by the investigator, and within standard of care.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or Merck for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

Informed Consent

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

General Informed Consent

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/ERC's 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/ERC requirements, applicable laws and regulations and Sponsor requirements.

Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

Prior and Concomitant Medications Review

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded.

Disease Details and Treatments

The investigator or qualified designee will obtain prior and current details regarding disease status.

Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

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 Trial Flow Chart 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 (see APPENDIX I). 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).

Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

1. Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 9.0). Vital signs may include temperature, pulse, respiratory rate, weight and blood pressure. Height may be measured at screening only.

2. Karnofsky Performance Status Scale and ECOG Performance Scale

The investigator or qualified designee may assess ECOG and/or KPS status at screening. ECOG status may be assessed prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart. After the initial assessment, ECOG alone during subsequent follow-up may be the minimum that is required on the trial.

3. Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5. Peripheral blood for serum biomarker analysis will also be obtained, as defined in section 9.0 at the appropriate time intervals.

Table 5: Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free thyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or bicarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		PK
	Calcium		
	Chloride		**Blood for correlative studies**
	Glucose		• **see biomarkers section 10.1** • **The additional blood that is collected will be sent to Dr Rafi Ahmed's lab for this analysis**
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
‡ If considered standard of care in your region.

Laboratory tests for screening or entry into the Second Course Phase should be performed within **14 days +/- 7 days** prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 7 days prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

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. Subjects who a) attain a CR or b) complete at least 24 months of treatment with pembrolizumab may stop taking the drug and discontinue the trial, at the discretion of the treating physician. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit and then proceed to the Follow-Up Period of the study.

Blinding/Unblinding

Not Applicable, as this is an open pilot study.

Visit Requirements

Visit requirements are outlined in Section 8.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 9.0 - Trial Procedures.

Screening

The screening period will be 28 days from enrollment.

Enrollment and Treatment Period

Enrollment period to accrue all 24 patients will be over two years. 12 patients will be allowed to not have measurable myeloma disease.

Treatment period will last from cycle 1, day 1 until disease progression and/or at least 24 months of pembrolizumab being delivered q3wks. Pembrolizumab 200 mg IV q3 weeks will be given for at least 2 years as described above or until disease progression. Safety evaluations should be conducted during the first day of every other cycle (minimum criteria), as detailed in the flow sheet in section 9.0. All AEs that occurred leading up to these treatment visits should be recorded. Post-Treatment Visits and all subsequent imaging and myeloma assessments will be per standard of care. All required blood and imaging will be per standard of care, except for the biomarker analysis, as outlined in section 9.0.

Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

Follow-up Visits

Subjects who complete treatment after 2 years or discontinue trial treatment for a reason other than disease progression should be assessed every 12 weeks (84 ± 14 days) or at physician's discretions by radiologic imaging to monitor disease. Subjects who show disease progression after the initial week 12 scan must have another assessment 4-6 weeks later by radiologic imaging to confirm evidence of disease progression. If disease progression is evident, treatment should be discontinued and subject should be assessed every 12 weeks (84 ± 14 days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as part of second phase enrollment. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Follow-up Visits for Patients Who Undergo Allogeneic Transplant:

Patients who undergo allogeneic transplant will be monitored for adverse events. For subjects who have an allogeneic SCT within 24 months of last study treatment, transplant parameters will be collected and specific events will be collected for 18 months from the date of the allogeneic transplant to include graft-versus-host-disease (acute and/or chronic), veno-occlusive disease, febrile syndrome (a steroid-requiring febrile illness without an infectious cause), and encephalitis, for all grades, and regardless of relationship to study drug. Additional medically important adverse events post-allogeneic SCT may be submitted at the Investigator's discretion. If available and relevant to an event post-allogeneic SCT, concomitant medications and/or laboratory results may also be reported.

Second Course Phase (Retreatment Period)

Subjects who stop pembrolizumab with SD or better may be eligible for up to one year of additional pembrolizumab therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- **Either**
    - Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to IMWG, and

- Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy
- Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

OR

- Had SD, PR or CR and stopped pembrolizumab treatment after 24 months of study therapy for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined confirmed disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subject 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. Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Male subject 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.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might 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.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab. Treatment will be administered for up to one additional year.

Visit requirements are outlined in Section 9.0 – Trial Flow Chart.

Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject associated with the use of a test article 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 or radiotherapy, 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 or SRS 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 that occur after the consent form is signed but before treatment allocation/randomization must be reported to Merck and the PI by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be documented by the investigator. Such events will be

recorded 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 9 and 10. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose, for a 100 kg patient). 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.

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)

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) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Merck product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies 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)

Immediate Reporting of Adverse Events to the Sponsor and to Merck

Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of a drug 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 an other important medical event

- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
    - Is a new cancer (that is not a condition of the study);
    - Is associated with an overdose.

Refer to Table 6 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, 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 must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, 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, whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

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 following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck Global Safety.

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

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 15 Day Reports and Annual Progress Reports is 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.

Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and 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).

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 11 - 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.

4. Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck as described section related to “Immediate Reporting of Adverse Events to the Sponsor and to Merck”, unless there

is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Sponsor within 24 hours and to Merck Global Safety within 2 working days either by electronic or paper media.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Merck Global Safety as a SAE within 2 working days of determination that the event is not progression of the cancer under study

Hospitalization related to convenience (e.g.transportation issues etc.) will not be considered a SAE.

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 6 Evaluating Adverse Events

Known acute side effects for SRS include: Alopecia within the portal sites, fatigue, headache, nausea, vomiting, worsening baseline neurological deficits due to increased edema or radionecrosis, seizure, skin irritation or redness; Late side effects include radiation necrosis, secondary cancer, seizure, worsening neurological deficit due to edema, death, hair loss within the portal fields.

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 investigational 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 for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); 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) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	

	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. 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 to the Sponsor and to Merck within 2 working days..	
	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 Merck product to be discontinued?	
Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that 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 Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to 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 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

Sponsor Responsibility for Reporting Adverse Events

Written IND safety reports will be submitted to the FDA by the IND sponsor, for serious, unexpected suspected adverse reactions within 15 calendar days of learning of its occurrence. If the event is fatal or is deemed to be life threatening, the report will be made within 7 calendar days. The IND sponsor will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB, which, in turn will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

11. STATISTICAL ANALYSIS PLAN

1.Statistical Analysis Plan Summary

Study Design

The study is a pilot study to look at the safety of concurrent PD-1 inhibitor and SRS for relapsed/refractory myeloma. A total of 24 patients will be enrolled on the trial (20 is the minimum, with an additional 4 patients, to make for any attrition and/or loss to follow-up). 12 patients will be allowed to not have measurable myeloma disease in this trial. Once 10 patients are enrolled, we will stop trial for 3 months to assess for acute toxicity, and then resume the trial. The estimated exact Clopper-Pearson 95% confidence interval for a 20% rate based on 5 responses in 20 patients is (0.087, 0.491), with a precision of 0.185. If we see lower than 20% difference in rate of toxicity at 3 months, the combination will be deemed safe.

A minimum of 20 patients are required to complete full treatments. An additional 20% is allowed for drop out/failure to adhere to required follow-up and treatment recommendations. Thus, 24 patients will be allowed to be enrolled on the trial to make for any attrition and/or loss to follow-up. 12 patients will be allowed to not have measurable myeloma disease.

# of Responses / # of Patients	95% confidence interval
5 / 20	(0.087, 0.491)
6 / 24	(0.098, 0.467)

Populations for analysis

- Enrolled set: All subjects who signed an informed consent.
- Safety set: All subjects who received at least one dose of any study drug.
- Full analysis set: All subjects from the safety set who have the required follow-up and treatment adherence to evaluate response and safety over time.

2.Statistical Analyses

1. Response

IMWG criteria will be used to assess response. Proportion of patients achieving stable

disease or better will be reported at **6 months** and **12 months**; Response rates will be reported along with 95% confidence intervals will be estimated using the Clopper-Pearson method.

2. Safety

Proportion of acute (at **3 months**) and late toxicity (**6 and 12 months**) will be reported, and 95% confidence intervals will be estimated using the Clopper-Pearson method.

3. Overall Survival

For overall survival, death from any cause will be defined as the event. Patients will be censored at time of last follow-up. OS will be estimated using the Kaplan-Meier product-limit method. Overall survival will be analyzed at **6 months, and 12 months.**

4. Biological variables

Descriptive statistics for the frequency and absolute cell counts for the major lymphocyte populations (CD3, CD4, CD8, CD19) T cells and monocytes (CD14) along with other markers listed above will be estimated.

12. LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

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 7.

Table 7 Product Descriptions

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

2.Packaging and Labeling Information

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

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.

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.

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.

13.0 DATA AND SAFETY MONITORING PLAN

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

14.1. **Data Collection:**

Data that will be captured in OnCore for the following procedures

- Inclusion/Exclusion Criteria
- Vital Signs
- Weight
- Karnofsky Performance Status (KPS) & ECOG
- HBcAb, HepC Ab
- PET/CT Diagnostic Imaging [RECIST]
- Adverse Events Assessment
- CBC with differential

- CMP
- T3, FT4, TSH
- Pregnancy Test – urine or serum b-HCG
- Urinalysis
- Uric Acid, MG, Phos, Coags (PTT, PT, INR) - [seconds]
- Serum Biomarkers
- Osseous, extra-osseous, bone marrow biopsy (if done, and what date it was done)

14.0 APPENDICES

APPENDIX I

CTCAE (Common Terminology Criteria for Adverse Events), version 4.03

The exact full criteria for toxicity assessment can be obtained at the NCI CTEP website at the following link:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

APPENDIX II

Tumor assessment via RECIST Criteria, Guideline Version 1.1

Eisenhauer, E.A., Therasse, P., Bogaerts, J., et al. New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (version 1.1). Europ J Cancer. 2009. 45; 228-247.

http://imaging.cancer.gov/clinicaltrials/imaging

APPENDIX III

Tumor Assessment per Immune-Related Response Criteria

Immune-related Response Criteria (irRC) are derived from modified World Health Organization (mWHO) conventions. Assessments of lymph nodes are derived from current RECIST guidelines.

a.) Definitions of Measurable/non-Measurable Lesions

All measurable and non-measurable lesions should be assessed at the initial Screening/enrollment, at the defined tumor assessment time points (see Time and Events Schedule), and during regular maintenance. Additional assessments may be performed, as clinically indicated for suspicion of progression. The Investigator will base response to treatment using the irRC.

i.) Measurable Disease

Measurable non-lymph node disease is defined as lesions that can be accurately measured in 2 perpendicular Diameters. Size criteria is defined based on the properties of the CT scan

-Spiral CT, 0.5cm thickness slice: both diameters must be at least $\geq$ 1.0cm

-For > 0.5cm thickness slices: larger diameter >2.0cm; the other > 1.0cm

Lymph nodes are measurable only if CT slice thickness is <0.5cm. Size criteria are that the lymph node be at least 15 mm in short axis.

ii.) Non-Measurable Lesions

Non-measurable (evaluable) lesions are all other lesions, including one-dimensional measurable disease and small lesions (not meeting the above criteria), and any of the following:

-lesions occurring in a previously irradiated, extracranial area (unless they are documented as new lesions since the completion of radiation therapy),

bone lesions,

-leptomeningeal disease,

-ascites,

-effusion (pleural or pericardial)

-cystic lesions

-abdominal masses not histological confirmed

Lymph nodes with a short axis < 10 mm are considered not pathological, and are not measurable.

b.) Definitions of Index/non-Index Lesions

i.) Index Lesions

Measurable lesions, up to a maximum of 5 lesions per organ and ten lesions in total, must be identified as index lesions to be measured at Screening. The index lesions should be representative of all involved organs. In addition, index lesions must be selected based on their size (e.g., lesions with the longest diameters), their suitability for accurate repeat assessment by imaging techniques, and how representative they are of the subject's tumor burden. At Screening, a Sum of the Product Diameters (SPD) for all index lesions will be calculated and considered the baseline SPD. The baseline sum will be used as the reference point to determine the objective tumor response of the index lesions at tumor

assessment.

ii.) Non Index Lesions

Measurable lesions, other than index lesions, and all sites of non-measurable disease, will be identified as non-index lesions. Non-index lesions will be evaluated at the same assessment time points as the index lesions. *After the initial assessment, changes in non-index lesions will contribute only in the assessment of complete response.*

c.) Calculation of Sum of Product of Diameters (SPD)

Sum of Product of Diameters is an estimate of tumor burden. The 2 greatest perpendicular diameters are used to estimate the size of each tumor lesion. The SPD is calculated as the sum of the product of the diameters for index tumor lesions. Several variations of the SPD are identified for the purpose of classification of tumor responses.

i.) SPD at Baseline

The sum of the product of the diameters for all index lesions identified at baseline prior to treatment on Day 1.

ii.) SPD at tumor assessment

For every on-study tumor assessment collected per protocol or as clinically indicated, the SPD at tumor assessment will be calculated using tumor imaging scans. All index lesions and all new measurable lesions that have emerged after baseline will contribute to the SPD at tumor assessment (irSPD).

iii.) SPD at NADIR

For tumors that are assessed more than 1 time after baseline, the lowest value of the SPD (SPD Baseline or SPD at tumor assessment) is used to classify subsequent tumor assessments for each subject. The SPD at tumor assessment using the irRC for progressive disease incorporates the contribution of new measurable lesions. Each net percentage change in tumor burden per assessment using irRC accounts for the size and growth kinetics of both old and new lesions as they appear. In this study the irRC as defined by the Investigator will serve as the basis of key endpoints for efficacy analyses and guide clinical care.

APPENDIX IV

International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma

http://myeloma.org/pdfs/IMWG_Response_criteria.pdf

APPENDIX V

KARNOFSKY PERFORMANCE SCALE

100 Normal; no complaints; no evidence of disease
90 Able to carry on normal activity; minor signs or symptoms of disease
80 Normal activity with effort; some sign or symptoms of disease
70 Cares for self; unable to carry on normal activity or do active work
60 Requires occasional assistance, but is able to care for most personal needs
50 Requires considerable assistance and frequent medical care
40 Disabled; requires special care and assistance
30 Severely disabled; hospitalization is indicated, although death not imminent
20 Very sick; hospitalization necessary; active support treatment is necessary
10 Moribund; fatal processes progressing rapidly
0 Dead

6. 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.

APPENDIX VI

Inclusion Criteria:

1) ≥ 18 years old; ISS stage I-III multiple myeloma;

2) Able to give informed consent;

3) ECOG Performance Status between 0 and 1;

4) Relapsed and/or refractory myeloma;

5) ≥ 1 osseous and/or extra-osseous lesion that can be radiated**;**

6) Candidate for pembrolizumab (as determined by physician, and adequate organ function as noted in **Table 1**);

7) Candidate for radiotherapy (as determined by physician);

8) Measurable myeloma disease **(urine protein > 200 mg in 24 hr urine collection, serum free light chain ratio> 100 with an abnormal k/l ratio, serum M protein > 0.5 g/dl) ; 12 patients of the 24 patients do not have to have to measurable myeloma disease;**

9) Negative urine pregnancy test within 2 weeks for female subjects;

Female subject of childbearing potential should have a negative urine or serum pregnancy within 2 weeks 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.

1. 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. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

2. 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.

3. Abstinence is acceptable, if this is the usual life style and preferred contraception for the patient.

Exclusion Criteria:

1) Previous anti-PD1 or anti-PD-L1;

2) Solitary plasmacytoma;

3) Smoldering (asymptomatic) multiple myeloma;

4) Currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment;

5) Has a diagnosis of immunodeficiency;

6) Known history of active TB (Bacillus Tuberculosis);

7) Hypersensitivity to pembrolizumab or any of its recipients;

8) 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);

9) 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);

10) Known history of, or any evidence of active, non-infectious pneumonitis;

11) Active infection requiring systemic therapy;

12) 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.

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

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

15) 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.

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