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TITLE: A Phase I/II Study of Anti PD-1 (MK 3475), Pomalidomide and Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma

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TRIAL SUMMARY

Abbreviated Title	Anti-PD-1 (MK-3475) and IMiD (Pomalidomide) and Dexamethasone Combination Immunotherapy in Relapsed/Refractory Multiple Myeloma
Trial Phase	Phase I/II
Clinical Indication	Relapsed and/or Refractory multiple myeloma
Trial Type	Open label dose escalation
Type of control	None
Route of administration	Anti PD1/ MK-3475 - Intravenous Pomalidomide and dexamethasone - Oral
Trial Blinding	N/A
Treatment Groups	Run up dose escalation for safety Phase 2 …expansion cohort for efficacy and safety
Number of trial subjects	Maximum 48 patients
Estimated duration of trial	24 months
Duration of Participation	12 months with an option to continue for responding/stable patients.

Table of Contents

1.0 Trial Design	5
2.0 Objectives & Hypothesis	6
3.0 Background	6
4.0 Rationale	11
5.0 Patient Selection	14
6.0 Treatment	17
7.0 Trial Flow Chart	32
8.0 Trial Procedures	37
9.0 Statistical Analysis Plan	49
10.0 Labeling, Packaging, Storage and Return of Clinical Supplies	50
11.0 Compliance with Laws and Regulations	54
12.0 List of References	56
Appendices	57

1.0 TRIAL DESIGN

1.1 Trial Design

This phase I/II study is focused on patients with relapsed or refractory multiple myeloma. (MM); 48 patients will be enrolled at University of Maryland. Patients must sign informed consent, complete pretreatment evaluations and fulfill all eligibility criteria before enrollment. Pomalidomide is given at standard dose of 4 mg daily orally for 21 days and dexamethasone is given at 40 mg orally on days 1, 8, 15, & 22. MK-3475 will be given as an intravenous infusion at 200 mg every 2 weeks (days 1 and 15). The drug is infused over 30 minutes. Treatment will be administered on an outpatient basis. A run off stage (6 patients) will be treated with MK-3475 at 200 mg every 4 weeks, to establish safety of the combination. If dose limiting toxicity (DLT, defined in Appendix B) is seen in 2 of 6 patients we will review the dosing schedule and consider amending the protocol before the expansion cohorts are started, though this is very unlikely considering the side effect profile of each drug. Additional 6 patients will be treated with MK-3475 at 200 mg on days 1 and 15; DLT will be assessed after cycle-1. If no toxicity is seen will continue the expansion cohort. If DLT is seen in 2/6 patients will consider MK-3475 at 200 mg every 4 weeks the appropriate dose for the expansion cohort.

1.2 Trial Schema

Day	**1**	**8**	**15**	**22**	**28**
Pomalidomide 4 mg Daily Orally Days 1-21	4 mg →				
MK-3475 Intravenously Days 1 and 15	200 mg *		200 mg*		
Dexamethasone Orally weekly**	40 mg PO	40 mg PO	40 mg PO	40 mg PO	

- * In a run off phase, 6 patients will receive MK-3475 intravenously 200 mg on day 1.
- The study will enroll up to 48 patients with possible additional 2 patients allowing for 5% non-evaluable patients.
- Cycles are repeated every 28 days up to 24 months for responding/stable patients, at the assigned dose of pomalidomide and MK-3475 (given on day 1 and day 15 of each 28 day cycle).
- **Elderly patients (over age 70 years) will receive 20 mg of dexamethasone with 2 dose reductions at 12 mg weekly (dose level -1) and 12 mg on days 1 & 15 (dose level -2).

Maintenance

After 24 months of study drugs, stable and responding patients can continue on the study in the maintenance phase until progression, adverse side effects, principal investigator's decision to remove or patient's wish or inability to comply with the study procedure. While on the maintenance phase patients will receive the following:

- Pomalidomide 4 mg daily x 21 days (patients on lower doses due to toxicity will continue on the designated dose).

- Pembrolizumab 200 mg once monthly (patients on lower doses due to toxicity will continue on the designated dose). .
- Dexamethasone 20-40 mg PO will be given weekly (patients on lower does due to toxicity will continue on the designated dose).

Patient follow-up will be monthly to include CBC, chemistry profile, 24 hour urine, and MM staging. A standard of care bone marrow aspirate will be done once yearly. TSH, T3, T4 will be checked every 3 months during the maintenance period.

2.0 OBJECTIVES & HYPOTHESIS

The broad expression of PD-1 and its ligands on malignant plasma cells and bone marrow microenvironment in Relapsed/Refractory Multiple Myeloma (RRMM) patients establishes the importance of the PD-1 pathway in the immune evasion by MM cells. Immune-mediated inflammatory diseases (IMiDs) can down regulate PD-1 and its ligand on T cells and plasma cells respectively. Further inhibition of PD-1/PDL-1 pathway would provide immunotherapeutic benefit as supported by preclinical data. Currently no data is available concerning interaction between Anti-PD-1 and IMiDs. In this study we will evaluate this combination in RRMM patients. Besides establishing the safety and efficacy of the regimen we will focus on correlative studies to identify markers/profiles that can help select patients for future anti-PD-1 therapy.

2.1 Primary Objectives

2.1.1 Establish the safety and tolerability of Pomalidomide and Dexamethasone in combination with MK-3475.

2.1.2 To determine the objective response rate

2.2 Secondary Objectives

2.2.1 Establish time to disease progression in responding RRMM patients.

2.2.2 Exploratory Correlative Studies

a. Identify a biomarker for response by evaluating PD-1/PDL-1 expression in patients' samples.

b. Pharmacogenomics correlation between peripheral blood and bone marrow gene expression profiling and response to therapy.

3.0 BACKGROUND

3.1 Disease

Multiple myeloma (MM) is a clonal plasma cell malignancy characterized by the accumulation of plasma cells in the bone marrow and secretion of immunoglobulin leading to end organ damage that commonly results in anemia, bone destruction, hypercalcemia, and renal failure.[1] MM accounts for 1% of all cancers and 10-15% of hematologic malignancies. In the United States (US), approximately 23,000 cases of MM are diagnosed each year, and 10,650 die yearly.[2] MM survival has dramatically improved over the last decade. This is due to the widespread use of stem cell transplantation, and the introduction of 2 classes of drugs immune modulator (IMiDs) such as thalidomide, lenalidomide and

pomalidomide and the proteasome inhibitors (PI) bortezomib and carfilzomib. Most patients receive multiple lines of therapy over the course of their disease; however, responses remain transient. Patients who relapse and are refractory to these IMiDS and PI do fairly poorly with overall survival of less than 9 months.[3] There are few effective salvage therapies available, so it is crucial to consider innovative targets to improve outcome in the advanced setting.

3.2 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades.[4] Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies[5]. 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.[6]

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) [7; 8]. The structure of murine PD-1 has been resolved [9]. 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. [7] 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. [8] 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. [9] Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. [10] 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. [11] Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell

expansion in subjects with melanoma. [12] 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.

3.3 Agents

MK-3475

Summarized from the Investigator's Brochure (IB). MK-3475 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. MK-3475 strongly enhances T-lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. In T-cell activation assays using human donor blood cells, the EC50 (concentration where 50% of the maximum effect is achieved) has been ~0.1 to 0.3 nM. In addition to interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFN), and levels of other cytokines were found to be modulated by MK-3475. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T-cells.

Using an anti-murine PD-1 analog antibody, PD-1 blockade has been shown to significantly inhibit tumor growth in a variety of syngeneic murine tumor models. In these experiments in mice, anti-PD-1 therapy is synergistic with chemotherapeutic agents such as gemcitabine and 5-fluorouracil (5-FU) and combination therapy results in increased complete tumor regression rates in vivo. After intravenous (IV) administration of MK-3475 to cynomolgus monkeys, systemic exposure to MK-3475 independent of sex, increased with increasing dose. Systemic exposure for the 7-day dosing interval increased after repeated dosing from 40 to 200 mg/kg. Area under the concentration-time curve (AUC) for the 7-day dosing interval (AUC[0-7 days]) after one dose appeared to be dose-proportional from 0.3 to 200 mg/kg, suggesting dose-independent pharmacokinetics (PK). Terminal half-life ($t_{½}$) values from individual animals after repeated IV dosing ranged from 11.8 to 23.7 days (mean values ranged from 15.7 to 22.3 days) across the doses tested. There was no test article-related mortality, and test article-related changes were limited to an increased incidence of inguinal swelling, and increased splenic weights in males receiving 200 mg/kg. The presence of anti-drug antibodies (ADA) in monkeys did not impact the pharmacodynamic response. The presence of ADA was observed in five out of ten animals at 6 mg/kg/dose during the dosing phase, which correlated with an apparent increased rate of elimination of MK-3475 in these animals. No anti-MK-3475 antibodies were detected at 40 or 200 mg/kg/dose. The potential for systemic toxicity was assessed in cynomolgus monkeys administered an IV dose of 6, 40, or 200 mg/kg once every other week for approximately 6 months (a total of 12 doses) followed by a 4-month treatment free period. MK-3475 was well tolerated at all dose levels. There were no test article-related antemortem findings.

Six clinical trials are currently evaluating MK-3475: PN001, PN002, PN006, PN010, PN011, and PN012.

- PN001 is the Phase I first in human (FIH) study of MK-3475, a dose-escalation study in patients with progressive locally advanced or metastatic carcinomas, along with subject expansion cohorts in MEL and NSCLC. Part A examined 3 dose levels (1, 3,

and 10 mg/kg) in patients with solid tumors. With no DLTs observed and no MTD reached, additional PK cohorts were examined at various doses (Parts A-1 and A-2).

- PN002 is a Phase II study designed to evaluate 2 doses of MK-3475 versus a chemotherapy control arm in patients with IPI-refractory metastatic melanoma. Patients are randomized in a 1:1:1 ratio to receive blinded MK-3475 2 mg/kg Q3W or MK-3475 10 mg/kg Q3W, or chemotherapy (according to current clinical practice).
- PN006 is a randomized, controlled, open-label, three-arm pivotal study of two dosing regimens of MK-3475 versus IPI in patients with unresectable or metastatic MEL who have not received IPI treatment. Patients are randomized in a 1:1:1 ratio to receive 10 mg/kg Q2W, 10 mg/kg Q3W, or ipilimumab.
- PN010 is multi-center, worldwide, randomized, adaptively designed Phase II/III trial of MK-3475 at two dosing schedules versus docetaxel in patients with NSCLC with PD-L1 positive tumors who have experienced disease progression after platinum-containing systemic therapy. Patients are randomized to receive 10 mg/kg Q3W, 2 mg/kg Q3W, or docetaxel 75 mg/m2 Q3W.
- PN011 is an open-label, non-randomized, multi-center Phase I study of MK-3475 alone in Japanese patients with advanced solid tumors, and in combination with cisplatin/pemetrexed and carboplatin/paclitaxel in patients with advanced NSCLC.
- PN012 is a multicenter, nonrandomized, multi-cohort trial of MK-3475 in patients with PD-L1 positive advanced solid tumors. All patients will receive MK-3475 10 mg/kg Q2W.

Clinical data from 789 patients treated in PN001 with MK-3475 as a 30-minute IV infusion. MK-3475 has been generally well-tolerated at doses up to 10 mg/kg every other week without DLTs. One (0.002%) patient assayed to date had samples confirmed positive for ADA, but no impact on safety has been observed. Five other clinical studies (PN002, PN006, PN010, PN011, and PN012) are ongoing however preliminary data analyses are not yet available. The observed pharmacokinetic profile of MK-3475 was typical of other IgG mAbs with a half-life ($t_{1/2}$) of approximately 2 to 3 weeks. There was no indication of dose dependency of half-life in the 3 dose groups and a dose related increase in exposure was observed from 1 to 10 mg/kg. The long half-life supports a dosing interval of every 2 or 3 weeks. Durable objective responses have been reported in patients with melanoma and NSCLC. Adverse events have generally been manageable and infrequently require discontinuation of MK-3475 treatment.

Of importance, and based on the literature review, and consideration of mechanism of action of MK-3475, potential immune-related adverse events (irAEs) are the primary events of clinical interest (ECI). Given that immune-related events can involve different organ systems, Merck is providing a guidance document based on the major potential target organs that could be affected by MK-3475 and other molecules that function via an immune mechanism. It is possible that irAEs other than those listed in this document may be observed in patients receiving MK-3475; therefore, all adverse events (AEs) of unknown etiology associated with drug exposure should be evaluated to determine if they are possibly immune-related. See Appendix D for document of ie AEs and ECI.

Pomalidomide:

Pomalidomide, which is an analog of thalidomide, is an immunomodulatory agent with antineoplastic activity. The agent enhances T cell and natural killer cell–mediated immunity and inhibits monocyte production of pro-inflammatory cytokines (e.g., tumor necrosis factor alpha and interleukin-6). It has shown anti-angiogenic activity in animal tumor models and in vitro in the umbilical cord model. In cellular assays, pomalidomide inhibits proliferation and induces apoptosis of hematopoietic tumor cells. It has been found to inhibit proliferation of lenalidomide-resistant multiple myeloma cell lines and to exhibit synergistic activity in inducing apoptosis when combined with dexamethasone in both lenalidomide-sensitive and lenalidomide resistant cell lines. [13-15]

Phase 1 Studies Using Pomalidomide:

An open-label dose-escalation (1, 2, 5, and 10 mg) phase 1 trial established pomalidomide as being well tolerated in doses ranging from 1 to 5 mg/d continuously or on alternate days with response. The maximum tolerated dose (MTD) of pomalidomide given for 21 of 28 days per cycle in patients with RRMM was grade 4 neutropenia at 5 mg/d; the MTD was 4 mg/d. This study determined the dose of 4 mg daily for 21 of 28 days as the recommended dose. A series of phase 2 studies used doses of 2 mg and 4 mg continuously for 28 days with dexamethasone 40 mg once a week. In the first Mayo Clinic trial, responses of PR or better were seen in 63% of patients treated with 2 mg daily. The median duration of response was 21 months, and median progression-free survival was 13 months. Follow-up trials in lenalidomide-refractory patients using pomalidomide 2 mg and 4 mg daily showed responses of PR or better in 32% and 38% of patients, respectively. Among patients refractory to both lenalidomide and bortezomib, responses of PR or better were seen in 26% of the patients treated with 2 mg daily and in 29% of those treated with 4 mg daily. Similar results were reported by the French Intergroup. An analysis of 345 patients enrolled in the Mayo Clinic studies suggested the strongest predictors of response and survival were the number and type of prior regimens. A large multicenter randomized phase 3 trial that compares pomalidomide and low-dose dexamethasone with high-dose (HD) dexamethasone in 455 patients with MM refractory to lenalidomide and bortezomib confirmed the above benefits which is also seen in patients with high-risk cytogenetic. The major toxicity described in pomalidomide myeloma trials is neutropenia. Grade 3-4 neutropenia is reported in 26%-66% of patients and is affected by dose (2 mg or 4 mg) as well as the number of prior treatment regimens. Thrombocytopenia and anemia are also common side effects of therapy. However, grade 3 toxicity is seen in only 13% of patients, and grade 4 is seen in 17% of patients. Non-hematologic toxicities are uncommon. Fatigue is the most commonly reported adverse effect, with 62% of patients experiencing any fatigue and 8% experiencing fatigue of grade 3 or higher. The incidence of thromboembolic events in patients treated with pomalidomide is similar to that in patients treated with the other IMiDs. Venous thromboembolism occurred at a rate of 2-3%. Prophylactic treatment with aspirin is a reasonable strategy for preventing thromboembolic complications. The risk of neuropathy has varied from zero to 33%, but these data are confounded by preexisting neuropathy in these heavily pretreated populations. Infections were seen in 12% of patients, primarily pneumonia, which was seen in 10% of patients. Acute noninfectious pulmonary toxicity has been described in 2 patients. This injury seems to respond to corticosteroids, and reintroduction of pomalidomide has been successful. Finally, skin rash is commonly seen with lenalidomide and thalidomide but rarely seen with

pomalidomide. Pomalidomide induces less constipation, asthenia, and neuropathy than thalidomide. [17, 18, 20-22]

Dexamethasone:

The addition of dexamethasone to all MM therapies (melphalan and prednisone vincristine, doxorubicin, and dexamethasone-VAD) and more recently to IMiDs and PI improves responses rates and in few studies the duration of response. Findings from an ECOG trial which was mostly toxicity profile of high dose dexamethasone led to widespread use of weekly dexamethasone regimens in the recent years. Side effects of dexamethasone are predictable and very manageable.

4.0 RATIONALE

MM patients have an impaired cellular immune response that may contribute to the development and aggressiveness of the malignant clone. The PD1/PDL1 pathway is a critical component of immune suppression in MM. B7-H1 (PDL-1) is differential expressed on malignant plasma cells, especially in the relapsed and refractory setting and is significantly associated with more aggressive features such as high lactate dehydrogenase (LDH). Moreover, increased PD-1 expression was observed on T cells and NK cells isolated from MM patients compared to controls, thus increasing apoptosis of antigen-specific T cells and inhibiting tumor immune surveillance. [23-26]

It is interesting to note that after autologous transplantation, T-cell expression of PD-1 returned to levels seen in normal controls. Similar results were noted in lenalidomide treated patients, resulting in T cell polarization to T-helper-1 phenotype and enhancement of T-cell proliferation and suppression of T-regs. Moreover, lenalidomide treatment led to decrease in PDL-1 expression on plasma cells in MM patients. These emerging data suggest that PD-1/PDL-1 pathway is critical for the immune-modulatory activities of IMiDs. Pre-clinical data suggest that PDL-1 inhibition improves survival of mice after failure of cell-based vaccine in syngeneic transplants.[27-29]

We hypothesize that immunotherapeutic combination with an IMiD (pomalidomide) and anti-PD-1 (MK-3475) can improve overall response in RRMM by combining direct tumor kill and improving T cell immune functions: proliferation and activation.[29]

This is based on

- The broad expression of PD-1 and its ligands on malignant plasma cells and bone marrow microenvironment in RRMM patients.
- The importance of the PD-1 pathway in the immune evasion by MM cells.
- Preclinical data suggesting immunotherapeutic benefit from DP-1/DPL-1.

4.1 Rationale for the Trial and Selected Subject Population

The broad expression of PD-1 and its ligands on malignant plasma cells and bone marrow microenvironment in RRMM patients establishes the importance of the PD-1 pathway in the immune evasion by MM cells. IMiDs can down regulate PD-1 and its ligand on T cells and plasma cells respectively. Further inhibition of PD-1/PDL-1 pathway would provide immunotherapeutic benefit as supported by preclinical data.

4.2 Rationale

4.2.1 Efficacy Endpoints

Currently no data is available concerning interaction between Anti-PD-1 and IMiDs. In this study we will evaluate this combination in RRMM patient with safety and efficacy as the primary endpoints. Considering none overlapping side effects of the 3 drug combination in this trial we do not expect cumulative increase in toxicity.

As far as overall response and its durability, we expect an incremental increase of approximately 15% with the addition of MK-3475 to pomalidomide and dexamethasone. The median duration of response to pomalidomide and weekly dexamethasone was 21 months, and median progression-free survival was 13 months. In RRMM patients, especially lenalidomide-refractory patients, pomalidomide showed responses of PR or better in approximately 30% of patients (range: 29-39%), and lower 25% among patients refractory to both lenalidomide and bortezomib (26%)

4.2.2 Biomarker Research

Besides establishing the safety and efficacy of the regimen, we will focus on correlative studies to identify markers/profiles that can help select patients for future anti-PD-1 therapy. Baseline bone marrow and blood samples will be evaluated for PD-L1 and correlate positive expression with overall responses. Staining for PD1, CD3 and T cell markers CD4, CD8, CD45RO, and FoxP3

Evaluating PDL-1 Expression in Patients' Bone Marrow
In collaboration with University of Chicago we have shown that PD-L1 expression can be detected using anti PD1 antibody used in the study , which was Mab from abcam , clone NAT105, cat # ab 62687. PD-L1 expression on BM bxs was very hard to detect and we are not sure whether the level of expression detected is not affected by BM fixation and decalcification. We have presented preliminary data at ASH 2015. With the significant impact of such finding on patients (correlation with response and later decision to treat) we are refining the methodology for evaluation of PD-L1 expression including comparative study of PDL1 expression by flow cytometry versus paraffin tissue sections. FC is more sensitive than IHC and there is available published literature in this matter. Furthermore, FC measures directly levels of Ag expression whereas IHC uses different amplification systems to increase sensitivity and is difficult to quantify. In addition, fixation and decalcification of BM bxs greatly destroys the antigenicity of some antigens/epitopes, especially PDL-1. Therefore, the results of IHC for PD-L1 on BM bxs may be biased. Since PD-L1 is class II antibody (e.g. interpreted for therapeutically purposes), the PD-L1 stain on BM biopies (fixed and decalcified) has to be calibrated in reference to standard, which has to be defined. It may be the level of PD-L1 expression on PCs by FC and/or IHC on formalin fixed (but not decalcified) plasma cells from the patient's BM aspirate samples. To get

hands on the methodology, we will first to calibrate PD-L1 IHC on Myeloma cell lines, which express PD-L1 and are readily available, and then on patient's samples. The purpose of this calibration is to compare PD-L1 expression by FC vs clots of plasma cell from cell culture, pelleted and resuspended in fibrinogen and clotted with thrombin, vs myeloma cells processed in the same way as patient's BM biopies (fixed and decalcified). Once this is done and we get an idea how they relate (how much PD-L1 Ag is destroyed by fixation and decalcification) we could move to patient's samples.

Evaluate the Expression of PD-1 in Bone Marrow Samples on T Cell Subjects.
To determine whether T-cell expression of PD-1 correlate with clinical features and prognosis among MM patients receiving pembrolizumab, pomalidomide and dexamethasone. This work will be done with Myeloma Service and Immunotherapeutics, Core Memorial Sloan-Kettering Cancer Center. Previous studies suggest that PD-1 expressing CD3+ T cells in newly diagnosed MM had poor overall survival, suggesting the possibility that T cell exhaustion represents a high risk disease characteristic. **The University of Maryland laboratory will perform i**mmunohistochemistry (IHC) on formalin-fixed paraffin-embedded specimens using an anti-human CD3 monoclonal antibody (mAb) (Dako, Clone F7.2.38) and an anti-human PD-1 mAb (Cell Marque, catalog #315M-95). CD3 and PD1 IHC staining were graded as negative (<5% for CD3, < 1% for PD1), or positive (≥5% for CD3, ≥1% for PD1).

4.2.3 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated, and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10mg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity. PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and

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

Pomalidomide has been effective in therapy of MM at doses ranging from 2-5 mg daily for 21 days; the approved dose is 4 mg with dexamethasone 40 mg weekly.

This study will evaluate the combination of Pomalidomide given at standard dose of 4 mg daily orally for 21 days, dexamethasone is given at 40 mg orally on days 1, 8, 15, & 22 and MK3475 given as an intravenous infusion at 200 mg every 2 weeks (days 1 and 15). A run off stage (6 patients) will be treated with MK3475 at 200 mg every 4 weeks (day 1), to establish safety of the combination. Once safety is established however, these 6 patients will always receive D1 dosing only.

5.0 PATIENT SELECTION

5.1 Inclusion Criteria:

1. Confirmed diagnosis of relapsed and/or refractory MM according to International Myeloma Working Group guidelines (2003); refractory disease is defined as documented disease progression during or within 60 days after their most recent line of anti-myeloma therapy.

2. Received two lines of prior therapy that includes an IMiD (lenalidomide or thalidomide) and a proteosome inhibitor (bortezomib and/or carfilzomib) (used either separately or in combination).
    a. Prior pomalidomide therapy is permitted, provided the patient achieved at least a partial remission and had not progressed for 3 months after stopping therapy.
3. Measurable disease as defined by one or more of the following criteria (assessed within 28 days prior to registration):
    a. Serum paraprotein ≥ 5 g/L (for IgA patients whose disease can only be reliably measured by serum quantitative immunoglobulin (IgA): ≥ 7.5 g/L)
    b. Urine Bence Jones Protein: ≥ 200 mg/24 h
    c. Serum light chain assay: Involved free light chain (FLC) level ≥ 100 mg/L, provided serum FLC ratio is abnormal
4. Be willing and able to provide written informed consent/assent for the trial.
5. Be ≥ 18 years of age on day of signing informed consent.
6. Have a performance status of < 2 on the ECOG Performance Scale.
7. Demonstrate adequate organ function as defined in Table 1 below, all screening labs should be performed within 28 days of treatment initiation.

Table 1

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,000 /mcL
Platelets	≥75,000 / mcL
Hemoglobin	≥9 g/dL
Serum creatinine **OR** creatinine clearance (if Cr > 2 mg/dL)	≤2 mg/dl ≥60 mL/min
Serum total bilirubin	≤ 1.5 X ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
International Normalized Ratio (INR) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN ≤1.5 X ULN If on anticoagulant therapy (PT or PTT should be therapeutic)
[a]Creatinine clearance should be calculated per institutional standard.	

8. Female subject of childbearing potential should have a negative serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
9. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

5.2 Exclusion Criteria

1. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.
2. Has a diagnosis of immunodeficiency (HIV) or is receiving systemic steroid therapy (in excess of 20 mg of prednisone daily) or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
3. Has had a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
4. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent. Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
5. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
6. Has known active central nervous system disease and/or carcinomatous meningitis.
7. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study.
8. Has evidence of interstitial lung disease or active, non-infectious pneumonitis.
9. Has an active infection requiring systemic therapy.
10. 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.
11. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

12. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
13. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or other antibody or drug specifically targeting T-cell co-stimulation).
14. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
15. Has known active Hepatitis B (HBsAg reactive) or Hepatitis C (HCV RNA [qualitative] is detected).
16. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

6.0 TREATMENT

6.1 Study schedule

The treatment to be used in this trial is outlined below

Table 2

Drug	Dose Level	Dose Frequency	Route of Administration	Treatment Period
MK-3475	200 mg	Every 2 weeks*	IV infusion	Days 1 and 15
Pomalidomide	4 mg	Daily	PO	Days 1-21
Dexamethasone	40 mg	Weekly	PO	Days 1, 8, 15, & 22

* In a run off phase, 6 patients will receive MK-3475 200 mg intravenously day 1.

- Dose adjustment due to toxicity as described in Section 6.2.
- Trial treatment should begin on the day of registration or as close as possible to the date on which treatment is allocated/assigned.

6.2 Dose Modification

Following the DLT evaluation Cycle-1 for the first 6 patients on the monthly schedule and 6 in the twice monthly schedule, the dose of MK-3475, pomalidomide and dexamethasone could be modified as outlined in Tables below. Subjects, who discontinue pomalidomide or dexamethasone due to toxicity, may continue receiving MK-3475 until unacceptable toxicity or progression. Subjects who discontinue MK-3475 due to untoward toxicities may not continue on the study receiving only pomalidomide and dexamethasone.

After any study medication has been held for any reason it may be restarted when clinically indicated according to any applicable dose modification guidelines and the dosing schedule conforms to the schedule of the normal dosing Cycle (e.g. MK-3475 must always be given on Day 1 or Day 15 and cannot be given on Day 21).

If dose modifications are necessary during the DLT observation period due to drug-related AEs that do not meet DLT criteria, then this would be considered a DLT in the run-off phase.

6.2.1 Dexamethasone

Dexamethasone doses will be modified due to toxicity as follows:

Table 3: Dose modification guidelines for Dexamethasone-related adverse events

Toxicity	Grade	Hold Treatment (Y/N)	Timing for Restarting Treatment	Dose/Schedule for Restarting Treatment	Discontinue Subject (after consultation with sponsor)
Non-hematological toxicity	1	No	N/A	N/A	N/A
	2	Consider withholding for persistent symptoms	Toxicity resolves to Grade 0-1 or baseline	Clinical AE resolves within1 week: Same dose and schedule	N/A
	3, 4	Yes	Toxicity resolves to Grade 0-1 or baseline	May decrease the dosing one level for each occurrence	Toxicity does not resolve within 4 weeks

- Dexamethasone doses will be modified due to toxicity as follows:
    - Original dose Level: Dexamethasone 40 mg by mouth on days 1, 8, 15, & 22of a 28-day cycle.
    - Dose level -1: Dexamethasone 20 mg by mouth on days 1, 8, 15, & 22 of a 28-day cycle.
    - Dose level -2: Dexamethasone 20 mg by mouth on days 1&15) of a 28-day cycle.

- Elderly patients (over age 70 years) will receive 20 mg of dexamethasone with 2 dose reductions at 12 mg weekly (dose level -1) and 12 mg on days 1, & 15 (dose level -2).

6.2.2 MK-3475

MK-3475 will be withheld for drug-related Grade 4 hematologic toxicities, non-hematologic toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per Tables below.

Table 4: Dose Modification Guidelines for Hematological Drug-Related Adverse Events

Toxicity	Grade	Hold Treatment (Y/N)	Timing for Restarting Treatment	Dose/Schedule for Restarting Treatment [1]	Discontinue Subject (after consultation with sponsor)
Hematological	1, 2, 3	No	N/A	N/A	N/A

Toxicity	Grade	Hold Treatment (Y/N)	Timing for Restarting Treatment	Dose/Schedule for Restarting Treatment [1]	Discontinue Subject (after consultation with sponsor)
Toxicity	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*
[1] See below for dose levels of MK-3475					

Table 5 Dose Modification Guidelines for Non-Hematological Drug-Related Adverse Events

Toxicity	Grade	Hold Treatment (Y/N)	Timing for Restarting Treatment	Dose/Schedule for Restarting Treatment [1]	Discontinue Subject (after consultation with Sponsor)
Non-hematological toxicity Note: Exceptions to be treated similar to Grade 1 toxicity • Grade 2 alopecia • Grade 2 fatigue For additional information regarding Adverse Events with a potential Immune-Etiology reference Section 6.5 with tables 8 and table 9.	1	No	N/A	N/A	N/A
	2	Consider withholding for persistent symptoms [2, 3]	Toxicity resolves to Grade 0-1 or baseline	*Clinical AE resolves within 4 weeks*: Same dose and schedule (reference Section 6.5.1.f for recommendations regarding pneumonitis) *Clinical AE does resolve within 4 weeks:* May decrease dose to next lower dose level for each occurrence	Toxicity does not resolve within 4 weeks of last infusion
	3	Yes [4]	Toxicity resolves to Grade 0-1 or baseline	May decrease dose to next lower dose level for each occurrence	Toxicity does not resolve within 4 weeks of last infusion
	4	NA	NA	NA	MK-3475 will be Permanently discontinued
[1] See below for dose levels of MK-3475. [2] During DLT evaluation period, depending on the nature of AE, for subjects who develop **Grade 2** non-heme drug-related AE, MK-3475 will not be held, if symptoms improve with appropriate supportive care					

Toxicity	Grade	Hold Treatment (Y/N)	Timing for Restarting Treatment	Dose/Schedule for Restarting Treatment [1]	Discontinue Subject (after consultation with Sponsor)
and symptomatic treatment within 3 days. [3] During DLT evaluation period, depending on the nature of AE, for subjects who develop **Grade 2** non-heme drug-related AE, MK-3475 will be held, if symptoms do not improve with appropriate supportive care and symptomatic treatment within 3 days and it will be considered DLT. [4] During DLT evaluation period, for subjects who develop **Grade 3** non-heme drug-related AE, MK-3475 will be held (except for inadequately treated nausea, hypersensitivity reactions, or fatigue lasting less than 3 days) and it will be considered DLT.					

MK-3475 doses will be modified due to toxicity as follows:

- Original dose level: MK-3475 200 mg IV on days 1and 15 of a 28-day cycle.
- Dose level -1: MK-3475 200 mg IV every 4 weeks of a 28-day cycle.
- Dose level -2: MK-3475 100 mg IV on days 1 and 15 of a 28-day cycle
- Dose level -3: MK-3475 100 mg IV every 4 weeks of a 28-day cycle.

For toxicity related to MK-3475 that does not resolve to Grade 0-1 within 4 weeks after last infusion, trial treatment (i.e., MK-3475+Pom+Dex) should be discontinued after consultation with the Principal Investigator. For information on the management of adverse events, see Section 6.2.2.

- For subjects who experience a recurrence of the same AE(s) at the same grade or greater with rechallenge of MK3475, the subject must discontinue trial treatment.

- In subjects who continue on trial treatment after experiencing an adverse event warranting potential dose modification, if considered drug-related by the investigator, once the subject has recovered to ≤ Grade 1 the dose of MK-3475 in subsequent cycles will be decreased to next lower dose level (e.g., if the subject is receiving 200 mg, it will be reduced to 100 mg every 4-weeks). Following such dose reduction due to toxicity, an additional dose reduction may be allowed. For example, subjects who began the study receiving 200 mg on a 2 week dosing schedule, and have stopped drug twice due to a drug-related toxicity that meets the above criteria, should now be dosed 100 mg every 4 weeks. Subjects who experience a DLT in Cycle 1 should be discontinued from the study. However, if it has been determined that the subject is deriving clinical benefit from the study therapy, the subject may be allowed to continue at a lower dose as indicated in table 5. It should be noted that if the dose of MK-3475 is reduced due to toxicity, the pomalidomide and dexamethasone should continue to be administered per study guidelines.

- In an individual subject, following a reduction in the dose of MK-3475, pomalidomide and dexamethasone, a subsequent increase in the dose will not be permitted.

6.2.3 Pomalidomide

Pomalidomide will be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per Table 6 below.

Table 6: Dose Modification Guidelines for Pomalidomide-Related Adverse Events

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with Sponsor)
Neutropenia or Febrile neutropenia (fever ≥ 38.5°C and ANC < 1,000/μL)	1, 2, 3 4	No Yes, for the reminder of the cycle	N/A Toxicity resolves to Grade 1 or baseline. Can use granulocyte colony-stimulating factor (GCFS) N/A	N/A If ANC ≥ 1000/μLcontinue same dose otherwise decrease 1 dose level	N/A Toxicity does not resolve within 4 weeks
Thrombocytopenia	1, 2, 3 4	No Yes, for the reminder of the cycle	N/A Toxicity resolves to Grade 1 or baseline.	N/A Decrease one dose level	N/A Toxicity does not resolve within 4 weeks
Rash	3 4	Yes, for the reminder of the cycle Discontinue	Toxicity resolves to Grade 1 Discontinue	Decrease one dose level Discontinue	Rash does not resolve within 4 weeks Discontinue
Deep Vein Thrombosis (DVT)	1, 2, 3 4	No Yes, for the reminder of the cycle	N/A Initiate anticoagulation treatment. Maintain dose level when dosing restarted at next cycle at discretion of treating physician.	N/A Initiate anticoagulation treatment. Maintain dose level when dosing restarted at next cycle at discretion of treating physician.	N/A Initiate anticoagulation treatment. Maintain dose level when dosing restarted at next cycle at discretion of treating physician.
Peripheral neuropathy	2, 3, 4	Yes, for the reminder of the cycle	neuropathy must resolve to ≤ Grade 1	Decrease one dose level	If painful neuropathy persist for > 4 weeks

Other Non-hematological toxicity Note: Exceptions to be treated similar to grade 1 toxicity • Grade 2 alopecia • Grade 2 fatigue	1 2 3,4	No Consider withholding for persistent symptoms Yes	N/A Toxicity resolves to Grade 0-1 or baseline Toxicity resolves to Grade 0-1 or baseline	N/A *Clinical AE resolves within 1 week*: Same dose and schedule May decrease the dosing one level for each occurrence	N/A N/A Toxicity does not resolve within 4 weeks.

Pomalidomide doses will be modified due to toxicity as follows:

- Original dose level: Pomalidomide 4 mg /day PO on days 1-21 of a 28-day cycle
- Dose level -1: Pomalidomide 3 mg/day PO on days 1-21 of a 28-day cycle
- Dose level -2: Pomalidomide 2 mg/day PO on days 1-21 of a 28-day cycle
- Dose level -3: Pomalidomide 1 mg/day PO on days 1-21 of a 28-day cycle

6.3 Timing of Dose Administration

All trial treatments will be administered on an outpatient basis.

Cycles are repeated every 28 days.

MK-3475 should be administered on Day 1 and 15 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). In a run off phase, 6 patients will receive MK-3475 intravenously on day 1. Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. No delays are allowed for day 15. On day 15 if the MK-3475 is not given the dose is cancelled. MK-3475 will be administered as a 30 minute IV infusion (treatment cycle intervals may be increased due to toxicity as described in Section 6.2.2). 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).

Pomalidomide will be given orally days 1-21. Pomalidomide capsules should be swallowed whole, and should not be broken, chewed or opened. Pomalidomide should be taken without food, at least 2 hours before or 2 hours after a meal. If a dose of pomalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up, rather it should be taken at the next scheduled time point. Patients who take more than the prescribed dose of pomalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

Dexamethasone will be given orally on days 1, 8, 15, & 22.

6.4 Concomitant Medications

6.4.1 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 will 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 and events of clinical interest (ECIs) as defined in Section 7.2.

6.4.2 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:

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than MK-3475
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion is allowed.

- 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, chicken pox, yellow fever, rabies, Bacillus Calmette-Guerin (BCG), and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- 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.

6.5 Supportive Care Guidelines

6.5.1 For MK-3475

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below:

a. **Diarrhea:** 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). In symptomatic subjects, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.
    - In subjects with severe enterocolitis (Grade 3), MK-3475 will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.
    - In subjects with moderate enterocolitis (Grade 2), MK-3475 should be withheld and anti-diarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Regarding guidelines for continuing treatment with MK-3475, see Section 6.2.
    - All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be given via IV infusion.

b. **Nausea/vomiting:** Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic

antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

c. **Anti-infectives**: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

d. **Infusion Reactions:** Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: allergic reaction/hypersensitivity (including drug fever); arthralgia (joint pain); bronchospasm; cough; dizziness; dyspnea (shortness of breath); fatigue (asthenia, lethargy, malaise); headache; hypertension; hypotension; myalgia (muscle pain); nausea; pruritis/itching; rash/desquamation; rigors/chills; sweating (diaphoresis); tachycardia; tumor pain (onset or exacerbation of tumor pain due to treatment); urticaria (hives, welts, wheals); vomiting.

Table 7 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of MK-3475.

Table 7 : 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**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of MK-3475 with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	premedication should be permanently discontinued from further trial treatment administration.	
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. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

e. Immune-related Adverse Events (irAEs)

Events of clinical interest of a potential immunologic etiology (irECIs) may be defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. irAEs may be predicted based on the nature of the MK-3475 compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE. Information on how to identify and evaluate irAEs has been developed and is included in the Event of Clinical Interest and Immune-Related Adverse Event Guidance Document located at the end of this protocol document. Subjects who develop a Grade 2 or higher irAE should be discussed immediately with the Sponsor.

Recommendations to managing irAEs not detailed elsewhere in the protocol are detailed in Table 8.

Table 8 General Approach to Handling irAEs

irAE	Withhold/Discontinue MK-3475?	Supportive Care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold MK-3475	Consider systemic corticosteroids in addition to appropriate symptomatic treatment
Grade 3	Withhold MK-3475 Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 12 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.

f. Supportive Care Guidelines for Pneumonitis

Subjects with symptomatic pneumonitis should immediately stop receiving MK-3475 and have an evaluation. The evaluation may include bronchoscopy and pulmonary function tests to rule out other causes such as infection. If the subject is determined to have study drug associated pneumonitis, the suggested treatment plan is detailed in Table 9.

Table 9 Recommended Approaches to Handling Pneumonitis

Study drug associated pneumonitis	Withhold/Discontinue MK-3475?	Supportive Care
Grade 1 (asymptomatic)	No action	Intervention not indicated
Grade 2	Withhold MK-3475, may return to treatment if improves to Grade 1 or resolves within 12 weeks	Systemic corticosteroids are indicated. Taper if necessary.
Grade 3 and Grade 4	Discontinue MK-3475	Systemic corticosteroids are indicated. The use of infliximab may be indicated as appropriate. Refer to the Event of Clinical Interest and Immune-related Adverse Event Guidance Document for additional recommendations.

For Grade 2 pneumonitis that improves to ≤ Grade 1 within 12 weeks, the following rules should apply:

- First episode of pneumonitis
    - May increase dosing interval by one week in subsequent cycles
- Second episode of pneumonitis – permanently discontinue MK-3475 if upon rechallenge subject develops pneumonitis ≥ Grade 2

6.5.2 For Pomalidomide

Pomalidomide increases the risk of thrombotic events in patients who are at high risk or with a history a thrombosis, in particular when combined with other drugs known to cause thrombosis. Consideration should be given to the use of aspirin (81 or 325

mg) or some other form of prophylaxis as deemed appropriate. Low molecular weight heparin may be utilized in patients that are intolerant to aspirin (ASA). Coumadin should be used with caution and close monitoring of INR.

6.5.3 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.

6.6 Diet/Activity/Other Considerations

6.6.1 Diet

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

6.6.2 Contraception

Subjects should be informed that taking pomalidomide 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. 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. 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.

MK-3475 may have adverse effects on a fetus in utero. Furthermore, it is not known if MK-3475 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).

6.6.3 Use in Pregnancy

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on pomalidomide and MK-4375 , or within 28 days of the subject's last dose are considered immediately reportable events. Both pomalidomide and MK-4375 are to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Merck Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Merck immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Merck Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspect is related to the in utero exposure to the pomalidomide and MK-3475 should also be reported.

Male Subjects: If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking pomalidomide and MK-4375should notify the Investigator immediately, and the pregnant female partner should be advised to call their healthcare provider immediately.

Drug Safety Contact Information:

Merck Global Safety. (Attn: Worldwide Product Safety; FAX (215) 993-1220)

6.6.4 Use in Nursing Women

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.

6.7 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 8.4.

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

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 8.4
- Unacceptable adverse experiences as described in Section 6.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of treatment with MK-3475
- Administrative reasons

The End of Treatment (EOT) and Follow-up visit procedures are listed in Trial Flow Chart and Section 8.6 (Visit Requirements). 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 in Section 8.6. 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.

6.8 Subject Replacement Strategy

If the patient did not finish at least one cycle of therapy he/she will be considered un-evaluable and will be replaced; unless the patient stopped therapy for an SAE related to drug.

6.9 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's decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

7.0 TREATMENT PHASE TRIAL FLOW CHART

Trial Period:	Screening Phase	Treatment Period (28 Day Cycles)				EOT	Post-Treatment		
Treatment Cycle/Title:	Main Study Screening	Cycles 1 through 12[17]		Cycles 13-24		Discontinuation	Safety Follow-up	Follow Up Visits	Survival Follow-Up
Scheduling Window (Days):	-28 to -1	D 1[12,16]	D 15[16]	D 1[12,16]	D 15[16]	At time of discontinuation	30 days post discontinuation	Every 8 weeks post discontinuation	Every 12-16 weeks
Administrative Procedures									
Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Demographics	X								
Medical History	X								
Prior and Concomitant Medication Review	X	X	X	X	X	X	X		
IV MK-3475 administration		X	X	X	X				
Oral POM dosing		Days 1-21							
Oral Dex dosing		Days 1, 8, 15 and 22							
Dispense/Collect / Review drug diary		X	X	X	X	X			
Post-study anticancer therapy status								X	
Survival Status									X
Clinical Procedures/Assessments									
Adverse Events		X	X	X	X	X	X		
Full Physical Examination	X	X		X		X	X		
Directed Physical Examination[6]			X		X				
Vital Signs, Height[5] and Weight	X	X	X	X	X	X	X		
ECOG Performance Status	X	X		X		X	X		
12 Lead EKG	X								
Laboratory Procedures									
Pregnancy Test:[1] Urine or Serum -HCG-1	X	X		X		X	X		
PT/INR and aPTT,[15]	X	X				X	X		
CBC with Differential	X	X	X	X	X	X	X		
Comprehensive Serum Chemistry Panel[2,]	X	X	X	X	X	X	X		
Urinalysis [15]	X	X				X	X		
T3, FT4 and TSH,[15]	X	X				X	X		
Efficacy Measurements									
SPEP, IF, quant immunoglobulin[3,10]	X	X		X		X		X	

Trial Period:	**Screening Phase**	**Treatment Period (28 Day Cycles)**				**EOT**	**Post-Treatment**		
Treatment Cycle/Title:	**Main Study Screening**	**Cycles 1 through 12[17]**		**Cycles 13-24**		**Discontinuation**	**Safety Follow-up**	**Follow Up Visits**	**Survival Follow-Up**
Scheduling Window (Days):	**-28 to -1**	**D 1[,12,16]**	**D 15[16]**	**D 1[,12,16]**	**D 15[16]**	**At time of discontinuation**	**30 days post discontinuation (+/- 7 days)**	**Every 8 weeks post discontinuation (+/- 7 days)**	**Every 12-16 weeks**
Serum free light chains[10]	X	X		X		X		**X**	
24-hour urine for UTP, UPEP, UIF[3,10]	X	X		X		X		X	
B-2-M, CRP[3,10]	X	X		X		X		X	
Bone marrow Aspirate and Biopsy[4]	X	X[13]							
Skeletal Scan	X								
PET/CT OR MRI[7]	X	X							
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood (Optional)									
Bone Marrow Aspirate	X	X[14]							
Correlative Studies Blood Collection[8,9]	X	X	X						

1. Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Pregnancy tests must occur 10 – 14 days before the first dose of POMALIDOMIDE and again within 24 hours prior to the first dose of POMALIDOMIDE. Once on study the following applies – Pregnancy test every week during the first 4 weeks of treatment. After the first 4 weeks are complete females with regular menstrual cycles will have a pregnancy test done every 4 weeks (including breaks in therapy). Females with irregular cycles will have a pregnancy test done every 2 weeks. Pregnancy testing will also be done at discontinuation of study and at Day 28 post the last dose of pomalidomide.
2. Includes sodium, potassium, chloride, CO2, calcium, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, SGOT/AST, SGPT/ALT, LDH, uric acid, magnesium, phosphorous
3. SPEP = serum protein electrophoresis; IF = serum immunofixation; UTP = urine total protein; UPEP = urine protein electrophoresis; UIF = urine immunofixation; B2M = beta-2 microglobulin; CRP = C-reactive protein
4. Bone marrow will be repeated to confirm complete remission or as clinically indicated.
5. Required at screening only
6. Day 15 if clinically indicated
7. PET/CT OR MRI of neck/chest/abdomen/pelvis as clinically indicated.
8. At initial screening, Day 1 and 15 of cycle 1, 2 and 3 and at time of relapse
9. Correlative Studies Blood Collection to be drawn at time of relapse also.
10. Required from Cycle 2 onwards on day 1. Also on C1D1 if screening is > 14 days from C1D1.
11. ECOG will be done every other cycle after Cycle 8
12. After Cycle 1, pre-dose lab 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.
13. Standard of care Bone marrow will be repeated on Cycle 3 Day 1 (+/- 3 days) to confirm complete remission or as clinically indicated.

14. To be collected on Cycle 3 Day 1 (+/- 3 days) only if standard of care bone marrow sample is done.
15. Day 1 of cycles 3 and 6 only.
16. Run off phase patients have study visits only on Day 1 of every cycle. Day 15 study visit is applicable only if they have Correlative blood collections or for clinical care.
17. During cycle 1 only, subjects will come in on week 2 and week 4 for safety lab checks.

7.1 Maintenance Trial Flow Chart

Trial Period	Maintenance				
Maintenance Treatment Cycle	**Once Weekly**	**Days 1-21**	**Once Monthly**	**Every 3 Months**	**Once Yearly**
Administration Procedures					
IV MK-3475 Administration[1]			X		
Oral POM Dosing		X			
Oral Dexamethasone Dosing	X				
Laboratory Procedures					
CBC with Differential			**X**		
Comprehensive Serum Chemistry Panel (refer to footnote 2 on trial flow chart)			**X**		
SPEP, IFE, 24-hour urine for UTP, UPEP, , UIFE			**X**		
T3, FT4 and TSH				**X**	
Bone marrow Aspirate and Biopsy					**X**
Free serum light chain			**X**		
Beta-2 microglobulin (B2M)			**X**		
C-reactive protein-CRP			**X**		

Quantitative immunoglobulin (IgG, IgA, IgM)			**X**		

1. Day 1 of each month

8. TRIAL PROCEDURES

8.1 Administrative Procedures

8.1.1 Informed Consent

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

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

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

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject 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.

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

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

8.1.2 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.

8.1.3 Subject Study Oral Study Drug Diary

All subjects will be given a study diary to record the oral study drug administration. The diary will be given at cycle 1 day 1.

8.1.4 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.

8.1.5 Prior and Concomitant Medications Review

a. 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.

b. 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 as defined in Section 8.12.1, and 8.12.2.

8.1.6 Disease Details and Treatments

a. Disease Details

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

b. Prior Treatment Details

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

c. 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.

8.2 Clinical Procedures/Assessments

8.2.1 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 4.0. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with MK-3475 exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (irAE). See Appendix D for the separate guidance document regarding the identification, evaluation and management of AEs of a potential immunological etiology.

Please refer to section 7.9 for detailed information regarding the assessment and recording of AEs.

8.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period and day 1 of all cycles. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

8.2.3 Directed Physical Exam

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

8.2.4 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 7.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

8.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix A) at screening, and prior to the administration of trial treatment on Day 1 of each cycle,and at discontinuation of trial treatment as specified in the Trial Flow Chart. After Cycle 8 assessment of ECOG status will be performed every other cycle in conjunction with the directed or full physical exam.

8.2.6 Multiple Myeloma Response Assessment

Myeloma objective response rate will be assessed using the International Myeloma Working Group Uniform Response Criteria (See Appendix C1 & C2). Response rate categories that will be evaluated include Stringent Complete Response, Complete Response, Very Good Partial Response, Partial Response, Stable Disease, Plateau Disease, Minimal Response and Disease Progression.

Progression-Free Survival and Overall Survival PFS will be defined as the time from first treatment day until objective or symptomatic progression or death. OS will be defined as the time from first treatment day until death.

8.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

All patients will be encouraged to consent for correlative studies. We will collect from consenting patients: peripheral blood (10 ml) at initial screening, Day 1 and 15 of cycle 1, 2 and 3 and at time of relapse

Bone marrow aspirate (5 ml) will be obtained at initial screening and confirmation of remission as well as at progression. The response or lack off for each patient will be correlated with the PD-1/PDL-1 expression in patients' samples and possibly pharmacogenomics using gene expression profiling. Staining for PD1, CD3 and T cell markers CD4, CD8, CD45RO, and FoxP3

See lab manual for more information regarding collection and processing of samples.

8.3 Laboratory Procedures/Assessments

8.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 10. The amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), are all standard of care. Less than 30 ml will be collected as research over the study period.

Table 10 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	SPEP = serum protein electrophoresis; IF = serum immunofixation,
Hemoglobin	Alkaline phosphatase	Glucose	Serum β-human chorionic gonadotropin†
Platelet count	Alanine aminotransferase (ALT)	Protein	(β-hCG)†
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
	(CO_2 or biocarbonate)	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid	UTP = urine total protein; UPEP = urine protein electrophoresis; UIF = urine immunofixation	B2M = beta-2 microglobulin, CRP = C-reactive protein
	Calcium		Free serum light chains
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		
	Creatinine		
† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. ‡ If considered standard of care in your region.			

8.4 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the discontinuation trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.9 - Assessing and Recording Adverse Events. After discontinuing treatment following assessment of complete disease response (CR), these subjects should return to the site for a Safety Follow-up Visit (described in Section 8.6 and then proceed to the Follow-Up Period of the study (described in Section 8.7).

8.5 Visit Requirements

Visit requirements are outlined in Section 7.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 8.0, Trial Procedures.

8.6 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days **(+/- 7 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 30 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

8.7 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 8 weeks (56 ± 7 days) by restaging 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, or end of the study as detailed in Section 6.2.2. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

8.8 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 12-16 weeks or via the patient's medical record review to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

8.9 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 protocol therapy 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.

Investigational 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 trial 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.

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 8.12.

If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

8.10 Definition of an Overdose for This Protocol and Reporting of Overdose to Merck

For purposes of this trial, an overdose will be defined as any dose exceeding 1000mg for MK-3475 by 20% over the prescribed dose or extra-doses of Pomalidomide. No specific information is available on the treatment of overdose of MK-3475 or pomalidomide. In the event of overdose, therapy should be discontinued and 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 MK-3475 or pomalidomide, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of MK-3475 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.

8.11 Reporting of Pregnancy and Lactation to Merck

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 pregnancy outcome must also be reported.

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

8.12 Immediate Reporting of Adverse Events to Merck

Serious adverse events (SAE) are defined below. The investigator must inform Merck in writing of any SAE within 2 business days of being aware of the event. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required.

Reporting of Adverse Events

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting the UMGCC DSM/QAC to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient. Any adverse experiences which occur at any time during the clinical study or within 30 days of receiving the last dose of study medication, whether or not related to the study drug will be reported as per institutional policy.

Adverse events will be tracked starting from Dose 1. The AE grading scale will be based on CTCAE version 4 to grade the severity of the events. Expeditious reporting to the IRB, based according to the UM IRB Reportable New Information (RNI) criteria, will follow HRPO's current guidelines. All AEs whether or not related to the study drugs will be reported to the DSM/QAC according to the UMGCC DSM/QAC SOP.

8.12.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of the investigational 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 11 for additional details regarding each of the above criteria.

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

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 the protocol therapy, must be reported locally to the site Institutional Review Board (IRB) per local policy and within 2 working days to Merck Global Safety. The sponsor will then report the event to Merck Global Safety (Attn: Worldwide Product Safety; FAX: 215 993-1220) using FDA Form 3500A (MedWatch Form) within 2 working days of becoming aware of the event. The event should also be reported locally to the site Institutional Review Board (IRB) per local policy. The serious adverse event must also be reported to the FDA using FDA Form 3500A (MedWatch Form) within 7 days. If the serious event is unexpected fatal, or life threatening it must be reported to the FDA as soon as possible but no later than 7 calendar days following the sponsor's initial receipt of the information.

Additionally, any serious adverse event considered by an investigator (who is a qualified physician) to be related to protocol therapy that is brought to the attention of the study team at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor. The sponsor will then report the event to Merck using FDA Form 3500A (MedWatch Form).

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 protocol therapy that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck.

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

A copy of all 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 for the duration of the SAE to determine outcome.

8.12.2 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 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 7.10 - 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.

3. In the event a subject develops any of the following AEs, a detailed narrative of the event should be reported as an ECI to Merck Global Safety within 2 working days of the event:

   a. Grade ≥ 3 diarrhea

   b. Grade ≥ 3 colitis

   c. Grade ≥ 2 pneumonitis

   d. Grade ≥ 3 hypo- or hyperthyroidism

Potential Skin Events of Clinical Interest:
Every attempt should be made by the study team to take photographs of the actual ECI skin lesion or rash as soon as possible. If affected, photographs should be taken of:

- the head (to assess mucosal or eye involvement)
- the trunk and extremities
- a close-up of the skin lesion/rash.

If possible, a ruler should be placed alongside the site of the skin occurrence as a fixed marker of distance.

- The time/date stamp should be set in the 'ON' position for documentation purposes.
- Photographs should be stored with the subject's study records.
- Merck may request copies of photographs.

In addition to the photographs, the following documents from the Merck Pembrolizumab Program (MK-3475) Event of Clinical Interest Guidance Document (at the end of the protocol) need to be completed and faxed to Merck Global Safety (Attn: Worldwide Product Safety, FAX: 215-993-1220) within 2 business day of the subject's presentation with the dermatologic event:

- Appendix 2—Past Medical History Related to Dermatologic Event
- Appendix 3—Presentation of the Dermatologic Event

- Appendix 4—Focused Skin Examination

A separate guidance document has been provided entitled "event of Clinical Interest and Immune-Related Adverse Event Guidance Document." This document provides guidance regarding identification, evaluation and management of ECIs and irAEs. Additional ECIs are identified in this guidance document and also need to be reported to Merck Global Safety within 2 working days of the event.

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.

ECIs that occur in any subject from the date of first dose through 90 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the Merck's product, must be reported to Merck Global Safety within 2 working days.

8.12.3 Evaluating Adverse Events

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

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

8.12.4 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.

Table 11 Evaluating Adverse Events

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 study treatment 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.)

9.0 STATISTICAL ANALYSIS PLAN

The main objectives in this study of the study in patients with relapsed/refractory multiple myeloma are assessment of the efficacy and safety of the new combination immunotherapy. The primary endpoint used to evaluate the efficacy is the overall response (CR, VGPR, PR). A true overall response (OR) rate of at least 42.5% would be considered active in this particular patient population. The Simon's two-stage design will be used for the study to ensure that the number of patients exposed to this new treatment is minimized. Twenty six patients will be initially entered. If there are at least six responses among the 20 patients, an additional 22 patients will be entered. If at least 15 patients among the forty two patients responded to the treatment, then the combination will be considered a promising treatment. The probability of stopping early if the true response rate is 25% is 0.62, and 0.09, if the true response rate is 42.5%. If the true overall response rate is 42.5%, the probability of concluding that the combination has sufficient activity is 0.82 (power of the study), and 0.07 if the true rate is 25%.

Total accrual is 42 subjects plus 6 patients in the runoff phase, since we expect about 5% of patients to be not evaluable.

The toxicity data will be monitored closely through the therapy. Addressing the safety of the combination, a maximum width 90% confidence interval for any grade 3 or higher toxicity will be about 26%. For 44 patients in the study, if the true unknown probability of a rare toxicity is 10%, the probability of observing 1 or more toxicities is 99%, for 5% it is 90%, and, if the true toxicity rate is 3%, then the probability of observing one or more rare toxicities is 74%.We do not anticipate additional toxicity with the addition of MK-3475.

Given current accrual rate for patients with relapsed/refractory MM in the GCC system, we would anticipate about 25 patients per year. If the study continues, about 2 year time period will be required to complete accrual.

Secondary endpoints

The most clinically relevant endpoint for this MM population is progression free survival (PFS) where failure is defined as death or the appearance of symptomatic myeloma. Progression-free survival (PFS) functions will be estimated using the Kaplan-Meier approach. PFS will be compared between patients' subgroups by the log-rank test. PFS medians and the 95% CI will be reported. The Cox regression model will be used to assess plausible risk factors in patients PFS.

All demographic and patients-on-study characteristics will be summarized and reported. The response rates will be estimated with the corresponding 95% confidence intervals (CI). Due to a rather small sample size all tests will be exact, 2-sided and done at type I error of 0.05.

Statistical analysis will be done in R (x64, v.3.0.3), and conducted by the GCC BSS.

However, the exploratory studies involving biomarkers and pharmacogenomics analyses will be done by Merck's central scientific laboratory. Correlative samples will be used for microarray data analysis. These tasks can be accomplished using various software such as MAS 5.0 from Affy, or the R packages affy, affycomp, gcrma, and affyPLM.

10.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

10.1 MK-3475

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

Clinical Supplies will be provided by Merck as summarized in Table 11.

Table 12 Product Descriptions

Product Name & Potency	Dosage Form
MK-3475 100 mg/ 4mL	Solution for Injection

10.1.1 Packaging and Labeling Information

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

10.1.2 Clinical Supplies Disclosure

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

10.1.3 Storage and Handling Requirements

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

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

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

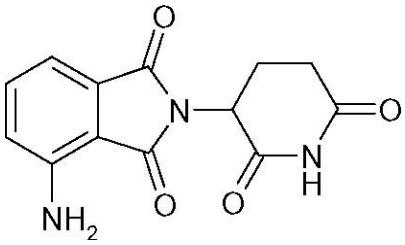
10.1.4 Returns and Reconciliation

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.

10.2 Pomalidomide

Pomalidomide, 4-amino-2-(2,6-dioxo-3-piperidyl)isoindoline-1'-one)-1,3-dione, belongs to the IMiDs class of compounds. The Chemical Abstract Service (CAS) registry number for CC-4047 is 19171-19-8. The chemical structure of the active pharmaceutical ingredient (API) is as follows:



Pomalidomide has an asymmetric carbon atom and can therefore exist as the optically active forms S (-) and R (+). Pomalidomide is being developed as a racemate.

10.2.1 Clinical Pharmacology

Mechanism of Action:

Pomalidomide is a novel immunomodulatory drug under development for the treatment of MM. Pomalidomide is a member of a class of pharmaceutical compounds known as immunomodulatory drugs (IMiDs). It shares a number of the beneficial pharmacologic properties of thalidomide and lenalidomide, but it is a more potent anti-proliferative immunomodulating agent than either drug. The pharmacodynamic properties of pomalidomide are of potential therapeutic benefit in the treatment of MM.

Dose and tolerability:

Pomalidomide was safe at doses of up to 5 mg in a phase 1 single dose study in normal, healthy male volunteers and up to 5 mg QOD or 2 mg QD in a phase 1 multidose clinical study in subjects with relapsed or refractory multiple myeloma; DLTs seen in subjects receiving higher doses were predominantly hematopoietic (i.e., neutropenia), and lower grade, self-limited neutropenia was also seen in some of the 1 and 2 mg QD and 5 mg QOD recipients. In a multidose, phase 2 clinical study of subjects with prostate cancer, 2 mg QD dosing was well tolerated and, unlike the multiple myeloma subjects who received 1 and 2 mg QD doses, only an overall shift to lower neutrophil counts was noted. No clinically relevant neutropenic AEs were observed, and no grade 3 or 4 neutropenic events occurred. It is, therefore, likely that subjects with solid tumors that do not extensively involve the bone marrow will have a higher pomalidomide MTD than subjects with hematologic malignancies.

Supplier(s)

POMALYST® (pomalidomide) is available commercially, and the patient's insurance will be charged for it.

Dosage form

Pomalidomide will be supplied as 1.0 mg, 2.0 mg, 3.0 mg and 4.0 mg capsules for oral administration.

Packaging

Pomalidomide will be shipped directly to patients or to the clinic site for IND studies. Bottles will contain a sufficient number of capsules for one cycle of dosing**.**

Labeling

Pomalidomide supplies are dispensed in individual bottles of capsules. Each bottle will identify the contents as study medication.

Pregnancy Testing

Must follow pregnancy testing requirements outlined in the POMALYST REMS™ program.

- All study participants must be registered into the mandatory POMALYST REMS™ program, and be willing and able to comply with the requirements of the POMALYST REMS™ program.
- Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the POMALYST REMS™ program. Able to take aspirin (81 or 325 mg) daily as prophylactic anticoagulation (patients intolerant to ASA may use warfarin or low molecular weight heparin).

Dosing

Pomalidomide capsules should be swallowed whole, and should not be broken, chewed or opened. Pomalidomide should be taken without food, at least 2 hours before or 2 hours after a meal.

If a dose of pomalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up, rather it should be taken at the next scheduled time point.

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

Special Handling Instructions

Females of childbearing potential should not handle or administer pomalidomide unless they are wearing gloves.

Record of administration

Accurate records will be kept of all study drug administration (including dispensing and dosing) in the source documents.

10.3 Dexamethasone

Dexamethasone

For further information on dexamethasone please refer to the approved package insert.

10.3.1 Other Names

Decadron, Hexadrol, Dexameth, Dexone, DXM, others.

10.3.2 Classification

Adrenal corticosteroid.

10.3.4 Mode of Action

Dexamethasone is a potent synthetic glucocorticoid that affects almost every body system. It has anti-inflammatory, immunosuppressant, antineoplastic, and antiemetic properties and very little mineralocorticoid activity. As an antineoplastic agent, dexamethasone may bind to specific proteins (receptors) within the cell forming a steroid-receptor complex. Binding of the receptor steroid complex with nuclear chromatin alters mRNA and protein synthesis within the cell.

10.3.5 Storage and Stability

The drug is stored at room temperature in a dry place.

10.3.6 Dose Specifics

Patients will be given 40 mg of dexamethasone on days 1, 8, 15, & 22, as outlined in Section 6.2.1.

10.3.7 Route of Administration

Oral.

10.3.8 Availability

Commercially available.

10.3.9 Side Effects

Gastrointestinal: Nausea, vomiting, anorexia, increased appetite, weight gain, aggravation of peptic ulcers.

Dermatologic: Rash, skin atrophy, facial hair growth, acne, facial erythema, ecchymoses.

Genitourinary: Menstrual changes (amenorrhea, menstrual irregularities).

Neurological: Insomnia, euphoria, headache, vertigo, psychosis, depression, seizures, muscle weakness.

Cardiovascular: Fluid retention and edema, hypertension; rarely, thrombophlebitis.

Ocular: Cataracts, increased intraocular pressure, exophthalmos.

Metabolic: Hyperglycemia, decreased glucose tolerance, aggravation or precipitation

of diabetes mellitus, adrenal suppression (with Cushingoid features), hypokalemia.

Hematologic: Leukocytosis.

Other: Osteoporosis (and resulting back pain), appearance of serious infections including herpes

zoster, varicella zoster, fungal infections, Pneumocystis carinii, tuberculosis, muscle wasting,

delayed wound healing, suppression of reactions to skin tests.

10.3.10 Nursing/Patient Implications

(Monitor regularly for hypertension, CHF, and other evidence of fluid retention.

(Advise patient of possible mood or behavioral changes, i.e., depression, euphoria, insomnia, even psychosis. Instruct patient to report any suspected changes to healthcare team.

(Assess for symptoms of gastric ulcer, heartburn, or gastritis. Suggest antacids. Instruct patient to report symptoms to healthcare team if unable to control.

(Evaluate signs of infection, particularly local candidal infections and treat appropriately.

(Monitor blood glucose frequently.

(Instruct patient to report frequent, unrelenting headaches or visual changes to healthcare team.

(Advise patient that easy bruising is a side effect. Dexamethasone may have an effect on liver microenzymes such as CYP, and hence patients on both arms should be monitored closely if on warfarin.

11.0 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in accordance with current U.S. Food and Drug Administration (FDA) Regulations, Good Clinical Practices (GCPs) and International Counsel on Harmonization (ICH) E6 Guidelines.

ADMINISTRATIVE AND REGULATORY DETAILS

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the trial and its results will be submitted 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.

11.1.1 Institutional Review Board (IRB)

This protocol will be submitted to the University of Maryland IRB. Study procedures will begin once IRB approval is secured. All amendments, instances of reportable new information (i.e. unanticipated problems, data breaches, etc.) and continuing review reports will be submitted to the University of Maryland IRB.

11.1.2 Clinical Trial Monitoring

Data safety and verification monitoring will be conducted in accordance with the Greenebaum Cancer Center Sponsor-Investigator Monitoring Standard Operating Procedure (SOP), the Code of Federal Regulations (CFR), and FDA and International Counsel on Harmonization (ICH) E6 Guidelines.

11.1.3 Data Safety and Monitoring Board (DSMB)

DSMB oversight will be conducted in accordance with the Greenebaum Cancer Center DSMB standard operating procedures.

11.1.4 FDA Reporting

The FDA Annual Report will be submitted to the Agency within +/- 60 days of the date on the IND approval letter. Major amendments will be submitted to FDA at the time of IRB

submission. Minor amendments will be reported to FDA at the time of the next major amendment or at the next FDA Annual Report (whichever comes first).

11.1.5 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records will be maintained in secure offsite storage after completion of study follow-up and data analysis.

11.2 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.

11.3 Data Management

Clinical data will be entered into the OnCore® database by the designated data manager at the University of Maryland Marlene and Stewart Greenebaum Cancer Center (UMGCC). Oncore® is 21CRF11.10 (electronic medical records) compliant and is equipped for HIPAA-compliant internet-based entry of protocol tracking and review information.

All study data will be collected by the research team at each and every study visit and recorded in the research record. This data will then be entered in to the OnCore® study database.

All source documents will be obtained and retained along with any study forms, and placed into the patient's research folder.

11.4 DATA QUALITY ASSURANCE

Accurate, consistent, and reliable data will be ensured through the use of standard practices and procedures. This study will be conducted per Good Clinical Practice Guidelines (GCP) and policies and procedures defined by the University of Maryland HRPO. ONCORE will be used to develop study specific CRFs.

The UMGCC Data Safety Monitoring/Quality Assurance Committee (DSM/QAC) will review research subject safety and the integrity of this study related to the patient safety and quality control by reviewing all internal and external serious adverse event (SAE) and protocol-designated significant adverse event (AE) experiences per UMGCC DSM/QAC guidelines. The DSM/QAC will also make recommendations on proceeding with the trial by reviewing successive levels of accrual. DSM/QAC functions are in addition to, not in place of, the IRB or other sponsor reporting/ monitoring that may be required within certain timetables. UMGCC

will be the auditing entity by serving to monitor activities at minimum to include verifying that research documents (e.g. informed consent, eligibility checklist, case report forms), and attesting that the regulatory binder are complete and current.

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APPENDICES

A. 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.	

B. Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

- Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

In addition, volumetric analysis will be explored by central review for response assessment.

DEFINITION OF DOSE LIMITING TOXICITY:

The occurrence of any of the following toxicities during Cycle 1 in the first 6 patients of the run off phase and the expansion phase respectively will be considered a DLT, if judged by the Investigator to be possibly, probably or definitely related to MK-3475 in combination with pomalidomide/dexamethasone. Please refer to Section 6.2 for dose level guidelines following DLT evaluation of Cycle 1.

1. Grade 4 hematologic toxicity lasting ≥7 days.

2. Grade 4 non-hematologic toxicity (not laboratory).

3. Grade 3 non-hematologic toxicity (not laboratory) will be considered a DLT, except for inadequately treated nausea, hypersensitivity reactions, or fatigue lasting ≤3 days.

4. Any Grade 3 non-hematologic laboratory value if:

    1. Renal or liver function abnormality
    2. Medical intervention is required to treat the subject, or
    3. The abnormality leads to hospitalization, or
    4. The abnormality persists for >1 week.

5. Febrile neutropenia Grade 3 or Grade 4:

- Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour.
- Grade 4 is defined as ANC <500/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour, with life-threatening consequences and urgent intervention indicated.

6. Thrombocytopenia <25,000/mm^3 if associated with:

   - A bleeding event which does not result in hemodynamic instability but requires an elective platelet transfusion, or
   - A life-threatening bleeding event which results in urgent intervention and admission to an Intensive Care Unit.

7. Grade 5 toxicity (i.e., death).

8. A delay of > 1 week due to drug-related toxicity in initiating Cycle 2.

9. Unable to complete at least 80% of any of the three treatments during the first course of therapy due to treatment-related toxicity (even if not meeting above DLT criteria).

C 1. The International Myeloma Working Group Response Criteria

Response	***IMWG criteria***
sCR	CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow[3] by immunohistochemistry or immunofluorescence[4]
CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow[3]
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h
PR	≥ 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to < 200 mg/24 h If the serum and urine M-protein are unmeasurable,[5] 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 not measurable, and serum free light assay is also not measureable, ≥ 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
MR	See Appendix C2 below.
No change/Stable disease	Not meeting criteria for CR, VGPR, PR, or progressive disease
Plateau	NA

Progressive disease[5]	Increase of ≥ 25% from lowest response value in any one or more of the following: • Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL)[6] • 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 percentage must be ≥ 10%[7] • 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 hypercalcaemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder
Relapse	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features).[6] It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice • Development of new soft tissue plasmacytomas or bone lesions • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion • Hypercalcemia (> 11.5 mg/dL) [2.65 mmol/L] • Decrease in haemoglobin of ≥ 2 g/dL [1.25 mmol/L] • Rise in serum creatinine by 2 mg/dL or more [177 mmol/L or more]
Relapse from CR[5] (To be used only if the end point studied is DFS)[8]	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[7] • Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcaemia)

BGM Durie *et al.* International uniform response criteria for multiple myeloma. *Leukemia* (2006) [1]-

Adapted from Durie BGM, et al. Leukemia 2006; 20: 1467-1473; and Kyle RA, Rajkumar SV. Leukemia 2008; 23:3-9. Note: A clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26–1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a >90% decrease in the difference between involved and uninvolved free light chain (FLC) levels.[3] Confirmation with repeat bone marrow biopsy not needed.[4] Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda 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 kappa/lambda of > 4:1 or < 1:2.[5] 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. In the IMWG criteria, CR patients must also meet the criteria for progressive disease shown here to be classified as progressive disease for the purposes of calculating time to progression and progression-free survival. The definitions of relapse, clinical relapse and relapse from CR are not to be used in calculation of time to progression or progression-free survival.[6] For progressive disease, serum M-component increases of ≥1 gm/dL are sufficient to define relapse

if starting M-component is ≥5 g/dL.[7] Relapse from CR has the 5% cut-off versus 10% for other categories of relapse.[8] For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

C 2. Definition of Minimal Response per EBMT Criteria

Criteria MR[a] - ≥ 25 but < 49% reduction in serum M-protein and a 50–89% reduction in 24-hour urinary M-protein, which still exceeds 200 mg per 24 h. For patients with non-secretory myeloma only, 25–49% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, if biopsy is performed

If the serum and urine M-protein are not measurable, a decrease of 25%–49% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. 25–49% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination)

No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response). Sources: Bladé 1998; Kyle 2009.

EBMT = European Group for Blood and Marrow Transplantation; MR = minimal response.

a **The response category MR requires 2 consecutive assessments** made at any time before the institution of any new therapy, as well as no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments are not required to be confirmed by repeat testing.

D. Pembrolizumab Event of Clinical Interest Guidance Document

PEMBROLIZUMAB PROGRAM

(MK-3475)

EVENT OF CLINICAL INTEREST

GUIDANCE DOCUMENT

Version 5.0

~~Confidential ✪ Limited Access~~

Pembrolizumab Event of Clinical Interest Guidance Document

REVISION HISTORY LOG

Version	Effective Date*	Revision Author	Action
1	08-Aug-2012	Kevin Gergich	Initial Release of guidance document for MK-3475
2	07-June-2013	Marty Huber, Kevin Gergich, Holly Brown	Revised title, formerly was "MK-3475 Immune-Related Adverse Event Identification, Evaluation and Management Guidance Document for Investigators" Revised the format of irAE Guidance document, including layout, font, sectioning, etc. for consistency with Sponsor Events of Clinical Interest guidance documents. Modified Categories for irAEs: – Replaced GI with Colitis category. – Removed Neurologic category. – Added Renal category. Removed detail in the irAE Guidance document that can be located in the Investigator's Brochure for MK-3475. Removed details regarding non-MK-3475 compounds. Added ECI reporting guidelines. Included a Table Events of Clinical Interest: Immune-Related Adverse Events that includes the key terms. – Also placed a pull-out quick-review sheet in the Appendix. Updated background, diagnosis and course of treatment details for irAEs.

3	10-Sep-2014	Marty Huber, Kevin Gergich, Holly Brown	Renamed the document: "Pembrolizumab Program (MK-3475) - Events of Clinical Interest Guidance Document". Introduced generic name: pembrolizumab (MK-3475) and inserted throughout the document. Updated Overview – Section 1 - Clarified the scope of the document and the reporting window for ECIs - Updated Table 1 with medDRA Preferred Terms for adverse events to correspond with reporting of terms to clinical database, rearranged the order, and updated the reporting criteria. - Updated the dose modification/discontinuation section to clarify discontinuation and hold terminology. Updated Section 2 – ECI Reporting Guidelines

			– Clarified that ECIs must be reported to Merck **within 24 hours** regardless of attribution to study treatment or etiology. Updated Section 3 – For All Sections, removed the Course of Action for Grade 1 events. - Section 3.1 Pneumonitis – Moved Pneumonitis to beginning of ECI Section – Updated management guidelines for Grade 2 and Grade 3-4 events - Section 3.2 Colitis: - Updated AE terms and ECI criteria, updated course of action language for clarity - Section 3.3 Endocrine: - Updated ECI criteria and updated course of action language for clarity. - Added subsections for hypophysitis, hyperthyroidism and hypothyroidism to clarify management guidelines. - Section 3.4 Hematologic: - New section added. - Section 3.5: Hepatic: - Updated terms and added additional guidance for reporting of DILI ECI; updated course of action for clarity - Section 3.6 Neurologic: - New section added. - Section 3.7 Ocular: - Changed the name of this section from Eye to Ocular - Added the term “iritis”, updated ECI guidance, and updated course of action language for clarity - Section 3.8 Renal: - Updated section for clarity. - Section 3.9 Skin: - Updated list of terms and added terms for reporting of other skin ECIs; added section 3.9.1: Immediate Evaluation for Potential Skin ECIs - Section 3.10 Other: - Updated list of terms for clarity; revised course of action for clarity.

			- Section 3.11 Infusion Reactions: - New section added. - Section 3.12: Follow-up to Resolution: - New section added. - Section 4: - References updated. - Section 5: - ECI table updated for consistency with Table 1. - Section 6: Appendix 2 – Past Medical History Related to Dermatologic Event: New section added. - Section 7: Appendix 3 – Presentation of the Dermatologic Event: New section added. - Section 8: Appendix 4 – Focused Skin Examination: New section added.
4	04-Dec-2014	Scot Ebbinghaus, Oswaldo Bracco, Holly Brown, Kevin Gergich	- Table 1 - Updated Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE) Section to include: - Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA) - Created new section in Table 1 – Endocrine (reported as ECI) and added: - Type 1 diabetes mellitus (if new onset) - Hepatic: Clarified Transaminase elevations as: - Transaminase elevations (ALT and/or AST) - Section 3.2 Colitis - Updated the duration of diarrhea requirments under the Course of Action for Grade 2 and Grade 3 - Section 3.3 Endocrine - Clarified Course of Action for hyperthyroidism and hypothyroidism - Added Course of Action section for Type 1 diabetes mellitus (if new onset) and ≥ Grade 3 hyperglycemia - Section 5 - Updated Reference Table in Appendix 1
5	18-Dec-2014	Holly Brown Kevin Gergich	- Section 3.3 Endocrine - Updated the Course of Action for Hypophysitis - Merged Grades 2-4 into one course of action

*Ensure that you are using the most current version of this document.

Pembrolizumab Event of Clinical Interest Guidance Document

TABLE OF CONTENTS

1. OVERVIEW 6
2. ECI REPORTING GUIDELINES 8
3. ECI CATEGORIES AND TERMS 8
3.1 Pneumonitis 9
3.2 Colitis 10
3.3 Endocrine 12
3.4 Hematologic 15
3.5 Hepatic 16
3.6 Neurologic 18
3.7 Ocular 19
3.8 Renal 20
3.9 Skin 21
3.9.1. Immediate Evaluation for Potential Skin ECIs 22
3.10 Other 23
3.11 Infusion Reactions 24
3.12 Follow-up to Resolution 26
4. REFERENCES 27
5. APPENDIX 1 –Events of Clinical Interest (ECI) – Reference Table 28
6. APPENDIX 2 – Past Medical History Related to Dermatologic Event 29
7. APPENDIX 3 – Presentation of the Dermatologic Event 30
8. APPENDIX 4 – Focused Skin Examination

1. OVERVIEW

The purpose of this document is to provide study sites with guidance on the identification and management of Events of Clinical Interest for the MK-3475 (also known as pembrolizumab) program.

Based on the literature review [1-11], and consideration of mechanism of action of pembrolizumab, potential immune-related adverse events (irAEs) are the primary Event of Clinical Interest (ECI). Immune-related AEs are adverse events associated with the treatment of patients with immunotherapy treatments that appear to be associated with the immune therapy's mechanism of action. Based on these potential irAEs, the sponsor has defined a list of specific adverse event terms (ECIs) that are selected adverse experiences that **must be reported to Merck within 24 hours** from the time the Investigator/physician is aware of such an occurrence, regardless of whether or not the investigator/physician considers the event to be related to study drug(s). In addition, these ECIs require additional detailed information to be collected and entered in the study database. ECIs may be identified through spontaneous patient report and / or upon review of subject data. **Table 1** provides the list of terms and reporting requirements for AEs that must be reported as ECIs for MK-3475 protocols. Of note, the requirement for reporting of ECIs applies to all arms, including comparators, of MK-3475 clinical trials

Given that our current list of events of clinical interest is not comprehensive for all potential immune-related events, it is possible that AEs other than those listed in this document may be observed in patients receiving pembrolizumab. Therefore any Grade 3 or higher event that the investigator/physician considers to be immune-related should be reported as an ECI regardless of whether the specific event term is in Table 1 **and reported to Merck within 24 hours** from the time the Investigator/physician is aware of such an occurrence. Adverse events that are both an SAE and an ECI should be reported one time as an SAE only, however the event must be appropriately identified as an ECI as well in in the database.

Pembrolizumab Event of Clinical Interest Guidance Document

Table 1: Events of Clinical Interest

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
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

Pembrolizumab Event of Clinical Interest Guidance Document

Each of the events above is described within this guidance document, along with site requirements for reporting these events to the Sponsor. The information collected should be entered into the narrative field(s) of the Adverse Event module in the database (please note, if narrative entry into the database is not available, please use the narrative text box on the 1727/AER Form). If additional Medical History or Concomitant Medications are reported, the Medical History and Concomitant Medication modules in the database must be updated.

In addition, the guidelines include recommendations on the management of these ECIs. These guidelines are intended to be applied when the physician determines the events to be related to pembrolizumab. Note: if after the evaluation the event is determined not to be related, the physician is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (below). Therefore, these recommendations should be seen as guidelines and the treating physician should exercise individual clinical judgment based on the patient. For any question of dose modification or other treatment options, the specific language in the protocol should be followed. Any questions pertaining to the collection of this information or management of ECIs should be directed to your local Sponsor contact.

Dose Modification/Discontinuation
The treatment guidance provides specific direction when to hold and/or discontinue pembrolizumab for each immune related adverse event. Of note, when the guidance states to "discontinue" pembrolizumab this is the permanent discontinuation of treatment with pembrolizumab. "Hold" means to stop treating with pembrolizumab but resumption of treatment may be considered assuming the patient meets the criteria for resumption of treatment.

2. ECI REPORTING GUIDELINES

ECIs are selected non-serious and serious adverse experiences that must be reported to Merck **within 24 hours** regardless of attribution to study treatment. The AEs listed in this document and any event that meets the ECI criteria (as noted) in Table 1 or in the respective protocol (event term and Grade) must be reported regardless of physician-determined causality with study medication and whether or not considered immune-related by the physician (unless otherwise specified). Physicians/study coordinators/designated site personnel are required to record these experiences as ECIs on the Adverse Experience electronic Case Report Forms (eCRFs) (or on paper) and to provide supplemental information (such as medical history, concomitant medications, investigations, etc.) about the event.

– Please refer to the Data Entry Guidelines (DEGs) for your protocol.
– Please refer to protocol for details on reporting timelines and reporting of Overdose and Drug Induced Liver Injury (DILI).

3. ECI CATEGORIES AND TERMS

This section describes the ECI categories and outlines subject management guidelines when an ECI is reported.

3.1 Pneumonitis

The following AE terms, if considered ≥ Grade 2, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

– Pneumonitis
– Interstitial lung disease
– Acute interstitial pneumonitis

If symptoms indicate possible new or worsening cardiac abnormalities additional testing and/or a cardiology consultation should be considered.

All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection**. It is important that patients with a suspected diagnosis of pneumonitis be managed as per the guidance below until treatment-related pneumonitis is excluded. Treatment of both a potential infectious etiology and pneumonitis in parallel may be warranted. Management of the treatment of suspected pneumonitis with steroid treatment should not be delayed for a therapeutic trial of antibiotics.** If an alternative diagnosis is established, the patient does not require management as below; however the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
– Report as ECI
– Hold pembrolizumab.
– Consider pulmonary consultation with bronchoscopy and biopsy/BAL.
– Consider ID consult
– Conduct an in person evaluation approximately twice per week
– Consider frequent Chest X-ray as part of monitoring
– Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4
weeks.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or
equivalent per day within 12 weeks.
– Second episode of pneumonitis – discontinue pembrolizumab if upon re-challenge the patient develops
a second episode of Grade 2 or higher pneumonitis.

Grade 3 and 4 events:
– Report as ECI
– Discontinue pembrolizumab.
– Hospitalize patient

– Bronchoscopy with biopsy and/or BAL is recommended.
– Immediately treat with intravenous steroids (methylprednisolone 125 mg IV). When symptoms improve to Grade 1 or less, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks.
– If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, treat with additional anti-inflammatory measures. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures, as needed
– Add prophylactic antibiotics for opportunistic infections.

3.2 Colitis

The following AE terms, if considered ≥ Grade 2 or resulting in dose modification or use of systemic steroids to treat the AE, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

– Colitis
– Colitis microscopic
– Enterocolitis
– Enterocolitis hemorrhagic
– Gastrointestinal perforation
– Intestinal obstruction
– Necrotizing colitis
– Diarrhea

All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, a Clostridium difficile titer and endoscopy. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 Diarrhea/Colitis (4-6 stools/day over baseline, dehydration requiring IV fluids < 24 hours, abdominal
pain, mucus or blood in stool):
– Report as ECI
– Hold pembrolizumab.
– Symptomatic Treatment
– For Grade 2 diarrhea that persists for greater than 3 days, and for diarrhea with blood and/or mucus,

- Consider GI consultation and endoscopy to confirm or rule out colitis
- Administer oral corticosteroids (prednisone 1-2 mg/kg QD or equivalent)

– When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
– If symptoms worsen or persist > 3 days treat as Grade 3

Grade 3 Diarrhea/Colitis (or Grade 2 diarrhea that persists for > 1 week):
– Report as ECI
– Hold pembrolizumab.
– Rule out bowel perforation. Imaging with plain films or CT can be useful.
– Recommend consultation with Gastroenterologist and confirmation biopsy with endoscopy.
– Treat with intravenous steroids (methylprednisolone 125 mg) followed by high dose oral steroids (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6 to 8 weeks in patients with diffuse and severe ulceration and/or bleeding.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
– If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider treatment with additional anti-inflammatory measures as described in the literature [5]. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures as needed.

Grade 4 events:
– Report as ECI
– Permanently discontinue pembrolizumab. –
Manage as per Grade 3.

3.3 Endocrine

The following AE terms, if considered Grade 3 or if Grade 2 and require holding/discontinuation/ modification of pembrolizumab dosing, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

– Adrenal insufficiency
– Hyperthyroidism
– Hypophysitis
– Hypopituitarism
– Hypothyroidism
– Thyroid disorder
– Thyroiditis

Pembrolizumab Event of Clinical Interest Guidance Document

All attempts should be made to rule out other causes such as brain metastases, sepsis and/or infection. However the AE should be reported regardless of etiology.

Hypophysitis or other symptomatic endocrinopathy other than hypo- or hyperthyroidism

Grade 2-4 events:
– Report as ECI if appropriate
– Hold pembrolizumab
– Rule out infection and sepsis with appropriate cultures and imaging.
– Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
– Pituitary gland imaging should be considered (MRIs with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis).
– Treat with prednisone 40 mg p.o. or equivalent per day. 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.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
– Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis.
– Consultation with an endocrinologist may be considered.

Pembrolizumab Event of Clinical Interest Guidance Document **Hyperthyroidism and 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, Grade 2-4 hypothyroidism events:
– Report as ECI if appropriate (see Table 1)
– Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until
returned to baseline values.
– Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency.
– Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
– 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.
– Consultation with an endocrinologist may be considered.

Grade 3 hyperthyroidism events:
– Report as ECI
– Hold pembrolizumab.
– Rule out infection and sepsis with appropriate cultures and imaging.
– Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day. 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.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4
hyperthyroidism
events: – Report
as ECI
– Discontinue
pembrolizumab. –
Manage as per Grade
3

Pembrolizumab Event of Clinical Interest Guidance Document

Type 1 diabetes mellitus (if new onset) and ≥ Grade 3 Hyperglycemia

The following AE terms are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

– Type I diabetes mellitus (T1DM), if new onset, including diabetic ketoacidosis (DKA)
– Grade 3 or higher hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA).

Immune-mediated diabetes may present as new onset of Type 1 diabetes or an abrupt worsening of preexisting diabetes associated with laboratorial evidence of beta cell failure. All attempts should be made to rule out other causes such as type 2 diabetes mellitus (T2DM), T2DM decompensation, steroid-induced diabetes, physiologic stress-induced diabetes, or poorly controlled pre-existing diabetes (either T1DM or T2DM), but events meeting the above criteria should be reported as ECIs regardless of etiology. The patients may present with hyperglycemia (abrupt onset or abrupt decompensation) with clinical evidence of diabetic ketoacidosis or laboratory evidence of insulin deficiency, such as ketonuria, laboratory evidence of metabolic acidosis, or low or undetected c-peptide.

Course of Action

T1DM should be immediately treated with insulin.

T1DM or Grade 3-4 Hyperglycemia events:
- Report as ECI if appropriate (see Table 1)
- Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure, and resume pembrolizumab when patients are clinically and metabolically stable.
- 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.
- Consultation with an Endocrinologist is recommended.
- Consider local testing for islet cell antibodies and antibodies to GAD, IA-2, ZnT8, and insulin may be obtained.

3.4 Hematologic

The following AE term, if considered Grade ≥3 or requiring dose modification or use of systemic steroids to treat the AE, are considered an ECI and should be reported to the Sponsor within 24 hours of the event:

– Autoimmune hemolytic anemia
– Aplastic anemia
– Disseminated Intravascular Coagulation (DIC)
– Haemolytic Uraemic Syndrome (HUS)
– Idiopathic (or immune) Thrombocytopenia Purpura (ITP)
– Thrombotic Thrombocytopenic Purpura (TTP)
– Any Grade 4 anemia regardless of underlying mechanism

All attempts should be made to rule out other causes such as metastases, sepsis and/or infection. Relevant diagnostic studies such as peripheral blood smear, reticulocyte count, LDH, haptoglobin, bone marrow biopsy or Coomb's test, etc., should be considered to confirm the diagnosis. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
– Report as ECI
– Hold pembrolizumab
– Prednisone 1-2 mg/kg daily may be indicated
– Consider Hematology consultation.
Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3 events:
– Report as ECI
– Hematology consultation.
– Hold pembrolizumab Discontinuation should be considered as per specific protocol guidance.
– Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:
– Report as ECI
– Hematology consultation
– Discontinue pembrolizumab for all solid tumor indications; refer to protocol for hematologic malignancies.
– Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate

3.5 Hepatic

The following AE terms, if considered 2 Grade 2 or greater (or any grade with dose modification or use of systemic steroids to treat the AE), are considered ECIs and should be reported to the Sponsor within 24 hours of the event:
– Autoimmune hepatitis –
Hepatitis
– Transaminase elevations

All attempts should be made to rule out other causes such as metastatic disease, infection or other hepatic diseases. However the AE should be reported regardless of etiology.

Drug Induced Liver Injury (DILI)
In addition, the event must be reported as a Drug Induced Liver Injury (DILI) ECI, if the patient meets the laboratory criteria for potential DILI defined as:

- An elevated alanine transaminase (ALT) or aspartate transaminase (AST) lab value that is greater than or equal to three times (3X) the upper limit of normal (ULN) and
- An elevated total bilirubin lab value that is greater than or equal to two times (2X) ULN and
- At the same time, an alkaline phosphatase (ALP) lab value that is less than 2X ULN,
- As a result of within-protocol-specific testing or unscheduled testing.

Note that any hepatic immune ECI meeting DILI criteria should only be reported once as a DILI event.

Course of Action
Grade 2 events:
– Report as ECI
– Hold pembrolizumab when AST or ALT >3.0 to 5.0 times ULN and/or total bilirubin >1.5 to 3.0 times ULN.
– Monitor liver function tests more frequently until returned to baseline values (consider weekly).
  - Treat with 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume pembrolizumab per protocol

– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
– Permanently discontinue pembrolizumab for patients with liver metastasis who begin treatment with Grade 2 elevation of AST or ALT, and AST or ALT increases 250% relative to baseline and lasts 21 week.

Grade 3 events:
– Report as ECI
– Discontinue pembrolizumab when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN.
– Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary – Treat with high-dose intravenous glucocorticosteroids for 24 to 48 hours. When symptoms improve to Grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1 to 2 mg/kg should be started and continued over no less than 4 weeks.
– If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity.

Pembrolizumab Event of Clinical Interest Guidance Document

– Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:
– Report as ECI
– Permanently discontinue pembrolizumab –
Manage patient as per Grade 3 above

3.6 Neurologic

The following AE terms, regardless of grade, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

– Autoimmune
neuropathy –
Demyelinating
polyneuropathy –
Guillain-Barre syndrome
– Myasthenic syndrome

All attempts should be made to rule out other causes such as metastatic disease, other medications or infectious causes. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
– Report as ECI
– Moderate (Grade 2) – consider withholding pembrolizumab.
– Consider treatment with prednisone 1-2 mg/kg p.o. daily as appropriate
– Consider Neurology consultation. Consider biopsy for confirmation of diagnosis.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or
equivalent per day within 12 weeks.

Grade 3 and 4 events:
– Report as ECI
– Discontinue pembrolizumab
– Obtain neurology consultation. Consider biopsy for confirmation of diagnosis
– Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. If
condition worsens consider IVIG or other immunosuppressive therapies as per local guidelines

When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

3.7 Ocular

The following AE terms, if considered Grade ≥2 or requiring dose modification or use of systemic steroids to treat the AE, is considered an ECI and should be reported to the Sponsor within 24 hours of the event:

– Uveitis –
Iritis

All attempts should be made to rule out other causes such as metastatic disease, infection or other ocular disease (e.g. glaucoma or cataracts). However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
– Evaluation by an ophthalmologist is strongly recommended.
– Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.
– Discontinue pembrolizumab as per protocol if symptoms persist despite treatment with topical immunosuppressive therapy.

Grade 3 events:
– Evaluation by an ophthalmologist is strongly recommended
– Hold pembrolizumab and consider permanent discontinuation as per specific protocol guidance. – Treat with systemic corticosteroids such as prednisone at a dose of 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:
– Evaluation by an ophthalmologist is strongly recommended –
Permanently discontinue pembrolizumab.
– Treat with corticosteroids as per Grade 3 above

3.8 Renal

The following AEs if ? Grade 2 are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

– Nephritis
– Nephritis
autoimmune –
Renal failure
– Renal failure acute

Creatinine elevations ? Grade 3 or any grade with dose modification or use of systemic steroids to treat the AE.

All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury due to other chemotherapy agents. A renal consultation is recommended. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
– Hold pembrolizumab
– Treatment with prednisone 1-2 mg/kg p.o. daily.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or
equivalent per day within 12 weeks.

Grade 3-4 events:
– Discontinue pembrolizumab
– Renal consultation with consideration of ultrasound and/or biopsy as appropriate
– Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone IV or equivalent once per
day.

When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

3.9 Skin

Rash and Pruritus

The following AEs should be considered as ECIs, if ≥ Grade 3 and should be reported to the Sponsor within 24 hours of the event:

– Pruritus
– Rash
– Rash generalized
– Rash maculo-papular
– In addition to CTCAE Grade 3 rash, any rash that is considered clinically significant, in the physician's judgment, should be treated as an ECI. Clinical significance is left to the physician to determine, and could possibly include rashes such as the following:

- rash with a duration >2 weeks; OR
- rash that is >10% body surface area; OR
- rash that causes significant discomfort not relieved by topical medication or temporary cessation of study drug.

Other Skin ECIs

The following AEs should **always** be reported as ECIs, regardless of grade, and should be reported to the Sponsor within 24 hours of the event:

– Dermatitis exfoliative
– Erythema multiforme
– Steven's Johnson syndrome –
Toxic epidermal necrolysis

Please note, the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
– Symptomatic treatment should be given such as topical glucocorticosteroids (e.g., betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral anti-pruritics (e.g., diphenhydramine HCl or hydroxyzine HCl).
– Treatment with oral steroids is at physician's discretion for Grade 2 events.

Pembrolizumab Event of Clinical Interest Guidance Document

Grade 3 events:
– Hold pembrolizumab.
– Consider Dermatology Consultation and biopsy for confirmation of diagnosis.
– Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:
– Permanently discontinue pembrolizumab.
– Dermatology consultation and consideration of biopsy and clinical dermatology photograph.
– Initiate steroids at 1 to 2 mg/kg prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Pembrolizumab Event of Clinical Interest Guidance Document **3.9.1.**

3.9.1 Immediate Evaluation for Potential Skin ECIs

A. Photographs:
Every attempt should be made to get a photograph of the actual ECI skin lesion or rash as soon as possible**. Obtain appropriate consent for subject photographs if a consent form addendum is required by your IRB/ERC.**

– Take digital photographs of:
- the head (to assess mucosal or eye involvement),
- the trunk and extremities, and
- a close-up of the skin lesion/rash.

– If possible, a ruler should be placed alongside the site of a skin occurrence as a fixed marker of distance.
– The time/date stamp should be set in the 'ON' position for documentation purposes. –
Photographs should be stored with the subject's study records.
– The Sponsor may request copies of photographs. The local study contact (e.g., CRA) will provide guidance to the site, if needed.

B. Past Medical History:
Collect past medical history relevant to the event, using the questions in Appendix 2 (Past Medical History Related to Dermatologic Event) as a guide. Any preexisting conditions not previously reported (e.g., drug allergy) should be entered into the Medical History eCRF.

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C. Presentation of the Event:

Collect information on clinical presentation and potential contributing factors using the questions in Appendix 3 (Presentation of the Dermatologic Event) as a guide. This information should be summarized and entered in narrative format in the AE eCRF. Please use the available free-text fields, such as Signs and Symptoms. Note pertinent negatives where applicable to reflect that the information was collected. Any treatments administered should be entered on the Concomitant Medication eCRF.

D. Vitals Signs and Standard Laboratory Tests:

Measure vital signs (pulse, sitting BP, oral temperature, and respiratory rate) and record on the Vital Signs eCRF. Perform standard laboratory tests (CBC with manual differential and serum chemistry panel, including LFTs).

E. Focused Skin Examination:

Perform a focused skin examination using the questions in Appendix 4 (Focused Skin Examination) as a guide. Information should be summarized and entered on the Adverse Experience eCRF as part of the narrative.

F. Dermatology Consult

Refer the subject to a dermatologist as soon as possible.
– For a **"severe rash"**, the subject must be seen within **1-2 days** of reporting the event. – For **clinically significant rash**, the subject should be seen within **3-5 days**.

The dermatologist should submit a biopsy sample to a certified dermatopathology laboratory or to a pathologist experienced in reviewing skin specimens.

The site should provide the dermatologist with all relevant case history, including copies of clinical photographs and laboratory test results.

3.10 Other

The following AEs, regardless of grade, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

Myocarditis – Pericarditis

Pancreatitis – Any additional Grade 3 or higher event which the physician considers to be immune related.

All attempts should be made to rule out other causes. Therapeutic specialists should be consulted as appropriate. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events or Grade 1 events that do not improve with symptomatic treatment:
– Withhold pembrolizumab.
– Systemic corticosteroids may be indicated.
– Consider biopsy for confirmation of diagnosis.
– If pembrolizumab held and corticosteroid required, manage as per grade 3 below.

Grade 3 events:
– Hold pembrolizumab
– Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day.
– When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks. Otherwise, pembrolizumab treatment may be restarted and the dose modified as specified in the protocol

Grade 4 events:
– Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. –
Discontinue pembrolizumab

Pembrolizumab Event of Clinical Interest Guidance Document

3.11 Infusion Reactions

The following AE terms, regardless of grade, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:
– Allergic reaction
– Anaphylaxis
– Cytokine release syndrome
– Serum sickness
– Infusion reactions
– Infusion-like reactions

Please note, the AE should be reported regardless of etiology.

Course of Action
Refer to infusion reaction table in the protocol and below.

Infusion Reactions

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.** 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 with: Diphenhydramine 50 mg p.o. (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg p.o. (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. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

3.12 Follow-up to Resolution

Subjects should be followed to resolution. The Adverse Experience eCRF should be updated with information regarding duration and clinical course of the event. Information obtained from the consulting specialist, including diagnosis, should be recorded in the appropriate AE fields. Free-text fields should be used to record narrative information:

– Clinical course of the event –

Course of treatment

– Evidence supporting recovery –

Follow-up to the clinical course

Any treatments administered for the event should also be entered in the Concomitant Medication eCRF.

4. REFERENCES

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5. APPENDIX 1 –Events of Clinical Interest (ECI) – 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		

6. APPENDIX 2 – Past Medical History Related to Dermatologic Event

Past Medical History:
Any preexisting conditions not previously reported (e.g., drug allergy) should be entered into the Medical History eCRF.

1. Does the subject have any allergies? □ Yes □ No

If yes, please obtain the following information:

a. Any allergy to drugs (including topical or ophthalmic drugs)? □ Yes □ No List the drug name(s) and describe the type of allergic response (e.g. rash, anaphylaxis, etc):

_____

b. Any allergy to external agents, such as laundry detergents, soaps, poison ivy, nickel, etc.? □ Yes □ No

Describe the agent and type of allergic response:

_____

c. Any allergy to food? □ Yes □ No

Describe the food and type of allergic response:

d. Any allergy to animals, insects? □ Yes □ No

Describe the allergen and type of allergic response:

_____

e. Any other allergy? □ Yes □ No

Describe the allergen and type of allergic response:

_____

2. Does the subject have any other history of skin reactions, skin eruptions, or rashes? □ Yes □ No

If so what kind? _____

3. Has the subject ever been treated for a skin condition? □ Yes □ No

If so what kind? _____

4. Is the current finding similar to a past experience? □ Yes □ No
Pembrolizumab Event of Clinical Interest Guidance Document

7. APPENDIX 3 – Presentation of the Dermatologic Event

Presentation of the event:
Collect information on clinical presentation and potential contributing factors. Key information should be summarized and entered on the Adverse Experience eCRF. Any treatments administered should be entered on the Concomitant Medication eCRF.

1. What is the onset time of the skin reaction, skin eruption, or rash relative to dose of study drug?

_____
_____

2. Has the subject contacted any known allergens? □ Yes □ No

If so what kind? _____

3. Has the subject contacted new, special, or unusual substances (e.g., new laundry detergents, soap, personal care product, poison ivy, etc.)? □ Yes □ No

If so what kind?_____

4. Has the subject taken any other medication (over the counter, prescription, vitamins, and supplement)? □ Yes □ No

If so what kind?_____

5. Has the subject consumed unaccustomed, special or unusual foods? □ Yes □ No

If so what kind?_____

6. Does the subject have or had in the last few days any illness? □ Yes □ No

If so what kind?_____

7. Has the subject come into contact with any family or house members who are ill? □ Yes □ No

If so who and what? _____

8. Has the subject recently been near children who have a skin reaction, skin eruption, or rash (e.g. *Molluscum Contagiosum*)? □ Yes □ No

9. Has the subject had recent sun exposure? □ Yes □ No

10. For the current rash, have there been any systemic clinical signs? □ Yes □ No

If so what kind?

i. Anaphylaxis? □ Yes □ No
ii. Signs of hypotension? □ Yes □ No
iii. Signs of dyspnea? □ Yes □ No
iv. Fever, night sweats, chills? □ Yes □ No

11. For the current rash, has the subject needed subcutaneous epinephrine or other systemic catecholamine therapy? □ Yes □ No

If so what kind?

12. For the current rash, has the subject used any other medication, such as inhaled bronchodilators, antihistaminic medication, topical corticosteroid, and/or systemic corticosteroid? □ Yes □ No

List medication(s) and dose(s):

_____

13. Is the rash pruritic (itchy)? □ Yes □ No

8. APPENDIX 4 – Focused Skin Examination

Focused Skin Examination:
Key information should be summarized and entered on the Adverse Experience eCRF.

Primary Skin Lesions Description
Color:

General description:

_____
_____

Describe the distribution of skin reaction, skin eruption, or rash on the body:

_____
_____

Is skin reaction, skin eruption, or rash resolving or continuing to spread?

_____
_____

Any associated signs on physical examination?

_____