

**TITLE: Testing the ability of Pembrolizumab to alter the Tumor Immune MicroEnvironment (TIME) of high risk DCIS**

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**Merck Supplied Agent:** Pembrolizumab

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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), Institutional Review Board (IRB), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable IRB 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](http://www.clinicaltrials.gov) website.
5. I agree to maintain adequate and accurate records in accordance with IRB policies, Federal, state and local laws and regulations.

### UCSF Principal Investigator / Study Chair

**Laura Esserman, MD, MBA**

\_\_\_\_\_  
Printed Name

\_\_\_\_\_  
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\_\_\_\_\_  
Date

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## 1.0 TRIAL SUMMARY

### 1.0 Trial Summary

Abbreviated Title	Testing the ability of Pembrolizumab to alter the tumor immune microenvironment of high risk DCIS
Trial Phase	Single agent pilot study
Clinical Indication	High risk DCIS
Trial Type	Pilot
Type of control	Untreated, proceed to surgical treatment at least 2 weeks after diagnosis
Route of administration	Intralesional
Trial Blinding	None
Treatment Groups	Controls; Intralesional injection of agent
Number of trial subjects	3 dose cohorts using a 3+3 cohort dose escalation design (9 patients) 30 in dose expansion group (10 controls, 20 treatment) total of 39 patients
Estimated enrollment period	42 months – June 2016 – December 2020
Estimated duration of trial	48 months – June 2020 target date for submission of publication
Duration of Participation	9 weeks (dose escalation), 5-9 weeks or 8-15 weeks (dose expansion)

## 2.0 TRIAL DESIGN

### 2.1 Trial Design Summary

#### 2.1 Trial Design Summary

We propose a pilot study to investigate the change in the immune microenvironment of high risk ductal carcinoma in situ (DCIS) after short term exposure to pembrolizumab. This study will include 3 dose cohorts using a 3+3 cohort dose escalation design (see figure 1) followed by a 4<sup>th</sup> cohort at the maximum tolerated dose. Unless a dose limiting toxicity (DLT), defined any grade 3 or 4 toxicity, is observed requiring expansion of a cohort or a subject withdraws, 3 subjects will be enrolled into each cohort in the dose escalation phase. Subjects, upon diagnosis with high risk DCIS, will be offered 2 doses of pembrolizumab injected intralesionally (IL) 3 weeks apart (+/- 1 week) with surgery 3 weeks (+/- 2 weeks) after the 2<sup>nd</sup> dose. The subject will then undergo the surgical treatment as determined by the surgeon and the subject (partial mastectomy or

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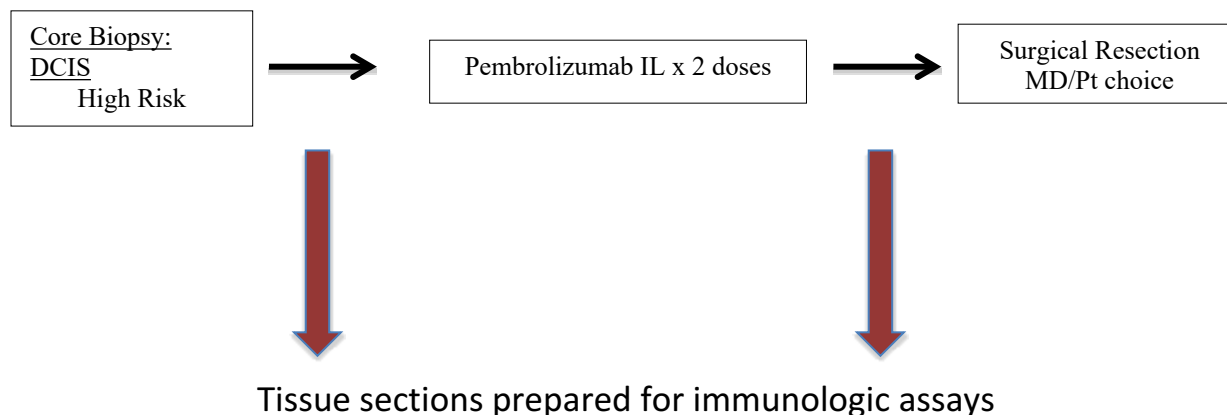
mastectomy). The primary objective of this phase of the study will be safety and feasibility of intralesional injection of pembrolizumab. The maximum tolerated dose will be used in the expansion phase. The expansion cohort will have a target enrollment of 30 subjects enrolled to either the control group or the treatment group. The treatment group will consist of 20 subjects who agree to receive the treatment. The control group will consist of 10 eligible subjects who decline treatment and agree to tissue collection and to the use of tissue for research purposes. The control group will proceed to surgery alone within a 4 month timeframe following the diagnosis of high risk DCIS. The treatment group will receive 4 doses of intralesional pembrolizumab 3 weeks apart (+/- 1 week) prior to surgery. All subjects in the expansion cohort will also undergo a baseline MRI at diagnosis and undergo a 2<sup>nd</sup> MRI prior to surgery. Baseline and pre-surgical MRI images will be evaluated for changes in tumor volume.

Cohort	Pembrolizumab Dose	Number of Subjects
1	2 mg	3-6
2	4 mg	3-6
3	8 mg	3-6
4	8 mg	30*

\* 10 patient control group, 20 patient treatment group

## 2.2 Trial Diagram

### Dose Escalation Cohort

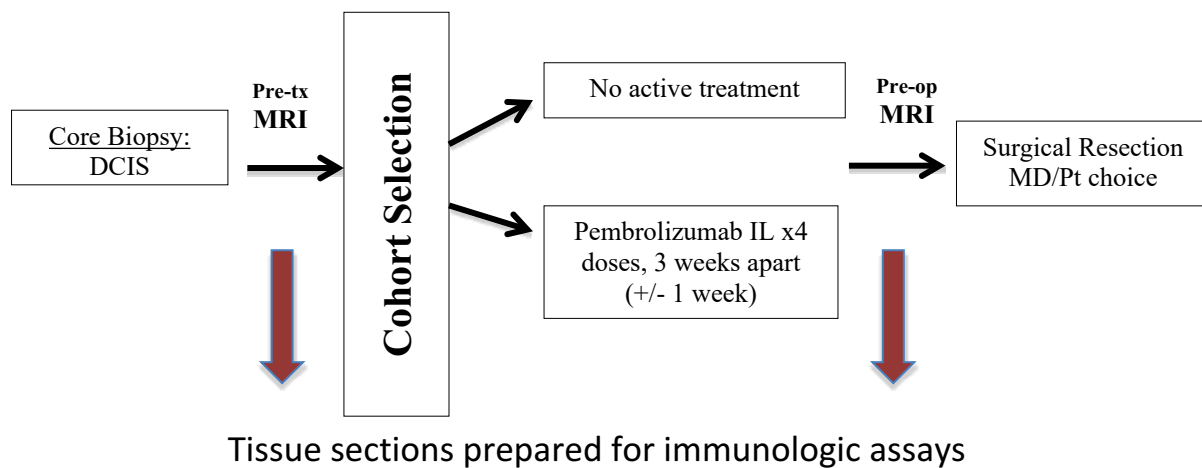




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## Dose Expansion Cohort



## 3.0 OBJECTIVES

### 3.1 Primary objectives (dose escalation phase)

3.1a) To determine the maximum tolerated dose (MTD), and recommended dose for subsequent expansion cohort, of intralesionally administered pembrolizumab in patients with ductal carcinoma in situ (DCIS) of the breast.

3.1b) To define the dose-limiting toxicities (DLTs), tolerability, and feasibility of intralesional administration of pembrolizumab in patients with DCIS.

### 3.2 Primary objective (dose expansion phase)

3.2a) To determine the response rate to intralesional pembrolizumab in patients with DCIS, as measured by an increase (baseline vs. post treatment) in intralesional CD8<sup>+</sup> T cells, compared to untreated controls.

### 3.3 Exploratory objectives

3.3a) To determine whether intralesional pembrolizumab decreases tumor volume on MRI imaging.

3.3b) To determine the extent of cell death within the DCIS lesions (pre- vs. post-therapy) using a cleaved caspase 3 IHC assay.

3.3c) To characterize changes in the immune landscape of DCIS following intralesional administration of pembrolizumab.

3.3d). To characterize changes in peripheral blood-based immune biomarkers.

## 4.0 BACKGROUND & RATIONALE

### 4.1 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies.

Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator brochure.

#### 4.1.1 Pharmaceutical and Therapeutic Background

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 $\zeta$ , PKC $\theta$  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<sup>+</sup> and CD8<sup>+</sup> 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.

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

#### **4.1.2 Preclinical and Clinical Trial Data**

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

### **4.2 Rationale**

#### **4.2.1 Rationale for the Trial and Selected Subject Population**

Ductal carcinoma in situ (DCIS) of the breast is a premalignant condition. Although DCIS is treated as an obligate precursor of invasive ductal carcinoma, the rate and latency of progression from DCIS to invasive breast cancer (IBC) in the absence of treatment are unknown. DCIS itself is not a lethal condition, but women with DCIS are at higher risk of developing subsequent local or metastatic IBC over a time period of 1-20 years depending on DCIS subtype.

DCIS is not one condition, but rather a spectrum of disease ranging from indolent lesions more akin to markers of increased risk for ER positive disease over 20 years and true precursors of triple negative or Her2 positive cancers that are likely to arise in a one to two year timeframe. The latter likely only comprises about 20% of the DCIS diagnosed.

Features of DCIS that are associated with high risk of recurrence include large size (> 5cm), high grade, comedo necrosis, palpable mass, hormone receptor (HR) negativity, and HER2 positivity. We selected such cases to investigate the immune microenvironment.<sup>1-3</sup>

Our studies, as well as those of others, have shown that high grade, HR-negative invasive breast cancers have a greater inflammatory component (significant macrophage and T cell infiltration) compared with low grade, HR-positive tumors.<sup>4-8</sup> Importantly, tumor associated macrophages are associated with early recurrence in HR-negative invasive breast cancer. High grade DCIS are also

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characterized by a high proportion of macrophages as measured by CD68 positive cells by immunohistochemistry.<sup>9-11</sup>

To further characterize the immune microenvironment of DCIS, we recently completed an IHC study of 53 cases of high grade DCIS, enriched for large lesions and history of recurrence, age matched with 65 cases of non-high grade DCIS. Immunohistochemical analyses were performed as single color stains for the following antigens: CD115, FoxP3, Ki-67, and HER2. Two color IHC was performed for the following antigen pairs: CD68/PCNA; CD68/Mac 387; CD8/HLA-DR; CD68/MRC1, and CD4/CD20. Stromal TILs were visually estimated from H&E stained sections as a percentage of total stroma per section. HR status was determined from ER and PR staining results in pathology reports. For each case, 3 hot spots were identified and marked on 10 consecutive sections. Nuance multispectral imaging software was used to image each hot spot. Protocols for automated image analysis were developed using CellProfiler software. Clinical parameters of interest included tumor palpability, recurrence, and Van Nuys Prognostic Index, (VNPI, 12 point scale-margins, age, size, grade). Associations were identified with non-parametric Spearman correlation test.

In general, immune infiltrates were correlated with high risk DCIS features (high VNPI, palpability, high grade, comedo necrosis, high proliferation, HER2-positivity, and HR-negativity). Comparing the mean percentages of immune cell populations in cases with a recurrence versus those without, we found no cell types that, by themselves, were associated with outcomes. We then constructed a prognostic model using the RPART function in R. A classification tree was generated using as input 16 immune cell populations along with 8 clinical parameters (grade, VNPI, tumor size, palpable, comedonecrosis, HR status, HER2 status, and DCIS density). Of the 24 input parameters, the best RPART model was built using only 3 immune cell populations: CD8<sup>+</sup>HLADR<sup>+</sup> cells, CD8<sup>+</sup>HLADR<sup>-</sup> cells and CD115<sup>+</sup> cells. This model had an accuracy of 87% (sensitivity=76%; specificity=89%). Importantly, all four cases with metastatic recurrences were correctly predicted.

The highest risk of recurrence was in cases with low numbers of activated CD8<sup>+</sup>HLADR<sup>+</sup> cells. Cases with high CD8<sup>+</sup>HLADR<sup>+</sup> cells, but also high numbers of non-activated CD8<sup>+</sup>HLADR<sup>-</sup> cells and high numbers of CD115<sup>+</sup> cells were also at a high risk for recurrence. In contrast, cases with high CD8<sup>+</sup>HLADR<sup>+</sup> cells and low CD8<sup>+</sup>HLADR<sup>-</sup> cells or high CD8<sup>+</sup>HLADR<sup>+</sup> cells, high CD8<sup>+</sup>HLADR<sup>-</sup> cells, and low CD115<sup>+</sup> cells were at a low risk for recurrence.

Using HLA-DR as a marker of T cell activation, we observed that activated CD8<sup>+</sup>HLA-DR<sup>+</sup> T cells were associated with good outcomes whereas non-activated or suppressed CD8<sup>+</sup>HLA-DR<sup>-</sup> T cells were associated with increased risk of recurrence. This suggests that activating the CD8<sup>+</sup>HLA-DR<sup>-</sup> T cells, perhaps via checkpoint blockade, could potentially alter disease progression.

These high-risk DCIS lesions truly represent an opportunity to prevent cancer. Tools to measure the complexity of the tumor immune microenvironment may provide an early measure of preventative potential. The focus of this proposal is to see if the immune microenvironment can be changed with short term exposure to an immunomodulating agent, pembrolizumab. This setting

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will provide an ideal opportunity to evaluate short term single agent exposure, using diagnostic core biopsies (pre) and surgical resection specimens (post).

#### 4.2.2 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 pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab 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. Recent data from other clinical studies within the pembrolizumab program has shown that a lower dose of pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

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 pembrolizumab 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. Pembrolizumab 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 pembrolizumab 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.

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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.

Preclinical studies in mice have demonstrated the efficacy of immunomodulatory antibodies administered intratumorally at 1/100<sup>th</sup> the standard systemic dose.<sup>12</sup> The intratumoral injection reduces systemic toxicities by giving it locally and at a lower dose. In a mouse lymphoma model, intratumoral administration of 1 ug/dose anti-CTLA4 is as effective as systemic administration of 100 ug/dose. There are additional mouse studies that demonstrate the efficacy of low-dose intratumoral injection of other immunomodulatory antibodies as well (anti-CD40 and anti-CD137).<sup>12-16</sup>

In the dose escalation phase of this study, no systemic adverse events were observed at the highest dose of 8 mg. Therefore, we propose to use this dose in the expansion cohort. Although we observed dramatic increases in CD8+ T cell infiltrates in the majority of patients post therapy, this was not accompanied by a reduction in the extent of DCIS in these patients. This was likely due to the short time interval between the initiation of treatment and surgical excision. We therefore propose to extend the time between initiation of therapy and surgery, and add additional injections of pembrolizumab during this time. We hypothesize that this will give the immune response more time to act and result in the reduction or elimination of the DCIS lesions.

### **4.3 Correlative Studies**

#### **4.3.1 Characterization of the immune landscape in DCIS**

H&E stained sections will be obtained from core biopsies (pre-treatment) and surgical specimens (post-treatment). Tumor infiltrating lymphocyte (TIL) counts will be performed using an automated counting algorithm in QuPath. Stromal TIL, intra-lesional TIL, and total TIL counts will be compared in pre and post samples.

Formalin-fixed paraffin embedded (FFPE) tissues from core biopsies (pre-treatment) and surgical specimens (post-treatment) will be obtained from all enrolled patients. Multiplex immunofluorescence staining for panels of immune markers will be performed using Opal staining kits (Perkin Elmer). A multispectral imaging platform (Vectra, Perkin Elmer) will be used to analyze stained sections for various populations of infiltrating immune cells. Analysis of samples from control patients (initial core biopsy vs. surgical specimen) will be used to determine what effects (if any) the biopsy procedure has on the local immune microenvironment. Analysis of samples from pembrolizumab treated patients (initial core biopsy vs. surgical specimen) will be used to determine what effects (if any) pembrolizumab treatment has on the local immune microenvironment. In addition, we will use an IHC assay for apoptosis (cleaved caspase 3 staining) to determine if the increase in CD8+ cytotoxic T cells is associated with increased cell death within the DCIS lesions.

#### **4.3.2 Analysis of peripheral blood immune biomarkers.**

From complete blood count data we will calculate the following leukocyte ratios as potential biomarkers of systemic immune activity:



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- a. neutrophil-to-lymphocyte ratio; NLR
- b. platelet-to-lymphocyte ratio; PLR
- c. monocyte-to-lymphocyte ratio; MLR
- d. neutrophil-to-monocyte ratio; NMR
- e. eosinophil-to-lymphocyte ratio; ELR
- f. basophil-to-lymphocyte ratio; BLR

These ratios, as well as absolute cell counts, LDH levels, and CRP levels, will be obtained from pre-treatment, on-treatment, and post-treatment samples. This will yield a dynamic picture of peripheral immunity across the course of therapy. We will run correlation analyses between these peripheral blood immune biomarkers and immune cell populations identified by multiplex immunofluorescence in pre- and post-treatment tissue samples to determine if changes in peripheral blood biomarkers predict changes in the tissue immune microenvironment, and ultimately with changes in the extent of DCIS.

## **5.0 METHODOLOGY**

### **5.1 Entry Criteria**

#### **5.1.1 Diagnosis/Condition for Entry into the Trial**

The patient must have high risk, biopsy proven DCIS. Patients who were previously enrolled on the dose escalation arm are eligible to enroll on the dose expansion arm.

#### **5.1.2 Subject Inclusion Criteria**

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

1. Plan on having surgical treatment for her DCIS.
2. Have at least 2 of the following high risk features associated with her DCIS – high-grade (grade II-III), palpable mass, hormone receptor negative (less than 1%), Her2 positive, young age (less than 45 years old), and large size (greater than 5 cm).
3. Patients with a history of tamoxifen and/or aromatase inhibitor use for treatment or prevention are eligible but should discontinue these medications at least 2 weeks prior to starting this trial.
4. Be willing and able to provide written informed consent/assent for the trial.
5. Be  $\geq 18$  years of age on day of signing informed consent.
6. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 (defined in Appendix 1).

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7. Demonstrate adequate organ function as defined in Table 1 Adequate Organ Function Laboratory Values. All screening labs should be performed within 10 days of treatment initiation.

**Table 1.** Adequate Organ Function Laboratory Values

System	Laboratory Value
<b>Hematological</b>	
Absolute neutrophil count (ANC)	$\geq 1,500$ /mcL
Platelets	$\geq 100,000$ / mcL
Hemoglobin	$\geq 9$ g/dL or $\geq 5.6$ mmol/L without transfusion or EPO dependency (within 7 days of assessment)
<b>Renal</b>	
Serum creatinine <b>OR</b> Measured or calculated <sup>a</sup> creatinine clearance (GFR can also be used in place of creatinine or CrCl)	$\leq 1.5$ X upper limit of normal (ULN) <b>OR</b> $\geq 60$ mL/min for subject with creatinine levels $> 1.5$ X institutional ULN
<b>Hepatic</b>	
Serum total bilirubin	$\leq 1.5$ X ULN <b>OR</b> Direct bilirubin $\leq$ ULN for subjects with total bilirubin levels $> 1.5$ ULN
AST (SGOT) and ALT (SGPT)	$\leq 2.5$ X ULN
Albumin	$\geq 2.5$ mg/dL
<b>Coagulation</b>	
International Normalized Ratio (INR) or Prothrombin Time (PT)	$\leq 1.5$ X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	$\leq 1.5$ X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

<sup>a</sup>Creatinine clearance should be calculated per institutional standard.

8. A female participant is eligible to participate if she is not pregnant (see Appendix 1.1), not breastfeeding, and at least one of the following conditions applies:
- Not a woman of childbearing potential (WOCBP) as defined in Appendix 1.1 **OR**
  - A WOCBP who agrees to follow the contraceptive guidance in Appendix 1.1 during the treatment period and for at least 90 days corresponding to time needed to eliminate any study treatment plus 30 days (a menstruation cycle) after the last dose of study treatment.
9. A male participant must agree to use a contraception as detailed in Appendix 1.1 of this protocol during the treatment period and for at least 90 days corresponding to time needed to eliminate any study treatment plus an additional 120 days (a spermatogenesis cycle) after the last dose of study treatment and refrain from donating sperm during this period.



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### 5.1.3 Subject Exclusion Criteria

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

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
3. Is not interested in surgical treatment for her DCIS.
4. Has invasive breast cancer. This does not include microinvasion.
5. Has a known history of active TB (Bacillus Tuberculosis).
6. Hypersensitivity to pembrolizumab or any of its excipients.
7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
8. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
9. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
10. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
11. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
12. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
13. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

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14. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. Note: no testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.
15. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

## 5.2 Study design and investigational treatment

This is a pilot study in patients with DCIS. The primary objective of this trial is to define the MTD and recommended dose of intralesional pembrolizumab. The dose escalation phase of this study followed a standard 3+3 trial design (Table 2).

The initial dose of intralesional pembrolizumab (2 mg) were chosen to be 1:100 the standard IV dose (200 mg) based on preclinical studies with immunomodulatory mAbs. Doses were escalated 2-fold as shown in Table 3.

Patients enrolled in the expansion cohort will receive intralesional pembrolizumab at the MTD as determined from the escalation phase. If a MTD is not reached, patients in the expansion cohort will receive the highest dose evaluated (8 mg).

**Table 2.** Dose escalation 3+3 trial design.

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Escalate dose to next higher dose level
1 out of 3	<p>Enter at least 3 more patients at this dose level</p> <p>If 0 of these 3 additional patients experience DLT (1 of 6), proceed to the next dose level</p> <p>If 1 or more of the 3 additional patients suffer DLT (2 of 6), then dose escalation is stopped and this dose is declared the maximal administered dose (highest dose administered)</p> <p>Determination of the MTD will continue at the next lowest dose cohort, at which an additional 3 patients will be added, for a total of 6 (unless that cohort already has 6 patients)</p>
≥ 2 out of 3	Dose escalation will be stopped

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	<p>This dose level is declared the maximal administered dose</p> <p>The next lower cohort will be expanded to 6 patients</p> <p>If &lt; 1 experience DLT, this dose is the maximal tolerated dose (MTD)</p>
<p>≤ 1 out of 6 at highest dose level below the maximal administered dose</p>	<p>This is generally the recommended Phase 2 dose</p> <p>At least 6 patients must be entered at the recommended Phase 2 dose</p>

### 5.2.1 Definition of Dose-Limiting Toxicities

All toxicities will be graded using National Cancer Institute (NCI) CTCAE Version 4.0 (Appendix 12.2). The occurrence of any of the following toxicities during Cycle 1 will be considered a DLT:

- Grade 4 non-hematologic toxicity
- Grade 3 non-hematologic toxicity lasting ≥3 days despite optimal supportive care
- Any Grade 3 or 4 non-hematologic laboratory value if:
  - Medical intervention is required to treat the patient, or
  - The abnormality leads to hospitalization, or
  - The abnormality persists for ≥1 week
- Neutropenia that is:
  - Grade 3 or 4 (i.e., ANC <1000 per mm<sup>3</sup>) and associated with fever (oral temperature ≥39°C) requiring antibiotic therapy
  - Grade 4 which lasts >7 days or leads to use of therapeutic G-CSF
- Grade 4 thrombocytopenia (i.e., platelets <25,000 per mm<sup>3</sup>) or Grade 3 thrombocytopenia (i.e., platelets <50,000 per mm<sup>3</sup>) with bleeding

**Table 3.** Trial Treatment

#### Dose Escalation

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	2 mg (1:100 IV dose)	2 doses 3 weeks apart (+/- 1 week)	Intralesional injection	Day 1 of each 3 week cycle	Experimental

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Pembrolizumab	4 mg (1:50 IV dose)	2 doses 3 weeks apart (+/- 1 week)	Intralesional injection	Day 1 of each 3 week cycle	Experimental
Pembrolizumab	8 mg (1:25 IV dose)	2 doses 3 weeks apart (+/- 1 week)	Intralesional injection	Day 1 of each 3 week cycle	Experimental

### Dose Expansion

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	8 mg (1:25 IV dose)	4 doses 3 weeks apart (+/- 1 week)	Intralesional Injection	Day 1 of each 3 week cycle	Experimental

The patient will proceed to the operating room for the operation as determined by the subject and the surgeon (partial mastectomy versus mastectomy) 3 weeks (+/- 2 weeks) after the 4<sup>th</sup> dose of intralesional pembrolizumab.

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

### 5.2.2 Dose Selection/Modification

#### 5.2.2.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale. Briefly, based on preclinical studies in mice that have demonstrated the efficacy of immunomodulatory antibodies administered intratumorally at 1/100<sup>th</sup> the standard systemic dose, we chose a starting dose of 2 mg (1:100 the standard i.v. dose of pembrolizumab). Doses will be escalated 2-fold in each subsequent escalation cohort.

Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Pharmacy Manual.

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### 5.2.2.2 Dose Modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 4.

**Table 4.** Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:				
<ol style="list-style-type: none"> <li>1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.</li> <li>2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to <math>\leq 10</math> mg prednisone or equivalent per day within 12 weeks.</li> <li>3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.</li> </ol>				
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	<ul style="list-style-type: none"> <li>• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor participants for signs and symptoms of pneumonitis</li> <li>• Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment</li> <li>• Add prophylactic antibiotics for opportunistic infections</li> </ul>
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		

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Diarrhea / Colitis	Grade 2 or 3	Withhold	<ul style="list-style-type: none"> <li>Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper</li> </ul>	<ul style="list-style-type: none"> <li>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).</li> <li>Participants with <math>\geq</math> Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis.</li> <li>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.</li> </ul>
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	<ul style="list-style-type: none"> <li>Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper</li> </ul>	<ul style="list-style-type: none"> <li>Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)</li> </ul>
	Grade 3 or 4	Permanently discontinue	<ul style="list-style-type: none"> <li>Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper</li> </ul>	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of $\beta$ -cell failure	Withhold	<ul style="list-style-type: none"> <li>Initiate insulin replacement therapy for participants with T1DM</li> <li>Administer anti-hyperglycemic in participants with hyperglycemia</li> </ul>	<ul style="list-style-type: none"> <li>Monitor participants for hyperglycemia or other signs and symptoms of diabetes.</li> </ul>
Hypophysitis	Grade 2	Withhold	<ul style="list-style-type: none"> <li>Administer corticosteroids and initiate hormonal replacements as clinically indicated.</li> </ul>	<ul style="list-style-type: none"> <li>Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)</li> </ul>
	Grade 3 or 4	Withhold or permanently discontinue <sup>1</sup>		

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Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue <sup>1</sup>		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) 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: Guillain-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).

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.

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### 5.2.3 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 7 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.

#### Dose Escalation Cohort

For intralesional injection, concentrated pembrolizumab will be injected into the palpable DCIS or in the vicinity of the non-palpable lesion. Injections will be given on 2 occasions 3 weeks apart ( $\pm$  1 week). The surgeon, in clinic, will use ultrasound imaging (an ultrasound visible clip placed at the time of initial biopsy) to guide the placement of the single injection. If a hydromark clip was not used, we will work with the radiologists to localize the clip and perform the injection.

#### Dose Expansion Cohort

Given satisfactory safety data an additional 20 patients will be treated with intralesional injections and 10 patients will act as the control group. The control group will proceed directly to surgery.

In the intralesional treated cohort, concentrated pembrolizumab will be injected into the palpable DCIS or in the vicinity of the non-palpable lesion. Injections will be given on four occasions, 3 weeks apart ( $\pm$  1 week). The surgeon, in clinic, will use ultrasound imaging (an ultrasound visible clip placed at the time of initial biopsy) to guide the placement of the single injection. If a hydromark clip was not used, we will work with the radiologists to localize the clip and perform the injection.

The patient will proceed to the operating room for the operation as determined by the subject and the surgeon (partial mastectomy versus mastectomy) 3 weeks ( $\pm$  2 weeks) after the 4<sup>th</sup> dose of intralesional pembrolizumab.

The Pharmacy Manual contains specific instructions for the preparation of the Pembrolizumab for injection. A 50 mg lyophilized powder single use vial will be reconstituted with sterile water and then diluted to the correct dose for injection using normal saline. The total injection volume will be 2 milliliters.

Dose	Volume of NS to 1 mL of 25 mg/mL pembrolizumab	Volume of injection
2 mg/2 mL	24 mL	2.05 mL
4 mg/2 mL	11.5 mL	2.05 mL



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8 mg/2mL	5.25 mL	2.05 mL
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#### 5.2.4 Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered. The immune markers will be performed and evaluated by a team that does not know treatment status (blinded to study arm).

#### 5.3 Treatment Allocation

In the dose escalation cohort, target enrollment was 3-6 patients at each dose.

In the expansion cohort, target enrollment in the expansion study will be 10 patients in the control arm and 20 patients in the treatment arm. Patients who agree to receive treatment will be enrolled to the treatment arm. Patients who are eligible to participate but decline treatment will be enrolled to the control arm. The core biopsies and surgical specimen of control patients will be banked for research.

#### 5.4 Stratification

Based on the limited number of patients in the study, we will not stratify.

#### 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.

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### 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
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

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

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

## 5.6 Rescue Medications & Supportive Care

### 5.6.1 Supportive Care Guidelines

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

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 5.2.1 for dose modification.

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

- **Pneumonitis:**

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

- **Diarrhea/Colitis:**

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

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

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

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

- **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 liothyronine, 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 Local Reactions:** Signs and symptoms may develop during or shortly after drug injection and generally resolve completely within 24 hours of completion of injection. .

5 below shows treatment guidelines for subjects who experience a local reaction associated with administration of pembrolizumab.

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**Table 5. Injection Reaction Treatment Guidelines**

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
<b>Grade 1</b> Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
<b>Grade 2</b> Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	<b>Stop Infusion.</b> 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 participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. <b>Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment</b>	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of _____ with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
<b>Grades 3 or 4</b> 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	<b>Stop Infusion.</b> Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. <b>Participant is permanently discontinued from further study drug treatment.</b>	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at <a href="http://ctep.cancer.gov">http://ctep.cancer.gov</a>		

## **5.7 Diet/Activity/Other Considerations**

### **5.7.1 Diet**

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

### **5.7.2 Contraception**

Pembrolizumab may have adverse effects on a fetus in utero. Refer to Appendix 12.1.1 for approved methods of contraception.

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.5.2-Reporting of Pregnancy and Lactation to the Sponsor and to Merck. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

### **5.7.3 Use in Pregnancy**

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

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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 7.2.5.2.

#### **5.7.4 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.

#### **5.8 Subject Withdrawal/Discontinuation Criteria**

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.5 – 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.
- Unacceptable adverse experiences as described in Section 7.2
- Intercurrent illness that prevents further administration of treatment
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- 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
- Recurrent Grade 2 pneumonitis
- Completion of 35 treatments (approximately 2 years) with pembrolizumab

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.6 (Visit Requirements). After the end of treatment, each subject will be followed

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for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2).

### **5.9 Subject Replacement Strategy**

This is an intent to treat study with a short course of therapy. Our goal is to have 20 evaluable patients (as long as there is no safety contraindication after the dose escalation phase). Patients who withdraw consent or opt to go elsewhere for surgical treatment without enabling us to obtain blocks will be replaced. Enrollment will re-open, and an additional eligible patient will be enrolled until we reach a cohort of 20 evaluable patients.

### **5.10 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.



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## 6.0 TRIAL FLOW CHART

### 6.1 Study Flow Chart

Trial Period	Treatment Cycles					End of Treatment	Post-Treatment	
Treatment Cycle/Title	Screening	1 <sup>st</sup> dose	2 <sup>nd</sup> dose	3 <sup>rd</sup> dose	4 <sup>th</sup> dose	Surgical treatment	Safety Follow-up/Post-op Visit <sup>o</sup>	Follow Up Visits
Scheduling Window	-28 to 0 days	± 1 wk	± 1 wk	± 1 wk	± 1 wk	1-5 wks post second dose	1- 3 wks post-surgery	8 wks +/- 2 weeks post-surgery
Informed Consent <sup>a</sup>	x							
Review of eligibility criteria <sup>b</sup>	x							
Demographics and Medical History <sup>c</sup>	x							
Prior and Concomitant Medication Review <sup>d</sup>	x	x	x	x	x		x	x
Intralesional injection pembrolizumab <sup>e</sup>		x	x	x	x			
Review Adverse Events <sup>f</sup>	x	x	x	x	x		x	x
Full Physical Examination <sup>g</sup>	x							
Directed Physical Examination <sup>h</sup>		x	x	x	x		x	x
Vital Signs and Weight <sup>i</sup>	x	x	x	x	x		x	x
ECOG Performance Status <sup>j</sup>	x	x	x	x	x	x	x	x
Tissue Collection <sup>k</sup>	Core biopsy (archival)					Surgical specimen		
<b>Laboratory Procedures<sup>l</sup></b>								
Pregnancy Test – Urine or Serum <sup>m</sup>	x		x					
Coagulation	x		x				x	
CBC with Differential	x		x				x	
Comprehensive Serum Chemistry Panel(BMP and LFTs)	x		x				x	
Urinalysis	x		x				x	
Thyroid Function	x		x				x	
<b>Imaging Procedure<sup>n</sup></b>								

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Trial Period	Treatment Cycles					End of Treatment	Post-Treatment	
Treatment Cycle/Title	Screening	1 <sup>st</sup> dose	2 <sup>nd</sup> dose	3 <sup>rd</sup> dose	4 <sup>th</sup> dose	Surgical treatment	Safety Follow-up/Post-op Visit <sup>o</sup>	Follow Up Visits
Scheduling Window	-28 to 0 days	± 1 wk	± 1 wk	± 1 wk	± 1 wk	1-5 wks post second dose	1- 3 wks post-surgery	8 wks +/- 2 weeks post-surgery
MRI scan (dose expansion group only)	x					x		

<sup>a</sup>**During dose expansion cohort:** At the time of enrollment patients will be assigned an enrollment number. Patients and their corresponding enrollment numbers will be logged and organized in OnCore.

<sup>b</sup>Patients with a diagnosis of high risk DCIS will come in to the clinic for a screening visit and identified as a potential candidate for the study during their clinic visit (i.e., eligibility). Eligible subjects, identified in clinic by the treating surgeon, will be assigned a screening number by the study coordinator at the time of identification. Screening numbers will be stored in an encrypted, secure Microsoft Excel file.

<sup>c</sup>Medical history includes all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator.

<sup>d</sup>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.

<sup>e</sup>**During dose escalation and patients on the treatment arm during dose expansion:** On Day 1 of each 3 week (+/- 1 week) cycle. Treatment window is +/- 7 days of scheduled Day 1 administration of each cycle due to administrative reasons.

<sup>f</sup>Significant baseline AEs prior to treatment and surgery will be collected.

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

<sup>h</sup>The investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

<sup>i</sup>Vital signs include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

<sup>j</sup>At screening, prior to the administration of each dose of trial treatment, and at discontinuation of trial treatment.

<sup>k</sup>Patients will receive a core biopsy upon diagnosis as part of standard clinical procedure. At surgery, tissue will be banked and sectioned for immunohistological analysis.

<sup>l</sup>Repeat labs not necessary provided baseline lab results within normal range. See Table 6 Laboratory Tests for specific tests

<sup>m</sup>Pregnancy test must be negative within 3 days prior to Day 1 except in dose expansion cohort who are enrolled to control arm (surgical treatment only).

<sup>n</sup>**During dose expansion cohort:** Patients will undergo MRI imaging of the breast to evaluate the extent and volume of DCIS. Patients will be offered an additional breast MRI pre-surgery. Breast MRI images will be evaluated for changes in tumor volume and tumor immune microenvironment.

<sup>o</sup>Safety follow-up visit and post-op visit will typically occur during the 2 week mark.

<sup>p</sup>Screening procedures can occur on the same day as C1D1. Vital signs, ECOG performance status, adverse event review, and concomitant medication review from that day will be recorded for both visits.

## 7.0 TRIAL PROCEDURES

### 7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

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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.

### **7.1.1 Administrative Procedures**

#### **7.1.1.1 Informed Consent**

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

#### **7.1.2 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 UCSF IRB'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 UCSF IRB requirements, applicable laws and regulations and Sponsor requirements.

#### **7.1.2.1 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.

#### **7.1.2.2 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

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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.

#### **7.1.2.3 Prior and Concomitant Medications Review**

##### **7.1.2.3.1 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.

##### **7.1.2.3.2 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.

#### **7.1.2.4 Disease Details and Treatments**

##### **7.1.2.4.1 Disease Details**

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

##### **7.1.2.5 Assignment of Screening Number**

Eligible subjects, identified in clinic by the treating surgeon, will be assigned a screening number by the study coordinator at the time of identification. Any identifying information associated with this number will be destroyed if the patient does not consent to participate in the study. Screening numbers will be stored in an encrypted, secure Microsoft Excel file.

##### **7.1.2.6 Assignment of Enrollment Number**

At the time of treatment selection, patients on study in the expansion cohort will be assigned an enrollment number. Patients and their corresponding enrollment numbers will be logged and organized in OnCore – The Online Collaborative Research Environment. This secure system will keep all patient personal health information secure and standardized.

##### **7.1.2.7 Trial Compliance (Medication/Diet/Activity/Other)**

Pembrolizumab will be administered in clinic. Subjects on the treatment arm will be required to be present for treatment. Patients will be advised not to change diet or activity and to remain compliant with home medications.

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### **7.1.3 Clinical Procedures/Assessments**

#### **7.1.3.1 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 (see Section 11.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see the separate ECI guidance document in Appendix 4 regarding the identification, evaluation and management of potential irAEs.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

#### **7.1.3.2 Full Physical Exam**

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

#### **7.1.3.3 Directed Physical Exam**

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

#### **7.1.3.4 Vital Signs**

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

#### **7.1.3.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale**

The investigator or qualified designee will assess ECOG status (see Section 11.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

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**7.1.3.6 Tumor Imaging and Assessment of Disease**

Patients will undergo MRI imaging of the breast to evaluate the extent and volume of DCIS pre-treatment and pre-surgery. Breast MRI images will be evaluated for changes in tumor volume and tumor immune microenvironment.

**7.1.3.7 Tumor Tissue Collection and Correlative Studies Blood Sampling**

Patients will receive a core biopsy upon diagnosis as part of standard clinical procedure. At surgery, tissue will be banked and sectioned for immunohistological analysis.

Peripheral blood will be collected from patients prior to each injection of pembrolizumab for standard blood counts and chemistries. An additional EDTA tube will be collected at baseline and prior to surgery from which plasma will be frozen for subsequent assays of cytokines and chemokines and white blood cells will be processed and frozen for subsequent flow cytometry or CyTOF analyses.

**7.1.4 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 Table 6.

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**Table 6.** Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum $\beta$ -human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	( $\beta$ -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 ( <i>If abnormal</i> )	Total triiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free thyroxine (T4)
Absolute Lymphocyte Count	( <i>CO<sub>2</sub> or biocarbonate</i> )	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
Monocyte count	Uric Acid		
Platelet count	Calcium		
Eosinophil count	Chloride		
Basophil count	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin ( <i>If total bilirubin is elevated above the upper limit of normal</i> )		
	Total protein		
	Blood Urea Nitrogen		
	Creatinine		
	CRP		
† 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.			

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### **7.1.5 Other Procedures**

#### **7.1.5.1 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.

#### **7.1.5.2 Blinding/Unblinding**

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.

### **7.1.6 Visit Requirements**

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

#### **7.1.6.1 Screening**

##### **7.1.6.1.1 Screening Period**

We will determine eligibility at initial patient consult based on pathology and imaging results. Patients who choose to participate in the study will be enrolled on the day that they sign consent.

Core biopsy specimens will be archived during screening.

The screening visit can occur on the same day as the first injection (C1D1). The patient will be seen in clinic and complete all screening procedures and labs. Once the patient is deemed eligible for enrollment and has provided informed consent, the patient will be able to receive the first injection that same day. We will record the vital signs, ECOG performance status, adverse event review, and concomitant medication review from that day for both the screening visit and the C1D1 visit.

#### **7.1.6.2 Treatment Period**

Patients will be seen in clinic on the day of each treatment administration. For the dose escalation cohort, there will be two drug administrations, 3 weeks (+/- 1 week) apart. In the expansion cohort, for patients on the treatment arm, there will be four drug administrations, 3 weeks (+/- 1 week) apart. In both cohorts, surgery will occur 3 weeks (+/- 2 weeks) after the 2<sup>nd</sup> or 4<sup>th</sup> dose of intralesional pembrolizumab.



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### **7.1.6.3 Post-Treatment Visits**

Patients will be seen on a standard post-operative visit (2-3 weeks after surgery).

#### **7.1.5.3.1 Safety Follow-Up Visit**

The mandatory Safety Follow-Up Visit should be conducted approximately 8 weeks post-surgery (+/- 2 weeks). All non-surgically-related AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

### **7.1.6.4 Follow-up Visits**

#### **7.1.6.4.1 Survival Follow-up**

This is a short term study using surgical endpoints. We will follow patients for toxicity (8 weeks post-surgery (+/- 2 weeks)).

## **7.2 Assessing and Recording Adverse Events**

### **7.2.1 Definitions of Adverse Events**

#### **7.2.1.1 Adverse Event**

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an adverse event (can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

#### **7.2.1.2 Adverse reaction**

An adverse reaction is defined as any adverse event caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

#### **7.2.1.3 Suspected**

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, “reasonable possibility” indicates that there is evidence to suggest a causal relationship between

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the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

#### 7.2.1.4 Unexpected

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

“Unexpected,” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

Some adverse events are listed in the Investigator Brochure as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered *unexpected* until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the ACE inhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes.

#### 7.2.1.5 Serious

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

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent

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one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

#### 7.2.1.6 Life-threatening

An adverse event or suspected adverse reaction is considered *life-threatening* if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

### 7.2.2 Recording of an Adverse Event

All Grade 3 and above adverse events will be entered into OnCore®, whether or not the event is believed to be associated with use of the study drug. Data about these events and their severity will be recorded using the NCI CTCAE v4.0.

If there are specific data plans to this study, such as Grade 1 & 2 AEs are also being entered into OnCore, describe that process here.

The Investigator will assign attribution of the possible association of the event with use of the investigational drug, and this information will be entered into OnCore® using the classification system listed below:

Relationship	Attribution	Description
Unrelated to investigational drug/intervention	Unrelated	The AE is <i>clearly NOT related</i> to the intervention
	Unlikely	The AE is <i>doubtfully related</i> to the intervention
Related to investigational drug/intervention	Possible	The AE <i>may be related</i> to the intervention
	Probable	The AE is <i>likely related</i> to the intervention
	Definite	The AE is <i>clearly related</i> to the intervention

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE. When specific adverse events are not listed in the CTCAE they will be graded by the Investigator as *none, mild, moderate* or *severe* according to the following grades and definitions:

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- Grade 0 No AE (or within normal limits)
- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2 Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

### 7.2.3 Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For selected adverse events for which administration of the investigational drug was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the Investigator.

### 7.2.4 Adverse Events Monitoring

All adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, as noted above.

The Investigator will assess all adverse events and determine reportability requirements to the UCSF Data and Safety Monitoring Committee (DSMC) and UCSF's Institutional Review Board, the Institutional Review Board (IRB); and, when the study is conducted under an Investigational New Drug Application (IND), to the Food and Drug Administration (FDA) if it meets the FDA reporting criteria.

[The manufacturer and/or grant sponsor may also need to be notified, as applicable.]

All adverse events entered into OnCore® will be reviewed by the Helen Diller Family Comprehensive Cancer Center Site Committee on a weekly basis. The Site Committee will review and discuss at each weekly meeting the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

All grade(s) 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 the attribution of relationship of the adverse event to the administration of the study drug(s).

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In addition, all suspected adverse reactions considered “serious” entered into OnCore®, will be 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.

For a detailed description of the Data and Safety Monitoring Plan for a Multicenter Phase 2 or 3 Institutional Study at the Helen Diller Comprehensive Cancer Center please refer Appendix 4 Multicenter Institutional Studies.

## **7.2.5 Expedited Reporting**

### **Reporting to the Data and Safety Monitoring Committee**

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

### **Reporting to UCSF Institutional Review Board (IRB)**

The Principal Investigator must report events meeting the UCSF IRB definition of “Unanticipated Problem” (UP) within 10 business days of his/her awareness of the event.

### **Expedited Reporting to the Food and Drug Administration**

If the study is being conducted under an IND, the Sponsor-Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

The Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor-Investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction - A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the treatment or procedure caused the adverse event. For the purposes of IND safety reporting, “reasonable possibility” indicates that there is evidence to suggest a causal relationship between the treatment or procedure and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.
- Unexpected - An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

“Unexpected,” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of treatment or procedure or as anticipated from the pharmacological properties of the treatment or procedure, but are not specifically mentioned as occurring with the particular treatment or procedure under investigation.

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Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

Some adverse events are listed in the Investigator's Brochure as occurring with the same class of treatment, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered *unexpected* until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the ACE inhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes.

- Serious - An adverse event or suspected adverse reaction is considered *serious* if, in the view of either the investigator or sponsor, it results in any of the following outcomes:
  - Death
  - Life-threatening adverse event
  - Inpatient hospitalization or prolongation of existing hospitalization
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
  - Congenital anomaly/birth defect

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

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

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**Expedited Reporting to Merck.**

Investigators must report all SAEs to Merck within 24 hours of becoming aware of the event.

**7.2.5.1 Pembrolizumab overdose**

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

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

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

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

**7.2.5.2 Reporting of Pregnancy and Lactation to the Sponsor and to Merck**

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

Pregnancies and infant exposures during breastfeeding that occur after the consent form is signed but before treatment must be reported by the investigator if they cause the participant 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 infant exposures during breastfeeding that occur from the time of treatment through 120 days following cessation of Sponsor’s product, or 30 days following cessation of treatment if the participant 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.



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Such events must be reported within 24 hours to the Sponsor and within 2 working days [REDACTED]  
[REDACTED]

#### 7.2.5.3 Immediate Reporting of Adverse Events to the Sponsor and to Merck

#### 7.2.5.4 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 any 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 7 for additional details regarding each of the above criteria.

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

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

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

**SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229**

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



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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.

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

#### 7.2.5.5 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. [REDACTED]

For the time period beginning when the consent form is signed until treatment, any ECI, or follow up to an ECI, that occurs to any participant must be reported within 2 working days to Merck Global Safety if it causes the participant 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 through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant 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 2 working days to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 7.2.5.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.\*

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

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### **7.2.6 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.

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**Table 7.** Evaluating Adverse Events

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

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

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

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### **7.2.7 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.

## **8.0 STATISTICAL ANALYSIS PLAN**

### **8.1 Analysis of primary endpoints (dose escalation cohort)**

The primary endpoint of this study is the MTD of two intralesional injections of pembrolizumab in patients with DCIS. The primary safety endpoint is DLT. The MTD is defined as the dose at which no more than 1/6 patients experience a DLT. Safety and tolerability will also be assessed by clinical review of all relevant parameters including adverse events (AEs), laboratory tests, and physical exam. Adverse events will be summarized as counts and frequencies for each dose level. Other safety endpoints will be summarized as appropriate. These data are descriptive in nature and statistical analysis tools will not be required. The recommended expansion dose will be explored in an additional cohort of 30 patients with DCIS (20 to receive pembrolizumab and 10 untreated control subjects).

#### **8.1.2 Analysis of primary endpoint (dose expansion cohort)**

The secondary endpoint (dose expansion cohort) is the response rate to intralesional pembrolizumab as measured by an increase in intralesional CD8+ T cells. For this study, we will define a responder to pembrolizumab as demonstrating a  $\geq 50\%$  increase (baseline to surgical sample) of intralesional CD8+ T cells. In a recent study in melanoma, 44% of patients treated with pembrolizumab demonstrated a  $\geq 50\%$  increase in intratumoral CD8+ T cells (Tumeh et al., 2014). Point estimate of the response rate and its 95% confidence interval will be obtained by arm, and two-sample proportion test will be used to test if the response rate is different between the two arms. For the expansion cohort, a sample size of 30 patients (2:1 – treatment:control) will have 80% power, with an alpha of 0.05, to detect a 44% or greater response rate in the treatment arm compared to the control arm.

### **8.2 Accrual objectives**

A 3x3 dose escalation design will be followed, so sample size will be between 12 and 18 for this phase. The expansion cohort will consist of 30 additional patients with DCIS. We anticipate accruing 2-3 patients per month and estimate that it will require approximately 16-20 months to complete the study.

### **8.3 Stratification factors**

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There are no planned patient stratification factors.

## 9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

### 9.1 Investigational Product

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

Clinical Supplies will be provided by Merck as summarized in Table 8.

**Table 8.** Product Descriptions

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

### 9.2 Packaging and Labeling Information

### 9.3 Clinical Supplies Disclosure

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

### 9.4 Storage and Handling Requirements

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

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

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

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## **9.5 Returns and Reconciliation**

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

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

## **10.0 ADMINISTRATIVE AND REGULATORY DETAILS**

### **10.1 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.

### **10.2 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 (IRB). 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.

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### 10.3 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.

### 10.4 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.

### 10.5 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.

### 10.6 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.



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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.

## 10.7 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 12.4 Data and Safety Monitoring Plan for a Phase 1/2 Institutional Study, for additional information.

## 10.8 Regulatory Documentation

Prior to implementing this protocol at UCSF HDFCCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the UCSF Institutional Review Board (IRB). Prior to implementing this protocol at the participating sites, approval for the UCSF IRB approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to UCSF HDFCCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list

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- Participating Site IRB membership list form ce number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals

Upon receipt of the required documents, UCSF HDFCCC will formally contact the site and grant permission to proceed with enrollment.

## **10.9 Protection of Human Subjects**

### **10.9.1 Protection from Unnecessary Harm**

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

### **10.9.2 Protection of Privacy**

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

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## 12.0 APPENDICES

### 12.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

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### 12.1.1 Contraceptive Guidance and Pregnancy Testing

#### Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

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## Contraception Requirements

### Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 9 during the protocol-defined time frame in Section 5.1.2.

### Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in section 5.1.2:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 9 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
- Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

### Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test and in accordance with local requirements. This test should be repeated a maximum of 72-hours before each dose.

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**Table 9.** Highly Effective Contraception Methods

<p><b>Highly Effective Contraceptive Methods That Are User Dependent <sup>a</sup></b>  <i>Failure rate of &lt;1% per year when used consistently and correctly.</i></p>
<ul style="list-style-type: none"> <li>● Combined (estrogen- and progestogen- containing ) hormonal contraception <sup>b, c</sup> <ul style="list-style-type: none"> <li>○ Oral</li> <li>○ Intravaginal</li> <li>○ Transdermal</li> <li>○ Injectable</li> </ul> </li> </ul>
<ul style="list-style-type: none"> <li>● Progestogen-only hormonal contraception <sup>b, c</sup> <ul style="list-style-type: none"> <li>○ Oral</li> <li>○ Injectable</li> </ul> </li> </ul>
<p><b>Highly Effective Methods That Have Low User Dependency</b>  <i>Failure rate of &lt;1% per year when used consistently and correctly.</i></p>
<ul style="list-style-type: none"> <li>● Progestogen- only contraceptive implant <sup>b, c</sup></li> <li>● Intrauterine hormone-releasing system (IUS) <sup>b</sup></li> <li>● Intrauterine device (IUD)</li> <li>● Bilateral tubal occlusion</li> </ul>
<ul style="list-style-type: none"> <li>● <b>Vasectomized partner</b>  A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.</li> </ul>
<ul style="list-style-type: none"> <li>● <b>Sexual abstinence</b>  Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)</li> </ul>
<p>Notes:  Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.</p> <p>a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly).  b) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.</p>



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## **12.2 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)**

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

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### **12.3 UCSF Policy/Procedure for required regulatory documents for single site and multicenter investigator-initiated oncology clinical trials**

#### **Purpose**

This policy defines the required Regulatory Documents for Single Site and Multicenter Investigator Initiated Oncology Clinical Trials at the Helen Diller Family Comprehensive Cancer Center (HDFCCC) for both IND and IND-exempt trials.

#### **Background**

The International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines define Essential Regulatory Documents as those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of data produced. These documents serve to demonstrate compliance with standards of GCP and with all applicable regulatory requirements. Filing essential documents in a timely manner can greatly assist in the successful management of a clinical trial.

The Regulatory Documents will consist of electronic files in both iRIS and OnCore®, as well as paper files in the Regulatory Binders for both the Coordinating Site and the Participating Site(s) in the HDFCCC Investigator Initiated Oncology Clinical Trials.

#### **Procedures**

##### ***1. Single Site (HDFCCC) Therapeutic Essential Regulatory Documents:***

##### **Documents Filed in iRIS:**

- Current and prior versions of the Informed Consent Form(s) (ICFs).
- IRB approvals for initial submission of application, all modifications, and continuing annual renewals.
- Current and prior approved protocol versions.
- IRB roster
- Current and prior versions of the Investigator Brochure (IB).
- Serious Adverse Event (SAE) Reports.
- Subject diary and handouts (if applicable).
- Single Patient Exception (SPE) Report(s) to IRB with Approval Letter(s) from IRB.
- Protocol Violation (PV) Reports with acknowledgement from the IRB.

##### **Documents Filed in OnCore®:**

- Package Insert (if the study drug is commercial).
- Protocol signature page(s) with PI signature(s) for all protocol versions.

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- Protocol Review Committee (PRC) approved protocols, protocol amendments and Summary of Changes (SOC) document.
- Screening/enrollment log.
- Data and Safety Monitoring Committee (DSMC) monitoring reports.
- DSMC dose escalation approvals with study status summary forms.
- Case Report Form (CRF) completion manual.
- Drug Destruction Standard Operating Procedure (SOP).
- Completed Food and Drug Administration (FDA) 1572 document with Principal Investigator's signature.
- For all Principal Investigators and Sub-Investigators listed on the FDA 1572, will need Financial Disclosure Forms, CVs, MD Licenses, and Staff Training Documents (i.e., Collaborative Institute Training Initiative (CITI), etc.).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center.
- Serious Adverse Event (SAE) reports to IRB and sponsor.
- MedWatch reporting to FDA and sponsor.
- Drug Destruction Standard Operating Procedure (SOP).
- For all laboratories listed on the FDA 1572, will need CUA certifications, CAP certifications, lab licenses, CV(s) and Medical License(s) of Lab Director(s), and laboratory reference ranges.

**Documents Filed in Regulatory Binder:**

- Delegation of Authority Log with signatures (to be scanned in OnCore once the trial is complete).

**2. Additional Essential Documents for Therapeutic Multicenter Trials for the Coordinating Center (filed in OnCore or Zip Drive):**

- Institutional Review Board (IRB) approval letters, IRB roster, Informed Consent Form (ICF), and Health Insurance Portability and Accountability Act (HIPAA) Consent Form for the Participating Site(s).
- For all Principal Investigators and Sub-Investigators listed on the 1572 at the Participating Site(s), will need Financial Disclosure Forms, CVs, MD Licenses, and Staff Training documents (i.e. Collaborative Institute Training Initiative (CITI), etc.) (for investigational New Drug Application).
- Site Initiation Visit (SIV) minutes and correspondence with the Participating Site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center for the Participating Site(s).

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- Protocol Violations (PV) Reports to IRB with acknowledgement from IRB for Participating Site(s).
- Single Patient Exception (SPE) Reports to IRB with IRB Approval Letters for Participating Site(s).
- Drug Destruction Standard Operating Procedure (SOP) for the Participating Site(s).
- Data and Safety Monitoring Committee (DSMC) monitoring reports for the Participating Site(s).
- For all laboratories listed on FDA 1572, will need CUA certifications, CAP certifications, lab licenses, CVs and Medical License(s) of Lab Director(s), and laboratory reference ranges for the Participating Site(s).
- Copy of the Data and Safety Monitoring Plan (DSMP) Monitoring Plan for all participating site(s) in Multicenter studies or Contract Research Organization (CRO) Monitoring Plan (if an outside CRO is used for the study).
- Serious Adverse Event (SAE) forms submitted to the IRB for the Participating Site(s).

**3. Required Multicenter Essential Regulatory Document Checklist for Therapeutic and Non-Therapeutic Trials (For Start-Up Only):**

- See attached checklist(s).

**4. Required Essential Regulatory Documents for Single Site and Multicenter Therapeutic IND-Exempt Studies (filed in OnCore):**

- For IND Exempt studies, the Essential Regulatory Documents for UCSF would include all documents in Section #1 of this policy. The Essential Regulatory Documents from the participating site(s) for Multicenter Trials when UCSF is the Coordinating Center would only include the signed protocol signature page, CV of the PI, and the IRB approval letters. All other documents in Section #2 of this policy would be the responsibility of the Participating Site(s).

**5. Required Essential Regulatory Documents for Single Site Non-Therapeutic Studies (filed in OnCore):**

- For Single Site non-therapeutic trials, all Regulatory Documents in Section #1 of this policy are required except for: current and prior versions of the Investigator Brochure (IB), package insert (if the study drug is commercial), DSMC dose escalation approvals with study status summary forms, approvals for Biosafety Committee, Radiation Committee, and Infusion Center, and drug destruction SOPs.

**6. Required Essential Regulatory Documents for Multicenter Non-Therapeutic Studies (filed in OnCore):**

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- For Multicenter non-therapeutic trials with UCSF as the Coordinating Site, all required Regulatory Documents listed above in Section #5 for Single Site non-therapeutic trials are required for the Coordinating Site. The only required Regulatory Documents from the Participating Site(s) will be: IRB approval letters, IRB roster, and ICF and HIPAA consent forms, the Delegation of Authority Log (with NIH or CITI human subject protection training certificates or GCP training certification), Protocol Violations and Single Patient Exception (SPE) reports to the IRB with supporting fax documentation (if applicable), Serious Adverse Event (SAE) forms submitted to both the IRB and the sponsor, and the Data and Safety Monitoring Committee (DSMC) monitoring reports for the Participating Site(s). If applicable, a copy of the Data and Safety Monitoring Plan (DSMP) Monitoring Plan for all participating site(s) in Multicenter studies or Contract Research Organization (CRO) Monitoring Plan (if an outside CRO is used for the study) will be required.

### **Alternate Procedures**

There are no alternate procedures to the HDFCCC policy for requirements for Essential Regulatory Documents for Multicenter Investigator-Initiated Oncology Clinical Trials.

### **References**

- ICH Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance (current version).
- International Conference on Harmonization: Good Clinical Practice: Consolidated Guideline (current version).
- International Conference on Harmonization: Essential Documents for the Conduct of a Clinical Trial (current version).
- 21CFR50
- 21 CFR56.11
- 45CFR46
- 21 CFR312

Required Regulatory Documents for Sub-sites Participating in Therapeutic UCSF Investigator Initiated Multicenter trial

Directions: Scan the documents in a zip drive and upload to OnCore.

**1572**

☐ PI and Sub investigators:

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- CV and Medical license
- Financial disclosure form
- NIH or CITI human subject protection training certification

☐ Laboratories:

- CLIA &CAP and Lab Licenses
- CV and Medical License of Lab Director
- Laboratory reference ranges

**Local Institutional Review Board**

- ☐ IRB Approval letter
- ☐ Reviewed/Approved documents
  - Protocol version date: \_\_\_\_\_
  - Informed consent version date: \_\_\_\_\_
  - Investigator Brochure version date: \_\_\_\_\_
  - HIPAA

☐ Current IRB Roster

Other

- ☐ Delegation of Authority Log
  - Include NIH or CITI human subject protection training certificates or GCP training certification
- ☐ Pharmacy
  - Drug destruction SOP and Policy
- ☐ Protocol signature page
- ☐ Executed sub contract

#### **12.4 Data and Safety Monitoring Plan for a Phase 1/2 Institutional Study**

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

- Review of subject data in each cohort for the Phase 1 portion of trial
- Review of suspected adverse reactions considered “serious”
- During the Phase 1 portion of trial, approval of dose escalation by DSMC Chair (or qualified alternate)
- Monthly monitoring (depending on study accrual) for the Phase 1 portion of trial and biannual monitoring for the Phase 2 portion of trial.
- Minimum of a yearly regulatory audit

#### **Monitoring and Reporting Guidelines**

Investigators will conduct continuous review of data and subject safety and discuss each subject’s treatment at weekly Site Committee meetings. The discussions are documented in the Site Committee meeting minutes. For each dose level, the discussion will include the number of subjects, significant toxicities in accordance with the protocol, doses adjustments, and observed responses.

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All institutional Phase 1/2 therapeutic studies are designated with moderate to high-risk assessment; therefore, during the Phase 1 portion of trial, the data is monitored once per month, as subjects are enrolled, through the DLT period and, during the Phase 2 portion of the trial, the data is monitored twice per year, with twenty percent of the subjects monitored (or at least three subjects if the calculated value is less than three).

#### Adverse Event Review and Monitoring

##### During Phase 1:

All clinically significant adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System.

All clinically significant adverse events entered into OnCore® will be reviewed on a weekly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

In addition, all suspected adverse reactions considered “serious” are entered into OnCore® and will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at the DSMC meetings, which take place every six (6) weeks.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair or his qualified alternate within **1 business day** of knowledge of this event. The contact may be by phone or e-mail.

##### Dose Escalations (During Phase 1)

At the time of dose escalation, a written report will be submitted to the DSMC Chair (or qualified alternate) describing the cohorts, dose levels, adverse events, safety reports, and any Dose Limiting Toxicities observed, in accordance with the protocol. The report will be reviewed by the DSMC Chair (or qualified alternate) and written authorization to proceed or a request for more information will be issued within **2 business days** of the request. Approval for dose escalation by the DSMC (or qualified alternate) must be obtained prior to implementation.

##### Increase in 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, a report should be submitted to the DSMC 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.



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If at any time the Investigator stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within **1 business day** via e-mail.

The DSMC must receive a formal letter within **10 business days** and the CHR must be notified.



\* DSMP approved by NCI 09/February2012

## 12.5 EVENT OF CLINICAL INTEREST GUIDANCE DOCUMENT (V3.0)

### REVISION HISTORY LOG

Version	Effective Date*	Revision Author	Action
1	08-Aug-2012	Kevin Gergich	Initial Release of guidance document for MK-3475

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2	07-June-2013	Marty Huber, Kevin Gergich, Holly Brown	<p>Revised title, formerly was “MK-3475 Immune-Related Adverse Event Identification, Evaluation and Management Guidance Document for Investigators”</p> <p>Revised the format of irAE Guidance document, including layout, font, sectioning, etc. for consistency with Sponsor Events of Clinical Interest guidance documents.</p> <p>Modified Categories for irAEs:</p> <ul style="list-style-type: none"> <li>– Replaced GI with Colitis category.</li> <li>– Removed Neurologic category.</li> <li>– Added Renal category.</li> </ul> <p>Removed detail in the irAE Guidance document that can be located in the Investigator’s Brochure for MK-3475.</p> <p>Removed details regarding non-MK-3475 compounds.</p> <p>Added ECI reporting guidelines.</p> <p>Included a Table Events of Clinical Interest: Immune-Related Adverse Events that includes the key terms.</p> <ul style="list-style-type: none"> <li>– Also placed a pull-out quick-review sheet in the Appendix.</li> </ul> <p>Updated background, diagnosis and course of treatment details for irAEs.</p>
3		Marty Huber, Kevin Gergich, Holly Brown	<p>Renamed the document: “Pembrolizumab Program (MK-3475) - Events of Clinical Interest Guidance Document”.</p> <p>Introduced generic name: pembrolizumab (MK-3475) and inserted throughout the document.</p> <p>Updated Overview – Section 1</p> <ul style="list-style-type: none"> <li>- Clarified the scope of the document and the reporting window for ECIs</li> <li>- Updated Table 1 with medDRA Preferred Terms for adverse events to correspond with reporting of terms to clinical database, rearranged the order, and updated the reporting criteria.</li> <li>- Updated the dose modification/discontinuation section to clarify discontinuation and hold terminology.</li> </ul> <p>Updated Section 2 – ECI Reporting Guidelines</p>

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			<ul style="list-style-type: none"> <li>- Clarified that ECIs must be reported to Merck <b><u>within 24 hours</u></b> regardless of attribution to study treatment or etiology.</li> </ul> <p>Updated Section 3</p> <ul style="list-style-type: none"> <li>- For All Sections, removed the Course of Action for Grade 1 events.</li> <li>- Section 3.1 Pneumonitis <ul style="list-style-type: none"> <li>- Moved Pneumonitis to beginning of ECI Section</li> <li>- Updated management guidelines for Grade 2 and Grade 3-4 events</li> </ul> </li> <li>- Section 3.2 Colitis: <ul style="list-style-type: none"> <li>- Updated AE terms and ECI criteria, updated course of action language for clarity</li> </ul> </li> <li>- Section 3.3 Endocrine: <ul style="list-style-type: none"> <li>- Updated ECI criteria and updated course of action language for clarity.</li> <li>- Added subsections for hypophysitis, hyperthyroidism and hypothyroidism to clarify management guidelines.</li> </ul> </li> <li>- Section 3.4 Hematologic: <ul style="list-style-type: none"> <li>- New section added.</li> </ul> </li> <li>- Section 3.5: Hepatic: <ul style="list-style-type: none"> <li>- Updated terms and added additional guidance for reporting of DILI ECI; updated course of action for clarity</li> </ul> </li> <li>- Section 3.6 Neurologic: <ul style="list-style-type: none"> <li>- New section added.</li> </ul> </li> <li>- Section 3.7 Ocular: <ul style="list-style-type: none"> <li>- Changed the name of this section from Eye to Ocular</li> <li>- Added the term “iritis”, updated ECI guidance, and updated course of action language for clarity</li> </ul> </li> <li>- Section 3.8 Renal: <ul style="list-style-type: none"> <li>- Updated section for clarity.</li> </ul> </li> <li>- Section 3.9 Skin: <ul style="list-style-type: none"> <li>- Updated list of terms and added terms for reporting of other skin ECIs; added section 3.9.1: Immediate Evaluation for Potential Skin ECIs</li> </ul> </li> <li>- Section 3.10 Other: <ul style="list-style-type: none"> <li>- Updated list of terms for clarity; revised course of action for clarity.</li> </ul> </li> </ul>
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			<ul style="list-style-type: none"> <li>- Section 3.11 Infusion Reactions: <ul style="list-style-type: none"> <li>- New section added.</li> </ul> </li> <li>- Section 3.12: Follow-up to Resolution: <ul style="list-style-type: none"> <li>- New section added.</li> </ul> </li> <li>- Section 4: <ul style="list-style-type: none"> <li>- References updated.</li> </ul> </li> <li>- Section 5: <ul style="list-style-type: none"> <li>- ECI table updated for consistency with Table 1.</li> </ul> </li> <li>- Section 6: Appendix 2 – Past Medical History Related to Dermatologic Event: New section added.</li> <li>- Section 7: Appendix 3 – Presentation of the Dermatologic Event: New section added.</li> <li>- Section 8: Appendix 4 – Focused Skin Examination: New section added.</li> </ul>
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\*Ensure that you are using the most current version of this document.

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## 1. OVERVIEW

The purpose of this document is to provide study sites with guidance on the identification and management of

Events of Clinical Interest for the MK-3475 (also known as pembrolizumab) program.

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

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

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**Table 1: Events of Clinical Interest**

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



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Other (reported as ECI for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

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

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

### **Dose Modification/Discontinuation**

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

## **2. ECI REPORTING GUIDELINES**

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

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

## **3. ECI CATEGORIES AND TERMS**

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

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### 3.1 Pneumonitis

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

- Pneumonitis
- Interstitial lung disease
- Acute interstitial pneumonitis

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

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

#### Course of Action

Grade 2 events:

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

Grade 3 and 4 events:

- Report as ECI
- Discontinue pembrolizumab.
- Hospitalize patient
- Bronchoscopy with biopsy and/or BAL is recommended.
- Immediately treat with intravenous steroids (methylprednisolone 125 mg IV). When symptoms improve to Grade 1 or less, a high dose oral steroid (prednisone 1 to 2 mg/kg once

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per day or dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks.

- If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, treat with additional anti-inflammatory measures. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures, as needed
- Add prophylactic antibiotics for opportunistic infections.

### 3.2 Colitis

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

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

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

#### Course of Action

Grade 2 Diarrhea/Colitis (4-6 stools/day over baseline, dehydration requiring IV fluids < 24 hours, abdominal pain, mucus or blood in stool):

- Report as ECI
- Hold pembrolizumab.
- Symptomatic Treatment
- For Grade 2 diarrhea that persists >1 week, and for diarrhea with blood and/or mucus,
  - o Consider GI consultation and endoscopy to confirm or rule out colitis
  - o Administer oral corticosteroids (prednisone 1-2 mg/kg QD or equivalent)
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

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- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- If symptoms worsen or persist > 3 days treat as Grade 3

Grade 3 Diarrhea/Colitis (or Grade 2 diarrhea that persist for greater than 3 days):

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

Grade 4 events:

- Report as ECI
- Permanently discontinue pembrolizumab.
- Manage as per Grade 3.

### **3.3 Endocrine**

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

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

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

**Hypophysitis or other symptomatic endocrinopathy other than hypo- or hyperthyroidism**

Grade 2 events:

- Report as ECI if appropriate
- Hold pembrolizumab
- Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
- Pituitary gland imaging should be considered (MRIs with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis).
- Treat with prednisone 40 mg p.o. or equivalent per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Consultation with an endocrinologist may be considered.

Grade 3 events:

- Report as ECI
- Hold pembrolizumab.
- Endocrine consultation is recommended.
- Rule out infection and sepsis with appropriate cultures and imaging.
- Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis.
- Hospitalization and endocrine consultation should be considered.

Grade 4 events:

- Report as ECI
- Discontinue pembrolizumab.
- Manage as per Grade 3

**Hyperthyroidism and Hypothyroidism**

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**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 events (and Grade 3-4 hypothyroidism):

- Report as ECI if appropriate (see Table 1)
- Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
- Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency.
- Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
- In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
- In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
- Consultation with an endocrinologist may be considered.

Grade 3 hyperthyroidism events:

- Report as ECI
- Hold pembrolizumab.
- Rule out infection and sepsis with appropriate cultures and imaging.
- Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

- Report as ECI
- Discontinue pembrolizumab
- Manage as per Grade 3

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### 3.4 Hematologic

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

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

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

#### Course of Action

Grade 2 events:

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

Grade 3 events:

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

Grade 4 events:

- Report as ECI
- Hematology consultation



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- Discontinue pembrolizumab for all solid tumor indications; refer to protocol for hematologic malignancies.
- Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate

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### 3.5 Hepatic

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

- Autoimmune hepatitis
- Hepatitis
- Transaminase elevations

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

#### Drug Induced Liver Injury (DILI)

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

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

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

#### **Course of Action**

Grade 2 events:

- Report as ECI
- Hold pembrolizumab when AST or ALT  $>3.0$  to  $5.0$  times ULN and/or total bilirubin  $>1.5$  to  $3.0$  times ULN.
- Monitor liver function tests more frequently until returned to baseline values (consider weekly).
  - o Treat with  $0.5$ - $1$  mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume pembrolizumab per protocol
- Permanently discontinue for inability to reduce corticosteroid dose to  $10$  mg or less of prednisone or equivalent per day within 12 weeks.
- Permanently discontinue pembrolizumab for patients with liver metastasis who begin treatment with Grade 2 elevation of AST or ALT, and AST or ALT increases  $\geq 50\%$  relative to baseline and lasts  $\geq 1$  week.

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**Grade 3 events:**

- Report as ECI
- Discontinue pembrolizumab when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN.
- Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary
- Treat with high-dose intravenous glucocorticosteroids for 24 to 48 hours. When symptoms improve to Grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1 to 2 mg/kg should be started and continued over no less than 4 weeks.
- If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity.
- Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

**Grade 4 events:**

- Report as ECI
- Permanently discontinue pembrolizumab
- Manage patient as per Grade 3 above

### **3.6 Neurologic**

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

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

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

#### **Course of Action**

**Grade 2 events:**

- Report as ECI
- Moderate (Grade 2) – consider withholding pembrolizumab.
- Consider treatment with prednisone 1-2 mg/kg p.o. daily as appropriate

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- Consider Neurology consultation. Consider biopsy for confirmation of diagnosis.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3 and 4 events:

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

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

### 3.7 Ocular

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

- Uveitis
- Iritis

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

#### Course of Action

Grade 2 events:

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

Grade 3 events:

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

Grade 4 events:

- Evaluation by an ophthalmologist is strongly recommended
- Permanently discontinue pembrolizumab.
- Treat with corticosteroids as per Grade 3 above

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### **3.8 Renal**

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

- Nephritis
- Nephritis autoimmune
- Renal failure
- Renal failure acute

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

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

#### **Course of Action**

Grade 2 events:

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

Grade 3-4 events:

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

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

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### 3.9 Skin

#### Rash and Pruritus

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

- Pruritus
- Rash
- Rash generalized
- Rash maculo-papular
- In addition to CTCAE Grade 3 rash, any rash that is considered clinically significant, in the physician's judgment, should be treated as an ECI. Clinical significance is left to the physician to determine, and could possibly include rashes such as the following:
  - o rash with a duration  $>2$  weeks; OR
  - o rash that is  $>10\%$  body surface area; OR
  - o rash that causes significant discomfort not relieved by topical medication or temporary cessation of study drug.

#### Other Skin ECIs

The following AEs should **always** be reported as ECIs, regardless of grade, and should be reported to the

Sponsor within 24 hours of the event:

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

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

#### **Course of Action**

Grade 2 events:

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

Grade 3 events:

- Hold pembrolizumab.
- Consider Dermatology Consultation and biopsy for confirmation of diagnosis.

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

Grade 4 events:

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

### 3.9.1. Immediate Evaluation for Potential Skin ECIs

#### A.

##### **Photographs:**

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

- Take digital photographs of:
  - o the head (to assess mucosal or eye involvement),
  - o the trunk and extremities, and
  - o a close-up of the skin lesion/rash.
- If possible, a ruler should be placed alongside the site of a skin occurrence as a fixed marker of distance.
- The time/date stamp should be set in the 'ON' position for documentation purposes.
- Photographs should be stored with the subject's study records.
- The Sponsor may request copies of photographs. The local study contact (e.g., CRA) will provide guidance to the site, if needed.

#### **B. Past Medical History:**

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

#### **C. Presentation of the Event:**

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



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**D. Vitals Signs and Standard Laboratory Tests:**

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

**E. Focused Skin Examination:**

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

**F. Dermatology Consult**

Refer the subject to a dermatologist as soon as possible.

- For a “**severe rash**”, the subject must be seen within **1-2 days** of reporting the event.
- For **clinically significant rash**, the subject should be seen within **3-5 days**.

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

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

***3.10 Other***

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

- Myocarditis
- Pericarditis
- Pancreatitis
- Any additional Grade 3 or higher event which the physician considers to be immune related

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

**Course of Action**

Grade 2 events or Grade 1 events that do not improve with symptomatic treatment:

- Withhold pembrolizumab.
- Systemic corticosteroids may be indicated.
- Consider biopsy for confirmation of diagnosis.

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- If pembrolizumab held and corticosteroid required, manage as per grade 3 below.

Grade 3 events:

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

Grade 4 events:

- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day.
- Discontinue pembrolizumab

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### ***3.11 Infusion Reactions***

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

- Allergic reaction
- Anaphylaxis
- Cytokine release syndrome
- Serum sickness
- Infusion reactions
- Infusion-like reactions

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

#### **Course of Action**

Refer to infusion reaction table in the protocol and below.

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### Infusion Reactions

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
<u>Grade 1</u> 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
<u>Grade 2</u> Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	<b>Stop Infusion.</b> 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. <b>Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.</b>	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with:  Diphenhydramine 50 mg p.o. (or equivalent dose of antihistamine).  Acetaminophen 500-1000 mg p.o. (or equivalent dose of antipyretic).
<u>Grades 3 or 4</u> 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	<b>Stop Infusion.</b> 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. <b>Subject is permanently discontinued from further trial treatment administration.</b>	No subsequent dosing

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Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.  
For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at <http://ctep.cancer.gov>

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### ***3.12 Follow-up to Resolution***

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

- Clinical course of the event
- Course of treatment
- Evidence supporting recovery
- Follow-up to the clinical course

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