UCSF Helen Diller Family Comprehensive Cancer Center

NCT# 03396952

Prostaglandin Inhibition and PD-1/CTLA4 blockade in melanoma

Protocol Number: CC #17854
Study Drugs: Pembrolizumab, Ipilimumab, Aspirin

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Protocol Signature Page

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1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Committee on Human Research (CHR), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable CHR requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with CHR policies, Federal, state and local laws and regulations.

UCSF Principal Investigator / Study Chair

_____
Printed Name

_____ _____
Signature Date

Abstract

Title	Prostaglandin Inhibition and PD-1/CTLA4 blockade in melanoma
Patient population	Patients with stage III unresectable/ stage IV melanoma
Rationale for Study	Prostaglandin Inhibition may increase the efficacy of immunotherapy
Primary Objective	To evaluate the overall response rate (ORR) by week 12 in patients with stage III unresectable/stage IV melanoma.
Secondary Objectives	To determine the median progression free survival and the overall survival and toxicity profile of this combination.
Study Design	Prospective single arm Simon 2 stage Phase II trial
Number of patients	43
Duration of Follow up	Patients will be followed for 30 days after discontinuation of treatment or removal from study
Duration of study	The study is expected to complete accrual at 24 months.
Study Drugs	Aspirin Pembrolizumab Ipilimumab
Safety Assessments	CTCAE v. 4 will be used to assess toxicity.
Efficacy Assessments	RECIST version 1.1 will be used in this study for assessment of tumor response.
Unique Aspects of this Study	Combination trial with ipilimumab, pembrolizumab, and aspirin.

List of Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
AUC	area under the curve
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CHR	Committee on Human Research (UCSF IRB)
CR	complete response
CRC	Clinical Research Coordinator
CRF	case report form
CSF	cerebral spinal fluid
CT	computerized tomography
CTCEA	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trial Management System
DFS	disease-free survival
DLT	dose limiting toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group

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1 Introduction

1.1 Background on Indication

The combination of ipilimumab and nivolumab is considered one of the standard treatments for advanced melanoma(1). However, even with this treatment, 40% of patients do not have an objective response. Recently, it has been shown in a preclinical model that the addition of a cyclooxygenase (COX) inhibitor may reduce PD-1 resistance(2, 3) In the study by Zelenay et al, aspirin, which blocks both COX-1 and COX-2), was able to prevent PD-1 resistance in a melanoma model. While the initial ipilimumab nivolumab study used nivolumab as the PD-1 inhibitor, these results have been recently replicated with pembrolizumab, a very similar anti-PD-1 inhibitor (Long G, et al ASCO 2016).

1.2 Background on the Immunotherapy Combinations

1.2.1 Pembrolizumab

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. KeytrudaTM (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor(4-7).

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors(8).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control(5). The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD 1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors . Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-

hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

1.2.2 Ipilimumab

Successful stimulation of T cells by antigen presenting cells require both antigen presentation by the MHC molecule-antigen peptide complex to the T cell receptor as well as costimulation by the B7 molecule on the antigen presenting cells to the CD 80/86 molecule. Ipilimumab is a humanized monoclonal antibody to CTLA-4 which is a decoy receptor. The effect of ipilimumab binding to CTLA-4 is to increase costimulation and increase T cell activation.

The two currently approved immune checkpoint blockers are anti-CTLA-4 and anti-PD-1 antibodies. The first, anti-CTLA4 antibody, ipilimumab was evaluated for treatment of advanced melanoma in two phase III trials as a monotherapy, and in combination with dacarbazine(9)(10). In these studies, ipilimumab demonstrated an increase overall response rate (ORR), median progression free survival (PFS), and median overall survival (OS) compared to a gp100 vaccine or in combination with dacarbazine vs. dacarbazine alone. Ipilimumab both at the tested 3mg/kg dose and at the 10 mg/kg dose was associated with increased immune related toxicities such as colitis, diarrhea, dermatitis, as well as a characteristic immune related hypophysitis(11).

Following the successful development of ipilimumab in melanoma, the development of anti-PD1 agents proceeded rapidly following the FDA approval of ipilimumab for advanced melanoma. In initial phase I clinical trials, two anti-PD-1 agents, pembrolizumab and nivolumab exhibited favorable response rates between 20-40% with substantial decreased frequency for grade 3-4 adverse events (10-15%)(12-13). Subsequent phase III trials showed durable clinical benefit with improved ORR, OFS, and OS from both pembrolizumab and nivolumab administered as first line therapies when compared to ipilimumab (KEYNOTE-006(14), CheckMate 067 trials(15), respectively).

With the anti-tumor benefit of both anti-CTLA4 and anti-PD1 agents administered as monotherapies, the logical next step was the administration of both immunotherapies in combination. Phase II data of ipilimumab and nivolumab in combination followed by nivolumab maintenance exhibited an increased toxicity profile compared to agents administered as monotherapies (50% of patients with grade 3-4 adverse events)(16). Yet despite the heightened toxicity profile, the clinical benefit seen in the combination was promising with improved ORR and PFS when compared to either ipilimumab or nivolumab alone (CheckMate 067)(15). Thus, while the clinical benefit has been promising, an increased propensity to develop grade 3/4 adverse events remains a strong consideration in choosing the proper context to administer the combination of nivolumab and ipilimumab.

The dose of ipilimumab does not appear to play a role in response rate but the dose does appear to play a role in side effects and adverse events. A recent trial, the Keynote 029 trial showed that the combination of pembrolizumab at the 200 mg dose and ipilimumab 1 mg/kg X 4 was associated with a reduced incidence of grade 3/4 AE to ~ 20%and an ORR of 55%(17). This reduced ipilimumab dose appears to be a well tolerated and equi-efficacious dose compared to

the higher dose ipilimumab regimens. For combination therapies, this is considered to be a good regimen.

1.2.3 Aspirin

Aspirin, in the form of leaves from the willow tree, has been used for its health effects for at least 2,400 years. In 1853, chemist Charles Frédéric Gerhardt synthesized acetyl salicylic acid in the lab for the first time. In 1897, scientists at Bayer began studying acetylsalicylic acid as a less-irritating replacement for common salicylate medicines. In 1899, Bayer had named the drug Aspirin(18).

In 1971, British pharmacologist John Robert Vane, showed aspirin suppressed the production of prostaglandins and thromboxanes. Aspirin's ability to suppress the production of prostaglandins and thromboxanes is due to its irreversible inactivation of the cyclooxygenase enzyme required for prostaglandin and thromboxane synthesis. Aspirin acts as an acetylating agent where an acetyl group is covalently attached to a serine residue in the active site of the PTGS enzyme.

Low-dose aspirin use irreversibly blocks the formation of thromboxane A2 in platelets, producing an inhibitory effect on platelet aggregation during the lifetime of the affected platelet (8–9 days). This antithrombotic property makes aspirin useful for reducing the incidence of heart attacks in people who have had a heart attack, unstable angina, ischemic stroke or transient ischemic attack 40 mg of aspirin a day is able to inhibit a large proportion of maximum thromboxane A2 release provoked acutely, with the prostaglandin I2 synthesis being little affected; however, higher doses of aspirin are required to attain further inhibition.

COX-1 and COX-2 inhibition

At least two different types of cyclooxygenases, COX-1 and COX-2, are acted on by aspirin. Aspirin irreversibly inhibits COX-1 and modifies the enzymatic activity of COX-2. COX-2 normally produces prostanoids, most of which are proinflammatory. Aspirin-modified PTGS2 (prostaglandin synthetase 2) produces lipoxins, most of which are anti-inflammatory

However, several of the new COX-2 inhibitors, such as rofecoxib (Vioxx), have been withdrawn in the last decade, after evidence emerged that PTGS2 inhibitors increase the risk of heart attack and stroke. Endothelial cells lining the microvasculature in the body are proposed to express PTGS2, and, by selectively inhibiting PTGS2, prostaglandin production (specifically, PGI2; prostacyclin) is downregulated with respect to thromboxane levels, as PTGS1 in platelets is unaffected. Thus, the protective anticoagulative effect of PGI2 is removed, increasing the risk of thrombus and associated heart attacks and other circulatory problems. Since platelets have no DNA, they are unable to synthesize new PTGS once aspirin has irreversibly inhibited the enzyme, an important difference with reversible inhibitors.

Furthermore, aspirin, while inhibiting the ability of COX-2 to form pro-inflammatory products such as the prostaglandins, converts this enzyme's activity from a prostaglandin-forming cyclooxygenase to a lipoxygenase-like enzyme: aspirin-treated COX-2 metabolizes a variety of polyunsaturated fatty acids to hydroperoxy products which are then further metabolized to specialized proresolving mediators such as the aspirin-triggered lipoxins, aspirin-triggered resolvins, and aspirin-triggered maresins. These mediators possess potent anti-inflammatory activity. It is proposed that this aspirin-triggered transition of COX-2 from cyclooxygenase to lipoxygenase activity and the consequential formation of specialized proresolving mediators contributes to the anti-inflammatory effects of aspirin.

Recently, COX-2 inhibition has been proposed as a mechanism for reducing MDSC activity in some models of cancer and thereby assisting PD-1 effectiveness(3). In these preclinical models,

COX blockade synergizes with PD-1 inhibition in melanoma, colorectal cancer and in other syngeneic immunocompetent models. Furthermore the same COX signature was seen in cutaneous melanoma(3). The calculated human dose extrapolated from animal models is 1 gm twice daily.

1.3 Rationale for the Proposed Study

PD-1 inhibition is associated with dramatic and long lasting responses in melanoma. However, 40-60 % of patients do not respond to anti-PD-1 or anti-PD-L-1 blocking antibodies. Recent reports of PD-1+CTLA4 blocking combinations have shown increased response rates. The combination of ipilimumab and nivolumab has demonstrated response rates in the ~60% range (19). The combination of low dose ipilimumab and standard dose pembrolizumab has been explored in a recent clinical trial and shown an ORR of 55%. However, there remains a residual 40% of patients where this combination is still not effective.

Our analysis has shown that many PD-1 non-responders share certain characteristics such as elevated LDH, liver metastasis, as well as increased tumor burden and non-cutaneous origin (21-23). Collectively, many of these melanoma patients have low fractions of partially exhausted cytotoxic T lymphocytes (peCTL). For these “low peCTL” tumors, ipilimumab + PD-1 combination therapy with ipilimumab and PD-1 inhibitors is the current standard of care. We hypothesize that the addition of aspirin to this modified ipilimumab pembrolizumab regimen will increase response rates.

Recent reports have highlighted other pathways that may be involved (20) such as iNOS, COX-2 activation, Myeloid Derived Suppressor Cells and Treg activation. A recent report provides powerful support for the COX-2 pathway as an escape mechanism(3). These authors showed that ablation of the COX-2 pathway or PGE synthetase in mice with the BRAFV600E mutation or the NRAS G12D mutation shifts cells towards the classic PD-1 escape pathway and hence sensitizes them to anti-PD-1 antibodies. The dose of aspirin was extrapolated from these mouse experiments.

1.4 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. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

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

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and

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

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

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

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

The combination of ipilimumab and pembrolizumab is considered one of the most effective regimens currently in use (Long et al, ASCO 2016) with an ORR of >50% with reduced grade 3/4 toxicities compared to the combination of ipilimumab and nivolumab. Given that this current combination is adding a drug (ASA), ipilimumab pembrolizumab is a better choice for the baseline regimen

The addition of ASA is based on preclinical data showing the effectiveness of ASA in increasing responses to anti-PD-1 antibodies(3)In this study mice were administered aspirin orally at 600 µg/mL. translating this dose to a human dose, approximately 1,800-2,400 mg/day would be appropriate. In a twice daily dose this would be 975 mg (total 1,950 mg/day).

1.5 Correlative Studies

We have recently described the CD8+ CTLA-4 high/PD-1 high fraction in the tumor as being directly proportional to the response rate. We plan to determine the proportion of patients with this marker <20% who have a response as this will be representative of patients who we would not expect to have a response with monotherapy PD-1 alone(21).

2 Objectives of the Study

2.1 Primary

To evaluate the overall response rate (ORR) by week 12 in patients with stage III unresectable/ stage IV melanoma

2.2 Secondary

To determine the median progression free survival, overall survival, and toxicity profile of the combination of ipilimumab, pembrolizumab and high dose aspirin in patients with stage III unresectable/IV melanoma.

2.3 Endpoints

2.3.1 Primary Endpoints

- Objective Response Rate (ORR)

2.3.2 Secondary Endpoints

- Toxicity, according to CTCAE v. 4
- Profession Free Survival (PFS)
- Overall Survival (OS)

3 Study Design

3.1 Characteristics

This is a single arm, single institution, open label, prospective, Phase II clinical trial with a Simon stage II design with an early stopping rule. In the first stage 11 patients will be accrued. If ≤7 responses are seen here then the trial will be stopped for futility. If >7 responses are seen then the trial will be continued and a full 43 patients will be enrolled.

Patients will take aspirin daily and receive combination therapy with pembrolizumab and ipilimumab every 3 weeks for 4 cycles. After 4 cycles, ipilimumab will be discontinued and patients will receive pembrolizumab every 3 weeks and continue taking aspirin daily.

3.2 Number of Subjects

A total of 43 subjects will be enrolled.

3.3 Eligibility Criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

3.3.1 Inclusion Criteria

1. Patients must have histologically confirmed melanoma that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective
2. Age >18 years
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
4. Requirements for organ and marrow function:

Adequate bone marrow function:	
leukocytes	≥ 3,000/mcL
absolute neutrophil count	≥ 1,500/mcL
platelets	≥ 100,000/mcL
Adequate hepatic function:	
total bilirubin	within normal institutional limits
total bilirubin	≤1.5 X institutional upper limit
AST(SGOT)	≤ 2.5 X institutional upper limit of normal
ALT(SGPT)	≤ 2.5 X institutional upper limit of normal
Adequate renal function:	
creatinine	≤ 1.5 X ULN

5. Women of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study drug. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
6. Women of childbearing potential (Section 5.6.2) must be willing to use an adequate method of contraception, as outlined in Section 5.6.2 – Contraception, for the course of the study through 120 days after the last dose of study medication.

   Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
7. Men of childbearing potential (Section 5.6.2) must agree to use an adequate method of contraception as outlined in Section 5.6.2- Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

   Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
8. Ability to understand a written informed consent document, and the willingness to sign it.

3.3.2 Exclusion Criteria

1. Any mental or physical condition or disease or past medical history that mitigates against following the protocol
2. History of active autoimmune diseases such as but not limited to Crohn's disease, Ulcerative colitis, Sjogren's syndrome, requiring active immune suppression. Patient may have hay fever or controlled asthma
3. Any solid organ transplant or bone marrow transplant
4. Any other disseminated malignancy. Exceptions include: localized prostate cancer, basal or squamous cell skin cancer, localized cervical cancer, and localized breast cancer.

5. Uncontrolled CNS metastasis. Patients with CNS metastasis can be eligible if definitively treated with radiotherapy or surgery.
6. Any coexistent medical condition interfering with drug absorption
7. History of gastritis or malabsorption syndrome or aspirin intolerance or allergy
8. Live vaccination within the last 30 days
9. History of multiple sclerosis, Type 1 DM or Guellian-Barre syndrome
10. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.

3.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until:

- Disease progression
    - Note: For a clinically stable subject with first radiologic evidence of disease progression (e.g. unconfirmed), it is at the discretion of the primary investigator to continue treating the subject.
    - Note: A subject may be granted an exception, at the discretion of the primary investigator, to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved.
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patients decides to withdraw from the study
- Significant patient non-compliance with protocol
- General or specific changes in the patients' condition render the patient unacceptable for further treatment in the judgment of the investigator.

3.5 Duration of Follow Up

Patients will be followed for 30 days after completion of treatment or removal from study, or until death, whichever occurs first. Patients removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related adverse events to Grade 2 or lower.

3.6 Study Timeline

3.6.1 Primary Completion

The study is expected to complete accrual at 24 months.

3.6.2 Study Completion

The study will reach completion 36 months from the time the study opens to accrual.

4 Study Drugs

The drugs to be used in this study are outlined below.

4.1 Pembrolizumab

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

4.1.1 Packaging and Labeling Information

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

4.1.2 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.

4.1.3 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.

4.1.4 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.

4.1.5 Safety Information

Complete and updated adverse event information for pembrolizumab is available in the Investigational Drug Brochure and/or product package insert.

4.2 Ipilimumab

Ipilimumab used in this study will be commercial drug supply. Ipilimumab is to be stored as directed below.

Drug Name & Potency	Dosage Form
Ipilimumab 200 mg (5 mg/mL)	Solution for Injection 40 mL/vial (4 vials/carton)

4.2.1 Packaging and Labeling Information

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

4.2.2 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.

4.2.3 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. Store at 2° - 8°C. Protect from light and freezing.

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

- Do not shake product.
- Inspect parenteral drug products visually for particulate matter and discoloration prior to administration. Discard vial if solution is cloudy, there is pronounced discoloration (solution may have pale-yellow color), or there is foreign particulate matter other than translucent-to-white, amorphous particles.

Preparation of Solution

- Allow the vials to stand at room temperature for approximately 5 minutes prior to preparation of infusion.
- Withdraw the required volume of ipilimumab and transfer into an intravenous bag.
- Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare a diluted solution with a final concentration ranging from 1 mg/mL to 2 mg/mL. Mix diluted solution by gentle inversion.
- Store the diluted solution for no more than 24 hours under refrigeration (2°C to 8°C, 36°F to 46°F) or at room temperature (20°C to 25°C, 68°F to 77°F).
- Flush the intravenous line with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP after each dose.

4.2.4 Returns and Reconciliation

4.2.5 Safety Information

WARNINGS AND PRECAUTIONS

Ipilimumab can result in severe and fatal immune-mediated reactions [see Boxed Warning].

Immune-Mediated Enterocolitis

Immune-mediated enterocolitis, including fatal cases, can occur with ipilimumab.

Monitor patients for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms.

Permanently discontinue ipilimumab in patients with severe enterocolitis and initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. In clinical trials, rapid corticosteroid tapering resulted in recurrence or worsening symptoms of enterocolitis in some patients. Consider adding anti-TNF or other immunosuppressant agents for management of immune-mediated enterocolitis unresponsive to systemic corticosteroids within 3 to 5 days or recurring after symptom improvement.

Withhold ipilimumab dosing for moderate enterocolitis; administer anti-diarrheal treatment and, if persistent for more than 1 week, initiate systemic corticosteroids at a dose of 0.5 mg/kg/day prednisone or equivalent.

Metastatic Melanoma

In patients receiving ipilimumab 3 mg/kg in Trial 1, severe, life-threatening, or fatal (diarrhea of 7 or more stools above baseline, fever, ileus, peritoneal signs; Grade 3 to 5) immune-mediated enterocolitis occurred in 34 ipilimumab-treated patients (7%), and moderate (diarrhea with up to 6 stools above baseline, abdominal pain, mucus or blood in stool; Grade 2) enterocolitis occurred in 28 ipilimumab -treated patients (5%). Across all ipilimumab-treated patients (n=511), 5 patients (1%) developed intestinal perforation, 4 patients (0.8%) died as a result of complications, and 26 patients (5%) were hospitalized for severe enterocolitis.

The median time to onset of Grade 3 to 5 enterocolitis was 1.7 months (range: 11 days to 3.1 months) and for Grade 2 enterocolitis was 1.4 months (range: 2 days to 4.3 months).

Immune-Mediated Hepatitis

Immune-mediated hepatitis, including fatal cases, can occur with ipilimumab.

Monitor liver function tests (hepatic transaminase and bilirubin levels) and assess patients for signs and symptoms of hepatotoxicity before each dose of ipilimumab. In patients with hepatotoxicity, rule out infectious or malignant causes and increase frequency of liver function test monitoring until resolution.

Permanently discontinue ipilimumab in patients with Grade 3 to 4 hepatotoxicity and administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When liver function tests show sustained improvement or return to baseline, initiate corticosteroid tapering and continue to taper over 1 month. Across the clinical development program for ipilimumab, mycophenolate treatment has been administered in patients who have persistent severe hepatitis despite high-dose corticosteroids. Withhold ipilimumab in patients with Grade 2 hepatotoxicity.

Metastatic Melanoma

In patients receiving ipilimumab 3 mg/kg in Trial 1, severe, life-threatening, or fatal hepatotoxicity (AST or ALT elevations of more than 5 times the upper limit of normal or total bilirubin elevations more than 3 times the upper limit of normal; Grade 3 to 5) occurred in 8 ipilimumab-treated patients (2%), with fatal hepatic failure in 0.2% and hospitalization in 0.4% of ipilimumab-treated patients. An additional 13 patients (2.5%) experienced moderate hepatotoxicity manifested by liver function test abnormalities (AST or ALT elevations of more than 2.5 times but not more than 5 times the upper limit of normal or total bilirubin elevation of
more than 1.5 times but not more than 3 times the upper limit of normal; Grade 2). The underlying pathology was not ascertained in all patients but in some instances included immune- mediated hepatitis. There were insufficient numbers of patients with biopsy-proven hepatitis to characterize the clinical course of this event.

Immune-Mediated Dermatitis

Immune-mediated dermatitis, including fatal cases, can occur with ipilimumab.

Monitor patients for signs and symptoms of dermatitis, such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated.

Permanently discontinue ipilimumab in patients with Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations. Administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month. Withhold ipilimumab dosing in patients with moderate to severe signs and symptoms [see Dosage and Administration (2.3)].

For mild to moderate dermatitis, such as localized rash and pruritus, treat symptomatically. Administer topical or systemic corticosteroids if there is no improvement of symptoms within 1 week.

Metastatic Melanoma

In patients receiving ipilimumab 3 mg/kg in Trial 1, severe, life-threatening, or fatal immune-mediated dermatitis (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations; Grade 3 to 5) occurred in 13 ipilimumab-treated patients (2.5%). One patient (0.2%) died as a result of toxic epidermal necrolysis and one additional patient required hospitalization for severe dermatitis. There were 63 patients (12%) with moderate (Grade 2) dermatitis.

The median time to onset of moderate, severe, or life-threatening immune-mediated dermatitis was 22 days and ranged up to 4.0 months from the initiation of ipilimumab.

Seven ipilimumab-treated patients (54%) with severe dermatitis received high-dose corticosteroids (median dose 60 mg prednisone/day or equivalent) for up to 3.4 months followed by corticosteroid taper. Of these 7 patients, 6 had complete resolution; time to resolution ranged up to 3.6 months.

Of the 63 patients with moderate dermatitis, 25 (40%) were treated with systemic corticosteroids (median of 60 mg/day of prednisone or equivalent) for a median of 15 days, 7 (11%) were treated with only topical corticosteroids, and 31 (49%) did not receive systemic or topical corticosteroids. Forty-four patients (70%) with moderate dermatitis were reported to have complete resolution, 7 (11%) improved to mild (Grade 1) severity, and 12 (19%) had no reported improvement.

Immune-Mediated Neuropathies

Immune-mediated neuropathies, including fatal cases, can occur with ipilimumab.

Monitor for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Permanently discontinue ipilimumab in patients with severe neuropathy (interfering with daily activities) such as Guillain-Barré-like syndromes. Institute medical intervention as appropriate for management of severe neuropathy. Consider initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe neuropathies. Withhold ipilimumab dosing in patients with moderate neuropathy (not interfering with daily activities) [see Dosage and Administration (2.3)].

Metastatic Melanoma

In patients receiving ipilimumab 3 mg/kg in Trial 1, 1 case of fatal Guillain-Barré syndrome and 1 case of severe (Grade 3) peripheral motor neuropathy were reported. Across the clinical development program of ipilimumab, myasthenia gravis and additional cases of Guillain-Barré syndrome have been reported.

Immune-Mediated Endocrinopathies

Immune-mediated endocrinopathies, including life-threatening cases, can occur with ipilimumab.

Monitor patients for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism. Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms of endocrinopathies should be considered immune-mediated.

Monitor clinical chemistries, adrenocorticotropic hormone (ACTH) level, and thyroid function tests at the start of treatment, before each dose, and as clinically indicated based on symptoms. In a limited number of patients, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland.

Withhold ipilimumab dosing in symptomatic patients and consider referral to an endocrinologist. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent, and initiate appropriate hormone replacement therapy [see Dosage and Administration (2.3)].

Metastatic Melanoma

In patients receiving ipilimumab 3 mg/kg in Trial 1, severe to life-threatening immune-mediated endocrinopathies (requiring hospitalization, urgent medical intervention, or interfering with activities of daily living; Grade 3 to 4) occurred in 9 ipilimumab-treated patients (1.8%). All 9 patients had hypopituitarism and some had additional concomitant endocrinopathies such as adrenal insufficiency, hypogonadism, and hypothyroidism. Six of the 9 patients were hospitalized for severe endocrinopathies. Moderate endocrinopathy (requiring hormone replacement or medical intervention; Grade 2) occurred in 12 patients (2.3%) and consisted of hypothyroidism, adrenal insufficiency, hypopituitarism, and 1 case each of hyperthyroidism and Cushing's syndrome. The median time to onset of moderate to severe immune-mediated endocrinopathy was 2.5 months and ranged up to 4.4 months after the initiation of ipilimumab.

Of the 21 patients with moderate to life-threatening endocrinopathy, 17 patients required long-term hormone replacement therapy including, most commonly, adrenal hormones (n=10) and thyroid hormones (n=13).

Other Immune-Mediated Adverse Reactions, Including Ocular Manifestations

Permanently discontinue ipilimumab for clinically significant or severe immune-mediated adverse reactions. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe immune-mediated adverse reactions.

Administer corticosteroid eye drops to patients who develop uveitis, iritis, or episcleritis. Permanently discontinue ipilimumab for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy [see Dosage and Administration (2.3)].

Metastatic Melanoma

In Trial 1, the following clinically significant immune-mediated adverse reactions were seen in less than 1% of ipilimumab-treated patients: nephritis, pneumonitis, meningitis, pericarditis, uveitis, iritis, and hemolytic anemia.

Other Clinical Experience

Across 21 dose-ranging trials administering ipilimumab at doses of 0.1 to 20 mg/kg (n=2478), the following likely immune-mediated adverse reactions were also reported with less than 1% incidence: angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, iritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, arthritis, autoimmune thyroiditis, neurosensory hypoacusis, autoimmune central neuropathy (encephalitis), myositis, polymyositis, ocular myositis, hemolytic anemia, and nephritis.

Embryo-fetal Toxicity

Based on its mechanism of action and data from animal studies, ipilimumab can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of ipilimumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight), and higher incidences of infant mortality in a dose-related manner. The effects of ipilimumab are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with a ipilimumab-containing regimen and for 3 months after the last dose of ipilimumab [see Use in Specific Populations (8.1, 8.3)].

[redacted]

4.3 Aspirin (Acetyl Salicylic Acid)

Aspirin used in this study will be commercial drug supply. Aspirin is to be stored as directed below.

4.3.1 Packaging and Labeling Information

Aspirin will be provided from a commercial supplier as tablets 325 mg size.

4.3.2 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.

4.3.3 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location at room temperature. Protect from light and freezing. Clinical supplies may not be used for any purpose other than that stated in the protocol. Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

4.3.4 Returns and Reconciliation

Supplies will be tracked by the investigational pharmacist and dispensed directly to the patient.

4.3.5 Safety Information

Aspirin is associated with serious side effects including GI bleeding , renal side effects as well as platelet and bleeding abnormalities. The FDA has reviewed aspirin side effect and a comprehensive review is at https://www.drugs.com/monograph/aspirin.html.

5 Treatment Plan

5.1 Dosage and Administration

Table 1 Regimen Description

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
Ipilimumab	1 mg/kg	Q3wk X4	IV infusion	Day 1 of each 3 wk cycle, for 4 cycles	experimental
Aspirin	975 mg	PO BID	oral	Each day	experimental

Trial treatment should begin on the day of randomization or as close as possible to the date on which treatment is allocated/assigned.

5.2 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

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

Ipilimumab, 1 mg/kg will be administered for 4 cycles as a 60 minute intravenous infusion following the pembrolizumab. No premedication is used routinely. If any infusion reaction is suspected, the infusion may be stopped and antihistamines may be administered (Benadryl 50 mg PO or 25 mg IV) and the infusion restarted.

Aspirin, 975 mg PO Twice daily is taken orally by the patient. An adequate number of pills will be dispensed every 3 weeks and pill counts done to ensure compliance

5.3 Dose Modifications and Dosing Delays

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

5.3.1 Dose Modification for Pembrolizumab

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per 3 below. See Section 5.6 for supportive care guidelines, including use of corticosteroids.

Table 2 Pembrolizumab Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	

Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

5.3.2 Dose Modification for Ipilimumab

Note that ipilimumab is only used for Cycles 1-4. Therefore in the case of ipilimumab being held, Pembrolizumab may be continued if not specifically contraindicated. Aspirin may also be continued unless specifically contraindicated

Table 3 Ipilimumab Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks. Patients are to be treated with 1 mg/kg prednisone or equivalent if grade 2 or greater toxicity and tapered over several weeks
	3-4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold ipilimumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Discontinue permanently
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with ipilimumab can be continued while thyroid replacement therapy is instituted	Therapy with ipilimumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue

Toxicity	Hold For Grade	Timing for Restarting Treatment	Treatment Discontinuation
All Other Drug-Related Toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

5.3.3 Dose Modification for Aspirin

Note that aspirin is known to cause GI bleeding, ulceration and hemorrhage. Any evidence of GI bleeding or ulceration based on symptoms or endoscopy should be treated as described below. For Grade 1 or 2 adverse events, patients may have proton pump inhibitor or sucralfate treatment along with aspirin.

Table 4 Aspirin Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
GI Bleeding	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 2 weeks, or continued bleeding, or life threatening or serious Grade 3 or 4 hemorrhage
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 4 weeks
GI Ulceration	1-2	Use omeprazole or PPI or sucralfate if not currently being used	May continue aspirin if symptoms resolve with treatment
	3-4 or Severe	Toxicity resolves to Grade 1 or 0	Life threatening or serious Grade 3 or 4 toxicity

5.4 Rescue Medications & Supportive Care

5.4.1 Supportive Care Guidelines

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

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 5.3 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

- **Pneumonitis**:

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

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

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

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

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

- **Hypophysitis**:

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

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

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

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

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

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

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

Table 5 Infusion Reaction Treatment Guidelines

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

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or

vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.5.1 Acceptable Concomitant Medications

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

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.5.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.

Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

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

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary. Daily or regular use of NSAIDs should be avoided except for the aspirin as specified in the trial. Concomitant NSAID use more frequently than once per week may be allowed at the investigator's discretion.

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

There are no prohibited therapies for patients after they discontinue study treatment.

5.6 Diet/Activity/Other Considerations

5.6.1 Diet

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

5.6.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

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

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

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

OR

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

OR

3. has a congenital or acquired condition that prevents childbearing.

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

1. practice abstinence† from heterosexual activity;

OR

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

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

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

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

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.6.3 Use in Pregnancy

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

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 7.2.

5.6.4 Use in Nursing Women

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

5.6.5 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 6.3 - Other Procedures.

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression

Note: For a clinically stable subject with first radiologic evidence of disease progression (e.g., unconfirmed), it is at the discretion of the site investigator to continue treating the subject

Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved.

- Unacceptable adverse experiences as described in Section 7.4
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 6.3 - Other Procedures. After the end of treatment, each subject will be followed for 30 days for adverse event monitoring.

5.6.6 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR, at the discretion of the primary investigator.

5.6.7 Clinical Criteria for Early Trial Termination

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

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

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

6 Study Procedures and Observations

The Trial Flow Chart summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

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

6.1 Administrative Procedures

6.1.1 Informed Consent

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

General Informed Consent

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

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

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

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

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

6.1.2 Inclusion/Exclusion Criteria

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

6.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are

considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

6.1.4 Prior and Concomitant Medications Review

6.1.4.1 Prior Medications

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

6.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

6.1.5 Disease Details and Treatments

6.1.5.1 Disease Details

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

6.1.5.2 Prior Treatment Details

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

6.1.5.3 Subsequent Anti-Cancer Therapy Status

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

6.2 Clinical Procedures/Assessments

6.2.1 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.

For subjects receiving treatment all AEs of unknown etiology associated with treatment exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs).

Please refer to Section 7 for detailed information regarding the assessment and recording of AEs.

6.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam at screening, on C1D1 of each treatment cycle, and at discontinuation of treatment, as specified in the Study Flow Chart (Section 6.0). Clinically significant abnormal findings should be recorded as medical history.

6.2.3 Vital Signs

The investigator or qualified designee will take vital signs at screening, on C1D1 of each treatment cycle, and at discontinuation of treatment as specified in the Study Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

6.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 1) at screening, prior to the administration of each dose of trial treatment and at discontinuation of trial treatment as specified in the Study Flow Chart.

6.2.5 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in the table below.

Table 6 Laboratory Tests

Hematology	**Chemistry**	**Urinalysis**	**Other**
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		PK
	Calcium		
	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		

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

Laboratory tests for screening should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to initiation of each treatment cycle.

6.2.6 Tumor Tissue Collection

At screening, patients with archival tissue or fresh tissue samples available will have their samples collected and tested for PD-L1 expression. FFPE blocks will be requested from specimens containing melanoma tissue and 5 slides of 5uM thickness will be cut from each block. The unstained slides will be shipped to Qualtek for staining with the 22C3 antibody. The stained samples will be graded according to MEL score.

6.2.7 Tumor Imaging

Prefer imaging of chest/abdomen and pelvis. PET/CT, CT, or MRI are acceptable. Imaging to be performed every 12 weeks (every 4 cycles).

6.3 Other Procedures

6.3.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

6.3.2 Visit Requirements

Visit requirements are outlined in Table 6 Study Flow Chart. Specific procedure-related details are provided above in Section 6.2 - Clinical Procedures/Assessments.

6.3.3 Safety Follow-Up Visit

The Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first.

6.3.4 Follow-up Visits

Patients who discontinue treatment will be followed as clinically indicated.

7 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example),

symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product, is also an adverse event.

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

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

Adverse events may occur during the course of the use of Merck product in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an adverse event.

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

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.3. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. 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.

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

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

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. [redacted]

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

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

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

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. [redacted]

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

7.3.1 Serious Adverse Events

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event

- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.

    - Is a new cancer (that is not a condition of the study);
    - Is associated with an overdose.

Refer to Table 8 Evaluating Adverse Events for additional details regarding each of the above criteria.

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

For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment, or at the time that the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study , whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck Global Safety.

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

SAE reports and any other relevant safety information are to be forwarded to [redacted] Merck Global Safety [redacted]

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. [redacted] at the time of submission to FDA.

7.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. [redacted]

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

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

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 7.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

7.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Section 7.3 - Immediate Reporting of Adverse Events to the Sponsor and to Merck, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Sponsor within 24 hours and to Merck Global Safety within 2 working days either by electronic or paper media.

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

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

7.4 Evaluating Adverse Events

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

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

Table 7 Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor and to Merck within 2 working days..	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause Merck product to be discontinued?	
Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of	

	causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

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 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 Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to 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) Sponsor's 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 MERCK PRODUCT, OR IF REEXPOSURE TO MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR 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 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 Merck product relationship).**
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.
No, there is not a reasonable possibility of Merck product relationship	Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a subject with overdose without an associated AE.)

7.5 Sponsor Responsibility for Reporting Adverse Events

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

8 Statistical Analysis Plan

8.1 Statistical Analysis Plan Summary

This is a non-randomized prospective Phase II clinical trial with a Simon stage II design with an early stopping provision. The primary objective is to evaluate the overall response rate (ORR) by week 12 in patients with stage III unresectable/stage IV melanoma.The hypothesis is that the study treatment regimen will have a clinical meaningful improvement in ORR by week 12. H0 is for an ORR by week 12 = 60% while Ha is for an ORR by week 12= 80%. 60% is used as a threshold for the H0 based on published data (19).

8.2 Sample Size and Accrual Rate Considerations

8.2.1 Sample Size and Power Estimate

A two-stage Simon's optimal design is used for the study to test the null hypothesis that the ORR by week 12 is 60% or less versus the alternative hypothesis that the ORR by week 12 is greater than 80% using an one-sided test with 5% level of significance with the power of 80% for alternative hypothesis. An initial 11 evaluable patients will be accrued at the end of stage 1. If at least 4 or more overall responders (CR/PR per RECIST 1.1) from stage 1 are observed, the study will continue to enroll additional 32 evaluable patients in the stage 2. The null hypothesis will be rejected at the 5% level of significance (one-sided) if there are 30 or fewer ORR by week 12 among all 43 evaluable patients by the end of stage 2. If the ORR rate is 60%, the probability of ending the study during the first stage is 70%; if the ORR rate is indeed 80%, the probability of study will be terminated at the first stage is 16%. The significance level of the study is 0.05 and the power is 0.80 for the study design.

8.2.2 Replacement Policy

Patients who are of unknown clinical response and discontinued due to AEs will be treated as non-responders. Other missing data will simply be noted as missing on the appropriate table or listing. Patients with missing data will not be replaced.

8.2.3 Accrual Estimates

The study is planned to accrue a total of 43 evaluable patients. The accrual rate is expected to be approximately 2 to 3 patients per month. It is expected to take about 24 months to accrue all 43 evaluable patients. We expect to enroll up to 50 patients to offset the potential drop-outs or non-evaluable patients in the study.

8.3 Interim Analyses and Stopping Rules

The two stage sequential design of this study has a decision timepoint based on the counts of CR or PR (per RECIST 1.1) from stage 1 by at least 4 months post-initial treatment regimen of the 11 patients with measurable disease at baseline, to either stop or initiate stage 2 of the study. In the first stage 11 patients will be accrued. If ≤7 responses are seen here then the trial will be stopped

for futility. If >7 responses are seen then the trial will be continued an a full 43 patients will be enrolled.

8.4 Statistical Analysis Plan

This is a Simon 2 stage Phase II prospective clinical trial. The statistical plan will be for an optimal 2 stage design with the P_0=0.6 and P_1=0.8. If <30 responses are seen then the experimental hypothesis has been rejected. The type 1 error is 0.0489 and the power is 0.8024. The probability of early stopping if the response rate is P_0=20.5 %

8.4.1 Analysis of Primary Endpoints

The primary efficacy endpoint of the study is the objective response rate (ORR), which is defined as the proportion of subjects for whom the best overall response by week 12 at the time of data cutoff is confirmed CR or PR as per RECIST. 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. In the primary analysis, point estimates of ORR and 95% confidence intervals will be provided. Subjects who do not have any post-baseline tumor assessments will be considered as non-responders. Supportive analysis of ORR may be performed to include response based on investigator assessment. If sufficient responses are observed, additional supportive analyses may be conducted in subgroups defined by baseline characteristics.

8.4.2 Analysis of Secondary Endpoints

For analysis of secondary endpoints, progression-free survival at 6 months is defined as the proportion of subjects alive and progression-free 6 months (182 days) after study day 1. Duration of PFS is defined as the time from the study day 1 to the earlier of disease progression or death due to any cause. The analysis of PFS will include only objective progression events per RECIST and clinical progression determined by the investigator may not be considered disease progression. Subjects who do not have any post-baseline tumor assessments will be right-censored on the date of study day 1. Subjects who receive subsequent anti-cancer therapy before experiencing an event will be right censored at the data of the last tumor assessment prior to the date of initiation of subsequent therapy. Subjects who have not experienced an event (and are not otherwise censored) at the time of data cutoff will be right censored on the date of their last tumor assessment. PFS will be estimated as a sample proportion based upon the results of 6-month tumor assessment. Subjects for whom the assessment is not performed will be included as failure, even if known to be alive at this timepoint. 95% confidence intervals will be provided. Median of PFS and duration of PFS will also be estimated using Kaplan-Meier methods with associated confidence intervals.

For analysis of overall survival, duration of OS is defined as the time from study day 1 to death due to any cause. For subjects who are alive at the time of data cutoff or are permanently lost to follow-up, duration of OS will be right censored at the date the subject was last known to be alive.The median duration of OS will be estimated using the Kaplan-Meier methods with the associated confidence intervals.

8.4.3 Other Analyses

8.5 Evaluation of Safety

Each verbatim adverse event (AE) term recorded during the study will be mapped to a system organ class and preferred term using the MedDRA Dictionary, version 16.1. The duration of an

adverse event will be computed as the stop date/time minus the start date/time, expressed as days.

A treatment-emergent adverse event (TEAE) will be defined as one with a start date and time which occurred after the date and time of the first study drug administration. If the start date and time of an AE is incomplete or missing, the event will be assumed to be treatment emergent, unless the incomplete start date and time or the stop date (complete or incomplete) clearly indicates that the event started prior to the first dose of study drug. Incomplete/missing information will be reported as incomplete/missing in the subject data listings.

The relationship of each AE to study drug will be recorded as “not related,” “probably not related,” “possibly related,” “probably related” and “definitely related.” For all analysis “possibly related,” “probably related” and “definitely related” will be considered as related to study drug. If a relation is missing for a given event, the event will conservatively be assumed as “definitely related” for summarization.

The severity of each AE will be classified as mild, moderate, severe, or potentially life threatening. All summaries of AEs will present the number and percentage of subjects who experienced at least one event overall, by system organ class, and by preferred term. If a subject had multiple occurrences of a particular event, the subject was counted only once at the given level of summarization (overall, within system organ class, or within preferred term).

For summaries of adverse events by maximum severity or maximum relation to study drug, if a subject had multiple occurrences of a particular AE, the subject was counted only once at the maximum severity or relation to study drug at the given level of summarization (overall, within system organ class, or within preferred term).

9 Study Management

9.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

9.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g., advertisements used to recruit participants) will be reviewed and approved by

the UCSF Institutional Review Board. Prior to obtaining IRB approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

9.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

9.4 Changes in the Protocol

Once the protocol has been approved by the UCSF IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the Investigator must then notify the IRB in writing within five (5) working days after implementation. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

9.5 Handling and Documentation of Clinical Supplies

The UCSF Principal Investigator and each participating site will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included. The sponsor-investigator will maintain written records of any disposition of the study drug.

The Principal Investigator shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the Principal Investigator will not allow the investigational drug to be used in any manner other than that specified in this protocol.

9.6 Case Report Forms (CRFs)

The Principal Investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the Study Chair, the Trial Statistician, and the Protocol Project Manager.

9.7 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered “serious”. The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 3 Data and Safety Monitoring Plan for a Phase 2 or 3 Institutional Study, for additional information.

9.8 Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data (e.g., signed and dated consent forms and medical records, such as progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

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Appendix 1 Schedule of Study Procedures and Assessments

Trial Period:	**Screening Phase[a]**	**Treatment Cycles[b]**								**End of Treatment[e]**	**Post-Treatment Follow-up[f]**
						To be repeated beyond 8 cycles					
Treatment Cycle/Title:	Main Study Screening	1	2	3	4	5	6	7	8	End of Treatment (EOT) visit	Safety Follow-up Visit
Scheduling Window (Days):	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon
Administrative Procedures											
Informed Consent	X										
Inclusion/Exclusion Criteria	X										
Demographics and Medical History	X										
Prior and Concomitant Medication Review	X										
Post-study anticancer therapy status										X	X
Survival Status										X	X
Trial Treatment Administration											
Ipilimumab		X	X	X	X						
Pembrolizumab		X	X	X	X	X	X	X	X		
Aspirin		X	X	X	X	X	X	X	X		
Clinical Procedures/Assessments											
Review Adverse Events		X	X	X	X	X	X	X	X	X	X
Full Physical Examination	X	X	X	X	X	X	X	X	X	X	X
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X
Laboratory Procedures/Assessments											
Pregnancy Test – Urine or Serum-HCG[c]	X										
PT/INR and aPTT	X										
CBC with Differential	X	X	X	X	X	X	X	X	X		
Comprehensive Serum Chemistry Panel	X	X	X	X	X	X	X	X	X		
Urinalysis	X										
T3, FT4 and TSH	X	X	X	X	X	X	X	X	X		
Tumor Tissue Collection[g]	X										
Efficacy Measurements											
Tumor Imaging[d]	X				X				X		

a. Screening procedures to be completed within 28 days of C1D1, except laboratory tests for screening should be performed within 10 days prior to the first dose of treatment.

b. Patients will take aspirin daily and receive pembrolizumab and ipilimumab every 3 weeks for 4 cycles. After 4 cycles, ipilimumab will be discontinued and patients will continue receiving pembrolizumab every 3 weeks while taking aspirin daily.
c. Women of childbearing potential: negative urine or serum pregnancy test within 72 hours prior to receiving trial treatment. If urine test is positive or non-confirmatory, a serum pregnancy test will be required.
d. Prefer imaging of chest/abdomen and pelvis. PET/CT, CT, or MRI are acceptable.
e. End of Treatment (EOT) is defined as date patient and/or treating physician decides to discontinue study treatment. EOT visit and enter the post-treatment (follow-up) period. EOT visit should occur within 30 days of last dose of study drug or the decision to discontinue study drug. If a patient discontinues study drug at a scheduled visit, the EOT visit can occur the same day. The EOT assessments do not need to be repeated if done within the preceding14 days. The EOT visit can be combined with a safety follow-up visit.
f. Safety follow-up can be combined with the EOT visit.
g. If available, archival tissue samples will be collected at screening and processed for for PD-L1 expression testing. FFPE blocks will be requested from specimens containing melanoma tissue and 5 slides of 5uM thickness will be cut from each block. The unstained slides will be shipped to Qualtek for staining with the 22C3 antibody. The stained samples will be graded according to MEL score.

Appendix 2 Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
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)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active 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	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

Appendix 3 Data and Safety Monitoring Plan for a Phase 2 or 3 Institutional Study

Data and Safety Monitoring Plan for a Phase II or III Institutional Study

1. Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for auditing data quality and participant safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Semiannual auditing (depending on study accrual)
- Review of serious adverse events
- Minimum of biennial regulatory auditing

2. Monitoring and Reporting Guidelines

Investigators will conduct a continuous review of data and participant safety at monthly site committee meetings where the results of each participant's treatment are discussed and documented in the site committee minutes.

All institutional Phase II and III studies are designated with a moderate risk assessment. The data is audited semiannually with a random selection of twenty percent of the participants audited (or at least three participants if the calculated value is less than three). The DSMC Monitor/Auditor will audit a maximum of 5 cycles of treatment in the participants selected for the review, or until the selected participants discontinue study participation or the trial is closed with the IRB. Additionally, the assigned DSMC Monitor/Auditor will review no more than a total of 10 participant charts during the course of auditing this trial. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the auditing visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. Additionally, a regulatory audit will occur on a biennial basis to review all regulatory documents for the trial.

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 adverse events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the use of the investigational agent(s) or study procedure, will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to investigational agent or study procedure. Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or study procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or study procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or study procedure.
- **Unrelated** – the adverse event is clearly not related to the investigational agent(s) or study procedure.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and attribution assignment.

3.2 Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death.
- Life-threatening (i.e. results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Permanent or significant disability/incapacity
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:
https://irb.ucsf.edu/adverse-event

Med Watch forms and information:
www.fda.gov/medwatch/getforms.htm

All serious adverse events are entered into OnCore®, as well as submitted to the IRB (per IRB guidelines). The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE is sent to all required reporting agencies will be documented in OnCore®.

If the SAE involves a subject death, and is determined to be possibly, probably or definitely related to the investigational drug or any research related procedure, the event must be reported to the DSMC Chair (or Vice Chair) and DSMC Director within one business day.

1.3 Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Principal Investigator will notify the DSMC via report at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Investigator voluntarily holds enrollment or stops the study due to safety issues, the DSMC Chair (or Vice Chair) and the DSMC Director must be notified within one business day and the IRB must be notified as per IRB reporting regulations.

Data and Safety Monitoring Committee Contacts:

[redacted]
Box 1705
UCSF HDFCCC
San Francisco, CA 94158

DSMC Monitors
Box 0128
UCSF HDFCCC
San Francisco, CA
94143

Appendix 4 Prohibited Medications

Drug	Trade name (if applicable)
Aosetron:	Iotronex
Bosentan:	Tracleer
Candesartan:	Atacand
Celecoxib:	Celebrex
Diclofnac:	Volaren
Dronabinol:	Marinol
Flubiprofen:	Ansaid
Fluvastatin:	Lescol
Glimepiride:	Amaryl
Indomethacin:	Indocin
Irbesartan:	Avapro
Losartan:	Cozaar
Meloxicam:	Mobic
Montelukast:	Singulair
Nateglinide:	Starlix
Phenobarbital	
Phenytoin:	Dilantin
Piroxicam:	Feldene
Rosiglitazone:	Avandia
Rosuvastatin:	Crestor
Sulfmethoxazole	
Tolbutamide	
Torsemide:	Demadex
Valsartan:	Diovan
Warfarin:	Coumadin

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol

- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
- Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary. Daily or regular use of NSAID's should be avoided except for aspirin as specified in the trial. Concomitant NSAID use more frequently than once per week may be allowed at the investigator's discretion.

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

There are no prohibited therapies for patients after they discontinue study treatment.