TITLE: A phase II trial of the anti -PD-1 monoclonal antibody Pembrolizumab (MK-3475) + Lenalidomide + Dexamethasone as post autologous transplant consolidation in patients with high-risk multiple myeloma

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By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/ Ethics Committee (EC) procedures, instructions from the Sponsor, the Declaration of Helsinki, ICH Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.

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TRIAL SUMMARY

Abbreviated Title	Pembrolizumab + lenalidomide post autologous stem cell transplant in high-risk MM
Trial Phase	*II*
Clinical Indication	Multiple Myeloma
Trial Type	Single arm Phase II efficacy/safety study
Type of control	No treatment control (historical control)
Route of administration	IV
Trial Blinding	Unblinded open label
Treatment Groups	Fixed dose pembrolizumab 200 mg every 3 weeks and lenalidomide 25 mg po daily x 14 days and dexamethasone 40 mg once weekly for a 21-day cycle x 2 cycles followed by fixed dose pembrolizumab 200 mg every 3 weeks and lenalidomide 25 mg po daily x 14 days for a 21-day cycle x 2 cycles for a total of 4 cycles
Number of trial subjects	Approximately 43 subjects will be enrolled
Estimated enrollment period	*October 1, 2015 – October 1, 2016*
Estimated duration of trial	The trial will require approximately 24 months from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified contact. After a screening phase of 28 days, eligible subjects will receive assigned treatment appropriate for the trial stage in which they are enrolled as described below. The assigned treatment will continue for 4 cycles, until documented confirmed disease progression, unacceptable adverse event(s), documented confirmed disease progression, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons. After the end of treatment, each subject will be followed for 90 days for adverse event monitoring (serious adverse events will be collected until disease progression on an every 3 month basis +/- 3 months). Subjects who discontinue for reasons other than disease progression will have posttreatment follow-up of disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone or direct contact for overall survival until death, withdrawal of consent, or the end of the study

1.0 TRIAL DESIGN

1.1 Trial Design

This is an open-label, Phase II, single center trial of pembrolizumab (MK-3475), lenalidomide and dexamethasone in subjects with high risk Multiple Myeloma (hrMM) post high-dose chemotherapy with autologous stem cell transplantation (ASCT).

Patients with high-risk MM defined as those with one of the following abnormalities who have undergone induction therapy followed by single or tandem melphalan -based ASCT will be considered eligible.

1. International Staging System (ISS) stage 3 (See Appendix 3 for ISS Staging) and/or

2. Deletion 13q by cytogenetics and/or

3. 1q amplification, 1p deletion, p53 deletions (17p deletions), t(4;14), t(14;16), t(14;20), hypodiploidy by FISH and/or

4. High-risk gene expression profile (GEP) scores

Post engraftment, between days +60 and day +180 post ASCT patients will undergo restaging evaluation to include a screening BM aspirate and biopsy. Patients will then be initiated on pembrolizumab, lenalidomide and dexamethasone for 2 cycles followed by pembrolizumab and lenalidomide alone for 2 cycles for a total period of 4 months.

Adverse events will be monitored at every visit and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. (See Appendix 1).

Treatment with pembrolizumab, lenalidomide and dexamethasone for the first 2 cycles then pembrolizumab and lenalidomide will continue for cycle 3 and 4 for a total of four cycles or until unacceptable adverse event(s), documented confirmed disease progression, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons. After the completion of cycle 4, 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 treatment for reasons other than disease progression 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. All subjects will be followed by telephone contact for overall survival until death, withdrawal of consent or the end of the trial, whichever comes first.

The primary objectives of this trial are to establish the progression free survival (PFS) of ASCT followed by consolidative therapy with pembrolizumab plus lenalidomide and dexamethasone and to evaluate the safety of pembrolizumab plus lenalidomide and dexamethasone following ASCT. The immunological analysis of cells and cytokines pre and post-therapy will be determined from patient bone marrow aspirate and peripheral blood samples as exploratory objectives. The overall composition of the gut microbiome will also be determined in patient stool samples.

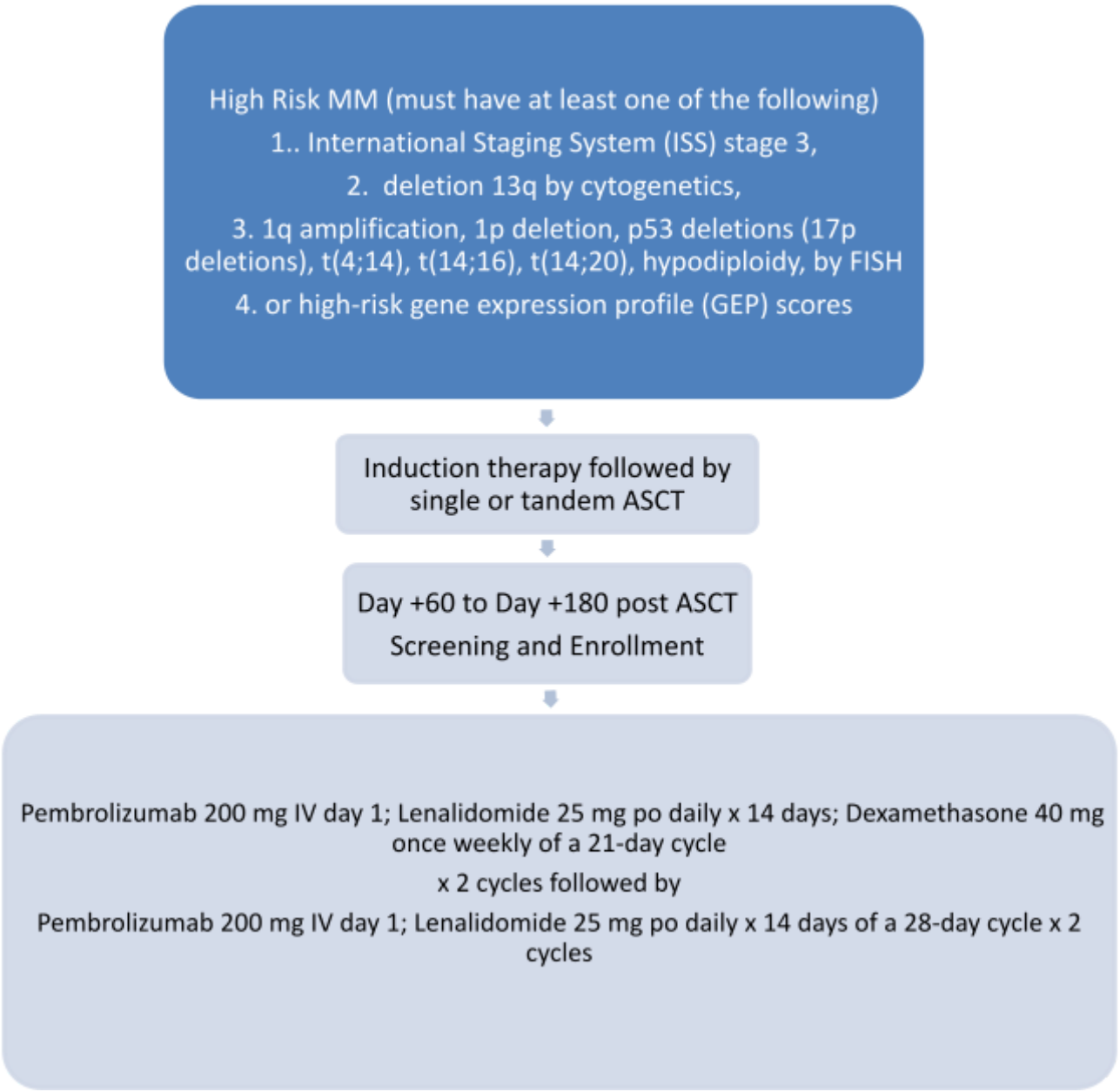
Patients will be followed by response, EFS/PFS/OS and safety endpoints on an every 3 week basis. Bone marrow aspirate specimens will be obtained at screening and at completing of the

study and peripheral blood specimens will be obtained on a monthly basis to evaluate in correlative studies.

This trial will be conducted in conformance with Good Clinical Practices. Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart – Section 5.0.

An interim efficacy analysis will be performed after 15 patients are accrued. The study will stop and treatment will be rejected if there are more than 8 patients (≥9 patients) who progress at 12 months. If 8 or more of the first 15 patients have not progressed at 12 months, a further 26 patients will be recruited into the second stage. If the overall PFS is 70% or above at 12 months, pembrolizumab, lenalidomide and dexamethasone will be considered to have shown worthwhile efficacy.

Trial Diagram



2.0 OBJECTIVES & HYPOTHESES

2.1 Primary Objective(s) & Hypothesis

(1) **Objective:** To establish the progression free survival (PFS) of high risk MM patients receiving pembrolizumab (MK-3475), lenalidomide and dexamethasone consolidation post autologous stem cell transplant (ASCT).

Hypothesis: The 12-month PFS of high risk MM patients receiving pembrolizumab (MK-3475), lenalidomide and dexamethasone consolidation post ASCT will be 70% or above. There will be an increase in the number of long-term remitters.

2.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: To determine the safety and tolerability of pembrolizumab (MK-3475), lenalidomide and dexamethasone following ASCT in subjects with high risk MM.

Hypothesis: Intravenous administration of pembrolizumab (MK-3475), lenalidomide and dexamethasone to subjects with high risk MM as consolidation therapy post ASCT is sufficiently well tolerated.

(2) **Objective:** To evaluate stringent complete response, complete response, and very good partial response rate (sCR + CR + VGPR rate) in subjects with high risk MM post-ASCT.

(3) **Objective**: To evaluate Overall Response Rate (ORR) in subjects with high risk MM post-ASCT.

(4) **Objective:** To evaluate Time to Progression (TTP) in subjects with high risk MM post-ASCT.

(5) **Objective**: To evaluate Duration of Response (DOR) in subjects with high risk MM post-ASCT.

(6) **Objective**: To evaluate Overall Survival (OS) in subjects with high risk MM post-ASCT.

2.3 Exploratory Objective

(1) **Objective:** To compare in bone marrow aspirates the extent of pre-pembrolizumab (MK-3475), lenalidomide and dexamethasone PD-L1 expression and change from baseline PD-L1 expression in responders versus non-responders in subjects with high risk MM post-ASCT.

Hypothesis: Subjects with deeper and longer duration of response to pembrolizumab, lenalidomide and dexamethasone will have a greater change from baseline PD-L1 expression compared to subjects without response or with shorter duration of response.

(2) **Objective:** To assess immune phenotype and T cell repertoire in bone marrow aspirates and peripheral blood samples and plasma cytokines before and after treatment in responders versus non-responders in subjects with high-risk MM post-ASCT. Assays for these studies include flow cytometry, TCR Immunoseq for Vbeta CDR3 highest frequency specificities, real-time PCR analysis and multiplex cytokine ELISA.

Hypothesis: Subjects with deeper and longer duration of response to pembrolizumab and lenalidomide will have an increase from baseline of inflammatory cytokines (TNF-alpha, IL-2, IL-4, IL-6, IL-10) and activated T cells (CD8+) compared to subjects without response or with shorter duration of response. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells will correlate with improved prognosis.

(3) Objective: To identify specific intestinal microbial strains associated with improved outcome in autologous stem cell transplantation patients treated with PEM+LEN+DEX compared to PEM+LEN. The overall microbial composition in stool samples of patients will be at screening or cycle 1, day 1, cycle 2 day 1, cycle 3 day 1, cycle 4 day 1, and at the completion of cycle 4 and every 12 weeks for the duration of follow up. Additional sample will be collected at confirmation of response. A 16S ribosomal RNA (rRNA) miSeq Illumina platform will be used for overall microbial composition and quantitative real-time PCR analysis will validate the specific microbial strains identified by miSeq.

Hypothesis: Subjects with deeper and longer duration of response to pembrolizumab and lenalidomide will have diverse gut microbiome compared to subjects without response or with shorter duration of response. This hypothesis is based on several studies demonstrating that the diversity of intestinal microbiota at the time of engraftment improves clinical outcome post-ASCT[1] and specific bacterial species boost immune responsiveness to chemotherapy[2, 3] and checkpoint inhibitors[4, 5]

3.0 BACKGROUND & RATIONALE

3.1 Background

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

3.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [6]. Accumulating evidence shows a correlation

between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [7-11]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [12, 13]. The structure of murine PD-1 has been resolved[14]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade[12, 15-17]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins[18, 19]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells[20, 21]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells[22]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors[18, 23-25]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues[18]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL)[26]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

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

disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

3.1.2 Preclinical and Clinical Trial Data

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

3.2 Rationale

3.2.1 Rationale for the Trial and Selected Subject Population

3.2.1.1 Rationale for evaluating anti-PD-1 Therapy in Patients with Multiple Myeloma

Multiple Myeloma (MM), accounting for 10% of all hematological malignancies, is a malignancy that results in the accumulation of clonal plasma cells in the bone marrow leading to bone destruction and marrow failure. It has an incidence of 20,000 cases per year in the United States with a median age of onset of 69 years[27-30]. The diagnosis of MM is made when there are more than 10% plasma cells in the bone marrow, presence of monoclonal proteins in serum, and/or in urine with one or more of end organ effects such as hypercalcemia, renal failure, anemia, or bone destruction (CRAB)[31, 32]. Patients with MM respond to systemic immunomodulator therapy such as thalidomide, lenalidomide, and pomalidomide. Although improvements in overall survival have been achieved with newer therapies such as proteasome inhibitors and immunomodulatory drugs (IMiDs), myeloma remains, in general, an incurable disease. Relapsed/refractory MM patients have an overall survival of 9 months, but only 3 months if they receive no therapy following relapse, thus reflecting the poor outcome among these patients[33-35].

PD-L1 is expressed on most MM plasma cells[36], and PD-L1 overexpression enhanced MM invasiveness and rendered tumor cells less susceptible to cytotoxic T lymphocytes (CTLs). This effect was alleviated by anti–PD-L1 antibody treatment, demonstrating the importance of the PD-1/PD-L1 pathway in disease progression[37]. In addition, a recent report demonstrated increased levels of PD-L1 on MM cells together with enhanced PD-1 expression on T cells with an "exhausted" phenotype. The immunosuppressive effects of myeloma are overcome by PD-L1 blockade[38]. A Phase 1 clinical trial conducted in advanced hematologic malignancies using CT-011, showed clinical responses in 6 of 17 patients including stable disease in multiple myeloma patients [39].

3.2.1.2 Rationale for Evaluating anti-PD-1 Therapy in Patients with High-Risk Multiple Myeloma Post High-Dose Chemotherapy followed by Peripheral Blood Autologous Stem Cell Transplant

Overall survival in MM ranges from several months to greater than 15 years. With modern therapy, survival in MM has increased from a median overall survival (OS) of 3–5 years to a 5-year survival rate of greater than 70% in transplant-eligible patients[40]. The improvement in survival, however, is not universal, and approximately 25% of patients have a median survival of 2 years or less[41]. The definition of high-risk MM has been in considerable flux. Some of the largest studies have used International Staging System

(ISS) and the presence of chromosome 13q abnormalities by cytogenetics as the primary definition[42]. The revised-ISS (R-ISS) combines ISS 3, high-risk cytogenetics, and elevated LDH as markers for inferior survival[43]. More recently, p53 deletions have been associated with PFS of 11.8 months[44]. Patients with high-risk gene expression profiling (GEP)-70 scores (and patients with chromosome 1q amplifications and 1p deletions by fluorescent in situ hybridization (FISH) show similar patterns[45]. Internal data from the Hackensack University Medical Center Multiple Myeloma division show that high-risk MM patients defined as those carrying 1q amplifications, 1p deletions, 13q deletions by cytogenetics, p53 deletions, high-risk GEP 70 scores, t(4;14), t(14;16) and t(14;20), hypodiploidy have a median event free survival (EFS) of 14 months post ASCT. The MRC IX trial showed that patients with high-risk MM by FISH have a 50% 12-month PFS from transplant[46].

While tandem ASCT remains a standard of care, the abovementioned high-risk patients will ultimately relapse within one to two years of first transplant and there are virtually no long-term remitters. In contrast, patients with smoldering (asymptomatic) MM that carry the same high-risk features are not significantly more likely to progress to active disease than are patients without high-risk markers[47]. One of the prevailing theories as to why smoldering MM patients, even those with high-risk disease, can remain stable for extended periods of time is that the host immune system can maintain homeostasis. For patients who are long term-remitters post transplant, it is likely that it is the reacquisition of this immune-competent phenotype, rather than a greater debulking of disease, that is responsible for long-term disease control. In fact, it may not be necessary to attain stringent levels of debulking in order to achieve long-term remission, as patients with easily measurable disease can achieve long periods of stable control without anti-myeloma therapies.

PDL-1 is routinely expressed on plasma cells of patients with MM[36]. While MM is a highly immunogenic tumor which can activate strong T-cell mediated immunity, MM is able to induce anergy, presumably via the PD-1/PDL-1 interaction. Re-establishing an effective immune response through blockade of PD-1 on responding activated T-cells has been shown to be possible, as discussed above. Our hypothesis is that in the post-transplant setting, where the host immune system is in significant flux, the PD-1/PDL-1 blockade will promote a recapturing of the smoldering MM phenotype. If we can establish that such a phenomenon is relevant for patients with high-risk MM then we can extend this intervention to the wider population of patients with standard-risk MM as well.

3.2.1.3 Rationale for IMiDs as a Combination Agent:

IMiDs (Thalidomide, Lenalidomide, and Pomalidomide) are a class of immunomodulatory agents, which are a mainstay in myeloma therapy, and could be rationally combined with anti-PD-1 therapy. IMiDs derive their designation as “Immunomodulators” designed as therapeutic immune stimulators derived from the parent compound thalidomide. Lenalidomide, and now pomalidomide, are approved therapies for multiple myeloma. The

immunostimulatory properties of IMiDs, in contrast to other active myeloma classes such as proteasome inhibitors, could synergize with anti-PD-1 therapies. Published literature suggests that IMiDs have T-cell co-stimulatory and positive effects on antigen presenting cells (APCs). T-cell co-stimulation has been demonstrated by increased IFN-g and IL-2 production, which result in clonal T-cell expansion and increased natural killer (NK) cell activity [28]. There is also evidence of increased IL-12 production in the setting of T-cell costimulation, which activates APCs[48].

3.2.1.4 Rationale for Lenalidomide and Low-dose Dexamethasone

Lenalidomide is a good choice among the three available IMiDs due to its better safety profile compared to thalidomide and broader use in earlier lines of therapy compared to the newer pomalidomide. Clinical studies have shown that lenalidomide has single-agent activity against relapsed/refractory MM, and synergistic effects when combined with dexamethasone [49-51]. Two recent pivotal Phase III studies (MM-009 and MM-010) have robustly demonstrated the clinical benefit of lenalidomide plus high-dose dexamethasone, over dexamethasone alone in subjects with relapsed/ refractory MM[51, 52]. A combined analysis of the data from the two pivotal Phase III studies demonstrated that lenalidomide plus high-dose dexamethasone achieved an OR in the region of 60%, including 15% of patients achieving CR, a median OS of 35 months, and a median TTP of 11 months [36]. In clinical trials, among the most common grade 3–4 adverse events according to the National Cancer Institute Common Toxicity Criteria associated with the use of lenalidomide plus dexamethasone in subjects with MM have been cytopenias, fatigue, muscle cramps, rash, infection, insomnia, and venous thromboembolism (VTE)[49, 51, 53, 54]. Such events are largely manageable through subject evaluation and monitoring, dose adjustment, or prophylactic intervention.

Lenalidomide was initially indicated in MM, in combination with dexamethasone, in patients who have received at least one prior therapy. The dose of dexamethasone approved by the FDA, in combination with lenalidomide in myeloma, is 40 mg q.d. p.o. on Days 1-4, 9-12, and 17-20 in the first 4 cycles and on Days 1-4 in Cycle 5 and above in each 28-day treatment cycle, which was defined as high dose dexamethasone. The Phase III registration studies of lenalidomide were done in combination with high dose dexamethasone versus high dose dexamethasone alone.

However, a more recent Phase III randomized study (known as E4A03) sponsored by the US National Cancer Institute (NCI), and conducted by a network of researchers led by the Eastern Cooperative Oncology Group (ECOG) compared combination treatment of lenalidomide and either high- or low-dose dexamethasone in 445 patients with myeloma[55]. The dose of dexamethasone considered "low-dose" in this trial was 40 mg on Days 1, 8, 15, and 22 (i.e. once weekly) in each 28-day cycle. Researchers found that patients in the study who received low-dose dexamethasone and lenalidomide had a one-year survival of 96 percent compared to 86 percent for patients treated with the standard or high -dose of dexamethasone and lenalidomide[56]. In addition, there were fewer side effects associated with the low-dose dexamethasone and lenalidomide. Based on this study, there is evidence that lowering the dexamethasone dose may reduce side effects and improve survival. The National Comprehensive Cancer Network (NCCN) MM guidelines also list

the lenalidomide, low dose-dexamethasone combination as an initial therapy for non-transplant candidates. There is an ongoing Phase I trial to establish the safety and the RP2D of pembrolizumab (MK-3475) in combination with lenalidomide and low-dose dexamethasone in subjects with relapsed/refractory MM who have failed at least two lines of prior therapy, including a proteasome inhibitor (e.g. bortezomib or carfilzomib) and an IMiD (thalidomide, pomalidomide, lenalidomide).

Biologically, this Phase 2 pilot study allows the combination of pembrolizumab, lenalidomide and dexamethasone to provide maximal cytoreduction post-ASCT for the first two cycles of therapy. And subsequently, the discontinuation of dexamethasone for the following 2 cycles will allow for maximization of potential long-term immunological benefits seen with pembrolizumab combined with lenalidomide alone.

3.2.2 Rationale for Dose Selection/Regimen/Modification

3.2.2.1 Rationale for Fixed Dose Pembrolizumab

In KEYNOTE-001, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab (MK-3475) at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed, and one randomized cohort evaluating of 10 mg/kg Q3W versus 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive MK-3475 at 2 mg/kg versus 10 mg/kg Q3W. The overall response rate (ORR) was 26% (21/81) in the 2mg/kg group and 26% (25/79) in the 10 mg/kg group (full analysis set (FAS)). The proportion of subjects with drug-related adverse events (AEs), grade 3-5 drug-related AEs, serious drug-related AEs, death or discontinuation due to an AE was comparable between groups or lower in the 10 mg/kg group. In Cohort B3, advanced melanoma subjects (irrespective of prior ipilimumab therapy) were randomized to receive MK-3475 at 10 mg/kg Q2W versus 10 mg/kg Q3W. Preliminary results demonstrate that the ORR was 32.8% (38/116) in the 10mg/kg Q2W group and 27.8% (30/108) in the 10 mg/kg Q3W group (FAS Population by irRC; data through 28-Feb-2014). The proportion of subjects with drug-related AEs, grade 3-5 drug-related AEs, serious drug-related AEs, death or discontinuation due to an AE was comparable between groups.

Available pharmacokinetic results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at a given dose among tumor types. Moreover, population PK analysis has been performed and has confirmed the expectation that intrinsic factors do not affect exposure to pembrolizumab (MK-3475) to a clinically meaningful extent. Importantly, the analysis revealed no significant impact of tumor burden on exposure. Taken together, this data support the use of lower doses (with similar exposure to 2 mg/kg Q3W) in all solid tumor indications. Selection of 200 mg as the appropriate dose for a switch to fixed dosing is based on simulation results indicating that 200 mg will provide exposures that are reasonably consistent with those obtained with 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. A population PK model which characterized the influence of body weight and

other patient covariates on exposure has been developed using available data from 476 subjects from KEYNOTE 001. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose, with some tendency for individual values to range slightly higher with the 200 mg fixed dose. The slight increase in PK variability predicted for the fixed dose relative to weight-based dosing is not expected to be clinically important given that the range of individual exposures is well contained within the range of exposures shown in the melanoma studies of 2 and 10 mg/kg to provide similar efficacy and safety. 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.

3.2.3 Rationale for Endpoints

3.2.3.1 Efficacy Endpoints

The primary efficacy objective of this trial is to determine Progression Free Survival (PFS) from the date of ASCT, with day 0 defined as date of stem cell infusion (if tandem transplant the 2nd of 2 transplants will be used) until the date of progression, defined as the date at which the patient starts the next line of therapy or the date of death. The Overall Survival (OS) will also be calculated from the date of ASCT as previously defined until the date of death.

The secondary efficacy objective of this trial is to evaluate the anti-tumor activity of pembrolizumab (MK-3475), lenalidomide and dexamethasone in subjects with high-risk MM post-ASCT. This will be complete response (CR) + stringent complete response (sCR) + very good partial response (VGPR) rate and objective response rate (ORR) as assessed by the investigator per International Myeloma Working Group (IMWG) uniform response criteria for MM[57].

Immunotherapeutic agents such as pembrolizumab (MK-3475), lenalidomide and dexamethasone may produce anti-tumor effects by potentiating endogenous cancer-specific immune responses, which may be functionally anergic. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard response assessment criteria may not provide a comprehensive response assessment of immunotherapeutic agents such as pembrolizumab (MK-3475), lenalidomide and dexamethasone. Disease response assessment will be performed every 21-day treatment cycles. PD must be confirmed prior to discontinuation from study.

3.2.3.2 Safety Endpoints

The primary safety objective of this trial is to characterize the safety and tolerability of pembrolizumab (MK-3475), lenalidomide and dexamethasone in subjects with high-risk MM post-ASCT. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE criteria version 4.03. Safety will be assessed by quantifying

the toxicities and grades experienced by subjects who have received pembrolizumab (MK-3475), lenalidomide and dexamethasone, including serious adverse events (SAEs).

Safety will be assessed by reported adverse experiences using CTCAE, Version 4.03. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes.

3.2.3.3 Biomarker Research

Additional research may evaluate factors important for predicting responsiveness or resistance to pembrolizumab (MK-3475), lenalidomide and dexamethasone therapy and other immunologic targets; or evaluate assay stability using clinical samples.

Assays may include but are not be limited

to: **Flow Cytometric Phenotype Analysis:**

Emerging data suggest that blockade of the PD-1/PDL-1 pathway results in enhanced T cell mediated immune response. To test the hypothesis that T cell activation mediated by pembrolizumab (MK-3475), lenalidomide and dexamethasone or pembrolizumab and lenalidomide treatment correlates with clinical response, T cell subsets in peripheral blood, e.g. PD-1+ T cells, effector, memory and regulatory T cells, will be assessed pre- and post-dose and in both responders and non-responders.

T Cells:

CD3; CD4; CD8; CD4+CD25+PD1+; CTLA-4

Follicular Helper T: CD3+,CD4+,CXCR5+,PD1+

CD4 and CD8 T naïve (RO-; CCR7+)

Central Memory: (T^{CM};RO+,CCR7-)

Effector Memory (T^{EM}, RO+,CCR7-)

Terminally differentiated effector memory (T^{EMRA}; RO-,CCR7-)

T regulatory cells (Treg): $CD4^{\pm}$,$CD25^{hi}$, $CD127^{low}$, $CD39^{\pm}$, $CD152^{hi}$, RO^{-} (resting); $CD4^{\pm}$,$CD25^{hi}$, $CD127^{low}$, $CD39^{\pm}$, $CD152^{hi}$, $RO^{\pm}$ (activated)

Dendritic Cells:

Lin-, CD11c+, CD1a+, $CD80\ (B7\text{-}1)^{low}$, $CD86\ (B7\text{-}2)^{low}$, $MHC\ Class\ II^{low}$ (DC resting); CD11c+, CD1a+, CD123-, $CD80^{hi}$, $CD86^{hi}$, $HLADR^{hi}$ (DC1 activated); $HLADR^{hi}$, CD11c-, CD123+ (DC2)

Macrophages:

HLADR+, CD14+, CD86+, CXCL9+, CD127 (M1); HLADR+, CD14+, CD206+, CD163+ (M2)

Myeloid derived suppressor cells:

HLADR-/low, CD11b+, CD14+,CD33+hi,CD34+, CD66b- (M-MDSC); HLADR-, CD11b+, CD14-,CD33+low,CD34+, CD66b+ (G-MDSC)

B Cells:

CD19+, B7-1^{low}, B7-2^{low}, MHC Class II^{low} (resting); CD19+, B7-1^{hi}, B7-2^{hi}, MHC Class II^{hi} (activated)

NK cells:

CD16+,CD3-,CD56+

NKT Cells:

CD16+,CD3+,CD56+

Real Time PCR Analysis

Real-time PCR analysis will be performed to determine the expression of T-cell and subsets;T-bet(Th1); STAT3, RORgamma t (TH17); STAT6 (Th2); FoxP3 (Treg) as well as checkpoint inhibitor induced markers such as granzyme A (GZMA) and perforin (PRF1)

T Cell Repertoire Analysis

To assess blood immune phenotype and TCR sequencing prior to and serially after Pem and Len , TCR Immunoseq for Vbeta CDR3 highest frequency specificities will be done.

Tumor Site Immune Phenotype and PD-L1/L2 Analysis

To assess tumor site immune phenotype and PD L1/2 expression in bone marrow aspirates available prior to and after last cycle of Pem +Len.

Gut Microbiome Analysis

Given that reduced diversity of intestinal microbiota leads to poor outcome post- allogeneic hematopoietic stem cell transplantation and specific intestinal bacterial species have been shown to boost responses to chemotherapy and checkpoint inhibitors, stool samples will be analyzed for the overall composition of the patient's gut microbiome prior and serially after PEM+ LEN treatments. A 16S ribosomal RNA (rRNA) miSeq Illumina platform will be used for overall microbial composition and quantitative real-time PCR analysis will validate the specific microbial strains identified by miSeq.

Multiparametric (Two-Color) IHC

Spatial association of PD-1+ tumor infiltrating lymphocytes (TILs) and PD-L1+ cells (tumor and myeloid cells) suggests "induction" of PD-L1. Interferon-gamma production by antigen-specific PD-1+ CD8+ T cells is hypothesized to drive local intratumoral upregulation of PD-L1 on adjacent tumor and myeloid cells, leading to a "stalled CTL" response, which may be predictive of response to pembrolizumab (MK-3475), lenalidomide, dexamethasone or pembrolizumab, and lenalidomide therapy. By assessing both of the

required elements, i.e. PD-L1 positive cells and PD-1+ T cells, a two-color IHC assay may be a better predictor of response than PD-L1 positivity alone.

Transcriptional Analyses

mRNA expression profiling in archival material will be completed to assess gene expression and to attempt to define a gene set critical for clinical response to pembrolizumab (MK-3475), lenalidomide and dexamethasone or pembrolizumab and lenalidomide. The hypothesis to be tested is that treatment responders will exhibit a "stalled Cytotoxic T Lymphocyte (CTL)" response within the tumor reflected in the physical proximity between PD-1 and PD-L1 expression and the presence of an aborted (e.g. weak but discernible) interferon-gamma transcriptional program will be detectable by profiling analyses. Global profiling will also be pursued.

Expression of individual genes related to the immune system may also be evaluated such as immune signatures and critical cytokines (e.g., IL-10).

Gene Sequencing

New data are emerging that suggest we can define certain tumor types as being 'hypermutated'. There is a potential that this hypermutated state may correlate with response to pembrolizumab (MK-3475), lenalidomide, dexamethasone or pembrolizumab, lenalidomide therapy, and/or that the converse, 'hypomutated' state may correlate with non-response.

4.0 METHODOLOGY

4.1 Entry Criteria

4.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with multiple myeloma (MM) of at least 18 years will be enrolled into this trial.

4.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide written informed consent/assent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Has a confirmed diagnosis of MM based on standard criteria. (See Appendix 2 for MM Diagnostic Criteria.)

4. Is between 60 and 180 days from peripheral blood autologous stem cell transplant.

5. At diagnosis, had MM with measurable disease, defined as:

   - A monoclonal immunoglobulin spike on serum electrophoresis of at least 0.5 g/dL and/or
   - Urine monoclonal levels of at least 200 mg/24 hours
   - For subjects without measurable serum and urine M-protein levels, an abnormal free light chain (FLC) ratio (normal value 0.26 – 1.65) with involved FLC ≥10 mg/dL
   - Radiographic evidence of disease for those without measurable M-spike or free light chains.

6. Has high-risk MM, which must be present at the time of diagnosis, and defined by:

   a. International Staging System (ISS) stage 3 (See Appendix 3 for ISS Staging), and/or

   b. Deletion 13q by cytogenetics, and/or

   c. 1q amplification, 1p deletion, p53 deletions (17p deletions), t(4;14), t(14;16), t(14;20), hypodiploidy, and/or

   d. High-risk gene expression profile (GEP) scores

7. Be able to provide a newly obtained bone marrow aspirate/biopsy material for biomarker analysis and disease assessment.

8. Have a performance status of ≤2 on the ECOG Performance Scale (See Appendix 4).

9. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 28 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,000 /mcL
Platelets	≥75,000 / mcL
Hemoglobin	≥8g/dL or ≥5.6 mmol/L without 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
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.	

10. All subjects must agree to follow the regional requirements for lenalidomide counseling, pregnancy testing, and birth control; and be willing and able to comply with the regional requirements (for example, periodic pregnancy tests, safety labs, etc.).
11. Female subjects of childbearing potential should have a negative urine or serum pregnancy test within 10-14 days prior to and again within 24 hours prior to receiving the first dose of pembrolizumab (MK-3475), lenalidomide and dexamethasone or pembrolizumab (MK-3475) and lenalidomide. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Female subjects of childbearing potential should agree to ongoing pregnancy testing.
12. Female subjects of childbearing potential must be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 4.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 2 years.
13. Male subjects must agree to use a latex condom during sexual contact with females of childbearing potential even if they have had a successful vasectomy starting with the first dose of study therapy through 120 days after the last dose of study therapy.
14. Subject is able to swallow capsules and is able to take or tolerate oral medications on a continuous basis.
15. 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.

4.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is 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.

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids may be used at the investigator's discretion.

3. Has received an allogeneic stem cell transplant.

4. Has received any myeloma-directed therapy after ASCT.

5. Has a known history of active TB (Bacillus Tuberculosis)

6. Hypersensitivity to pembrolizumab or any of its excipients.

7. Progressive disease from autologous transplantation at the time of screening. See Appendix 11.5 for criteria

8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

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). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

10. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

11. Has an active infection requiring intravenous systemic therapy.

12. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

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

14. 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.

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

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

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

18. 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.

4.2 Trial Treatments

Trial treatment should be administered starting with Day 1 of the first 28-day cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 5.0). Trial treatment may be administered up to 3 days before or after the scheduled day of administration due to administrative reasons. The treatment(s) to be used in this trial are outlined below in Table 2.

Table 2 Trial Treatments

Dose		
Pembrolizumab (MK-3475)	**Lenalidomide**	**Dexamethasone**
200 mg	25 mg	40 mg*
Pembrolizumab (MK-3475) will be administered every 3 weeks (on Day 1 of each 21-day cycle. Lenalidomide will be dosed on Days 1-14 of each 21-day cycle. Dexamethasone will be dosed on Days 1,8, and 15 of each 21-day cycle for the first 2 cycles only. * A dexamethasone dose of 20 mg on Days 1,8, and 15 of each 21-day cycle is recommend for **subjects aged >75**.		

Pembrolizumab (MK-3475)

Pembrolizumab (MK-3475) will be administered as a 30 minute IV infusion every three weeks (on Day 1) of a 21-day cycle (treatment dose may be reduced due to toxicity as described in Section 4.2.1.2). 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 starting dose of pembrolizumab (MK-3475) is 200 mg, fixed dose.

Lenalidomide

The recommended starting dose of lenalidomide is 25 mg once daily on Days 1 -14 of repeated 21-day cycles. If 25 mg dose of lenalidomide is not tolerated due to toxicity, the dose could be decreased to 15 mg. Lenalidomide should be taken orally at about the same time each day, either with or without food. Lenalidomide capsules should be swallowed whole with water. The capsules should not be opened, broken, or chewed. Refer to local product label for more details.

Dexamethasone

The recommended dose of dexamethasone is 40 mg once weekly on Days 1, 8, and 15of each 21-day cycle. A dexamethasone dose of 20 mg once weekly on Days 1, 8, and 15, in subjects aged **>75 years** is recommended. Refer to local product label for more details. Patients to receive dexamethasone in the first 2 cycles only.

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 trial treatments in accordance with the protocol and any applicable laws and regulations.

4.2.1 Dose Selection/Modification

4.2.1.1 Dose Selection

The dose amount required to prepare the pembrolizumab (MK-3475) infusion solution will be a fixed dose of 200 mg IV.

4.2.1.2 Dose Modification

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 4.6.1 and Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids.

Table 3a:

Dose Modification Guidelines for Pembrolizumab Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism	2-4	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[2]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

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

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

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

Table 3b:

Dose-Modification Guidelines for Hematological Toxicity

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment [1]	Discontinue Subject (after consultation with Sponsor)
Hematological Toxicity	1, 2, 3	No	N/A	N/A	N/A
	4	Yes	Toxicity resolves to Grade 0-1 or baseline	May decrease dose to next dose level below	Toxicity does not resolve within 4 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*

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

4.2.1.3 Dose Modification Guidelines for Lenalidomide

Dose modification guidelines are based on the recommendation provided by the Myeloma expert panel review[58] of the efficacy and toxicity of lenalidomide plus dexamethasone, and the guidance provided in the product label for lenalidomide. Any toxicity associated with lenalidomide that prompts a dose reduction of lenalidomide is outlined in the Sections below.

Lenalidomide is administered once daily from Day 1 through Day 14 in each 21 day cycle. If a subject receiving 5 mg of lenalidomide experiences an AE related to lenalidomide and is in need of dose modification, the subject should discontinue lenalidomide and continue only pembrolizumab (MK-3475) and dexamethasone, as 5 mg is the lowest dose used in

this trial. A maximum of three dose reductions of lenalidomide will be allowed in the order indicated in Table 6, where applicable. The duration of administration will remain the same.

A subject cannot be restarted on lenalidomide unless non-hematologic lenalidomide-related toxicities have returned to at least Grade 1 toxicity or baseline.

4.2.1.3.1 Dose Adjustments for Hematologic Toxicities during Multiple Myeloma Treatment

Dose modification guidelines, as summarized below in Table 4 and Table 5, are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia or other Grade 3 or 4 toxicities judged to be related to lenalidomide. Please refer to local product label for additional guidelines.

Table 4 Platelet Counts: Thrombocytopenia in MM

When Platelets	Recommended Course
Fall to <30,000/mcL Return to ≥30,000/mcL	Interrupt lenalidomide treatment, follow CBC weekly Restart lenalidomide at 15 mg daily
For each subsequent drop <30,000/mcL Return to ≥30,000/mcL	Interrupt lenalidomide treatment Resume lenalidomide at 5 mg less than the previous dose. Do not dose below 5 mg daily.

Table 5 Absolute Neutrophil Counts (ANC): Neutropenia in MM

When Neutrophils	Recommended Course[1]
Fall to <1,000/mcL Return to ≥1,000/mcL and neutropenia is the only toxicity	Interrupt lenalidomide treatment, add G-CSF, follow CBC weekly Resume lenalidomide at 25 mg daily
Return to ≥1,000/mcL and if other toxicity	Resume lenalidomide at 15 mg daily

For each subsequent drop <1,000/mcL Return to ≥1,000/mcL	Interrupt lenalidomide treatment Resume lenalidomide at 5 mg less than the previous dose. Do not dose below 5 mg daily.
1 If the subject is receiving Len 10 mg, the subject may resume Len at 5 mg.	

4.2.1.3.2 Other Grade 3/4 Toxicities in MM

For other Grade 3/4 toxicities, hold treatment and restart at the physician's discretion at next lower dose level when toxicity has resolved to ≤ Grade 2 as outlined below in Table 6.

Table 6 Lenalidomide Dose Reductions for Subjects with Other Grade 3/4 Toxicities

Modification	**Dose** 1, 2
Starting Dose	Lenalidomide 25 mg every day for 14 days, every 21 days
Dose Reduction 1	Lenalidomide 15 mg every day for 14 days, every 21 days
Dose Reduction 2	Lenalidomide 10 mg every day for 14 days, every 21 days
Dose Reduction 3	Lenalidomide 5 mg every day for 14 days, every 21 days
1 Do not dose below 5 mg daily 2 If the subject is receiving Len 10 mg, the subject may resume Len at 5 mg.	

4.2.1.3.3 Recommended Dose Adjustments for Subjects with Impaired Renal Function

Renal function may be impaired in subjects with MM by immunoglobulin light chains, amyloidosis. MM subjects with normal renal function may develop renal dysfunction or renal impairment during treatment with lenalidomide and dexamethasone. If renal toxicity occurs during study treatment, drug should not be restarted unless the toxicity resolved to ≤Grade 1.

4.2.1.4 Dose Modification Guidelines for Dexamethasone

Dexamethasone will be given at 40 mg q.d. p.o. on Days 1, 8, and 15 (i.e. once weekly) in each 21-day cycle. If a subject experiences adverse events, up to two dose reductions of dexamethasone will be allowed. The duration of administration will remain the same; however, the daily dose will be modified. For grade 3 or 4 toxicities, the dose will be modified from a starting dose of 40 mg to 20 mg, and a second dose reduction can be to 10 mg. For grade 3 or 4 toxicities in patients >75, in the starting dose of 20 mg can be dose reduced to 10 mg and then a second dose reduction can be to 4 mg. Additional supportive care guidelines specific to dexamethasone are indicated in Table 7.

A subject cannot be restarted on dexamethasone unless non-hematologic dexamethasone related toxicities have returned to at least Grade 1 toxicity or baseline.

4.2.1.4.1 Supportive Care Guidelines Specific to Dexamethasone

Table 7 Supportive Care Guidelines Specific to Dexamethasone

Body System	Symptom	Recommended Action
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1–2 (requiring medical management)	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by one dose level.
Gastrointestinal	> Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart and decrease one dose level of current dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Gastrointestinal	Acute pancreatitis	Discontinue dexamethasone and do not resume.
Cardiovascular	Edema >Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and decrease dexamethasone dose by one dose level; if edema persists despite above measures, decrease dose another dose level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction.
Neurology	Confusion or Mood alteration > Grade 2 (interfering with function +/- interfering with activities of daily living)	Hold dexamethasone until symptoms resolve. Restart with one dose level reduction. If symptoms persist despite above measures, discontinue dexamethasone do not resume.
Musculoskeletal	Muscle weakness > Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living)	Decrease dexamethasone dose by one dose level. If weakness persists despite above measures, decrease dose by one dose level. Discontinue dexamethasone and do not resume if symptoms persist.

Metabolic	Hyperglycemia > Grade 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by one dose level until levels are satisfactory.

4.2.2 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 5.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. 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).

4.2.3 Trial Blinding/Masking

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

4.3 Randomization or Treatment Allocation

No randomization or treatment allocation will be used in this trial as it is a single arm, open-label trial.

4.4 Stratification

No stratification based on age, sex or other characteristic will be used in this trial.

4.5 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 final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

4.5.1 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 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs.

4.5.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

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

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

4.6 Rescue Medications & Supportive Care

4.6.1 Supportive Care Guidelines

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

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 4.2.1 for dose modification.

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

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

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

- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

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

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

- **Hypophysitis**:

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

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

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):

- In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
- In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.

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

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

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

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

Table 8 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 8 Infusion Reaction Treatment Guidelines

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

4.7 Diet/Activity/Other Considerations

4.7.1 Diet

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

4.7.2 Contraception

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 6.2.2-Reporting of Pregnancy and Lactation to the Sponsor and to Merck. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

† Lenalidomide (REVLIMID®) is only available through a restricted distribution program called the REVLIMID REMSTM program (formally known as the "RevAssist® program").

Required components of the REVLIMID REMSTM program include the following:

- Prescribers must be certified with the REVLIMID REMSTM program by enrolling and complying with the REMS requirements. Study sites in the United States register with Celgene's Revlimid REMS® Program prior to prescribing the Celgene Product in accordance with the Revlimid REMS® guidelines and for investigators at Study sites outside of the United States register with the appropriate Celgene risk minimization program in that country prior to prescribing the Celgene Product

- Study investigators must follow Global Pregnancy Prevention Plan as presented by Revlimid REMS

- Subjects must sign a "Patient-Prescriber agreement form" and comply with the REMS requirements in the United States or the appropriate Celgene risk minimization program for countries outside of the United States. In particular,

female subjects of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements and males must comply with contraception requirements. Refer to local product label.

- Pharmacies must be certified with the REVLIMID REMSTM program, must only dispense to subjects who are authorized to receive lenalidomide (REVLIMID®) and comply with REMS requirements. At the termination or conclusion of the study sites shall direct all patients to return to Celgene any unused quantities of the Celgene Product in accordance with the Celgene REMS® Program.

- Further information about the REVLIMID REMSTM program is available at celgeneriskmanagement.com or by telephone at 1-888-423-5436.

Females of Reproductive Potential:

- Females of reproductive potential must avoid pregnancy for at least 4 weeks before beginning lenalidomide (REVLIMD®) therapy, during therapy, during dose interruptions and for at least 4 weeks after completing therapy.

- Females must commit either to abstain continuously from heterosexual intercourse or to use two methods of reliable birth control, beginning 4 weeks prior to initiating treatment with lenalidomide (REVLIMID®), during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of REVLIMID® therapy.

- Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing lenalidomide (REVLIMID) therapy and then weekly during the first month, then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. Refer to local product label for additional details.

- Pregnancy testing and counseling should be performed if a subject misses her period or if there is any abnormality in her menstrual bleeding. Lenalidomide (REVLIMID®) treatment must be discontinued during this evaluation.

Males of Reproductive Potential:

- Lenalidomide (REVLIMID®) is present in the semen of subjects receiving the drug. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking lenalidomide (REVLIMID) and for up to 28 days after discontinuing lenalidomide (REVLIMID®), even if they have undergone a successful vasectomy. Male subjects taking lenalidomide (REVLIMID®) must not donate sperm. Refer to local product label for additional details.

4.7.3 Use in Pregnancy

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

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 6.2.2.

> *Lenalidomide (REVLIMID®) can cause fetal harm when administered to a pregnant female. If lenalidomide is used during pregnancy or if the subject becomes pregnant while taking lenalidomide, the subject should be apprised of the potential hazard to the fetus. Refer to local product label for further details.**

4.7.4 Use in Nursing Women

It is unknown whether pembrolizumab (MK-3475), or lenalidomide 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. Because of the potential for serious adverse reactions in nursing infants, breast feeding must be discontinued for the duration of therapy with pembrolizumab (MK-3475), or lenalidomide, if applicable. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of drug to the mother. Please refer to lenalidomide local product labels for further information.

4.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the

trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 6.1.4 – Other Procedures.

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed disease progression, including biochemical disease progression, and radiographic disease progression
- Unacceptable adverse experiences as described in Section 4.2.1.
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 5 (Protocol Flow Chart). 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 as described). 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.

4.9 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.

5.0 TRIAL FLOW CHART

5.1 Study Flow Chart

Trial Period:	**Treatment Cycles[1, 4]**								**End of Treatment**	**Post-treatment[2]**		
		Cycle = 21 Days										
Treatment Cycle/Title:	Screening (Visit 1)	Cycle 1			Cycle 2		Cycle 3 and 4		At the completion of cycle 4	Post-Treatment Safety Follow-up	Follow-up Visits[3]	Survival Follow-up[7]
Cycle Day		1	8	15	1	15	1	15	At the completion of cycle 4	30 days post completion of cycle 4	Every 12 weeks post completion	Every 12 weeks
Scheduling Window (Days)[4]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7
Administrative Procedures												
Informed Consent	X											

Inclusion/Exclusion Criteria	X											
Demographics and Medical History	X											
Prior Multiple Myeloma treatment history	X											
International Staging System Criteria	X											
Prior and Concomitant Medication Review[5,9]	X	X	X	X	X	X	X	X	X	X		
Trial Treatment Administration		See Section 4.2										
Post-study anticancer therapy status											X	X
Survival Status [7]												X
Clinical Procedures/Assessments												
Review Adverse Events [8,9]	X	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X	X			X		X		X	X		
Directed Physical Examination [10]				X		X		X			X	
Vital Signs and Weight [11]	X	X	X	X	X	X	X	X	X	X	X	
Trial Period:	**Treatment Cycles[1,4]**								**End of Treatment**	**Post-treatment[2]**		
	Cycle = 21 Days											

Treatment Cycle/Title:	Screening (Visit 1)	Cycle 1			Cycle 2		Cycle 3 and 4		At the completion of cycle 4	Post-Treatment Safety Follow-up	Follow-up Visits[3]	Survival Follow-up[7]
Cycle Day		1	8	15	1	15	1	15	At the completion of cycle 4	30 days post completion of cycle 4	Every 12 weeks post completion	Every 12 weeks
12-Lead Electrocardiogram	X											
ECOG Performance Status	X	X	X	X	X	X	X	X	X			
Skeletal survey [12]	X											
MRI/CT/PET [12]	X											
International Uniform Response Criteria[13]	X	X			X		X		X_{13}		X_{13}	
Pregnancy Test – urine or serum Beta-HCG [14]	X	X	X	X	X	X	X	X				
CBC with differential [15]	X	X	X	X	X	X	X	X	X	X [16]		
Comprehensive blood chemistry panel [15]	X	X	X	X	X	X	X	X	X	X [16]		
LDH [15]	X	X			X		X					
Coagulation	X											

Urinalysis	X											
TSH, T3 and free T4 [15]	X				X		X					
Quantitative serum immunogloublins [13]	X	X			X		X		X		X	
Serum protein electrophoresis and serum immunofixation [13]	X	X			X		X		X		X	
Serum free light chain analysis [13]	X	X			X		X		X		X	
24 hour urine protein electrophoresis and urine immunofixation [13]	X	X			X		X		X		X	
M-protein quantitation (urine and/or serum) [13]	X	X			X		X		X		X	
Beta-2 microglobulin [13]	X	X			X		X		X		X	
Bone marrow aspiration and biopsy [17,19]	X								X			
Trial Period:	**Treatment Cycles[1, 4]**								**End of Treatment**	**Post-treatment[2]**		
		Cycle = 21 Days										
Treatment Cycle/Title:	Screening (Visit 1)	Cycle 1		Cycle 2		Cycle 3 and 4			At the completion of cycle 4	Post-Treatment Safety Follow-up	Follow-up Visits[3]	Survival Follow-up[7]

Cycle Day		1	8	15	1	15	1	15	At the completion of cycle 4	30 days post completion of cycle 4 of Cycle 4	Every 12 weeks post completion post Discon	Every 12 weeks
Bone marrow morphology, IHC, cytogenetics by standard karyotyping, FISH panel, and minimal residual disease (MRD) analysis [17, 19]		$X_{17, 19}$			X_{17}		X_{17}		X			
Correlative Studies – bone marrow and peripheral blood collection, stool samples [6]	X_6	X_6			X		X		X			

1. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 21 days. Unless otherwise noted, procedures should be on Day 1 of each Cycle.
2. Procedures outlined for visit, 30-day Safety-Follow-up and Survival Follow-up should be performed for subjects who complete the study or progress.
3. Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (84 ± 7 days) to monitor disease status. Every effort should be made to collect information regarding disease status
4. In general, the window for each visit is ± 3 days unless otherwise noted.
5. Record all medications taken from 28 days prior to cycle 1 day 1 to the 30 day post completion of cycle 4 visit.
6. For correlative studies, collection will be at screening or cycle 1 day 1, then every day 1 of each cycle, and at completion of cycle 4 and to confirm response.

7. After documented disease progression or the start of new antineoplastic therapy, each subject will be followed by telephone for overall survival until death, withdrawal consent or the end of the trial, whichever occurs first.
8. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.03. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness. AEs will be evaluated every two weeks, on Days 1 and 15 of each 21-day cycle.
9. Record all AEs occurring within 30 days after the last dose of study drug. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the last dose of trial treatment or the start of new anti-cancer treatment, whichever comes first. Afterwards, report only SAEs and ECIs that are related to trial treatment.
10. Directed PE performed to collect any new/clinically significant abnormalities (i.e. ECI/AE).
11. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.
12. Skeletal survey should include a chest (PA or AP; lateral), skull (lateral), upper extremities (shoulder to elbow), lower extremities (hip to knee; AP), pelvis (AP), cervical/thoracic/lumbar spine (AP and lateral). For suspected progression to bone disease bidimensional measurement of the target lytic lesions must be performed. MRI/CT/PET (MRI for subjects with bone disease and CT/PET for plasmacytomas) is required when clinically indicated for subjects with bony disease and should just include the bony lesions. Subjects with measurable plasmacytomas at baseline should have imaging performed every 12 weeks.
13. Disease response assessment is based upon the multiple myeloma response criteria (See Appendix 5). Myeloma lab assessments should be performed every 3 weeks, that is, on Day 1 of every 21-day treatment cycle. Disease assessments should occur at Day 1 of each 21-day treatment cycle (+/- 7 days) throughout the course of the trial.
14. For women of reproductive potential, a urine pregnancy test should be performed. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local trial site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be performed monthly (on Day 1 of each Cycle) for women with regular menstrual cycles, or every two weeks in women with irregular menstrual cycles. Pregnancy tests (urine and/or serum tests) may be performed more frequently if required by local guidelines. Pregnancy testing and counseling should be performed if a subject misses her period or if there is any abnormality in her menstrual bleeding. Lenalidomide (REVLIMID) treatment must be discontinued during this evaluation.
Pharmacies must be certified with the REVLIMID REMSTM program, and must only dispense to subjects who are authorized to receive REVLIMID® and comply with REMS requirements. Refer to Local Product Label.
15. After cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. Repeat lab samples on Days 1 each cycle.
16. Labs do not need to be repeated after the end of treatment if labs returned to baseline.
17. Bone marrow morphology, IHC, Cytogenetics by standard karyotyping, and FISH panel should be performed with bone marrow aspirate/biopsy, at screening/cycle 1 day 1, at completion of cycle 4, and to confirm complete response.
18. In subjects who discontinue study therapy without confirmed disease progression, a response assessment should be performed at the time of treatment discontinuation, then a repeat assessment at treatment discontinuation is not mandatory.
19. FISH panel should include del 1p, del 13, del 17p13, t(4;14), t(11;14), t(14;16), and 1q21 amplification.

6.0 TRIAL PROCEDURES

6.1 Trial Procedures

The Trial Flow Chart - Section 5.0 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.

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.

6.1.1 Administrative Procedures

6.1.1.1 Informed Consent

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

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

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

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

6.1.1.2 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.

6.1.1.3 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.

6.1.1.4 Prior and Concomitant Medications Review

6.1.1.4.1 Prior Medications

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.

6.1.1.4.2 Concomitant Medications

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.

6.1.1.5 Disease Details and Treatments

6.1.1.5.1 Disease Details

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

6.1.1.5.2 Prior Treatment Details

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

6.1.1.5.3 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.

6.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

6.1.1.7 Assignment of Randomization Number

This trial is an open-label single arm, phase II clinical trial and therefore does not require randomization.

6.1.1.8 Trial Compliance (Medication/Diet/Activity/Other)

Interruptions from the protocol specified treatment plan for 4 weeks require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of trial treatment will be witnessed by the investigator and/or trial staff. The total volume of pembrolizumab (MK-3475) infused will be compared to the total volume prepared to determine compliance with each dose of pembrolizumab (MK-3475) administered.

Medication Compliance

The instructions for preparing and administering pembrolizumab (MK-3475), will be provided / referenced in the Pharmacy Manual.

6.1.2 Clinical Procedures/Assessments

6.1.2.1 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 4.03 (see Appendix 1). 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.

Please refer to section 6.2 for detailed information regarding the assessment and recording of AEs.

6.1.2.2 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 and repeated as per the frequency defined in the Trial Flow Chart. After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

6.1.2.3 Directed Physical Exam

For cycle days 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. New clinically significant abnormal findings should be recorded as AEs.

6.1.2.4 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 5.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

6.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

6.1.2.6 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed using local standard procedures at Screening. Clinically significant abnormal findings should be recorded as medical history.

6.1.2.7 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

6.1.2.7.1 Myeloma Disease Measurements

Primary Myeloma Panel

The Primary Myeloma Panel that the Investigator followed for subject's disease status should be specified on trial eCRF. Along with other Myeloma Markers, the clinical site should consistently record and follow the Primary Myeloma Panel throughout the trial.

Monoclonal Protein Considerations

Laboratory tests for measurement of Serum M-protein level are quantitated using densitometry on SPEP except in cases where the SPEP is felt to be unreliable such as in patients with IgA monoclonal proteins migrating in the beta region. If SPEP is not available or felt to be unreliable (e.g., in some cases of IgA myeloma) for routine M -protein quantitation during therapy, then quantitative immunoglobulin levels on nephelometry or turbidometry can be accepted. However, this must be explicitly reported, and only nephelometry can be used for that patient to assess response and SPEP and nephelometric values cannot be used interchangeably.

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

See Appendix 5 for Myeloma Response Criteria.

6.1.2.7.2 Criteria for Assessment of Disease

Multiple Myeloma: International uniform response criteria for multiple myeloma[57].

The International Working Group criteria will be applied by the site as the primary measure for assessment of disease response and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of trial treatment).

6.1.2.8 Disease Assessment of Immunotherapeutic Agent

Immunotherapeutic agents such as pembrolizumab (MK-3475) may produce antitumor effects by potentiating endogenous cancer-specific immune responses, which may be functionally anergic. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard response assessment criteria may not provide a complete response assessment of immunotherapeutic agents such as pembrolizumab (MK-3475). Therefore in the setting where a subject's assessment shows PD, study drug should not be discontinued unless

progression is confirmed at least 3 weeks later, provided that the subject's clinical condition is stable.

6.1.2.9 Timing of Disease Assessments

Uniform disease response assessment will be performed every 21-day treatment cycle.

6.1.2.10 Initial Disease Assessment

Initial disease assessments must be performed within 28 days prior to the first dose of trial treatment (See 5.0 – Trial Flow Charts).

Bone marrow aspirates/biopsies performed as part of standard of care prior to signing informed consent may be used for screening if performed within 28 days of Day 1.

Myeloma laboratory disease assessments should be performed within 28 days prior to the first dose of trial treatment (See 5.0 – Trial Flow Charts).

6.1.2.11 Disease Assessment during Trial

Disease assessments should be performed per the frequency defined in Section 5.0 – Trial Flow Charts. There is a ±3 day window for assessments performed after Day 1. Disease assessments should not be delayed for delays in cycle starts.

Disease assessments should continue to be performed until documented disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. Disease assessments should be performed to confirm stringent CR or as clinically indicated.. Subjects who have unconfirmed disease progression may continue on treatment until progression is confirmed at the next scheduled assessment.

6.1.2.12 Confirmation Assessments

A subject with progression of disease may continue trial treatment until confirmation of progression of disease is documented per the respective response evaluation criteria at least 21 days later. Subjects may only receive treatment while waiting for confirmation of PD if the following criteria are met:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression;
- No decline in ECOG performance status
- Absence of rapid progression of disease.
- Absence of progressive tumor at critical anatomical sites (e.g. cord compression) requiring urgent alternative medical intervention.

After the first disease response assessment, it is at the discretion of the investigator to keep a clinically stable subject on trial treatment or to stop trial treatment until a repeat assessment is performed at least 21 days later. When feasible, subjects should not be discontinued until repeat disease response assessment is performed at least 21 days later.

6.1.2.13 Biopsy Collection and Correlative Studies Aspirate and Blood Collection

All subjects enrolled into this study must be able to provide an archived bone marrow biopsy sample for biomarker analysis and is willing to provide a newly obtained bone marrow aspirate/biopsy sample to be submitted for characterization. Bone marrow assessments will include a biopsy for morphologic and immunohistochemistry assessment, and aspirate for FISH panel, metaphase cytogenetics, and minimal residual disease assessment by ClonoSIGHT.

Bone marrow biopsies, aspirates and whole blood for correlative biomarker studies should be collected per Table 9A and 9B below:

Table 9A: Bone Marrow Biopsy Collection

Bone marrow biopsies will be collected as per Table 5 below: Table 5A Bone Marrow Biopsy Assessments **Indication**	**Timing of Biopsy**
Bone marrow aspirate and biopsy	Cycle 1 Day 1, to confirm Complete Remission and at End-of Study. (See Section 5.0 for Trial Flow Chart and Procedures Manual for further details).

Table 9B Blood Collection for Correlative Biomarker Studies

Peripheral Blood and Stool Collection	**Timing of Correlative Blood Collection**
	Screening or Cycle 1 Day 1, Cycle 2 day 1, Cycle 3 Day 1, Cycle 4 Day 1, and at the completion of cycle 4 every 12 weeks

Peripheral blood and stool	eve For subjects with Progressive Disease, a bone marrow aspirate and including confirmation of response. A window of +/- 7 days will be allowed for specimen collection An additional sample should be performed as part of confirmation of response Our patient A Jon Prusmack is on Sanofi TED14154 study and needs post infusion PK samples done Wednesday 2/3, Thursday 2/4 and Friday 2/5. As per the protocol, these samples do not have a window for collection and need to be obtained at exactly 8:30AM. We would appreciate it if our patient could have these research PK samples collected in the third floor infusion suite in an effort to ensure the samples are collected at 8:30AM. If the samples are not collected at exactly 8:30AM we will be deviating from the protocol and must submit deviations to the IRB. We will have the chart with the order and the tubes in the clinic at 8:00AM every day and the patient will be instructed to come in at 8:15AM for the 8:30AM collection. Please let us know if this is feasible on your end. I appreciate your help.

	(See Section 5.0 for Trial Flow Chart and Procedures Manual for further details).

6.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Procedures Manual.

Table 10 Laboratory Tests

Hematology	**Chemistry**	**Urinalysis**	**Other**
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin (β-hCG)
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR)
Platelet count	Alanine aminotransferase (ALT)	Protein	aPTT
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Total Thriodothyronine (T3)†
Red Blood Cell Count	Bicarbonate	Microscopic exam, if abnormal results are noted	Free tyroxine (T4)
Absolute Neutrophil Count	Calcium	Urine pregnancy test*	Thyroid stimulating hormone (TSH)
	Chloride		
	Creatinine		
	GFR		
	Uric Acid		
	Calcium		
	Glucose		
	LDH		

	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.

† Free T3 may be performed in place of Total T3 per local standards

Laboratory tests for Screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours 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.

6.1.3.1 Pharmacokinetic/Pharmacodynamic Evaluations

There will be no pharmacokinetetic or pharmacodynamics sampling for this protocol.

6.1.4 Other Procedures

6.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in the protocol. Visit Requirements

Visit requirements are outlined in Section 5.0 - Trial Flow Chart.

6.1.4.2 Screening

6.1.4.2.1 Screening Period

Approximately 28 days prior to enrollment, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 4.1. Visit requirements are outlined in Section 5.0 – Trial Flow Chart.

Written consent for the main study must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of trial treatment except for the following:

- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met.

6.1.4.3 Treatment Period

6.1.4.4 Post-Treatment Visits

6.1.4.4.1 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.

6.1.4.5 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (84 ± 7 days) 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. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

6.1.4.5.1 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.

6.2 Assessing and Recording Adverse Events

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

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

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

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

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

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

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

forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 6.2.3.1.

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

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

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

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

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

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

6.2.3 Immediate Reporting of Adverse Events to the Sponsor

6.2.3.1 Serious Adverse Events

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

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

Refer to Table 7 for additional details regarding each of the above criteria.

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

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

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

SAE reports and any other relevant safety information are to be reported to Georgetown DSMB, Hackensack eIRB, Merck Global Safety (FAX: 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.

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

6.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 6.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent). See Appendix 6 for ECI Reference Guidance.

1. Additional adverse events:

   A separate guidance document has been provided entitled "Event of Clinical Interest Guidance Document" (previously entitled, "Event of Clinical Interest and Immune-Related Adverse Event Guidance Document").

   ECIs (both non-serious and serious adverse events) identified in this guidance document from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220), regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

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

6.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.03. 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 11 Evaluating Adverse Events

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

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

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

6.2.5 Sponsor Responsibility for Reporting Adverse Events

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

7.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Post hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) will be issued for this study.

7.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Section 7.1.8).

7.1.1 Efficacy Analysis

The primary and key secondary endpoints, primary analysis population, and statistical methods that will be employed for the efficacy analysis are presented in Table 11 below.

The CR+sCR+VGPR response rate and objective response rate (ORR) per IMWG criteria based on investigator assessment will be conducted in the Full Analysis Set (FAS) population. No multiplicity adjustment is planned.

Table 12: Summary of Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time point)	Statistical Method	Analysis Population	Missing Data Approach
PFS	Kaplan Meier	FAS	Subjects with missing data are considered non-progressors
CR + sCR + VGPR response rate per IMWG criteria based on	Exact test of binomial parameter	FAS	Subjects with missing data are considered non-responders

investigator assessment			
ORR per IMWG criteria based on investigator assessment	Exact test of binomial parameter	FAS	Subjects with missing data are considered non-responders

7.1.2 Safety Analysis

The All-Subjects-as-Treated (ASaT) population will be employed for safety analyses. The ASaT population consists of all subjects who received at least one dose of trial treatment. Subjects who entered the study and did not take any of the study drug(s) and had this confirmed, will not be evaluated for safety.
Descriptive tables that summarize the number and percentage of subjects that experience adverse events as categorized in the NCI CTCAE Version 4 will be generated by dose level.

Stopping rules:

- Death greater than 10% of patients in any part independent of their relationship to study treatment.
- Grade 4 non-hematologic toxicity in greater than 10% of patients in any part independent of their relationship to study treatment.

The severity of the toxicities will be graded according to the NCI CTCAE v4.0 whenever possible. An interim safety analysis will be performed in between stages 1 and 2 of recruitment (See Section 7.1.3) at the same time as the planned efficacy analysis per the Simon-two-staged design.

7.1.3 Power and Sample Size

Using a Simon's two-stage design, this study has 80% power at a one-sided significance level of 0.05 to discount an 'ineffective' progression-free survival (PFS) rate of 50% (po) in favor of a PFS rate of at least 70% (p1).

A total of 15 patients will be accrued in stage one and, if successful, a further 28 patients will be accrued in stage two, bringing the total number of patients required to 43 evaluable patients. There will be a planned stopping rule in recruitment between stages 1 and 2.

The study will stop and treatment will be rejected if there are 8 or fewer patients are progression free at 12 months. If 9 or more of the first 15 patients have not progressed at 12 months, a further 28 patients will be recruited into the second stage, bringing the final size to 43. At the end of stage two, if 26 or fewer of the 43 patients are progression free then no further investigation of the 4-cycle PEM+LEN+DEX therapy is warranted. If 27 or more of the 43 patients are progression-free, then the hypothesis PFS is 59% will be rejected. The optimal design has an expected sample size of 23.5 and probability of early termination of 0.696. If the

overall PFS is 70% or above at 12 months, pembrolizumab will be considered to have shown worthwhile efficacy.

7.1.4 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistician of Hackensack University Medical Center.

The study will be done as an open-label study. The official database will be finalized after medical/scientific review has been performed, protocol violations have been identified, and data have been declared final and complete.

7.1.5 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0.

7.1.6 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated by dosing schedules, dose levels, and disease-specific cohorts are listed below.

7.1.6.1 Efficacy Endpoints

Key efficacy endpoints for the trial include the following as assessed by IMWG:

- PFS: defined as the time from Day 0 of ASCT to progressive disease (PD) or death, whichever occurs earlier, per IMWG criteria by investigator assessment. Subjects without documented PD/death will be censored at the last disease assessment date.

- Complete response, stringent complete response, and very good partial response rate (CR + sCR + VGPR) rate using IMWG criteria. Response rates will be determined with the following baselines 1) Prior to ASCT 2) Cycle 1 day 1 of study drug or screening visit, whichever is higher.

- ORR: Defined as the proportion of subjects who have achieved sCR, CR, VGPR or PR according to the IMWG criteria by investigator assessment. Subjects with missing outcome on objective response will be considered non-responders. Response rates will be determined with the following baselines 1) Prior to ASCT 2) Cycle 1 day 1 of study drug or screening visit, whichever is higher.

- DOR: defined as the time interval between the date of first response (sCR, CR, VGPR, PR) and the date of first documented disease progression.

- TTP: defined as the time from 1) Day 0 ASCT and 2) Date of enrollment to progressive disease (PD) per IMWG criteria by investigator assessment. Subjects without documented PD or death will be censored at the last disease assessment date, and subjects who died without documented PD will be censored at the time of death.

- OS: defined as the time from Day 0 ASCT to death from any cause.

In addition, overall survival (OS) and change from baseline in bone marrow/aspirate PD-L1 expression, T-cell subsets, and cytokine analysis will be evaluated.

7.1.6.2 Safety Endpoints

The primary safety endpoints include the AEs graded using CTCAE (Version 4.03) criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab (MK-3475), including serious AEs and events of clinical interest (ECIs). Immune-related AEs (irAEs), as defined in Section 6.2.3.2 will be collected. Other safety endpoints include laboratory safety assessments, vital signs and physical examinations. Safety measurements are described in Section 6.

7.1.7 Analysis Populations

7.1.7.1 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of response rate data in this study. The FAS population consists of all subjects who:

- receive at least one dose of study treatment
- have a post baseline disease assessment OR discontinue the trial due to progressive disease/drug-related AE

The Intent-to-Treat (ITT) population will serve as the primary population for the analyses of PFS, TTP and OS in this study. The ITT population consists of all enrolled subjects.

The analysis of response duration is based on all responders.

Details on the approach to handling missing data are provided in Section 7.1.8 Statistical Methods.

7.1.7.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this trial. The ASaT population consists of all subjects who received at least one dose of trial treatment. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of trial treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling missing data for safety analyses are provided in Section 7.1.8.1 Statistical Methods.

For safety analysis related to AE rate, the AE evaluable population will be used. The AE evaluable population consists of all AE evaluable subjects. In order to be considered evaluable, the subject must complete the first cycle of therapy or discontinue from the trial due to a drug-related adverse event. Subjects who discontinue prematurely due to a non-drug-related cause are not included in the AE evaluable population.

7.1.8 Statistical Methods

7.1.8.1 Statistical Methods for Efficacy Analysis

Kaplan-Meier estimates and corresponding 95% confidence intervals of time to event endpoints, including PFS, OS, TTP and DOR, will be provided.

For key efficacy endpoints including CR + sCR + VGPR rate + ORR, the point estimate, 90% confidence interval and p-value for testing response rate is greater than the historical control for each arm will be provided using exact binomial distribution.

Table 13 Summarizes key efficacy analyses.

Table 13 Analysis Strategies for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach	Analysis Population	Statistical Method	Missing Data Approach
Primary				
PFS	P	ITT	Summary statistics using Kaplan-Meier method	Censored at last disease assessment date
Secondary				
ORR per IMWG criteria based on investigator assessment	P S	FAS ITT	Exact test of binomial parameter	Subjects with missing data are considered as non-responders
CR+sCR+VGPR response rate per IMWG criteria based on investigator assessment	P S	FAS ITT	Exact test of binomial parameter	Subjects with missing data are considered as non-responders
OS	P	ITT	Summary statistics using Kaplan-Meier method	Censored at the last date known to be alive
TTP	P	ITT	Summary statistics using Kaplan-Meier method	Censored at the last non-PD assessment date
DOR	P	All responders	Summary statistics using Kaplan-Meier method	Non-responders are excluded in analysis

P=Primary approach; S=Secondary approach; FAS=Full Analysis Set; ITT=Intention to treat.

7.1.8.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), ECOG, laboratory tests, vital signs, and ECG measurements.

Summary statistics (median and range) for time to onset of first drug-related toxicity in each dose level will be provided. Adverse experiences will be summarized as counts, frequencies and grade by NCI CTCAE version 4.03. Laboratory values will be graded by NCI CTCAE version 4.03. The percentage of subjects with laboratory abnormalities by grades will be tabulated. The change of grades during the study will be summarized by a lab shift table. In this analysis, the percentage of subjects who improve or worsen from baseline for each laboratory test will be summarized. A clinically meaningful worsening in CTCAE grade was defined as a shift from less than Grade 3 at baseline to Grade 3 or above, or a shift from Grade 0 to Grade 2. Summary statistics for baseline, on-treatment, and change from baseline values of continuous measures such as changes from baseline in ECOG, laboratory, vital signs, and ECG parameters will be provided by dose-level in table format. Immune-related AEs (irAEs) that are designated as events of special interest will be summarized separately from other AEs.

7.1.8.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Demographic and Baseline Characteristics

Each relevant characteristic will be assessed by the use of tables/graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (such as age) and baseline characteristics will be summarized by treatment either by descriptive statistics or categorical tables.

The reason for exclusion from the Full Analysis Set (if any) will be summarized.

Exploratory Analyses

Change from baseline in bone marrow aspirate/biopsy PD-L1 expression will be summarized by dosing schedules using descriptive statistics.

Comparison of change from baseline in bone marrow aspirate/biopsy PD-L1 expression between responders with longer duration of response and non-responders or responders with a short duration of response will be performed using mixed regression analysis. Longitudinal analysis of bone marrow aspirate/biopsy PD-L1 expression over time will be examined using mixed model repeated measure design with levels observed serially over time and response type (long responders vs short responders/non-response) as a fixed variable.

Longitudinal analysis will be performed on blood samples collected at time points 1) screening visit 2) Day 1 of Cycle 1, 3) Day 1 of Cycle 2, 3) Day 1 of Cycle 3, 4) Day 1 of Cycle 4, 5) Post completion of Cycle 4. Discrete variables such as cell counts of the absolute number of inflammatory cytokines (TNF-alpha, IL-2, IL-4, IL-6, IL-10) and activated T cells (CD8+) will be examined for changes over time using Poisson Regression Analysis based on generalized estimating equations (GEE) method obtained by utilizing PROC GENMOD SAS 9.4 with Poisson distribution, log link function and independent covariance structure. The repeated counts will be compared between long responders vs short responders/non-responders.

Longitudinal analysis of specific intestinal microbial strains identified form blood and stool samples collected at time points 1) screening visit 2) Day 1 of Cycle 1, 3) Day 1 of Cycle 2, 3) Day 1 of Cycle 3, 4) Day 1 of Cycle 4, 5) Post completion of Cycle 4, will be performed using GEE method described above with type of responder as grouping variable.

7.1.9 Multiplicity

There is no multiplicity adjustment planned for this study.

7.1.10 Sample Size and Power Calculations

Using a Simon's two-stage design, this study has 80% power at a one-sided significance level of 0.05 to discount an 'ineffective' progression-free survival (PFS) rate of 50% (po) in favor of a PFS rate of at least 70% (p1).

A total of 15 patients will be accrued in stage one and, if successful, a further 28 patients will be accrued in stage two, bringing the total number of patients required to 43 evaluable patients. There will be a planned stopping rule in recruitment between stages 1 and 2.

7.1.11 Subgroup Analyses and Effect of Baseline Factors

There is no formal subgroup analysis for this study.

7.1.12 Interim Analysis

The study will stop and treatment will be rejected if there are 8 or fewer patients are progression free at 12 months. If 9 or more of the first 15 patients have not progressed at 12 months, a further 28 patients will be recruited into the second stage. The optimal design has an expected sample size of 23.5 and probability of early termination of 0.696. If the overall PFS is 70% or above at 12 months, pembrolizumab, lenalidomide and dexamethasone will be considered to have shown worthwhile efficacy. A safety analysis will also be conducted at this time and the study will be terminated if the safety stopping rules are met (See section 7.1.2).

7.1.13 Compliance (Medication Adherence)

Drug accountability data for trial treatment will be collected during the study. Compliance with pembrolizumab (MK-3475), lenalidomide and dexamethasone treatment administration will be measured by subjects: 1) receiving unscheduled study agent infusions/injections; or 2)

missing an infusion/injection. Numbers and percentages of subjects and infusion/injection visits with any deviation in these measures will be reported for the ITT population.

Compliance will be defined as the percentage of the "Number of Days on Therapy" over the "Number of Days Should be on Therapy". A day within the study will be considered an "On-Therapy" day if the subject takes study drug on a scheduled day for treatment administration without dose variation or with dose variation, including dose reduction and dose interruption, for reasons other than non-compliance. For each subject, the "Number of Days Should be on Therapy" is the total number of scheduled days for treatment administration from entry to the study to the date of discontinuation.

For each subject, percent compliance will then be calculated using the following formula:

$$\text{Percent Compliance} = \frac{\text{Number of Days on Therapy}}{\text{Number of Days Should be on Therapy}} \times 100.$$

Summary statistics will be provided on percent compliance by treatment group for the ASaT population.

8.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

8.1 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.

Table 14 Product Descriptions

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

8.2 Packaging and Labeling Information

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

8.3 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.

8.4 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.

8.5 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.

9.0 ADMINISTRATIVE AND REGULATORY DETAILS

9.1 Confidentiality

9.1.1 Confidentiality of Data

All information regarding this trial will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator,

except to the extent that it is included in a publication as provided in the Publications section of this protocol.

9.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

9.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator/subinvestigator(s) responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

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9.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to discarding trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

9.4 Compliance with Trial Registration and Results Posting Requirements

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

9.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

9.6 Data Management

Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific paper Case Report Forms (CRFs) when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a subject ID number and initials.

If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided by the Sponsor.

Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Query reports (Data Clarification Requests) pertaining to data omissions and discrepancies will be forwarded to the Investigators and study monitors for resolution. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

Monitoring

Monitoring visits will be conducted by representatives of the Sponsor according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

Subject Confidentiality

In order to maintain subject confidentiality, only a subject number and subject initials will identify all study subjects on CRFs and other documentation submitted to the Sponsor. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

9.7 Data and Safety Monitoring Committee (DSMC)

The Georgetown Lombardi Comprehensive Cancer Center will be responsible for the data and safety monitoring of this multi-site trial. As this study is an investigator initiated Phase II study utilizing an FDA approved drug for which the PI does not hold the IND it is considered a moderate risk study which requires real-time monitoring by the PI and study team and semi-annual reviews by the LCCC Data and Safety Monitoring Committee (DSMC).

The Principal Investigator and the Co-Investigators will review the data including safety monitoring at their weekly institution based disease group meetings and on monthly disease group teleconferences.

All Severe Adverse Events (SAEs) are required to be reported to the IRB. Based on SAEs, the IRB retains the authority to suspend further accrual pending more detailed reporting and/or modifications to further reduce risk and maximize the safety of participating patients.

Progress on the trial and the toxicities experienced will be reviewed by the LCCC Data and Safety Monitoring Committee every 6 months from the time the first patient is enrolled on the study. Results of the DSMC meetings will be forwarded to the IRB with recommendations regarding need for study closure.

DSMC recommendations should be based not only on results for the trial being monitored as well as on data available to the DSMC from other studies. It is the responsibility of the PI to ensure that the DSMC is kept apprised of non-confidential results from related studies that become available. It is the responsibility of the DSMC to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

A written copy of the DSMC recommendations will be given to the trial PI and the IRB. If the DSMC recommends a study change for patient safety or efficacy reasons the trial PI must act to implement the change as expeditiously as possible. In the unlikely event that the trial PI does not concur with the DSMC recommendations, then the LCCC Associate Director of Clinical Research must be informed of the reason for the disagreement. The trial PI, DSMC

Chair, and the LCCC AD for Clinical Research will be responsible for reaching a mutually acceptable decision about the study and providing details of that decision to the IRB. Confidentiality must be preserved during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and staff to seek advice to assist in reaching a mutually acceptable decision.

If a recommendation is made to change a trial for reasons other than patient safety or efficacy the DSMC will provide an adequate rationale for its decision. If the DSMC recommends that the trial be closed for any reason, the recommendation will be reviewed by the Associate Director for Clinical Research at G-LCCC. Authority to close a trial for safety reasons lies with the IRB, with the above described input from DSMC and the AD for Clinical Research.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript.

Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and

writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines

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11.0 APPENDICES

11.1 Common Terminology Criteria for Adverse Events V4.03 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

11.2 MM Diagnostic Criteria

Durie, Seminars in Oncology, Vol 13, No 3 (September), 1986: pp300-309:

1. Criteria for Diagnosis of Multiple Myeloma

Major criteria

I. Plasmacytoma on tissue biopsy.

II. Bone marrow plasmacytosis with >30% plasma cells.

III. Monoclonal globulin spike on serum electrophoresis exceeding 3.5 g/dL for IgG peaks or 2.0 g for IgA peaks, ≥1.0 g/24 h of κ or λ light chain excretion on urine electrophoresis in the absence of amyloidosis.

Minor criteria

a. Bone marrow plasmacytosis with 10% to 30% plasma cells.

b. Monoclonal globulin spike present, but less than the levels defined above.

c. Lytic bone lesions.

d. Normal IgM <50 mg, IgA <100 mg, or IgG <600 mg/dL.

Diagnosis will be confirmed when any of the following features are documented in symptomatic patients with clearly progressive disease. The diagnosis of myeloma requires a minimum of one major + one minor criterion or three minor criteria that must include a + b

1. I + b, I + c, I + d (I + a not sufficient)
2. II + b, II + c, II + d.
3. III + a, III + c, III + d.
4. a + b + c, a + b + d.

2. Criteria for Monoclonal Gammopathy of Undetermined Significance (MGUS), Indolent Myeloma and Smoldering Myeloma (Stage I or IIA)

i. MGUS

I. Monoclonal gammopathy

II. M component level

IgG ≤3.5 g/dL

IgA ≤2.0 g/dL

BJ ≤1.0 g/24 h

III. Bone marrow plasma cells <10%

IV. No bone lesions

V. No symptoms

ii. Indolent myeloma: Criteria as for myeloma (I above) with the following limitations:

I. No bone lesions or only limited bone lesions (≤3 lytic lesions); no compression fractures

II. M component levels

a. IgG <7 g/dL

b. IgA <5 g/dL

III. No symptoms or associated disease features

a. Performance status >70%*

b. Hemoglobin >10 g/dL

c. Serum calcium: normal

d. Serum creatinine <2.0 mg/dL

e. No infections

Smoldering Myeloma: Criteria as for indolent myeloma with additional constraints:

I. There must be no demonstrable bone lesions

II. Bone marrow plasma cells ≥ 10% ≤ 30%

11.3 International Staging System

Greipp PR et al, Journal of Clinical Oncology 2005, May 20:23 (15): 3412-20.

Stage	Criteria	Median survival (mos)
I	Serum Beta-2 microglobulin <3.5 mg/dL AND Albumin >3.5 mg/L	62
II	Neither I or III	45
III	Serum Beta-2 microglobulin >5.5 mg/L	29

11.4 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.

11.5 Multiple Myeloma Disease Response Criteria

Durie et al. International uniform response criteria for multiple myeloma. Leukemia. 2006; 20:1467-1473.

Criteria for multiple myeloma disease assessment:

Table 5 International Myeloma Working Group uniform response criteria: CR and other response categories

Response subcategory	*Response criteria*[a]
sCR	CR as defined below plus Normal FLC ratio and Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c]
CR	Negative immunofixation on the serum and urine and Disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in bone marrow[b]
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
PR	≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h If the serum and urine M-protein are unmeasurable,[d] a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30% In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
SD (not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates)	Not meeting criteria for CR, VGPR, PR or progressive disease

Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.
[a]All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.
[b]Confirmation with repeat bone marrow biopsy not needed.
[c]Presence/absence of clonal cells is based upon the k/λ ratio. An abnormal k/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/λ of >4:1 or <1:2.
[d]Refer to Table 4 for definitions of measurable disease.

Table 6 International Myeloma Working Group uniform response criteria: disease progression and relapse

Relapse subcategory	*Relapse criteria*
Progressive disease[a] To be used for calculation of time to progression and progression-free survival end points for all patients including those in CR (includes primary progressive disease and disease progression on or off therapy)	Progressive Disease: requires any one or more of the following: Increase of ≥25% from baseline in Serum M-component and/or (the absolute increase must be ≥0.5 g/dl)[b] Urine M-component and/or (the absolute increase must be ≥200 mg/24 h Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dl. Bone marrow plasma cell percentage: the absolute % must be ≥10%[c] Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium >11.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder
Clinical relapse[a]	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features)[b] It is not used in calculation of time to progression or progression-free survival but is listed here as as something that can be reported optionally or for use in clinical practice 1 Development of new soft tissue plasmacytomas or bone lesions 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcemia (>11.5 mg/dl) [2.65 mmol/l] 4. Decrease in hemoglobin of ≥2 g/dl [1.25 mmol/l] (see Table 3 for further details) 5. Rise in serum creatinine by 2 mg/dl or more [177 μmol/l or more]
Relapse from CR[a](To be used only if the end point studied is DFS)[d]	Any one or more of the following: Reappearance of serum or urine M-protein by immunofixation or electrophoresis Development of ≥5% plasma cells in the bone marrow[c] Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia see below)

Abbreviations: CR, complete response; DFS, disease-free survival.
[a]All relapse categories require two consecutive assessments made at anytime before classification as relapse or disease progression and/or the institution of any new therapy.
[b]For progressive disease, serum M-component increases of ≥1 gm/dl are sufficient to define relapse if starting M-component is ≥5 g/dl.
[c]Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.
[d]For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

11.6 Events of Clinical Interest Reference Table

Pneumonitis (reported as ECI if ≥ Grade 2)		
Acute interstitial pneumonitis	Interstitial lung disease	Pneumonitis
Colitis (reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotizing colitis	Diarrhea	
Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis	Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA)	
Endocrine (reported as ECI)		
Type 1 diabetes mellitus (if new onset)		
Hematologic (reported as ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Autoimmune hemolytic anemia	Aplastic anemia	Thrombotic Thrombocytopenic Purpura (TTP)
Idiopathic (or immune) Thrombocytopenia Purpura (ITP)	Disseminated Intravascular Coagulation (DIC)	Haemolytic Uraemic Syndrome (HUS)
Any Grade 4 anemia regardless of underlying mechanism		
Hepatic (reported as ECI if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE**)**		
Hepatitis	Autoimmune hepatitis	Transaminase elevations (ALT and/or AST)
Infusion Reactions (reported as ECI for any grade)		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic (reported as ECI for any grade)		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular (report as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Uveitis	Iritis	
Renal (reported as ECI if ≥ Grade 2)		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations (report as ECI if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	
Skin (reported as ECI for any grade)		
Dermatitis exfoliative	Erythema multiforme	Stevens-Johnson syndrome
Toxic epidermal necrolysis		
Skin (reported as ECI if ≥ Grade 3)		
Pruritus	Rash	Rash generalized
Rash maculo-papular		
Any rash considered clinically significant in the physician's judgment		
Other (reported as ECI for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

11.7 List of Abbreviations

Abbreviation/Term	Definition
AE	Adverse event
ADA	Anti-Drug Antibodies
ADCC	Antibody-Dependent Cell-Mediated Cytotoxicity
ALT	Alanine aminotransferase
AML	Acute Myelogenous Leukemia
ANC	Absolute neutrophil count
APC	Antigen Presenting Cells
aPTT	Activated partial thromboplastin time
AUC	Area Under Curve
AST	Aspartate aminotransferase
$^{\beta}$-HCG	Beta human chorionic gonadotropin
CBC	Complete blood count
CDC	Complement-Dependent Cytotoxicity
CNS	Central nervous system
CR	Complete response
CrCl	Calculated creatinine clearance
CRF	Case report form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTL	Cytotoxic T Lymphocytes
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
Dex	Dexamethasone
DL	Dose Level

DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of Response
ECI	Events of clinical interest
ECI-ie	Events of clinical interest with a potential immunologic etiology
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERC	Ethics review committee
FAS	Full analysis set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FLC	Free Light Chain
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
Hb	Hemoglobin

Abbreviation/Term	Definition
HBV	Hepatitis B
HCV	Hepatitis C
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IMiD	Immunomodulatory
IMWG	International Myeloma Working Group
INR	International normalized ratio
irAEs	Immune-related adverse events
IRB	Institutional Review Board
ISS	International Staging System
ITIM	Immunoreceptor tyrosine-based switch motif
ITSM	Immunoreceptor Tyrosine-based Switch Motif
IV	Intravenous
Kg	kilogram
LDH	lactate dehydrogenase
Len	Lenalidomide
LMWH	Low molecular weight heparin
mAb	Monoclonal antibody
MAD	Maximum administered dose
mcL	Millimeters
MEL	Melanoma

MG	Milligram
Mg/kg	Milligram per kilogram
ML	milliliter
MM	Multiple Myeloma
MRI	Magnetic resonance imaging
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MTD	Maximum tolerated dose
NA or N/A	Not Applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NK	Natural Killer
NSAID	Non-steroidal anti-inflammatory drug
ORR	Overall response rate
OS	Overall survival
OTC	Over-the-counter
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PGt	Pharmacogenetic
Abbreviation/Term	Definition
PK-PD	Pharmacokinetic-Pharmacodynamic
PO	Oral administration
PR	Partial response
PT	Prothrombin time
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 Dose

RR	Response rate
Q3W	Every 3 weeks
SAE	Serious adverse events
SAP	Statistical Analysis Plan
sCR	Stringent Complete Response
SFU	Survival follow-up
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SoC	Standard of Care
SJS	Stevens-Johnson Syndrome
SOP	Standard Operating Procedures
SPEP	serum protein electrophoresis
TEN	Toxic Epidermal Necrolysis
TIL	Tumor-infiltrating lymphocytes
TPI	Toxicity Probability Interval
TSH	Thyroid stimulating hormone
TTP	Time To Progression
ULN	Upper limit of normal
UPEP	urinary protein electrophoresis
VTE	Venous Thromboembolism
WHO	World Health Organization