TITLE:
A Phase II Study of Pembrolizumab in EGFR Mutant, Tyrosine Kinase Inhibitor Naïve Treatment Patients with Advanced Non-Small Cell Lung Cancer (NSCLC)

IND NUMBER:

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1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab in Frontline EGFR mutant, TKI-naïve NSCLC
Trial Phase	Phase II
Clinical Indication	The treatment of subjects with non-small cell lung cancer (NSCLC) whose tumors are positive for PD-L1 and harbor an EGFR mutation who have not been previously treated with an EGFR TKI
Trial Type	Interventional
Type of control	Active control without placebo
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	Pembrolizumab 200 mg every three weeks
Number of trial subjects	Approximately 25 patients will be enrolled.
Estimated enrollment period	We estimate that the trial will require approximately 16 months from the time the first subject signs the informed consent until the last subject's consent.
Estimated duration of trial	We estimate that the trial will require approximately 28 months from the time the first subject signs the informed consent until the subject's last visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified contact. After a screening phase of up to 28 days, eligible subjects will receive assigned treatment on Day 1 of the 3-week (Q3W) dosing cycle. Treatment with pembrolizumab will continue until radiographic progression, documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons. After progression on pembrolizumab, patients will be asked to undergo an additional biopsy and blood draw and be followed through periodic follow-up visits and calls (every 60 days) for evaluation of duration of response with the EGFR TKI as well as survival follow up
Estimated average length of treatment per patient	6 months

2.0 TRIAL DESIGN

2.1 Trial Design

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

This is a single-site Phase II trial of intravenous (IV) pembrolizumab in subjects with non-small cell lung cancer (NSCLC) with PD-L1 positive (≥1% by immunohistochemistry (IHC) 22C3 pharmDx test) and EGFR mutant tumors who have not been previously treated with a tyrosine kinase inhibitor (TKI). Approximately 25 subjects will be enrolled in this trial to examine the response to pembrolizumab in this TKI-naïve population. Subjects will all receive 200 mg every 3 weeks (Q3W). Assignment to pembrolizumab will be unblinded.

Subjects will be evaluated every 9 weeks (63 +/- 7 days) with radiographic imaging to assess response to treatment. All imaging obtained on study will be assessed using a modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for determination of objective response rate (ORR) and progression-free survival (PFS). Subjects will continue with the assigned study treatment until RECIST 1.1-defined progression of disease, unacceptable toxicity, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, administrative reasons, or the subject has received 35 trial treatments of pembrolizumab. Treatment may continue despite RECIST 1.1 defined progression if the subject is clinically stable and is considered to be deriving clinical benefit by the investigator. Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. After progression on pembrolizumab, patients will be asked to undergo an additional biopsy and blood draw and be followed through periodic follow-up visits and calls (every 60 days) for evaluation of duration of response with the EGFR TKI as well as survival follow up. Subjects will have post-treatment follow-up for disease status until death, withdrawing consent, or becoming lost to follow-up.

The primary objective of the trial is objective response rate (ORR) per RECIST 1.1. Safety, as assessed by a variety of parameters of adverse events (AEs), will be a secondary objective. Additional secondary objectives will be to determine ORR, PFS, and OS of subsequent EGFR TKI therapy in patients with EGFR-sensitizing mutation after pembrolizumab and to analyze tumor tissue biomarkers for potential correlation with response.

Participation in this trial will be dependent upon supplying tumor tissue from a newly obtained formalin-fixed specimen from locations not radiated prior to biopsy; no new systemic antineoplastic therapy may be administered between the PD-L1 biopsy and initiating study medication. The qualifying

biopsy does not need to be obtained after consent for this trial is signed. The specimen will be evaluated at a central laboratory or a CLIA-certified laboratory that uses the 22C3 antibody for expression status of PD-L1 in a prospective manner. Only subjects whose tumors demonstrate an EGFR mutation and PD-L1 will be eligible for this study. Any CLIA certified test to assess EGFR mutational status is acceptable.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** Determine efficacy [objective response rate (ORR)] of front-line pembrolizumab for Stage IIIB or IV metastatic EGFR mutation positive PD-L1+ (> 1% by IHC) NSCLC

Hypothesis: We hypothesize that over 26% of patients with Stage IIIB or IV EGFR mutation positive, EGFR TKI-naïve, PD-L1+ NSCLC will show a response with pembrolizumab.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: Determine safety [adverse event tabulation and grading] of front-line pembrolizumab for Stage IIIB or IV EGFR mutation positive PD-L1+ [> 1% by immunohistochemistry (IHC)]NSCLC

(2) **Objective:** Determine efficacy [progression free survival (PFS), overall survival (OS)] of front-line pembrolizumab for Stage IIIB or IV EGFR mutation positive PD-L1+ (>1% by IHC) NSCLC

(3) **Objective**: Determine ORR, PFS and OS of subsequent EGFR TKI therapy in patients with EGFR-sensitizing mutation after pembrolizumab

Hypothesis: We hypothesize that the safety, progression free survival, and overall survival among EGFR mutant patients who are EGFR TKI naïve and treated with pembrolizumab will be similar to what has been generally seen with pembrolizumab in the general population. Further, we hypothesize that the clinical outcomes from EGFR TKI treatment in patients with EGFR-sensitizing mutations after pembrolizumab will be similar to what would be expected in a treatment naïve patient population.

3.3 Exploratory Objective

(1) **Objective:** Analyze tumor tissue biomarkers for potential correlation with response

Hypothesis: We hypothesize that patients with high level of PD-L1 expression (> 50% by immunohistochemistry) are more likely to respond to an anti-PD-1 therapy.

4.0 BACKGROUND & RATIONALE

4.1 Background

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

In the United States, lung cancer is the leading cause of cancer-related deaths in both men and women with an estimated 160,340 deaths in 2012, with NSCLC comprising over 85% of all lung cancers (1). Approximately 10% of patients in Western countries have mutations in the epidermal growth factor receptor (EGFR) gene (2). These tumors are generally responsive to tyrosine kinase inhibitors (TKIs) directed against EGFR (2). Unfortunately, TKI benefits are transient, and recurrence inevitably occurs. Immunotherapies, specifically inhibitors of programmed cell death 1 (PD-1), are an emerging class of drugs that provide durable responses in some lung cancer patients (3).

Epidermal Growth Factor Receptor: Mutations and Targeted Therapies
Tyrosine kinase receptors play a major role in the tumorigenicity of neoplastic cells, particularly NSCLC (4). Up to half of NSCLC patients in Asian populations and approximately 10% in Western populations harbor EGFR mutations (5-6). To stop the proliferative signals of EGFR, TKIs such as gefitinib, erlotinib, and afatinib selectively block autophosphorylation of the EGFR intracellular tyrosine kinase domain (7). These drugs are approved in multiple countries for the treatment of locally advanced or metastatic NSCLC in 2nd or 3rd-line therapy.
Gefitinib showed superiority as a first line therapy compared to carboplatin-paclitaxel chemotherapy in progression-free survival (PFS) in EGFR mutant patients (hazard ratio (HR) for progression, 0.48; $p<0.001$) (8). As a result, EGFR TKIs have become the standard initial therapy in EGFR mutant NSCLC. Although there have been meta-analyses and subset analyses that have found improvement in survival with an EGFR TKI, individual studies have failed to show improvement in overall survival for EGFR TKIs in EGFR mutant patients, presumably based on patients in the chemotherapy arms crossing over to EGFR TKIs on progression (9).
Second generation TKIs including dacomitinib and afatinib have been evaluated (10-11). However, in approximately 60% of EGFR mutant patients, resistance is mediated by a secondary T790M mutation in EGFR, and 2nd generation agents have not been clinically successful in this setting (12).
Third generation drugs, including CO-1686 and AZD9291, have been designed to irreversibly inhibit the tyrosine kinase activity of mutant EGFR without affecting wild-type EGFR (13-15). Phase I/II trials are currently underway (NCT01526928 and NCT01802632), with preliminary data indicating over 50% objective response rate (ORR) in T790M–positive patients (16-17). However, this accounts for only a subset of patients with TKI resistance, leaving a significant proportion of patients without favorable options after progression on an EGFR TKI. Moreover, acquired resistance to these new agents is anticipated.

PD-1/PD-L1 Play a Role in Tumors Evading Immune Destruction
PD-1, encoded by the *Pdcd1* gene, is an immunoglobulin in the CD28 family. PD-1 is a type I transmembrane glycoprotein containing an extracellular Ig variable-type (V-type) domain involved in

ligand binding and a cytoplasmic tail involved in intracellular signaling. The cytoplasmic tail contains an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM) (18). Ligand binding to PD-1 induces recruitment of SHP-1 and SHP-2 to the ITSM motif, causing de-phosphorylation of CD3ζ, PKCθ, and ZAP70, which are involved in the CD3 T cell-signaling cascade (19-20).

One mechanism by which cancer cells evade immune surveillance is up-regulation of the ligand PD-L1, the binding partner of PD-1. PD-1 is expressed by CD4+ and CD8+ T cells, B cells, Tregs, and NK cells (21). In T cells, binding of PD-1 with PD-L1 (or its other ligand, PD-L2) conveys a signal to the T cell that down-regulates activation, preventing destruction of the antigen-presenting cell. Under healthy conditions, PD-L1 attenuates unwanted immune responses, such as autoimmunity (22).

Cytokines Can Create a Permissive Environment for Tumors

Cytokines are a group of small proteins released from cells that direct effects through autocrine or paracrine signaling mechanisms. Cytokines predominantly modulate the immune system by activating or inhibiting immune cells. When investigating the mechanism of PD-1 inhibition in cytotoxic T-lymphocytes (CTLs), cytokines of interest, such as IL-6 and TGF-β, have been implicated in creating a permissive microenvironment, including EGFR mutant NSCLC (23). For L858R tumors in mouse models, it was concluded that upregulation of IL-6 and TGF-β assisted in cell proliferation (23). TGF-β has also been implicated as an inducer of epithelial-mesenchymal transition (EMT), which is associated with inhibition of CTL-mediated tumor cell lysis, possibly by overexpression of PD-L1, in tumors exhibiting EMT (24-26).

Anti PD-1/PD-L1 Immunotherapy Have Led to Durable Responses in NSCLC

Since T lymphocytes recognize antigens derived from cellular compartments that are presented on the surface of tumor cells, T cells are a major focus in cancer immunotherapy (27). Recently, immunotherapies have shown promise in the treatment of a variety of cancers including NSCLC (28). These treatments act to disrupt immunosuppressive checkpoints, including PD-1/PD-L1, that are believed to play important roles in prevention of autoimmune responses but also allow tumors to evade destruction by the immune system (29).

Several monoclonal antibodies inhibiting PD-1 are currently in clinical development, including nivolumab (BMS936558) and pembrolizumab (MK-3475; lambrolizumab) (3, 30-31). We demonstrated safety and efficacy of pembrolizumab in previously treated NSCLC patients, with ORR of 20% (3). Similar results were seen with nivolumab (28). Response durations have been ongoing for more than 1 year. Recent data from the KEYNOTE 024 study has shown that front line treatment with pembrolizumab significantly improved progression free survival as well as overall survival in patients with PD-L1 positive (>50%) non-small cell lung cancer as compared to platinum based chemotherapy. Patients with EGFR mutations were excluded from this study. (37).

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.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor. Keytruda™ (pembrolizumab) has also been granted accelerated approval by the United States Food and Drug Administration to treat patients with metastatic non-small cell lung cancer (NSCLC) whose disease has progressed after other treatments and with tumors that express PD-L1 protein.

4.1.2 Preclinical and Clinical Trial Data

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

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Although tyrosine kinases directed against EGFR have revolutionized the care of patients with EGFR mutant tumors, progression is generally seen after approximately a year, and the benefit of newer inhibitors at the time of progression is generally less than a year. PD-1 inhibition is a promising option for NSCLC patients, but an optimal strategy in EGFR mutant patients has been elusive. The rationale for treating TKI naïve patients is corroborated by laboratory studies demonstrating that cell lines treated with EGFR TKIs have lower PD-L1 expression levels (33). PD-L1 expression has been positively correlated with benefit (34).

This trial could lead us to reevaluate the standard-of-care for non-small cell lung cancer (NSCLC) patients with mutations in EGFR. Programmed cell death-1 (PD-1) inhibitors have shown significant potential to induce durable responses in NSCLC. To date, responses have been less frequent in patients harboring EGFR mutations, although responses are seen (34). Predictors of response in this group are unclear. Although studies are being conducted in which EGFR mutant patients are given EGFR tyrosine kinase inhibitors (TKIs) and PD-1 inhibitors, the schemas are based on established clinical pathways (EGFR TKIs first) rather than objective preclinical and clinical data. It is not clear that the best strategy is to treat EGFR mutant patients with an EGFR TKI prior to a PD-1 inhibitor, and in addition, approximately 10% of EGFR mutant patients do not have a mutation that is sensitive to available EGFR TKIs. In a retrospective analysis in the BRAF-mutant melanoma population (a somewhat similar

clinical scenario), prior treatment with immunotherapies did not adversely impact response to BRAF inhibitors, while outcomes of immunotherapy following BRAF inhibition were poor (35).

Data from the KEYNOTE-001 trial revealed that prior TKI therapy in NSCLC EGFR mutant patients was strongly correlated with a lack of response to PD-1 inhibitor therapy (34). In contrast, out of the 29 EGFR mutant patients treated at UCLA, 2 of 3 EGFR TKI naïve patients had a partial response to pembrolizumab compared to only 1 of 26 patients who had been previously treated with an EGFR TKI. The only patient with a prior EGFR TKI who responded to pembrolizumab had an EGFR mutation that is typically not sensitive to available EGFR TKI's. In addition, based on our data from the clinical experience through the KEYNOTE 001 trial, when analyzing response in our EGFR mutant patients treated with an anti-PD-1 immunotherapy (N=29) and the subset who received a 9 week scan (N=18), response was significantly more favorable in those who did not receive a prior EGFR TKI in both subgroups ($p<0.001$).

Overall EGFR MT Population	PR	SD/PD	
No TKI	2	1	3
TKI	1	25	26
Total	3	26	29

EGFR MT/9 Week Scan	PR	SD/PD	
No TKI	2	0	2
TKI	1	15	16
Total	3	15	18

Of the 18 patients with 9 weeks scans, two EGFR mutant patients who were TKI-naïve were enrolled, one with a L858R mutation (enrolled prior to an amendment excluding such patients prior to an EGFR TKI) and one with an exon 20 insertion (generally EGFR TKI resistant). Both patients achieved a partial response (PR) according to RECIST 1.1. Only one of the 16 EGFR mutant patients (the patient had an exon 20 insertion) who received prior TKI treatment achieved a PR. A similar correlation was not seen when EGFR wild type patients were evaluated based on whether they were treated with an EGFR TKI.

In order to corroborate the results from the clinical trial, we conducted cell line experiments to evaluate potential immunomodulatory effects of EGFR TKIs, particularly with respect to the PD-1 pathway (Figure 1). Afatinib, an irreversible pan-HER inhibitor is associated with an $IC_{50} < 1\mu M$ in H1975, HCC827 and Calu-3. Erlotinib, a reversible EGFR inhibitor, inhibits only HCC827 at this level. Neither TKI inhibits H460 at this level. The cell lines that were effectively inhibited by the EGFR TKI also saw a decrease in PD-L1 levels, confirming results from others (23). When studying TKI-resistant, non-small cell lung cancer cell lines, PD-L1 expression was not reduced by EGFR TKIs. The results mimic what we saw clinically, in which pembrolizumab was not an effective therapy in patients with EGFR sensitizing mutations after a prior EGFR TKI.

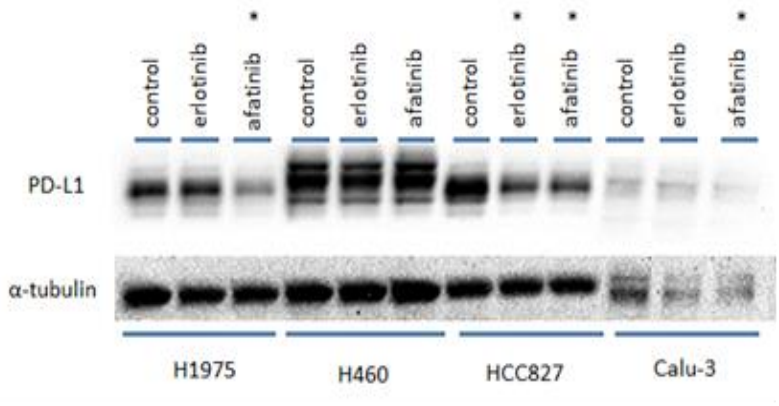

Figure 1: Western blot analysis of PD-L1 expression (PD-L1 mAb #13684, Cell Signaling Technology) in NSCLC cell lines in response to erlotinib and afatinib. NSCLC cell lines H1975 (EGFR L858R/T790M mutation), H460 (KRAS Q61H mutation), HCC827 (EGFR exon 19 deletion), and Calu-3 (*her2* amplification) were evaluated at baseline and after 24 hours of exposure to 1 μM erlotinib or afatinib. * indicates an $IC_{50} < 1\mu M$ for the respective drug in that cell line.

Data from the KEYNOTE 024 trial showed that first-line treatment with pembrolizumab significantly improved progression-free and overall survival in patients with PD-L1 positive (>50%) non-small cell lung cancer. Pembrolizumab was also associated with a higher overall response rate and a longer duration of response than platinum-based chemotherapy. Patients with EGFR mutations were excluded from this study (37).

This study will be the first to our knowledge to evaluate the role of PD-1 inhibitors in EGFR mutant patients who have not yet received an EGFR TKI. After progression on pembrolizumab, patients will be asked to undergo an additional biopsy and blood draw and be followed through periodic follow-up visits and calls (~every 2 months) for evaluation of duration of response with the EGFR TKI as well as survival follow up. The goal of this clinical trial is to evaluate a treatment sequence in which EGFR mutant NSCLC patients receive pembrolizumab prior to an EGFR TKI.

4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) was conducted to evaluate the safety and clinical activity of single agent pembrolizumab (34). 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 (34). All three dose levels were well tolerated and no dose-limiting toxicities were observed (34). This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No maximum tolerated dose (MTD) has been identified to date Recent data from other clinical studies within the pembrolizumab program has shown that a lower dose of pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of pembrolizumab 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 pharmacodynamics data provides scientific rationale for using 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 pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. pembrolizumab has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 200 mg Q3W. 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 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.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The primary endpoint will be objective response rate (ORR), while the secondary endpoints will be progression-free survival (PFS) and overall survival (OS). The rationale for using ORR as the primary endpoint is that this trial is a single-arm trial; assessing ORR will allow us to attribute the effect of treatment directly to pembrolizumab, not to the natural history of NSCLC.

Since ORR cannot comprehensively measure drug activity, PFS and OS will be used as secondary endpoints. This will allow us to account for deaths that are unrelated to cancer and to the effects of pembrolizumab. PFS is an acceptable measure of clinical benefit for a Phase 2 trial that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of effect is large and the therapy has an acceptable risk-benefit profile. Furthermore, it is an endorsed regulatory endpoint for 1L NSCLC trials with recent FDA and EMA approvals including the EGFR inhibitors afatinib and erlotinib. PFS will be assessed by RECIST 1.1 by an independent central radiologists' review. Although PFS assesses how long a patient is on trial without progressing, since we have seen that EGFR mutant patients have

a high response rate, we will also collect OS data to determine if pembrolizumab is comparable to TKI therapy or standard of care chemotherapy. Further, OS is a standard assessment of clinical benefit in subjects with advanced or metastatic NSCLC. OS will be assessed by RECIST 1.1 criteria by independent central radiology review.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Refer to sections 5.1.2 and 5.1.3 of the protocol for more detailed information.

5.1.2 Subject Inclusion Criteria

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

1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (PHI).

2. Be ≥18 years of age on day of signing informed consent.

3. Have a life expectancy of at least 3 months.

4. Have a histologically or cytologically confirmed diagnosis of Stage IIIB or IV non-small cell lung cancer (NSCLC) and have at least one measurable lesion as defined by modified RECIST 1.1. The target lesion(s) should also have bi-dimensional measurability for RECIST 1.1 evaluation on study.

5. Have an EGFR mutation (sensitizing or non-sensitizing) as determined by any CLIA certified laboratory.

6. Have a performance status of 0 or 1 on the ECOG Performance Scale.

7. Have adequate organ function

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)

Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated using the standard Cockcroft and Gault equation.	

8. Have provided tissue for PD-L1 biomarker analysis from either a newly obtained or archival formalin fixed tumor tissue from a biopsy of a tumor lesion not previously irradiated for analysis of PD-L1 expression. The tissue sample must be received and evaluated by the study site prior to start of treatment. Fine needle aspirates are not acceptable. Needle or excisional biopsies, or resected tissue is required.

9. Have a PD-L1 positive (either strongly or weakly) tumor as determined by the IHC 22C3 pharmDx test at the study site. If a patient's initial tumor specimen is not classified as PD-L1 positive a newly obtained specimen (different from the sample previously submitted) may be submitted for testing. If the newer specimen is classified as PD-L1 positive by the study site, the patient meets this eligibility criterion. Positivity can either be determined at the central laboratory or at any CLIA-certified laboratory using the 22C3 antibody.

10. Have resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except alopecia). If subject received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention.

11. Female subject of childbearing potential has a negative urine or serum pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the subject to be eligible.

12. Female subjects may be enrolled in the trial if they are:
    -of non-childbearing potential which is defined as a woman who is postmenarcheal, has not reached a postmenopausal state (at least 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
    -of childbearing potential who are willing to use either 2 adequate barrier methods or a barrier method plus a hormonal method of contraception to prevent pregnancy, or to abstain from heterosexual activity throughout the trial, starting with the screening visit (Visit 1) through 120 days after the last dose of pembrolizumab.
13. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

5.1.3 Subject Exclusion Criteria

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

1. Has received prior therapy with an EGFR tyrosine kinase inhibitor (such as erlotinib, gefitinib, afatinib, rociletinib, or AZD9291) for NSCLC.

2. Is currently participating or has participated in a study of an investigational agent or using an investigational device within 30 days of the first dose of trial treatment. The 30 day window should be applied to the last dose of an antineoplastic investigational agent or last use of an investigational device with antineoplastic intent.

3. Is receiving systemic steroid therapy within three days prior to the first dose of trial treatment or receiving any other form of immunosuppressive medication (corticosteroid use on study for management of ECIs is allowed).

4. Is expected to require any other form of systemic or localized antineoplastic therapy while on trial (including maintenance therapy with another agent for NSCLC or radiation therapy).

5. Has received prior systemic cytotoxic chemotherapy, antineoplastic biological therapy (e.g., cetuximab), major surgery within 3 weeks of the first dose of trial treatment; received thoracic radiation therapy of > 30 Gy within 6 months of the first dose of trial treatment.

6. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways). Has participated in another pembrolizumabclinical trial.

7. Has a known history of prior malignancy that in the opinion of the investigator interferes with the ability to interpret the radiographic results (e.g. a second active malignancy with some lesions being of uncertain origin).
8. Subjects with central nervous system (CNS) metastases and/or carcinomatous meningitis may participate provided they are clinically stable, and are using no steroids for at least seven days prior to study medication.

9. Has an active autoimmune disease, or a documented history of autoimmune disease that required systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be exception to this rule. Subjects that require inhaled steroid or local steroid injections will not be excluded from the study. Subjects with hypothyroidism who are stable on hormone replacement will not be excluded from the study.

10. Has had an allogeneic tissue/solid organ transplant.

11. Has interstitial lung disease or a history of pneumonitis that required oral or intravenous glucocorticoids to assist with management. Lymphangitic spread of the NSCLC is not exclusionary.

12. Has received or will receive a live vaccine within 30 days prior to the first administration of study medication. Seasonal flu vaccines that do not contain live virus are permitted.

13. Has an active infection requiring intravenous systemic therapy.

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

15. Has known active Hepatitis B or C. Active Hepatitis B is defined as a known positive HBsAg result. Active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay.

16. 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.

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

18. Is, at the time of signing informed consent, a regular user (including "recreational use") of any illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol).

19. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit (Visit 1) through 120 days after the last dose of pembrolizumab.

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 Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental

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

5.2.1 Dose Selection/Modification

5.2.1.1 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.

5.2.1.2 Dose Modification

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.6.1 for supportive care guidelines, including use of corticosteroids.

Table 3

Dose Modification Guidelines for Drug-Related Adverse Events

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

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

AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.

Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

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

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

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

5.3 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.3.1 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.

5.3.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy

- Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.

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

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

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.

5.4 Rescue Medications & Supportive Care

5.4.1 Supportive Care Guidelines

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

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance. 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.

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.

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

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

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

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

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

- **Hypophysitis**:

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

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

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

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

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

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

  Table 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 4 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	**Treatment**	**Premedication at subsequent dosing**
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds	**Stop Infusion and monitor symptoms.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	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.**	of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
<u>Grades 3 or 4</u> Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g.,	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	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.		

5.5 Diet/Activity/Other Considerations

5.5.1 Diet

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

5.5.2 Contraception

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.2-Reporting of Pregnancy and Lactation to UCLA DSMB. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.5.3 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 study site's Data Safety Monitoring Board without delay 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 UCLA Data Safety Monitoring Board (DSMB). If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the UCLA DSMB and followed as described above and in Section 7.2.2.

5.5.4 Use in Nursing Women

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

5.6 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 UCLA DSMB 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:

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

  Note: For unconfirmed radiographic disease progression, please see Section 5.2.2

  Note: A subject may continue on treatment with confirmed radiographic progression if clinically stable or clinically improved. Unacceptable adverse experiences as described in Section 5.2.1.2

- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment

- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.

  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.5

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). 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.

5.6.1 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.5.5.

5.7 Subject Replacement Strategy

A subject that discontinues from the trial will not be replaced.

5.8 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:	**Screening Phase**	**Treatment Cycles[a]**								**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:		1	2	3	4	To be repeated beyond 8 cycles 5	6	7	8	Discon	Safety Follow-up Visits[b]		Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	3 months post tx	6 months post tx	Approx.Q 2 months
Administrative Procedures													
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Demographics and Medical History	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X
Trial Treatment Administration		X	X	X	X	X	X	X	X				
Post-study anticancer therapy status										X	X	X	X
Survival Status										X	X	X	X
Clinical Procedures/Assessments													
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X

Trial Period:	**Screening Phase (Visit 1)**	**Treatment Cycles[a]**								**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:		1	2	3	4	To be repeated beyond 8 cycles 5	6	7	8	Discon	Safety Follow-up Visits[b]		Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	3 months post tx	6 months post tx	Approx.Q 2 months
Full Physical Examination	X												
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X												
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory													
Pregnancy Test – Urine or Serum □-HCG	X												
PT/INR and aPTT	X	X	X	X	X	X	X	X	X	X			
CBC with Differential	X	X	X	X	X	X	X	X	X	X			
Comprehensive Serum Chemistry Panel	X	X	X	X	X	X	X	X	X	X			
Urinalysis	X	X	X	X	X	X	X	X	X	X			
T3, FT4 and TSH	X	X	X	X	X	X	X	X	X	X			
Efficacy Measurements													

Trial Period:	**Screening Phase** (Visit 1)	**Treatment Cycles[a]**								**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:		1	2	3	4	To be repeated beyond 8 cycles 5	6	7	8	Discon	Safety Follow-up Visits[b]		Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	3 months post tx	6 months post tx	Approx.Q 2 months
Tumor Imaging	X				X			X		X	X	X	X
Brain Imaging	X[1]												
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood													
Archival or Newly Obtained Tissue Collection[2]	X									X[3]			
Correlative Studies Blood Collection		X	X	X						X			

1. Brain imaging needed if clinically indicated
2. If patient has not had a biopsy or if tissue is exhausted, patient must undergo a new biopsy for the trial
3. Patient has the option of undergoing an additional biopsy at end of treatment.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the 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 UCLA DSMB requirements.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

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

7.1.1.4.2 Concomitant Medications

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

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

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

7.1.1.5.2 Prior Treatment Details

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

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

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

7.1.1.6 Assignment of Screening Number

Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects. Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

7.1.1.7 Assignment of Randomization Number

Once an allocation number is assigned to a subject, it can never be re-assigned to another subject. A single subject cannot be assigned more than 1 allocation number. Note: although this is described as a "randomization number," this study is not randomized.

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

Interruptions from the protocol specified treatment plan for greater than 18 weeks between pembrolizumab doses due to toxicity will require written documentation on subject management.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (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.

7.1.2.2 Full Physical Exam

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

7.1.2.3 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.

7.1.2.4 Vital Signs

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

7.1.2.5 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.

7.1.2.6 12-Lead ECG

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

7.1.2.7 Tumor Imaging and Assessment of Disease

Subjects will be evaluated every 9 weeks (63 +/- 7 days) with radiographic imaging to assess response to treatment. All imaging obtained on study will be assessed using a modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for determination of objective response rate (ORR) and progression-free survival (PFS). Subjects will continue with the assigned study treatment until RECIST 1.1-defined progression of disease, unacceptable toxicity, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, administrative reasons, or the subject has received 35 trial treatments of pembrolizumab. Treatment may continue despite RECIST 1.1 defined progression if the subject is clinically stable and is considered to be deriving clinical benefit by the investigator. For further information, see Appendix Section 13.3.

7.1.2.8 Brain Imaging

For patients who have prior history of brain metastases, screening brain imaging will need to be obtained. MRI is the preferred imaging modality.

7.1.2.9 Tumor Tissue Collection and Correlative Studies Blood Sampling

For the first three cycles, prior to treatment, 100 mL of additional blood/serum will be collected for correlative research studies. These samples may be collected up to three days prior to treatment. An additional sample of 100mL of blood/serum will also be collected at the time of progression. All blood drawn must begin processing a maximum of two hours after being drawn. Samples from patients at sites close enough to UCLA to allow blood processing within two hours will be couriered for processing. Sites that are not near enough to allow blood processing within two hours at UCLA will process the correlative blood samples themselves. Sample collection, and storage instructions for serum samples will be provided in the lab manual.

7.1.3 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)*	Total triiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free thyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or bicarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

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

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results from the C1D1 tests and C1D1 of Second Course Phase are for information only and do not need to be checked prior to therapy. Other results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.5. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

7.1.4.2 Blinding/Unblinding

7.1.5 Visit Requirements

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

7.1.5.1 Screening

7.1.5.1.1 Screening Period

Approximately 28 days prior to start of treatment, potential subjects will be evaluated to determine that they fulfill the entry requirements. Screening procedures may be repeated after consultation with the UCLA DSMB.

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

- Laboratory tests are to be performed within 10 days prior to the first dose of trial treatment.
- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required.
- Tumor imaging must be performed within 30 days prior to the first dose of trial treatment.

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

7.1.5.2 Treatment Period

Visit requirements are outlined in Section 6.0 - Trial Flow Chart.

7.1.5.3 Post-Treatment Visits

The discontinuation visit should be conducted approximately within 28 +/- 7 days after the last dose of trial treatment or before the initiation of a new antineoplastic treatment, whichever comes first.

7.1.5.4 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-up Phase and should continue to be assessed every 9 weeks (63 ± 7 days) by radiologic imaging to monitor disease status. Follow-up Visit 1 should be scheduled 3 months after the last dose of trial treatment. Assessment for drug-related immune-related adverse events should occur at Follow-up Visit 1. Follow-up Visit 2 should occur 6 months after the last dose of trial treatment. After Follow-up Visit 2 subjects should continue to be assessed every 9 weeks (63 ± 7 days) by radiologic imaging to monitor disease status and initiation of new antineoplastic therapy. Unless otherwise noted in the flow chart, every effort should be made to collect subject information on the start of new tyrosine kinase inhibitor therapy in patients harboring EGFR-sensitizing mutations, disease progression, and death.

7.1.5.4.1 Survival Follow-up

Once a subject completes the follow-up visits, the subject moves into the survival follow-up phase and should come in for a visit (approximately every 2 months) for survival status and to receive scans until death, withdrawal of consent, or the end of the study, whichever occurs first. It is recognized that based on variability of post-study management, the frequency of this visit is anticipated to vary significantly. In patients for whom follow up is less frequent than every 3 months, we will call patients to evaluation vital status, and whether they are currently on an EGFR-TKI.

7.1.5.5 Second Course Phase

Subjects may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase if the treating investigator believes that the patient will benefit from the Second Course Phase. Patients will not need to be re-registered or re-screened in order to participate.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal

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

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

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

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

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

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

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1.

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the UCLA DSMB 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 UCLA DSMB and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.2 Reporting of Pregnancy and Lactation to UCLA DSMB and to Merck

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

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

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

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

7.2.3 Immediate Reporting of Adverse Events to UCLA DSMB and Merck

7.2.3.1 Serious Adverse Events

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

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

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

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

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

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the UCLA DSMB and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-993-1220).

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

For the time period beginning at treatment allocation/randomization through 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 Sponsor and within 24 hours to Merck Global Safety.

. Events of clinical interest for this trial include:

1. An overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose, that is not associated with clinical symptoms or abnormal laboratory results.

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

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Section 7.2.3.- Immediate Reporting of Adverse Events to the Sponsor and to Merck, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Sponsor within 24 hours and to Merck Global Safety within 2 working days either by electronic or paper media.

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

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

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

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. 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.

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

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 thathas 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 pembrolizumab 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 definitions, is reportable to the Sponsor within 24 hours and to Merck withint 2 working days to meet certain local requirements.); or	

	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor and to Merck within 2 working days.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Merck product to be discontinued?	
Relationship to Merck Product	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck Product	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve?

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

7.2.5 Responsibility for Reporting Adverse Events

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

8.0 DATA AND SAFETY MONITORING PLAN

8.1 JCCC DSMB Oversight

This trial will be overseen by the JCCC DSMB. The JCCC DSMB meets monthly to review all SAE reports for trials overseen by the JCCC DSMB. All SAE reports, which have been filed since the previous meeting, are presented to the committee for review.

For trials overseen by the JCCC DSMB, the DSMB reviews all dose-limiting toxicities (DLTs) for dose-escalation studies. Protocol suspensions and re-opening of accrual to the next cohort based on DLT evaluation fall under the purview of the DSMB.

For all JCCC oncology trials and TRIO-US studies where the JCCC DSMB has primary oversight, all SAEs shall be reported to the JCCC DSMB in a timely manner [ten days, two days for a death] regardless of relationship and expectedness. The JCCC ORC will review all submissions and the ORC staff will enter the information into the JCCC Clinical Trials database. Reports are generated for full JCCC DSMB review. For trials where the JCCC DSMB has primary DSMB review responsibility, the DSMB requires that the PI generate cumulative adverse event reports for quarterly, biannual or annual review.

The DSMB reviews each SAE report and determines whether or not protocol modifications are warranted to ensure subject safety. In this review, prior occurrences of similar toxicity with the therapy under study are taken into consideration, as well as the severity of the event and the likelihood that it was related to a study drug. The DSMB may recommend no changes to the study if the event is expected or related to other causes such as the subject's underlying condition. The DSMB may request an expert's advice of another non-Principal Investigator with national experience to support their deliberations and decisions.

The JCCC DSMB has the authority to recommend to the UCLA IRB the immediate halt to a study (i.e., discontinuation of any further treatment of enrolled subjects and discontinuation of enrollment of new subjects) should there be any serious unexpected toxicity that warrants further investigation.

Requests for single subject exceptions/waivers from the approved study protocol, including out of window procedures and eligibility deviations, must be reviewed and approved by a member of the DSMB. Each trial is assigned a primary and secondary reviewer who is responsible for reviewing each exception/waiver request for that trial. Approvals and disapprovals of the request are sent to the Principal Investigator via email and copied to the UCLA IRB. Requests for single subject exceptions/waivers are made by the Principal Investigator via email utilizing the "Single Subject Exception Request Form."

JCCC DSMB correspondences are addressed to the Principal Investigator and copied to the UCLA IRB. Minutes of the DSMB meetings are maintained in a computer file.

Confidentiality: Each member of the JCCC DSMB is responsible for maintaining strict confidentiality of the study data. Members will not share any study data or information about the study with any individual external to the JCCC DSMB or the statistical working group for the study. The DSMB members may contact the statistical working group directly with questions regarding the operational details associated with the data analysis and summary presentations. Communication of deliberations or recommendations of the JCCC DSMB, either written or oral, should not be made outside of the Committee or the statistical working group. Outcome results are strictly confidential and must not be divulged to any non-member of the JCCC DSMB except in those cases where DSMB is required to inform the UCLA IRB of its determinations. Disclosure of outcome results to the IRB must only occur with written approval of the DSMB. A member who believes he or she may have a potential intellectual or financial conflict of interest during the course of review of the data must inform the chairperson of the DSMB. In such case, the meeting minutes will record the disclosure of the potential conflict of interest and that the individual recuse himself from the discussions and abstains from voting on the DSMB decision.

8.2 Assignment of Risk – Level 2

All interventional clinical trials undergo scientific review by the Internal Scientific Peer Review Committee (ISPRC) which requires that a Data and Safety Monitoring Plan is in place before a trial can be approved to begin. For trials overseen by the JCCC DSMB, the JCCC DSMB will determine the degree of risk of the study and will ensure that there are procedures in place to ensure the safety of the subjects that are enrolled in the trial. The intensity level of study oversight is determined by the risk category. Some of the factors that are considered when assigning the Level of Risk category include:

- A biostatistical design and appropriate procedures for proper data management so that the information collected can be properly validated.
- Appropriate Serious Adverse Event reporting procedures must be in place.
- The study duration must be appropriate and must be based on a realistic rate of enrollment.
- Data collection and data management must be adequate to verify and ensure subject eligibility.

8.2.1 Assignment of Risk

This protocol is assigned a Level 2 Risk. Assigning risk ensures that the data and safety monitoring is based on the level of risk (low, medium, or high) to ensure that the data and

safety monitoring activities are appropriate. Level 2 Risk assignment includes the data and safety monitoring activities listed below:

- Compliance Officer meets with PI/Staff prior to study initiation; review regulatory requirements and operating system. Compliance Officer provides real time monitoring to determine eligibility prior to enrollment onto the protocol.
- Real time QA monitoring of the subjects and data collection occurs for all subjects entered onto the trial.
- Comprehensive QA auditing within first year or first 10 subjects enrolled, whichever comes first. Subsequent audit frequency will be annually.
- Frequency of DSMB Summary Report is typically on a biannual basis or approximately every six months.

8.3 Monitoring and Auditing Activities

The compliance officer of the JCCC Office of Regulatory Compliance [ORC] will monitor and audit the clinical records for all human subjects enrolled onto JCCC trials overseen by the JCCC DSMB. The JCCC compliance officer will perform real time review of informed consent processes and the meeting of all inclusion and exclusion criteria and screening results at study entry. Active monitoring will offer the JCCC study teams prospective information that can be used to enhance the quality of research being performed contemporaneously. Auditing is a review of historic performance of the research effort and is performed on case report forms, regulatory files and source documents to measure the quality of the research effort in a retrospective manner.

9.0 STATISTICAL ANALYSIS PLAN

9.1 Efficacy Endpoints

Primary

The primary efficacy analyses will be based on the Full Analysis Set (FAS). Patients with measureable disease at baseline who received at least one dose of study treatment will be included in the FAS. The primary efficacy endpoint is objective response rate (ORR) and will be determined by blinded central review. We will use an exact binomial test to evaluate the response rate to the null hypothesis value of 0.10.

Response duration is defined as the time from first documented evidence of response until progression, according to RECIST 1.1. Objective response rate is determined as the proportion of patients achieving complete response (CR) or partial response (PR) as respectively defined in RECIST 1.1. A 95% confidence interval will be provided for the objective response rate of the population. All patients

receiving at least one dose of pembrolizumab will be considered evaluable for efficacy and toxicity.

Secondary

Secondary efficacy endpoints, progression free survival and overall survival, will also be analyzed. Per RECIST 1.1, progression free survival (PFS) is defined as time from randomization to first documented progression and overall survival (OS) and is defined as time from randomization to death by any cause.

For patients harboring EGFR-sensitizing mutations, PFS, ORR, OS following TKI therapy will be assessed and analyzed against data on treatment-naïve EGFRm NSCLC treated with TKI as control.

9.2 Safety Endpoints

Safety measurements are described in section 7

9.3 Responsibility for Analyses

The statistical data obtained from this study will be the responsibility of Dr. Garon and the clinical biostatisticians in the UCLA Department of Medicine Medical Statistics Core.

9.4 Hypothesis / Estimation

Objectives and hypotheses of the study are stated in Section 3.0. The study is considered positive and to have met its primary efficacy endpoint if anti-tumor response rate of pembrolizumab meets or exceeds 26% (see sample size and power explanation below). The null hypothesis is derived from subpopulation data describing response rate in EGFR mutation positive NSCLC treated with TKI prior to single-agent pembrolizumab on KEYNOTE-001 study which is <8% in this population (36). Our study conservatively sets the null hypothesis at 10% objective response rate.

9.5 PD-L1 Biomarker

Pearson correlation will evaluate correlation between PD-L1 expression in tumor samples and percent decrease in tumor volume following therapy. When the sample size is 25, the linear regression test for the Pearson correlation will have 80% power to detect a correlation of at least 0.51 assuming a two-side 0.05 level of significance.

We will evaluate the relationship between PD-L1 expression at baseline with clinical outcomes using regression models. For PFS and OS we will use Cox-proportional hazards regression.

A futility analysis will be conducted after nine patients with ≤50% PD-L1 expression (i.e. 1-49%) reach their first set of scans. If all nine patients have failed to respond to therapy, we will revise the protocol to restrict the study population to patients with PD-L1 staining of >50%. Based on data to date, a response rate that low would not be anticipated for patients with >50% PD-L1 expression.

9.6 Sample Size and Power Calculations

With 25 TKI-naïve patients treated at 200mg q3w, an exact binomial test with a nominal 0.10 one-sided significance level will have 81% power to detect the difference between the Null hypothesis response rate of 10% and the Alternative hypothesis rate of 26%.

10.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

10.1 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

10.2 Packaging and Labeling Information

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

10.3 Clinical Supplies Disclosure

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

10.4 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.

10.5 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.

11.0 ADMINISTRATIVE AND REGULATORY DETAILS

11.1 Confidentiality

11.1.1 Confidentiality of Data

The investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

11.1.2 Confidentiality of Subject Record

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

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

11.1.3 Confidentiality of Investigator Information

The investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. Name, address, telephone number and e-mail address;

2. Hospital or clinic address and telephone number;

3. Curriculum vitae or other summary of qualifications and credentials; and

4. Other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. The investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

11.2 Compliance with Financial Disclosure Requirements

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

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

11.3 Compliance with Law, Audit and Debarment

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

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

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

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

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

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

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

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

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

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

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

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

11.4 Compliance with Trial Registration and Results Posting Requirements

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

11.5 Quality Management System

The investigator agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial. Clinical Research Unit of UCLA's Jonsson Comprehensive Cancer Center already has SOPs.

11.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. The investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate. Detailed information regarding Data Management procedures for this protocol will be provided by the Sponsor.

11.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

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

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically

for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

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

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13.0 APPENDICES

13.1 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.	

13.2 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)

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

RECIST v1.1 Tumor Assessment Worksheet Instructions

1. Refer to the protocol for specific tumor assessment requirements noting:
    a. any protocol specific modifications to RECIST v1.1 criteria – be sure to incorporate these into your assessment (i.e., imaging modality)
    b. screening window for tumor assessment
    c. time-points/windows/frequency of tumor assessments during treatment and follow-up when applicable
        - determine time-point that first assessment is to be done, i.e.,: 6 weeks from randomization date or 6 weeks from C1D1 (+/- 7days)
2. Standard method of assessment for RECIST v1.1 remains grounded in the anatomical assessment of disease by contrast CT of Chest, Abdomen, and Pelvis, and CT or MRI of brain when clinically indicated. If contrast CT is contraindicated, then a non-contrast CT of Chest and MRI of Abdomen and Pelvis should be done. Functional imaging or FDG-PET is not an acceptable method of tumor assessment per RECIST v1.1 criteria; rather it is used as an adjunct to determination of disease progression. Bone scan or plain films are not considered adequate imaging techniques to measure bone lesions; however these techniques can be used to confirm the presence or disappearance of bone lesions. Imaging based evaluation should always be done rather than clinical exam unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.
3. Radiologist should provide a thorough baseline assessment of all sites of disease, non-nodal and nodal, along with the longest diameter in mm of non-nodal disease and the short axis measurement in mm of nodal disease. Non-disease findings should also be documented in the radiology report and noted in the investigator's note (i.e.: simple cyst, fatty tissue).
4. Using the radiologist's assessment, the investigator should select a total of ten (10) target lesions (TL) with a maximum of five (5) lesions per organ on the basis of their size, be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. All other sites of disease should be identified as non-target lesions (NTL). The investigator should document his/her choice and rationale for selection of lesions for baseline assessment of overall tumor burden to be assessed for response. ***Note:*** You may record multiple non-target lesions involving the same organ as a single NTL on the form, i.e.: multiple bone mets, multiple liver mets; multiple enlarged pelvic lymph nodes.
    a. **Target Lesions (TLs)** are defined as non-nodal lesions with a minimum ***longest diameter (LD)*** of≥10mm by CT/MRI; 10mm caliper measurement by clinical exam (documented with photo and ruler); ≥20mm by chest X-ray (For the purpose of this study, CT is preferred); and lymph nodes ≥15mm in the ***short axis (SA)***. **Note:** Measure the longest diameter of the node first. Then determine the longest dimension perpendicular to the longest diameter and report that measurement as the short axis. (For example: a cervical lymph node is reported as being 17mm x 22mm. The SA

measurement would be 17mm). ***Note:*** Lytic or mixed lytic-blastic bone lesions with identifiable soft tissue components that can be evaluated by CT/MRI and meet the definition of measurability can be considered as measurable lesions

b. **Non-Target Lesions (NTLs)** are defined as non-measurable and include: any measurable lesions that were not selected as target lesions; non-nodal lesions <10mm in ***longest diameter***; lymph nodes that have a ***short axis*** ≥10mm and <15mm ***Note:*** SA nodal non-target lesion must have a reduction in SA to <10mm to be considered a CR; therefore, documenting nodal non-target lesions SA is recommended. ; blastic bone lesions, lytic or mixed lytic-blastic lesions without an identifiable soft tissue component that meets the definition of measurable, and lesions considered truly non-measurable which include: leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin/lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques. ***Note****:* lesions situated in a previously irradiated area are considered non-measurable lesions (non-target) unless there has been demonstrated progression in the lesion and then it may be considered a target lesion.

c. **Non-Pathological Lesions** include nodes that have a short axis of <10mm and simple cysts. These should not be recorded as target or non-target lesions.

5. List each selected baseline target lesion under the column "Lesion Description" and record the LD/SA (Largest Diameter(non-nodal)/Short Axis(nodal)) for each lesion in the corresponding Baseline LD/SA mm column. Baseline assessment of overall tumor burden is calculated by adding the longest diameter measurement of non-nodal target lesions and the short axis measurement for target nodal lesions in mm and reporting this as the baseline Sum of the Diameters (SOD). Add the baseline measurements and record the SOD in the corresponding space.
6. List all non-target sites of disease under the column "Lesion Description" and record as present in the corresponding Baseline Present/Absent column. Measurements are not required and should be followed as "present", "absent", or in rare cases "unequivocal progression" (write this in space when applicable). Note***:*** There are not a maximum number of non-target lesions; therefore, you may need to use an additional assessment form to document all non-target lesions. However, keep in mind that multiple non-target lesions involving the same organ may be recorded as a single item, i.e., multiple liver mets
7. Document the time-point response of Target Lesions in the row labeled "**TL Response"** that corresponds to the specific assessment time-point. Target lesion response is determined by the SOD of subsequent tumor assessments. **Note**: All Target Lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as "0"mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be recorded.
    a. **Complete Response (CR)**: Disappearance of all target lesions (each pathological lymph nodes must have a reduction in short axis to <10mm)

b. **Partial Response (PR)**: ≥30% decrease in the **baseline SOD**. To find the PR threshold, at baseline, multiple the baseline SOD x 0.7 and record this in the corresponding spaces for each tumor assessment time-point. *Note: This calculation only needs to be calculated at baseline*. For example: Baseline SOD = 32mm x 0.7 = 22.4mm; therefore, on subsequent assessments, the SOD would have to be ≤22.4mm to be documented and recorded as a PR.

c. **Progressive Disease (PD):** ≥20% increase in the **Nadir SOD** (this includes the Baseline SD if it is the smallest on study) **+ *an absolute increase of 5mm over the nadir SOD***. The appearance of one or more new lesions representing disease is also considered PD. To find the PD threshold, determine the smallest SD recorded and multiple it by 1.20 and record this calculation in the corresponding space for each tumor assessment time-point. *Note: This calculation must be done at each assessment*. Example: Baseline SOD = 43mm PD threshold = 43 x 1.20 = 51.6mm. Assessment #2 SOD = 35mm, = 1.2 x 35 = new PD threshold = 42mm Assessment #3 SOD = 37mm. PD threshold = 42mm (Nadir SOD of 35mm). Assessment #4 SOD = 43mm = >20% ↑ over nadir SOD (Assessment #2) and the SOD of 43mm is an absolute increase of 8mm over the nadir SOD of 35mm.

d. **Stable Disease (SD):** There is neither sufficient shrinkage (compared to baseline) to qualify for PR nor sufficient increase (taking as reference the smallest SOD while on study) to qualify for PD.

e. **Not All Evaluated (NE)**: When no imaging/measurement is done at all at a particular assessment time point or only a subset of lesion measurements are made at an assessment (unless documentation is made that the contribution of the individual missing lesion(s) measurements would not change the assigned time point response. This would most likely happen in the case of PD). ***Note:*** Make all attempts at obtaining/clarifying measurements for all baseline sites of disease at each subsequent assessment time-point.

8. Document the time-point response of Non-Target Lesions in the row labeled **"NTL Response"** that corresponds to the specific assessment time-point. Non Target Lesion response is defined as:

a. **Complete Response (CR)**: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis)

b. **Non CR/Non PD**: Persistence of one or more non-target lesions and/or maintenance of tumor marker level above normal limits

c. **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions. The appearance of one or more new lesions is also considered progression. ***Note:*** When there is measurable disease, to achieve unequivocal progression, there must be an overall level of substantial worsening in non-target disease, such that even in presence of SD or PR of target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. When there is only non-measurable disease, there needs to be an increase in tumor burden representing an additional 73% increase in volume (example: increase in pleural effusion from trace to large)

d. **Not All Evaluated (NE)**: When none or only some imaging is done at a particular assessment time point.

9. Document the presence or absence of any new lesion (Target or Non-Target) in the row labeled **"NEW LESION"** at each assessment time point after baseline. This represents disease progression; however, this finding should be unequivocal and not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (Example: a new bone lesion may represent healing or flare of pre-existing lesions).
    a. A lesion identified on a follow-up study in an anatomical location that **was not scanned at baseline is considered a new lesion** and will indicate disease progression
    b. If a new lesion is equivocal (i.e. because of small size), continued therapy and follow up evaluation may clarify if it truly represents new disease. Discuss and obtain approval from medical monitor to continue treatment and re-evaluate. If re-eval confirms it as a new lesion, then PD should be recorded as the date of initial scan.
10. Document the overall response in the row labeled **"OVERALL RESPONSE"** at each assessment time point after baseline. Refer to Table 1 (for subjects with Target +/- Non Target Disease) and Table 2 (for subjects with Non Target Disease only).
11. Document the review and confirmation date of the Clinical Investigator in the row labeled **"Investigator Signature/Date"** at baseline and each subsequent assessment time point. ***Important:*** This is source documentation that disease burden and response have been confirmed by the investigator prior to continued study treatment after each assessment time point. In addition, the investigator's documentation should reflect any clarifications related to imaging/treatment discussed with radiologist and/or study monitor.

Additional RECIST v1.1 Guidance:

1. **Special Notes on Response Assessment:**

Complete Response:

- When nodal disease is included in the Sum of Largest Diameter of target lesions and the nodes decrease to "normal" size (<10mm), measurements may still be reported on scans. The measurements should be recorded even though the nodes are normal to prevent the overstatement of progression should progression be based on increase in the size of the nodes. This means that responses with CR may not have a total sum of "zero".
- When it is difficult to distinguish residual disease from normal tissue and the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (FNA/Biopsy) before assigning a status of CR. FDG-PET may be used to upgrade a response to CR in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. *Note: both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.*

Progression:

- For equivocal findings of progression (i.e., very small and uncertain new lesions, cystic changes or necrosis in existing lesions), treatment may continue until the next

scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected. ***Note:*** The investigator's documentation should reflect the equivocal findings with decision to continue to treat until the next scheduled assessment.

- Patients with global deterioration of health status requiring discontinuation of treatment *without objective evidence of disease progression* at that time should be reported as **"symptomatic deterioration"**. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is a reason for discontinuing study therapy, not an objective response which is determined by evaluation of target and non-target disease.

Target Lesions that Split or Coalesce:

- When non-nodal lesions split, the longest diameters of the split portions should be added together to calculate the target lesion sum
- When a non-nodal lesion has coalesced (no longer separable), the vector of the longest diameter should be the maximal longest diameter for the coalesced lesion

Target Lesions that become "too small to measure":

- Actual measurements of all baseline nodal and non-nodal lesions should be recorded at each subsequent assessment, even when very small (i.e., 2mm). If the radiologist is not comfortable with assigning an exact measurement and the radiologist feels
  - that the lesion has likely disappeared, the measurement should be recorded as "0"mm
  - that the lesion is believed to be present and is faintly seen but too small to measure, a default value of "5"mm should be recorded

2. **Confirmatory Measurement of Response**
   a. In non-randomized trials where response is the primary endpoint, confirmation of CR and PR is required to ensure responses identified are not due to measurement error.
   b. In randomized (phase II or III) trials where SD or PD are the primary endpoints, confirmation of response is not required
   c. Stable Disease measurements must have met the SD criteria at least once after study entry at a minimum interval (in general ≥ 6-8 weeks) that is defined in the study protocol.

Modified RECIST Definitions:

- Definition for SD, PR, and CR are the same as RECIST 1.1.
- PD by modified RECIST: Although the same rules for progression apply for modified RECIST, if the subject is clinically stable, at the discretion of the PI, they may continue treatment until the next imaging time points ≥4 weeks later. If PD is confirmed, the date of PD is the same as the initial date of PD by RECIST. If PD is not confirmed, the date of PD is based on the second event for PD by imaging.

- The following scenarios defined confirmation of PD or lack thereof at the repeat imaging time point. Note that if PD is not confirmed, imaging should resume the regular interval per the schedule. Also, if a second PD event occurs, no further

confirmation of PD is required. Note; if PD is confirmed and the subject is achieving a clinically meaningful benefit, the site should speak with DSMB to discuss the potential to continue on treatment.

PD IS CONFIRMED:

1. If initial PD is due to increase in tumor burden ≥ 20% compared to nadir, PD is Confirmed if ANY of the following are met:
    - At follow-up scan tumor burden remains ≥ 20% compared to nadir + 5mm absolute increase if tumor burden is small
    - New unequivocal PD of non-target lesion (NTL) qualitative)
    - One or more new lesion(s)
    - Clinical instability

2. If initial PD is due to unequivocal PD of NTL, PD is CONFIRMED at follow up if ANY of the following conditions are met:
    - NT disease resulting in initial PD is worse (qualitative)
    - New additional unequivocal PD of NTL
        - (qualitatively assessed)
    - Additional new lesion (s)
    - New PD due to tumor burden (SOD) ≥ 20% compared to nadir+ 5 mm absolute increase if tumor burden is small

3. If PD is due to New Lesion, PD is CONFIRMED at follow up time point if ANY of the following conditions are met:
    - New lesion resulting in initial PD is worse (qualitative)
    - Additional new lesion (s)
    - New unequivocal PD of non target (qualitative)
    - New PD due to tumor burden (SOD) ≥ 20% compared to nadir + 5 mm absolute increase if tumor burden is small

PD IS NOT CONFIRMED AT FOLLOW UP IMAGING FOR THE FOLLOWING SCENARIOS :

4. If PD is due to increase in tumor burden by 20% compared to nadir, PD is NOT CONFIRMED at follow up if ALL of the following conditions are met
    - Tumor burden is <20% compared to nadir
    - No unequivocal PD of non target lesion (qualitative)
    - No new lesion(s)
    - Continued clinical stability

5. If PD is due to New Lesion(s), PD is NOT CONFIRMED at follow up time point if ALL of the following conditions are met:

- Previous new lesion (that was initially called PD) is not worse (qualitative)
- No additional new lesion(s)
- No unequivocal PD of non target (qualitative)
- No new PD due to tumor burden (SOD) ≥ 20% compared to nadir
- Continued clinical stability

6. If PD is due to unequivocal PD of non target, PD is NOT CONFIRMED at follow up if ALL of the following conditions are met:
   - Initial PD of non target disease is not worse (qualitative)
   - No additional new unequivocal PD of non target qualitative)
   - No new lesion(s)
   - No new PD due to tumor burden (SOD) ≥ 20% compared to nadir
   - Continued clinical stability

Time point response of Measurable Disease (Target Lesions) with or without Non-Measurable Disease (Non Target Lesions)

Target Lesion Response	Non Target Lesion	New Lesions	Overall Response
CR	**CR**	**No**	**CR**
CR	**Non-CR/Non-PD**	**No**	**PR**
CR	**NE**	**No**	**PR**
PR	**Non-PD or NE**	**No**	**PR**
SD	**Non-PD or NE**	**No**	**SD**
NE	**Non-PD**	**No**	**NE**
PD	**Any**	**Yes or No**	**PD**
Any	**PD**	**Yes or No**	**PD**
Any	**Any**	**Yes**	**PD**
CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease, and NE=Not All Evaluated			

Time point response of Non-Measurable Disease Only (Non Target Lesions)

Non Target Lesion Response	New Lesions	Overall Response
CR	**No**	**CR**
Non-CR/Non-PD	**No**	**Non-CR/Con-PD**
NE	**No**	**NE**

Unequivocal Progression	**Yes or No**	**PD**
Any	**Yes**	**PD**
CR=Complete Response, PD=Progressive Disease, and NE=Not All Evaluated **Non-CR/Non-PD is preferred over "Stable Disease" for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised**		

Note: If a CR is truly met at a time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that time point since disease must have reappeared after CR.