UCSF Helen Diller Family Comprehensive Cancer Center

CC# 166520: PembroX: Enhancing the Immunogenicity of Non-Small Cell Lung Cancer with Pembrolizumab +/- Stereotactic Radiotherapy Delivered in the Preoperative Window, A Randomized Phase II Study with Correlative Biomarkers

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PROTOCOL SIGNATURE PAGE

Protocol No.: 166520 **Version Date:** 03/29/2021

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 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

Printed Name

_____ _____

Signature Date

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1.0 TRIAL SUMMARY

Abbreviated Title	PembroX
Trial Phase	II
Clinical Indication	Non-small cell lung cancer, resectable
Trial Type	Randomized phase II
Type of control	Control arm of randomized schema
Route of administration	Intravenous
Trial Blinding	No
Treatment Groups	(1) Pembrolizumab followed by surgery (2) Stereotactic radiation therapy and pembrolizumab followed by surgery
Number of trial subjects	40
Estimated enrollment period	9 months: 4 patients per month
Estimated duration of trial	25 months
Duration of Participation	15 months
Estimated average length of treatment per patient	3 months, 12 months follow-up

2.0 TRIAL DESIGN

2.1 Trial Design

This is a randomized single-institution, phase II, open-label clinical trial of neoadjuvant pembrolizumab with or without low-dose stereotactic radiation therapy (SRT) in stage I- IIIA non-small lung cancer (NSCLC) patients who are planned to undergo surgical resection of their lung cancer.

Two consecutive run-in cohorts will administer pembrolizumab or pembrolizumab with SRT of 12 Gy to the lateral aspect of the primary tumor. Patients will receive pembrolizumab for 2 cycles prior to surgery or SRT and surgery. Surgical resection of all involved areas of tumor will occur within 6 weeks of the last administration of pembrolizumab. It should be noted that in almost all cases, surgery is expected to occur very expeditiously, within a much shorter window and 6 weeks would represent only the greatest allowable amount of delay.

If during the run-in, only the pembrolizumab-alone cohort meets pre-specified safety parameters, subsequently enrolled patients will enter a larger expansion cohort, with treatment given according to that cohort only. If during the run-in both cohorts meet pre- specified safety parameters, subsequently enrolled patients will enter the expansion cohort and be randomized between preoperative pembrolizumab versus pembrolizumab with SRT of 12 Gy.

Patients will be followed every 12 weeks for 1 year for disease status and survival.

2.2 Trial Diagram

Two consecutive run-in cohorts will be treated establishing the safety of neoadjuvant pembrolizumab and pembrolizumab-SRT delivered in the preoperative window. An expansion cohort will include a larger number of patients who will be treated with pembrolizumab alone or be randomized between the two arms.

Cohort 1: 6 patients. The patients will undergo 2 cycles of pembrolizumab prior to surgery. Surgery will occur no later than 6 weeks following the last dose of pembrolizumab.

If ≤33% of patients experience grade 3 immune-related toxicity attributable to study interventions (as determined within 30 days of date of surgery), or ≤ 1 patient progresses to unresectability over the course of study treatment, proceed to Cohort 2.

If >33% of patients experience grade 3 immune-related **t**oxicity attributable to study interventions (as determined within 30 days of date of surgery), or > 1 patient progresses to unresectability over the course of study treatment, the study will terminate.

Cohort 2: 6 patients. The patients will undergo 2 cycles of pembrolizumab then within the week (7 days +/- 3 days) following administration of the second cycle, a single fraction of SRT (12 Gy) will be delivered to 50% of the primary tumor only. Definitive surgical resection will occur

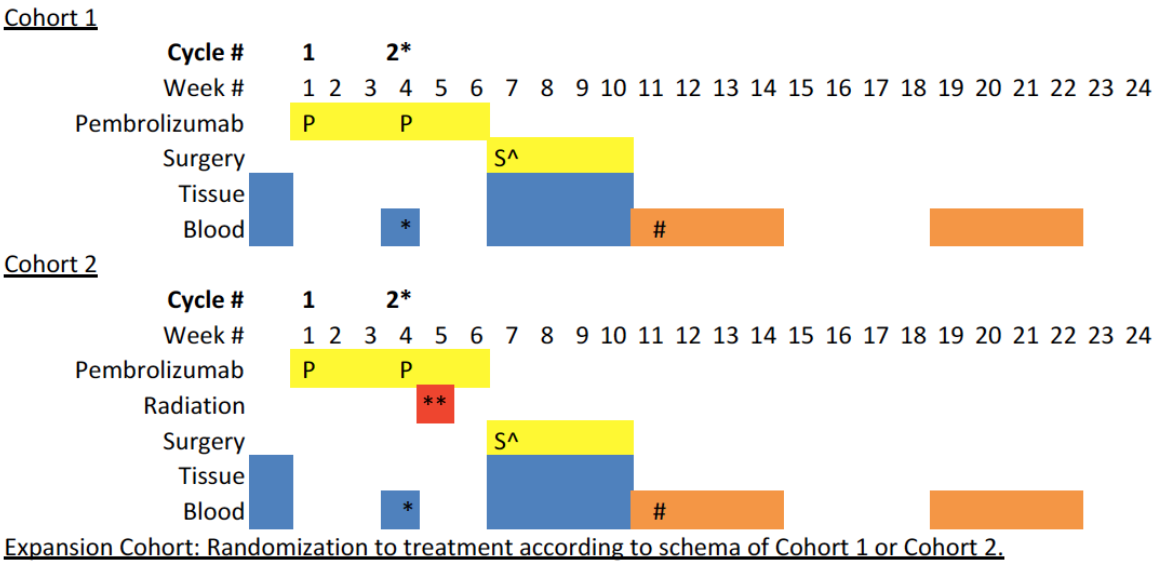
no later than 6 weeks following the last dose of pembrolizumab.

If ≤33% of patients experience grade 3 immune-related toxicity attributable to study interventions (as determined within 30 days of date of surgery), or ≤ 1 patient progresses to unresectability over the course of study treatment, proceed to Expansion Cohort (randomization between parameters of Cohort 1 and Cohort 2, e.g. randomization between preoperative pembrolizumab versus pembrolizumab and SRT).

If >33% of patients in Cohort 2 experience grade 3 immune-related toxicity attributable to study interventions (as determined within 30 days of date of surgery), or > 1 patient progresses to unresectability over the course of study treatment, then proceed to Expansion Cohort (parameters only of Cohort 1, e.g. preoperative pembrolizumab alone).

Expansion Cohort: 28 patients. The patients will be treated according to Cohort 1 if Cohort 2 failed to meet the specified safety milestones. If both cohorts met the safety milestones, then patients in this cohort will be randomized to parameters of either Cohort 1 or Cohort 2. Surgery will occur no later than 6 weeks following the last dose of pembrolizumab.

Stopping Rule: If at any point during the study, >15% of patients progress to unresectability over the course of the study treatment, then the study will terminate. This stopping rule will be cumulatively evaluated at all timepoints during the protocol, for all patients enrolled in any phase of the protocol. Each case of study-induced medical unfitness, tumor progression, or any other cause resulting in unresectability will trigger a re-evaluation of the 15% stopping rule.



* Cycle 2 of pembrolizumab should be given except as recommended per protocol, section 5.2.1.2.

** SRT is delivered within 7 days +/- 3 days of second pembrolizumab cycle. If second cycle is not given due to discontinuation, SRT should not be given (patient should continue to surgery

when deemed safe by treating surgeon).

^ Surgery will take place no later than 6 weeks following last dose of pembrolizumab, e.g. no later than week 7 if only one cycle of pembrolizumab was tolerated, or if two cycles of pembrolizumab were given, week 10.

Adjuvant blood collection will take place at follow-up visits (30d, 90d, 180d and 360d (±14d) after surgery).

Adjuvant therapy such as systemic therapy +/- radiation therapy following surgery will be administered according to the standard of care per judgment of the treating physician(s).

3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objectives & Hypotheses

(1) **Objective:** To determine the change in the number of infiltrating CD3+ T cells/ μm^2 in the lung cancer tissue between the paired biopsy and thoracotomy specimens, as quantified by immunohistochemistry (IHC) and image analysis.

Hypothesis: For resectable NSCLC, the administration of pembrolizumab +/- low-dose stereotactic SRT in the preoperative window will enhance tumor immunogenicity, resulting in two-fold greater infiltrating CD3+ T cells/ μm^2 in the primary and/or regional environment at the time of surgical resection, as compared to the time of initial biopsy.

3.2 Secondary Objectives & Hypotheses

(1) **Objective**: To assess the safety of preoperative pembrolizumab +/- SRT when combined with surgery;

Hypothesis: In patients scheduled for NSCLC resection, pembrolizumab, or pembrolizumab + SRT, given in the preoperative window, will meet safety criteria described by the protocol;

(2) **Objective**: To record the toxicity of preoperative pembrolizumab +/- SRT when combined with surgery, according to CTCAE v. 4, including immune-related adverse events (AEs);

Hypothesis: In patients scheduled for NSCLC resection, pembrolizumab, or pembrolizumab + SRT, given in the preoperative window, will result in acceptable short-term and perioperative toxicity;

(3) **Objective**: To determine the 1-year overall survival rate resulting from preoperative pembrolizumab +/- SRT when combined with surgery;

Hypothesis: In patients scheduled for NSCLC resection, pembrolizumab + SRT given in the preoperative window will result in a higher 1-year survival rate than pembrolizumab alone;

(4) **Objective**: To determine the 1-year relapse free survival rate resulting from preoperative pembrolizumab +/- SRT when combined with surgery;

Hypothesis: In patients scheduled for NSCLC resection, pembrolizumab + SRT given in the preoperative window will result in a higher 1-year relapse free survival rate than pembrolizumab alone;

(5) **Objective**: To determine the 1-year rate of distant metastases resulting from preoperative pembrolizumab +/- SRT when combined with surgery;

Hypothesis: In patients scheduled for NSCLC resection, pembrolizumab + SRT given in the preoperative window will result in a lower 1-year distant metastasis rate than pembrolizumab alone;

(6) **Objective**: To assess quality of life associated with preoperative pembrolizumab +/- SRT when combined with surgery;

Hypothesis: In patients scheduled for NSCLC resection, pembrolizumab, or pembrolizumab + SRT, given in the preoperative window, will result in acceptable short-term and perioperative quality of life;

(7) **Objective**: To determine the rate of unresectability that results from a program of preoperative pembrolizumab +/- SRT to be followed by a planned surgery;

Hypothesis: In patients scheduled for NSCLC resection, either pembrolizumab or pembrolizumab + SRT given in the preoperative window will both result in <15% overall rate of unresectability following the preoperative program;

3.3 Exploratory Objectives

(1) **Objective:** To determine the difference in the number of infiltrating T cell subsets (cytotoxic CD8+, helper CD4+ FOXP3-, and regulatory CD4+ FOXP3+ T cells) between the biopsy and the surgery specimens, as quantified by IHC and image analysis;

Hypothesis: Preoperative pembrolizumab +/- SRT will produce quantitatively detectable changes in the infiltrating T cell subsets as compared to pre-treatment biopsy;

(2) **Objective:** To determine the change in the intratumoral T-cell repertoire by TCR sequencing and single-cell T-cell profiling;

Hypothesis: Preoperative pembrolizumab +/- SRT will produce quantitatively detectable changes in the intratumoral T-cell repertoire as compared to pre-treatment specimens;

(3) **Objective:** To quantify treatment-induced changes in the circulating T cell immune response using TCR sequencing and enzyme-linked immunospot (ELISPOT) assays;

Hypothesis: Preoperative pembrolizumab +/- SRT will produce quantitatively detectable changes in the circulating T cell immune response as compared to pre-treatment specimens;

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475.

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+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). 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, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen

unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

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

The first-in-human phase I study showed that pembrolizumab was well tolerated at doses of up to 10 mg/kg every 2 weeks and demonstrated evidence of antitumor activity in multiple tumor types including melanoma, Merkel cell carcinoma, and NSCLC (Patnaik 2015). Based on these data, pembrolizumab was first approved in September 2014 by the FDA for the treatment of unresectable or metastatic melanoma and disease progression following ipilimumab and a BRAF inhibitor, in patients who were BRAF V600 mutation—positive (Robert 2014). In October 2015, the FDA granted accelerated approval for pembrolizumab to treat patients with advanced or metastatic NSCLC whose disease progressed after other treatments and with tumors that express PD-L1 based on the results of the KEYNOTE-001 trial (Garon 2015).

KEYNOTE-001

A total of 495 patients with locally advanced or metastatic NSCLC were assigned to 3 dose expansion cohorts and received at least 1 dose of pembrolizumab. Overall, 50% of patients were male with a median age of 64 (range, 28–93) and most had good Eastern Cooperative Oncology Group (ECOG) performance statuses of 0 or 1. Among 495 patients, about 80% had non-squamous histology and had previously received more than two lines of chemotherapy. Patients were treated with pembrolizumab alone at a dose of either 2 mg/kg every 3 weeks (Q3 W) (n = 6), or 10 mg/kg Q3 W (n = 287), or 10 mg every 2 weeks (Q2 W) (n = 202) (Garon 2015). Across patients regardless of dose, schedule, histology, and history of smoking, the overall response rate (ORR) was 19.4% [95% confidence interval (CI), 16.0–23.2] by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. ORR was 18.0% [95% CI, 14.4–22.2] for 394 patients previously treated and 24.8% [95% CI, 16.7–34.3] for 101 treatment-naïve patients. Stable disease was observed as the best overall response for 108 (21.8%) patients. Pembrolizumab demonstrated a response rate of 33.3% [95% CI, 4.3–77.7] at 2 mg/kg Q3 W, 19.2% [95% CI, 14.8–24.2] at 10 mg/kg Q3 W,

and 19.3% [95% CI, 14.1–25.4] at 10 mg/kg Q2 W. Patients with squamous histology (n = 85) showed an ORR of 23.5% [95% CI, 15.0–34.0] and the ORR for patients with non-squamous histology was 18.7% [95% CI, 15.0–22.9]. Smoking status influenced ORR (10.3% for never smokers vs. 22.5% for former/current smokers). Notably, the median duration of response was

12.5 months (range, 1.0–23.3) for all patients, 10.4 months (range, 1.0–10.4) for previously treated

patients, and 23.3 months (range, 1.0–23.3) in treatment-naïve patients. At the data collection cutoff (August 2014), the median duration of PFS was 3.7 months [95% CI, 2.9–4.1] in all patients (3.0 months [95% CI, 2.2–4.0] in previously treated patients, and 6.0 months [95% CI, 4.1–8.6] in treatment-naïve patients), and the median duration of OS was 12.0 months [95% CI, 9.3–14.7] in all patients (9.3 months [95% CI, 8.4–12.4] for previously treated patients and 16.2 months [95% CI, 16.2—not reached] for previously untreated patients) (Garon 2015). For adverse events (AEs) considered to be treatment related, fatigue, pruritus, and decreased appetite were the most common AEs and occurred in 10–20% of all patients. There was no clear difference between the incidence of AEs and the dose/schedule of pembrolizumab. AEs of grade 3 or higher were reported in 47 of 495 patients (9.5%). Immune-related AEs occurred in ≥2% of patients including hypothyroidism (*n* = 34, 6.9%), hyperthyroidism (*n* = 9, 1.8%), infusion-related reaction (*n* = 10, 2%), and pneumonitis (*n* = 18, 3.6%). There was a single case of grade 5 interstitial lung disease that resulted in death (Garon 2015).

KEYNOTE-010

The pivotal phase II/III randomized KEYNOTE-010 trial compared the effects of pembrolizumab and docetaxel in patients with previously treated NSCLC (NCT01905657). From August 2013 to April 2015, this international, open-label study randomized 1034 patients with PD-L1 positive NSCLC to the FDA-approved dose of 2 mg/kg of pembrolizumab, an elevated dose of 10 mg/kg of PD-1 inhibitor, or 75 mg/m2 of docetaxel. All three regimens were administered at 3-week intervals. All patients had progressed following platinum-based chemotherapy and eligible patients expressed PD-L1 on >1% of their tumor cells, and predefined subgroup analysis will be performed for those of strongly PD-L1-positive patients, defined as those expressing PD-L1 on

≥50% of their tumor cells. The primary endpoint was OS and secondary endpoint was PFS. Tumor response was measured by RECIST 1.1 at week 12, and then every 6 weeks thereafter. Promising results were recently published (Herbst 2016). Pembrolizumab improved overall survival versus docetaxel in both standard and higher-dose arms (median 14.9 and 17.3 months with 2 mg/kg and 10 mg/kg of pembrolizumab, respectively and 8.2 months with docetaxel), as well as in the overall study population and in the strongly PD-L1-positive subgroup. Hazard ratio (HR) for OS of 0.54 [95% CI, 0.38–0.77] and 0.50 [95% CI, 0.36–0.70] for the two dosing schedules of pembrolizumab (at 2 mg/kg and 10 mg/kg, respectively) was noted for the patients with the highest biomarker expression (tumor proportion score, TPS ≥ 50%) as compared to docetaxel. Interestingly, pembrolizumab also demonstrated a benefit in OS for patients in the total study population (>1% PD-L1 positivity in the tumor was required at study entry), with hazard ratios of 0.71 [95% CI, 0.58–0. 88] and 0.61 [95% CI, 0.49–0.75] in the pembrolizumab arms at 2 mg/kg and 10 mg/kg, respectively. PFS also significantly improved with both dosing schedules of pembrolizumab versus chemotherapy in high PD-L1 expressers (median 5.0 and 5.2 vs. 4.1 months). Based on the promising efficacy of pembrolizumab in previously treated NSCLC, several clinical trials of pembrolizumab as first-line therapy or adjuvant therapy for NSCLC after curative resection are currently underway.

KEYNOTE-042

Based on the promising results especially chemo-naïve NSCLC patients from early clinical trial,

pembrolizumab is being evaluated as first-line therapy. KEYNOTE-042 trial (ClinicalTrial.gov, NCT02220894), a randomized, open-label phase I trial will evaluate the efficacy and safety of pembrolizumab vs. platinum doublet chemotherapy as first-line therapy for PDL-1 positive advanced NSCLC. Eligible patients with advanced PDL-1 positive NSCLC without EGFR mutations or ALK translocation and ≥1 measurable lesion will be randomized 1:1 to pembrolizumab 200 mg every 3 weeks or investigator's choice of carboplatin plus paclitaxel or carboplatin plus pemetrexed (Mok 2015). Patients will be stratified by ECOG PS (0 vs. 1), histology (squamous vs. non-squamous), region (East Asia vs. non-East Asia), and PDL-1 expression (strong vs. weak [staining in ≥50% vs. 1–49% of tumor cells assessed by immunohistochemistry with the 22C3 antibody]). Primary end point is overall survival in patients with PDL-1 strongly positive tumors and secondary endpoints include progression-free survival in strongly positive patients and PFS and OS in all patients.

4.2 PD-L1 expression by immunohistochemistry

Pembrolizumab has been approved for use with a companion diagnostic, the PD-L1 immunohistochemistry (IHC) 22C3 pharmDx test, the first test designed to detect PD-L1 expression in NSCLC. The clinical trial assay was developed by Dako, an *in vitro* diagnostic manufacturer. In the KEYNOTE-001 trial, the overall prevalence of PD-L1 expression ≥1% was 60.8% among 824 patients including 58.6% of the 643 previously treated patients and 68.5% of the 181 previously untreated patients. The prevalence of a proportion score (PS) of at least 50% was 24.9% among previously untreated patients and 22.7% among previously treated patients (Garon 2015). Notably, the ORR (45.2% vs. 16.5% vs. 10.7%), PFS (6.4 vs. 4.1 vs. 4.0 months), and OS (not reached vs. 10.6 vs. 10.4 months) were significantly higher for patients whose tumors expressed PD-L1 membranous staining ≥50% compared to patients with a PS of 1–49% or those with a score less than 1%. A cutoff of ≥50% PD-L1 positivity in tumor cell membranes was determined as optimal by receiver operating characteristic (ROC) analysis. In contrast, PD-L1 expression was not associated with predictive markers of any efficacy endpoints in the Checkmate 017 study with nivolumab, in which patients with pretreated squamous NSCLC were compared with those treated with docetaxel (Brahmer 2015). There was a favorable trend of unstratified hazard ratios toward nivolumab in patients with higher PD-L1 expression (≥10%, ≥5%, and ≥1%) and similar rates of objective response were observed among patients with PD-L1 positive tumors and those with PD-L1 negative tumors. On the other hand, another trial of nivolumab in pretreated advanced non-squamous NSCLC (Checkmate 057) compared with docetaxel demonstrated a meaningful separation of the overall survival curves across all pre-specified PD-L1 expression levels (at ≥1%, ≥5%, and ≥10%) (Borghaei 2015). However, PD-L1 expression in both studies was evaluated retrospectively in pretreatment (archival or recent) tumor biopsy specimens using rabbit monoclonal antihuman PD-L1 antibody (clone 28-8, Epitomics). In a phase I study of anti-PD-L1 antibody MPDL3280A, PD-L1 was stained with an antihuman PD-L1 rabbit monoclonal antibody (clone SP142, Ventana) and PD-L1 expression was evaluated on both tumor cells and tumor-infiltrating immune cells. While the association of response to MPDL3280A treatment and tumor-infiltrating immune (TIL) cell PD-L1 expression was significant, the association with tumor cell PD-L1 expression was not (Herbst 2014).

Recent pooled sensitive analyses of phase I–III clinical trials of PD-1/PD-L1 inhibitors (nivolumab, pembrolizumab, or MPDL3280A) including 511 NSCLC patients showed that

patients with PD-L1 positive tumor achieved significantly more responses than PD-L1-negative patients (23.2% vs. 14.5%), with an absolute difference of 8.7% (95% CI 1.1–15.5) (Carbognin 2015). However, the use of PD-L1 IHC positivity as a predictive marker remains controversial in the context of different anti-PD-L1 antibodies, staining techniques, definitions of positive tumor cells or immune cells, tumor site (primary vs. metastasis), tumor type (archival vs. recent), and various cutoffs.

4.3 Rationale

4.3.1 Rationale for the Trial and Selected Subject Population

We hypothesize that neoadjuvant treatment with pembrolizumab and targeted stereotactic radiation therapy (SRT) will improve patients' immunogenic responses during and after surgical treatment of their non-small cell lung cancer. The timing of the interventions during the neoadjuvant phase will allow us to perform comprehensive analyses on tumor specimens before any treatment and after initial response to pembrolizumab alone or pembrolizumab with SRT.

In this study, patients are offered immunotherapy +/- SRT before surgery but are free to pursue chemotherapy +/- external beam radiation therapy after surgery. It is important to call attention to this deliberate aspect of the study design, which ends protocol-mandated treatment at the time of surgery, such that patients are allowed to pursue postoperative treatment appropriate to their surgical/pathologic stage. While chemotherapy is considered part of the perioperative standard of care for NSCLC patients undergoing resection, the only available randomized evidence showed no statistical difference in long-term disease-free survival, whether chemotherapy was administered preoperatively or postoperatively (Felip 2010). Thus, neoadjuvant chemotherapy given prior to surgery is not considered a standard of care, and in fact the extremely well established standard of care is to offer postoperative chemotherapy +/- radiotherapy depending on the pathologic outcome at surgery, as advocated by the guidelines issued by the European Society of Medical Oncologists on this subject (McElnay 2014). Likewise, there is no clear benefit to external beam radiotherapy whether given preoperatively or postoperatively. In addition, emerging recent evidence indicates that in several different tumor types, cisplatin may stimulate upregulation of PD-L1 and that this could be associated with subsequent cisplatin resistance (Zhang 2016, Mesnage 2016, Yan 2016). Therefore, the rationale for administration of immunotherapy prior to administration of cisplatin, with the possibility of inducing a durable immune response prior to surgery and expected postoperative therapy, may offer a more therapeutically effective strategy.

Furthermore, our thoracic surgery service has extensive experience performing operations on patients who are currently receiving immunotherapy for a variety of malignancies, and thus far there have been no issues with delays due to therapy. It is expected that the amount of delay of surgery will be relatively minimal, even accounting for administration of 1-2 cycles of pembrolizumab. Given the relatively poor outcomes for NSCLC, even among patients who are eligible for definitive surgical resection, novel approaches to treating this population are greatly needed.

The strategy offered in this study will allow us to define a rationale for therapies that, when

combined with standard surgical resection in the first-line setting, could result in more complete and durable responses for patients. The study design will allow us to investigate intratumoral and circulating immunologic changes as a result of preoperative therapy, as well as potential mechanisms of synergy between pembrolizumab and stereotactic radiation therapy in addressing local-regional and distant disease recurrence.

4.3.2 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 MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated, and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, was utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity.

Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

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

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

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W,

3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

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

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

4.3.3 Rationale for SRT Dosing

The dose of radiation therapy prescribed in this study is based on a number of preclinical and clinical studies that have investigated the immunologic effects of radiation doses in this range in combination with PD-1 antibodies.

For example, Verbrugge et al. irradiated triple-negative AT3 breast tumors in mice with a single fraction of 12 Gy with or without anti-CD137 antibody, a co-stimulatory molecule designed to boost immune-mediated antitumor effects of radiotherapy (Verbrugge 2012). Anti-CD137 therapy significantly enhanced radiotherapy-induced tumor control, but the response was short-lived. The addition of anti-PD-1 antibody to anti-CD137 antibody and radiation led to cures at the primary irradiated tumor site, while anti-PD1 monotherapy was not very effective. After testing of various radiation regimens, they found that 12 Gy x 1 fraction led to 100% cure, whereas the cure rates with 5 Gy x 4 fractions and 4 Gy x 5 fractions were 80% and 40%, respectively.

Zeng et al. found that a radiation regimen of 12 Gy x 1 fraction, when combined with anti-PD-1 antibody, led to long-term survival in a mouse glioma model whereas neither therapy by itself did (Zeng 2013). The combination therapy was associated with increased infiltration by cytotoxic T cells and decreased regulatory T cells within the tumor microenvironment. Deng et al. also used this radiation regimen (12 Gy x 1 fraction) and anti-PD- L1 therapy to show synergistic inhibition of TUBO mammary carcinoma and MC38 colon adenocarcinoma growth in mice (Deng 2014). Furthermore, they showed that PD-L1 expression was upregulated in tumor cells after radiotherapy and that radiation and anti-PD-L1 led to a synergistic reduction in the local accumulation of tumor-infiltrating myeloid-derived suppressor cells that normally suppress T cell function within the tumor microenvironment.

Twyman-Saint Victor et al. conducted preclinical studies using both anti-CTLA4 and anti-PD-1 (or PD-L1) therapy and radiation (Twyman-Saint Victor 2015). B16- F10 melanoma tumors were grown in the bilateral flanks of mice. Tumor in one flank was irradiated (20 Gy) and

growth was assessed in both the irradiated and the unirradiated tumors. Mice were treated with anti-CTLA4 antibody, anti PD-1/PD-L1 antibody or both prior to and after irradiation. In these experiments, the addition of radiation to anti-CTLA4 improved responses in irradiated and unirradiated tumors; however, resistance was common. Integrated genomic and immune profiling revealed that resistance was due to upregulation of PD-L1 on melanoma cells and associated with T cell dysfunction, known as exhaustion. Even in the presence of dual checkpoint blockade, omission of radiation resulted in high rates of relapse. Investigation into how each treatment impacted mechanisms that influence response revealed that anti-CTLA4 predominantly inhibits regulatory T cells (Treg) to increase the CD8+ T cell to Treg (CD8/Treg) ratio, radiation enhances the diversity of the T cell receptor repertoire of intratumoral T cells, and anti- PD-L1 reverses T cell exhaustion. Together, dual checkpoint blockade promotes expansion of T cells, while radiation shapes the T cell receptor repertoire of the expanded peripheral clones.

Many ongoing studies at present are testing comparisons between various single-fraction doses versus more fractionated regimens in combination with immunomodulatory compounds. At least based on available data from in vivo studies delivering radiation in combination with CTLA-4 antibody, it appears that 12 Gy is sufficient to enact a vaccine-like effect in the primary tumor when given with immunomodulatory agents. In combination with anti-PD-1 therapy, it also appears that 12 Gy is also likely to be effective, although prior studies have not analyzed effects

outside the primary tumor. For the purpose of this study, 12 Gy was chosen as a dose likely to produce a substantive immune effect but also very likely to be safe. Partial SRT (irradiation will be prescribed to approximately 50% of the primary tumor) will be given to avoid CD4+ and CD8+ T cell depletion within the irradiated primary tumor and allow for the assessment of local effects resulting from reshaping of the intratumoral T cell repertoire.

4.3.4 Rationale for Endpoints

The primary endpoint for this study is the change in number of infiltrating CD3+ T cells/ μm^2 in the lung cancer tissue from before and after pembrolizumab +/- SRT, based on quantification using immunohistochemistry (IHC) and image analysis. This endpoint was selected as a marker of T cell proliferation and activation. It is expected that immunologic activation would be reflected by the presence of this biomarker. The purpose of this study is to determine whether neoadjuvant pembrolizumab +/- SRT is sufficient to produce a two-fold change in the CD3+ T cell population, comparing pre-treatment biopsy tissue to post-treatment resection specimens.

Despite the generally high efficacy of surgery in producing local control for most NSCLC patients, a large percentage will succumb to regional or distant metastatic disease manifestation. Therefore, this study will also include exploratory objectives aimed at the possibility of a potential improvement in 1-year clinical outcomes from the addition of neoadjuvant immune modulation.

4.4 Secondary Objectives & Hypotheses

Secondary objectives include safety according to criteria described by the protocol (≤33% grade 3 immune-related toxicity); toxicity according to CTCAE v. 4, including immune-related adverse events (AEs); and quality of life.

Other secondary objectives include the 1-year overall survival rate, 1-year relapse free survival, 1 year rate of distant metastases, and rate of progression to unresectability following the preoperative program. These exploratory data will provide an initial basis for investigating which of these two programs might provide the best overall clinical benefits and merit further study.

4.5 Exploratory Objectives

4.5.1 Biomarker Research

PD-L1 expression will be tested in tumor specimens to investigate correlations to immune response from treatment with pembrolizumab.

Other exploratory objectives will further describe immune changes resulting from neoadjuvant pembrolizumab +/- SRT. These will include: changes in the number of infiltrating T cell subsets; change in the intratumoral T-cell repertoire by TCR sequencing and single-cell T-cell profiling; and treatment-induced changes in the circulating T cell immune response using TCR sequencing and enzyme-linked immunospot (ELISPOT) assays.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

1. Histologically or cytologically confirmed non-small cell lung cancer, performed on a biopsy that occurred within the last 120 days.
2. PET-CT within the last 75 days showing radiographic stage I to IIIa lung cancer (mediastinal staging biopsy is allowed but not required).
3. Documentation that the patient is a candidate for surgical resection of their lung cancer by an American Board of Thoracic Surgery-certified surgeon.
4. Measurable disease as defined by RECIST v1.1.
5. Adequate tissue specimens for correlative biomarker analysis. The patient should be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. Newly-obtained is defined as a specimen obtained up to 120 days prior to initiation of treatment on Day 1. Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the Principal Investigator.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
7. Resolution of all acute toxic effects of prior chemotherapy, radiotherapy or surgical procedures to NCI CTCAE Version 4.0 grade 1.

5.1.2 Subject Inclusion Criteria

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

1. Be willing and able to provide written informed consent/assent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Demonstrate adequate organ function as defined in Table 1. All screening labs should be performed within 10 days of treatment initiation, unless specified below.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin[a]	≥9 g/dL or ≥5.6 mmol/L
Renal	
Serum creatinine **OR** Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Patients cannot have received transfusion or erythropoietin (EPO) within 7 days of the hemoglobin (Hgb) lab test as this may artificially inflate the Hgb lab value. [b]Creatinine clearance should be calculated per institutional standard.	

4. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
5. Female subjects of childbearing potential (Section 5.7.2) must be willing to use an adequate method of contraception, as outlined in Section 5.7.2 – Contraception, for the course of the study through 120 days after the last dose of study medication.

   Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
6. Male subjects of childbearing potential (Section 5.7.1) must agree to use an adequate method of contraception as outlined in Section 5.7.1- Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

   Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

5.1.3 Subject Exclusion Criteria

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

1. Is ineligible for an operation based on medical or oncologic contraindications to surgery.
2. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
3. Has evidence of interstitial lung disease.
4. Has an active second malignancy, i.e. patient known to have potentially fatal cancer present for which he/she may be (but not necessarily) currently receiving treatment. Patients with a history of malignancy that has been completely treated, with no evidence of that cancer currently, are permitted to enroll in the trial if curative therapy has been completed, such as basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
5. 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.
6. 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.
7. Has a known history of active TB (Bacillus Tuberculosis)
8. Hypersensitivity to pembrolizumab or any of its excipients.
9. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
10. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.
    - Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
    - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
11. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

12. Has an active infection requiring systemic therapy.
13. 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.
14. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
15. 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.
16. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
17. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
18. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
19. Has received a live vaccine or live-attenuated vaccine within 30 days prior to the first dose of the study drug. Administration of killed vaccines is allowed.

    Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2.

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequenc	Route of Administratio	Regimen/Trea t- ment	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3-week cycle	Experimental

Stereotactic radiation therapy will be given at a prescription dosage of 12 Gy at the 80% isodose line, to be delivered in one single treatment session in one day, to 50% +/- 10% of the primary tumor volume, as determined by volumetric measurement of the total tumor volume and the volume of that tumor within the prescribed planning target volume (PTV). The lateral half of the tumor should be encompassed within the PTV and the medial aspect of the tumor relative to the patient should not be included in the PTV. Treatment may be delivered from either a linear accelerator or robotic SRT delivery system. SRT, if the patient is to receive it according to the terms of the protocol, should be given within 7 days (+/- 3 days) following the second administration of pembrolizumab. If the second cycle is not given, then SRT should not be given.

During dose expansion, trial treatment should begin on the day of randomization or as close as possible to the date on which treatment is allocated/assigned.

5.2.1 Dose Selection/Modification

5.3.2.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

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

5.2.1.1 Dose Modification (Escalation/Titration/Other)

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

If a patient continues to experience toxicity, or if dosing with study drug is interrupted for > 14 consecutive days due to toxicity, treatment should be discontinued unless otherwise agreed between the investigators before reintroduction of study drug.

The following dose modification rules will be used with respect to potential toxicity. Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0).

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to the combination, to stereotactic radiotherapy, or to pembrolizumab alone, for adverse events listed in Table 3, both interventions must be held according to the criteria in Table 3 Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Pembrolizumab.

Holding Study Interventions:

When study interventions are administered in combination, if the AE is considered immune-related, both interventions should be held according to recommended dose modifications.

Restarting Study Interventions:

Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in Table 3.

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions.

  If the toxicities do resolve and conditions are aligned with what is defined in Table 3, the combination of stereotactic radiotherapy and pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to stereotactic radiotherapy alone, re-initiation of pembrolizumab as a monotherapy may be considered at the principal investigator's discretion.

Table 3 Dose Modification and Toxicity Management Guidelines for Immune-Related AEs associated with pembrolizumab monotherapy and IO Combinations

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if irAEs are not controlled by corticosteroids.
2. Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last study intervention treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If study intervention has been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitor and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme

			equivalent) followed by taper	value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta- blockers (e.g., propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue1		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g., levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 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		
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		
Exfoliative	Suspected SJS, TEN, or	Withhold		

Dermatologic Conditions	DRESS		• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All other irAEs	persistent Grade 2	Withhold	• Based on severity of AE, administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the event[e]. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal;
bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal;
bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs.

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 Principal Investigator. The reason for interruption should be documented in the patient's study record.

5.2.2 Timing of Dose Administration

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

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30-minute IV infusion every 3 weeks, for 2 cycles. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

5.2.3 Trial Blinding/Masking

This trial is open label; therefore, the subject, the trial site personnel, the Principal Investigator and/or designee are not blinded to treatment.

5.3 Randomization or Treatment Allocation

For the run-in cohorts, consecutive patients will be enrolled.

In the expansion cohort, consecutive patients will be enrolled if only Cohort 1 conditions are fulfilled. If Cohort 1 and Cohort 2 both meet safety criteria, then patients will be enrolled in the Expansion Cohort using permuted-block randomization with block size of 4.

5.4 Stratification

No stratification is to be performed.

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

5.5.1 Acceptable Concomitant Medications

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

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

5.5.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy outside of that prescribed per protocol
- 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 Principal Investigator.

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

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

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

5.6.2 Pneumonitis:

5.6.2.1 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.

5.6.2.2 For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.

5.6.2.3 Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

5.6.3 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).

5.6.3.1 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.

5.6.3.2 For **Grade 2 diarrhea/colitis,** administer oral corticosteroids.

5.6.3.3 For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids followed by high dose oral steroids.

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

5.6.4 Type 1 diabetes mellitus*

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

5.6.4.1 For **T1DM** or **Grade 3-4** Hyperglycemia

5.6.4.1.1 Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.

5.6.4.1.2 Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

5.6.5 Hypophysitis:

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

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

5.6.6 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.

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

5.6.6.1.1 In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.

5.6.6.1.2 In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.

5.6.6.2 Grade 3-4 hyperthyroidism

5.6.6.2.1 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.

5.6.7 Hepatic:

5.6.7.1 For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).

5.6.7.1.1 Treat with IV or oral corticosteroids

5.6.7.2 For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.

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

5.6.8 Renal Failure or Nephritis:

5.6.8.1 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.

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

Table 3 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 3 Infusion Reaction Treatment Guidelines

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

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. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

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

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

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

OR

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

OR

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

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

(1) practice abstinence† from heterosexual activity; OR
(2) use (or have their partner use) acceptable contraception during heterosexual activity. Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

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

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

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)

- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

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

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

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

5.7.3 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 Principal Investigator and to Merck without delay and within 24 hours to the Principal Investigator and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Principal Investigator. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Principal Investigator and to Merck and followed as described above and in Section 7.2.2.

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 Principal Investigator 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 7.1.4 – Other Procedures.

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

5.9.5 The subject or legal representative (such as a parent or legal guardian) withdraws consent.
5.9.6 Confirmed radiographic disease progression
5.9.7 Intercurrent illness that prevents further administration of treatment per protocol
5.9.8 Investigator's decision to withdraw the subject
5.9.9 The subject has a confirmed positive serum pregnancy test
5.9.10 Noncompliance with trial treatment or procedure requirements
5.9.11 The subject is lost to follow-up
5.9.12 Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6. After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.9 Subject Replacement Strategy

Patients who drop out before starting pembrolizumab will be replaced. In addition, patients who come off study before completing surgery without grade ≥3 toxicity will be replaced. The frequency of each of these events will be reported and reasons for replacement reviewed.

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.

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	**Screeninga**		**Treatment Cyclesb**			**Surgical Treatment**	**Follow-Up**
Treatment Cycle:	Screening	1	2	End- Induction/ Safety Visit	SRTc	Surgical Treatment	Post-Treatment/ Safety Visitse
Scheduling Window:	-28d to -1d	± 3d	± 3d	No later than 7d (± 3d)	No later than 7d (± 3d)	no later than 6wksd	At 30d, 90d, 180d,360d after surgery (+14d)
Administrative Procedures							
Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Demographics and Medical History	X						
Prior and Concomitant Medication Review	X	X	X	X		X	X
Trial Treatment Administration		X	X				
Post-study anticancer therapy status							X
Survival Status							X
Clinical Procedures/Assessments							
Review Adverse Events		X	X	X		X	X
Full Physical Examination	X						
Directed Physical Examination		X		X			X
Vital Signs and Weight	X	X		X			X
ECOG Performance Status	X	X		X			X
Laboratory Procedures/Assessmentsf							
Pregnancy Test – Urine or Serum β-HCGg	X						
Coagulation	X						

Trial Period:	**Screeninga**		**Treatment Cyclesb**			**Surgical Treatment**	**Follow-Up**
Treatment Cycle:	Screening	1	2	End- Induction/ Safety Visit	SRTc	Surgical Treatment	Post-Treatment/ Safety Visitse
Scheduling Window:	-28d to -1d	± 3d	± 3d	No later than 7d (± 3d)	No later than 7d (± 3d)	no later than 6wksd	At 30d, 90d, 180d,360d after surgery (+14d)
Hematology	X	X	X	X		X	X
Comprehensive Serum Chemistry Panel	X	X	X	X		X	X
Urinalysis	X						X
Thyroid function	X			X			X
Efficacy Measurementsh							
Tumor Imaging (F-18 FDG PET/CT in screening with MRI/CT brain in stage II/III patients, and CT chest at 360d or as otherwise clinically indicated)	X						X
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Bloodi							
Archival or Newly Obtained Tissue Collection	X						X
Correlative Studies Blood Collection	X		X	X		X	X

[a]Screening procedures to be completed within 28 days of C1D1 with the exception of fresh tumor specimens and tumor imaging, please see information in footnotes, respectively.
[b]Patients receive 2 cycles of pembrolizumab. 1 cycle is defined as 3 week intervals.
[c]If patient is scheduled to receive SRT, the day of radiation therapy will be no later than 7d (+/- 3d) following the second cycle of pembrolizumab.
[d]No later than 6 weeks after the last dose of pembrolizumab.
[e]After surgery, patients to return for clinical and laboratory assessments at 30 days (first follow-up visit to occur), 90 days, 180 days, and 360 days (+ 21 days) after date of surgery.
[f]Screening labs performed within 10d of treatment initiation can be applied to Cycle 1 lab tests. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.
[g]Females of childbearing potential: negative urine or serum pregnancy test within 3d prior to receiving trial treatment. If urine test is positive or non-confirmatory, a serum pregnancy test will be required.
[h]All patients to have a full-body F-18 FDG PET/CT scan ≤75d prior to study treatment; patients with stage II and stage III disease should also have brain CT or MRI ≤75d prior to study treatment. Additional imaging during treatment will be under investigator discretion. During Follow-up phase, imaging studies are to be completed at the discretion of investigator or qualified designee.
[i]Newly obtained specimen is preferred, however archived tissue will be acceptable due to inaccessibility or subject safety concern. Specimens that are newly obtained are defined as collection up to 120d prior to initiation of study treatment.
For correlative studies and blood collection: research-donated blood will be collected pre-pembrolizumab infusion for cycle 1 and cycle 2, at the safety visit during cycle 2 (blood should be collected prior to SRT administration if patient will receive SRT), prior to surgical treatment, and at each post-treatment/safety follow-up visit (30d, 90d, 180d and 360d (+14d) after surgery).

6.2 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.

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

6.2.1 Administrative Procedures

6.1.1.1 Informed Consent

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

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

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

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

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

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

6.2.1.1 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.

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

6.2.1.3 Prior and Concomitant Medications Review

6.2.1.3.1 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.

6.2.1.3.2 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.

6.2.1.4 Disease Details and Treatments

6.2.1.4.1 Disease Details

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

6.2.1.4.2 Prior Treatment Details

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

6.2.1.4.3 Subsequent Anti-Cancer Therapy Status

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

6.2.1.5 Assignment of Screening Number

At the time of screening, the patient will be assigned a screening number.

6.2.1.6 Assignment of Randomization Number

At the time of randomization during dose expansion, the patient will be assigned a randomization number.

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

6.2.2 Clinical Procedures/Assessments

6.2.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow- up period according to NCI CTCAE Version 4.0 (see Section 11.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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

6.2.2.2 Full Physical Exam

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

6.2.2.3 Directed Physical Exam

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

6.2.2.4 Vital Signs

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

6.2.2.5 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.

6.2.2.6 Tumor Imaging and Assessment of Disease

All patients will undergo a full-body F-18 FDG PET/CT scan within 75 days prior to start of treatment or randomization (only during dose expansion). Patients with stage II and III disease should have a brain CT or MRI within 75 days prior to start of treatment.

Following the time of surgery, the investigator or qualified designee will assess disease with imaging studies according to the investigator's determination of the standard of care.

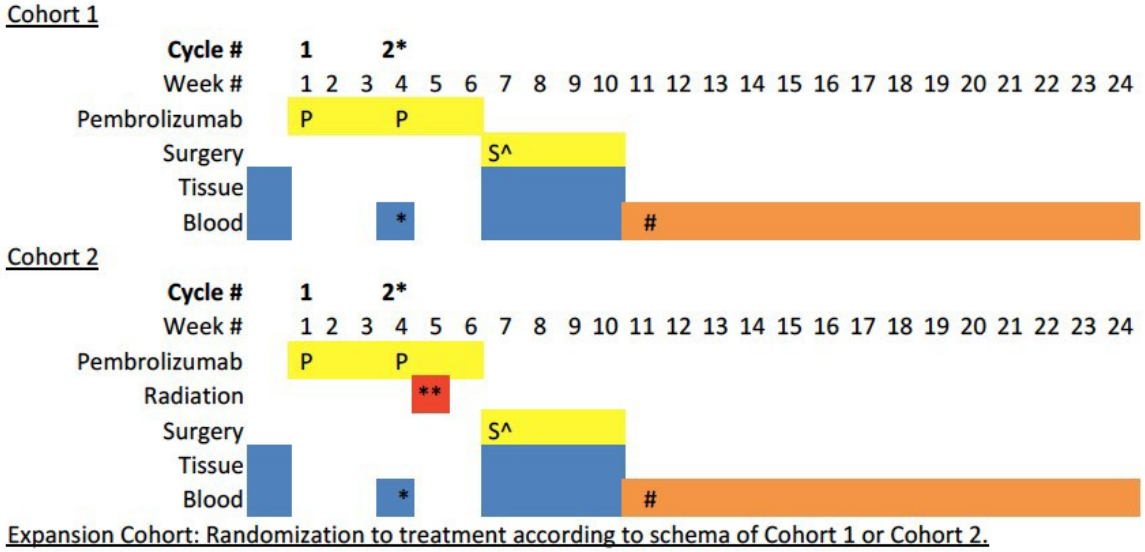
6.2.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

Prior to treatment or randomization (only during dose expansion), tissue collections include fresh sampling (preferred) of the primary tumor (core or excisional biopsy) or archival tissue, due to safety and inaccessibility, and blood samples (please see Table 6, Trial Flow for details).

If the patient has clinically involved lymph nodes and investigation of the nodes is clinically warranted, every effort should be made to collect tissue via core needle biopsy from the involved lymph nodes. If bronchoscopy is performed, it is highly encouraged to collect lavage specimens as well, although this is not mandatory.

Research-donated blood will be collected prior to pembrolizumab infusion during cycle 1 and cycle 2; prior to surgical treatment, and at each post-treatment/safety follow-up visit (30d, 90d, 180d and 360d (±14d) after surgery).

Overall Schema:



* Cycle 2 of pembrolizumab should be given except as recommended per protocol, section 5.2.1.2.
** SRT is delivered within 7 days +/- 3 days of second pembrolizumab cycle. If second cycle is not given due to discontinuation, SRT should not be given (patient should continue to surgery when deemed safe by treating surgeon).

^ Surgery will take place no later than 6 weeks following last dose of pembrolizumab, e.g. no later than week 7, or if two cycles of pembrolizumab were given, week 10.
# Adjuvant blood collection will take place at follow-up visits (30d, 90d, 180d and 360d (±14d) after surgery).

6.2.3 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 5.

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Free thyroxine (T4)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Thyroid stimulating hormone (TSH)
Absolute Lymphocyte Count	*(CO2 or biocarbonate)*	Urine pregnancy test †	PK
	Uric Acid		Blood for correlative studies
	Calcium		
	Chloride		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		
	Creatinine		

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

After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

6.2.4 Blood Collections

All patients will have 4 (four) 10mL green top tubes of blood specimens collected prior to pembrolizumab infusion during cycle 1 and cycle 2, prior to surgical treatment, and at each post-treatment/safety follow-up visit (30d, 90d, 180d and 360d (±14d) after surgery).

Sample collection, storage and shipment instructions for blood samples are provided in the Laboratory Manual.

6.2.5 Other Procedures

Fresh sampling (preferred) of the primary tumor (core or excisional biopsy) is required, or archival tissue may be substituted for reasons due to safety and inaccessibility.

If the patient has clinically involved lymph nodes and investigation of the nodes is clinically warranted, every effort should be made to collect tissue via core needle biopsy from the involved lymph nodes.

6.2.5.1 Pretreatment samples

Core biopsies of primary tumor +/- involved lymph nodes will be performed by a qualified radiologist, pathologist, surgeon, or pulmonologist. One to four core biopsies will be performed (number determined by safe accessibility and size of lesion at the discretion of the physician performing the biopsy). Core biopsies are required, however if it is deemed technically infeasible, or if a core biopsy is deemed very high risk by the physician performing the biopsy, then fine-needle aspiration (FNA) may be acceptable in 1-2 extremely select cases based on pre-approval by the study Principal Investigators.

For intraparenchymal lung biopsies, an 18G core needle biopsy is preferred. If this is not considered to be safe by the physician performing the procedure, then an FNA with a higher gauge needle will be acceptable.

Biopsy sites other than intraparenchymal lung should use a 16 G if possible, but 18 G or FNA will be acceptable if the physician performing the biopsy feels that it is safer. One to three needle passes at minimum will be obtained, but if the physician determines it is safe, up to 6 passes may be obtained.

Sample collection, storage and shipment instructions for pre-treatment tissue samples are provided in the Laboratory Manual.

6.2.5.2 Post-treatment samples:

Patients will undergo surgical resection of their primary tumor and associated lymph nodes. Patients in cohort 1 will have received pembrolizumab alone prior to resection, whereas patients in cohort 2 will have received pembrolizumab and radiation to half of the primary tumor.

In all cases, post-treatment excisional samples should be first taken from the primary tumor tissue that was treated with pembrolizumab only (medially oriented half of tumor). The portion of tumor which received radiation is the lateral aspect of the tumor relative to the patient.

Therefore, mandated post-treatment tissue samples should always be removed from the medial aspect of the tumor.

If it is feasible and specimen collection will not interfere with the patient's clinical care, tissue samples should also be collected from the radiated portion of the tumor (lateral aspect). These tumor samples should be labeled so that their orientation (medial vs lateral) is clear.

Samples from clinically involved lymph nodes are requested if feasible and if collection will not interfere with the patient's clinical care. These samples should be labeled by the designated nodal station.

Sample collection, storage and shipment instructions for post-treatment tissue samples are provided in the Laboratory Manual.

6.2.5.3 Lavage (fluid) specimens

If bronchoscopy is performed, it is highly encouraged to collect lavage specimens as well, although this is not mandatory. If a patient has clinical indication for bronchoscopy, lavage fluid may be obtained. Any excess leftover fluid, up to 1000mL, should be submitted.

Sample collection, storage and shipment instructions for fluid samples are provided in the Laboratory Manual.

6.2.6 Withdrawal/Discontinuation

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

6.2.7 Blinding/Unblinding

This trial is open label; therefore, the subject, the trial site personnel, the Principal Investigator and/or designee are not blinded to treatment.

6.2.8 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.

6.2.9 Screening

Screening period will be conducted days -28 to -1.

6.2.10 Treatment Period

Treatment will initiate with the first dose of pembrolizumab. A second dose of pembrolizumab will be delivered 3 weeks later, +/- 3 days.

If the patient is scheduled to receive SRT on the protocol, the day of radiation delivery will be no later than 7 days following the date anticipated for administration of the second cycle of pembrolizumab, +/- 3 days. If the second cycle is not given, then SRT should not be given.

Surgical resection, if the patient is medically and physically able to undergo the procedure, should be delivered no later than 6 weeks (42 days +/- 3 days) after the last dose of pembrolizumab.

6.2.11 Post-Treatment/Safety Follow-Up Visits

After the date of surgery, patients will return for clinical and laboratory assessments at 30 days (first follow-up visit), 90 days, 180 days, and 360 days (+/- 14 days) after the date of surgery. These assessments are required but imaging studies are to be ordered at the discretion of the investigator or a qualified designee.

All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Correlative blood samples will be collected at each follow-up visit. Details are provided in Section 6.0 – Trial Flow Chart

6.3 Assessing and Recording Adverse Events

6.3.1 Definitions of Adverse Events

6.3.1.1 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.

6.3.1.2 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.

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

6.3.1.4 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.

6.3.1.5 Serious

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

6.4.1.5.1 Death
6.4.1.5.2 Life-threatening adverse event
6.4.1.5.3 Inpatient hospitalization or prolongation of existing hospitalization
6.4.1.5.4 A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
6.4.1.5.5 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.

6.3.1.6 Life-threatening

An adverse event or suspected adverse reaction is considered *life-threatening* if, in the view of either the investigator or Principal Investigator, 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.

6.3.2 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:

Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or study procedure.

- **Probable** – The adverse event is likely related to the investigational agent(s) or study

procedure.

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

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:

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

6.3.3 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.

6.3.4 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).

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.

6.4.5 Expedited Reporting

6.4.5.1 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.

6.4.5.2 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.

6.4.5.3 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:

6.4.1.10.1 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.

6.4.1.10.2 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.

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.

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

6.4.1.10.3.1 Death

6.4.1.10.3.2 Life-threatening adverse event
6.4.1.10.3.3 Inpatient hospitalization or prolongation of existing hospitalization
6.4.1.10.3.4 A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
6.4.1.10.3.5 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)).

6.4.5.4 Expedited Reporting to Merck.

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

6.4.6 Definition of an Overdose for This Protocol and Reporting of Overdose to the Principal Investigator and to Merck

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

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

met.

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Principal Investigator and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX [redacted])

6.4.7 Reporting of Pregnancy and Lactation to the Principal Investigator and to Merck

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

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

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

Such events must be reported within 24 hours to the Principal Investigator and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX [redacted])

6.4.8 Immediate Reporting of Adverse Events to the Principal Investigator and to Merck

6.4.8.1 Serious Adverse Events

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

6.4.8.1.1 Results in death;
6.4.8.1.2 Is life threatening;
6.4.8.1.3 Results in persistent or significant disability/incapacity;
6.4.8.1.4 Results in or prolongs an existing inpatient hospitalization;

6.4.8.1.5 Is a congenital anomaly/birth defect;
6.4.8.1.6 Is another important medical event
6.4.8.1.7 **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.
6.4.8.1.7.1 is a new cancer (that is not a condition of the study);
6.4.8.1.7.2 is associated with an overdose.

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

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

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study, whether or not related to the Merck product, must be reported within 24 hours to the Principal Investigator and within 2 working days to Merck Global Safety.

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

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

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

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX [redacted]) at the time of submission to FDA.

6.4.8.2 Events of Clinical Interest

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

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

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

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Principal Investigator, 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.

6.4.8.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Principal Investigator within 24 hours and to Merck Global Safety within 2 working days either by electronic or paper media.

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

The Principal Investigator will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is

not progression of the cancer under study will be forwarded to Merck Global Safety as a SAE within 2 working days of determination that the event is not progression of the cancer under study

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

6.4.8.4 Evaluating Adverse Events

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

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

Table 6 Evaluating Adverse Events
An investigator, who is a qualified physician, will evaluate all adverse events as to:

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

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

Relationship	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
to Merck Product (continued)	**Dechallenge**	Was Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the product; or (3) the trial is a single-dose drug trial); or (4) product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY MERCK PRODUCT, OR IF REEXPOSURE TO MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE PRINCIPAL INVESTIGATOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency Trial Treatmen t Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or **with** toxicology?

The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

Record one of the following be	**Use the following scale of criteria as guidance (not all criteria must**	**present to be indicative of Merck product relationship).**
Yes, there is a reasonable of **possibility of Merck product relationship.**	There is evidence of exposure to Merck product. The temporal sequence The AE is more likely explained by Merck product than by another cause.	the AE onset relative to the administration of Merck product is reasonable.
No, there is not a reasonable possibility of Merck product product. **relationship**	Subject did not receive the Merck product OR temporal sequence of the the AE is more likely explained by another cause than the Merck	AE onset relative to administration of Merck product is not reasonable OR (Also entered for a subject with overdose without an associated AE.)

6.4.9 Principal Investigator Responsibility for Reporting Adverse Events

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

7.0 STATISTICAL ANALYSIS PLAN

7.1 Statistical Analysis Plan Summary

Forty evaluable subjects will be enrolled in the study. Two sequential run-in cohorts will be conducted to confirm safety, after which the remaining patients will be randomized between preoperative pembrolizumab versus preoperative pembrolizumab and SRT. The primary study endpoint is based on the anticipated degree of improvement in tumor immunogenicity as measured by the number of infiltrating CD3+ T cells/ μm^2 in the lung cancer tissue.

7.2 Statistical Analysis Plan

Sample size justification:

The sample size is based upon the anticipated number of patients who will have samples that will be useful for study of immunologic changes in the number of infiltrating CD3+ T cells/μm^2 in the lung cancer tissue between the pre-treatment (baseline) biopsy and post-treatment thoracotomy specimens.

The sample size is fixed at 40 patients. It assumes successful accrual of 6 patients from each of the two run-in cohorts and an additional 28 patients from the randomized expansion cohort, for a total of 40 patients. However, past clinical experience indicates that as many as one-third of patients may not be able to complete a new successful core needle biopsy procedure and only prior archived tissues will be available for any analysis (which may eventually turn out to be insufficient to evaluate for primary endpoint). These patients who enrolled but whose core biopsy is later found to be inadequate after initiation of therapy will be allowed to continue on the protocol but will not be included in the primary endpoint.

The null hypothesis is that a two-fold increase will be seen in 15% of the evaluable 26 patients (assuming up to one third of samples may be inevaluable for primary endpoint). The alternative hypothesis is that a two-fold increase will be seen in 40% of the evaluable 26 patients. This yields 90% statistical power, with one sided 5% alpha level based on an exact binomial test.

The goal of achieving a two-fold increase in 40% of the evaluable population is a reasonable one, as estimated from a previous study showing greater-than-three-fold increase in 57% of patients when CD3+ T cells/um^2 were measured in prostate cancer tissue treated with a cell- based cancer immunotherapy, with a null hypothesis having been set at a two-fold increase in 15% of the population (Fong 2014). The current study includes immunotherapy +/- stereotactic radiation therapy, both of which are anticipated to create increased immunogenicity against NSCLC.

It is anticipated that accrual will be completed in 10 months (4 patients per month), with each patient treated for approximately 2.5-3 months and then followed for 12 months after completing protocol therapy. Total study duration is 25 months.

A binomial exact test will be performed to compare the proportion of patients achieving a two-fold increase from baseline using a 1-sided test under the null hypothesis of 15%. Exact 95% confidence intervals will be presented with associated estimate. P <0.05 will be considered statistically significant.

8.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

8.1 Investigational Product

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

Clinical Supplies will be provided by Merck as summarized in Table 7.

Table 7 Product Descriptions

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

8.2 Packaging and Labeling Information

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

8.3 Clinical Supplies Disclosure

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

8.4 Storage and Handling Requirements

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

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

the trial site.

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

8.5 Returns and Reconciliation

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

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

9.0 ADMINISTRATIVE AND REGULATORY DETAILS

9.1 Pre-study Documentation

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

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

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

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

9.2 Institutional Review Board Approval

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

9.3 Informed Consent

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

9.4 Changes in the Protocol

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

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

9.5 Handling and Documentation of Clinical Supplies

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

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

9.6 Case Report Forms (CRFs)

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

and approve the completed CRFs.

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

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

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

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

9.7 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI- approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered "serious". The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 12.4 Data and Safety Monitoring Plan for a Phase 2 Institutional Study, for additional information.

9.8 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
- Participating Site IRB's Federal Wide Assurance 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.

9.9 Protection of Human Subjects

9.9.1 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.

9.9.2 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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APPENDIX 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.

APPENDIX 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).

APPENDIX 3 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

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

* As published in the European Journal of Cancer:

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

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

APPENDIX 4 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

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.
- Current 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 Pl signature(s) for all protocol versions.
- 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 Principal Investigator.
- MedWatch reporting to FDA and Principal Investigator.
- 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).

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).
- 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).

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

- See attached checklist(s).

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 Pl, and the IRB approval letters. All other documents in Section #2 of this policy would be the responsibility of the Participating Site(s).

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.

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

- 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 Principal Investigator, 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:
- 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 subcontract

APPENDIX 5 Data and Safety Monitoring Plan for a Phase II or III Institutional Trial

1. Oversight and Monitoring Plan

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

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

2. Monitoring and Reporting Guidelines

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

All institutional Phase II and III therapeutic trials are audited on a semiannual basis, with all data from twenty percent of the enrolled participants audited by the DSMC Monitor/Auditor. The assigned DSMC Monitor/Auditor will review no more than a total of 10 participant charts during the course of auditing this trial. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the auditing visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

Auditing of all enrolled participants in these trials will be complete after 20% of enrolled participants have been audited through five cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

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

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

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

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

3.2 Serious Adverse Event Reporting

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

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

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

UCSF IRB website for guidance in reporting serious adverse events:

https://irb.ucsf.edu/adverse-event

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

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

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

1.3 Review of Adverse Event Rates

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

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

Data and Safety Monitoring Committee Contacts:

Katie Kelley, MD (DSMC Chair)
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