ALLIANCE FOUNDATION TRIALS (AFT)

PROTOCOL NUMBER
AFT – 09

Randomized Phase II Trial Evaluating the Optimal Sequencing of PD-1 Inhibition with Pembrolizumab (MK-3475) and Standard Platinum-based Chemotherapy in Patients with Chemotherapy naive stage IV Non-small Cell Lung Cancer

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Investigational Agent: Pembrolizumab(MK-3475)
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Investigational Agent Supplier: Merck

ClinicalTrials.gov Identifier: NCT 02591615

Study Chair
Thomas Hensing, M.D.
NorthShore University Health System
University of Chicago
[redacted]
Evanston, IL 60201
[redacted]

Sponsor Principal Investigator
Monica M. Bertagnolli, MD
Alliance Foundation Trials
[redacted]
Boston, MA 02115
[redacted]

Study Resources

Adverse Event Reporting **via Medidata Rave® iMedidata Portal/Argus Safety Management** accessible via the AFT website, https://alliancefoundationtrials.org/
IRT – Randomization System accessible via the AFT website, https://alliancefoundationtrials.org/
Site Zone https://sitezone.mywingspan.com/sitezone/trials accessible via the AFT website, https://alliancefoundationtrials.org/ For Site Zone Help: [redacted]
BiOMS AFT Resource Site https://cbmiapps.wustl.edu/confluence/x/TaETAO

Protocol Contacts

Alliance Foundation Trials Project Manager [redacted]	**Alliance Foundation Trials Biorepository at Washington University** c/o Siteman Cancer Center Tissue Procurement Core 425 S. Euclid Avenue BJCIH Building, Room 5120 St. Louis, MO 63110-1005 [redacted]

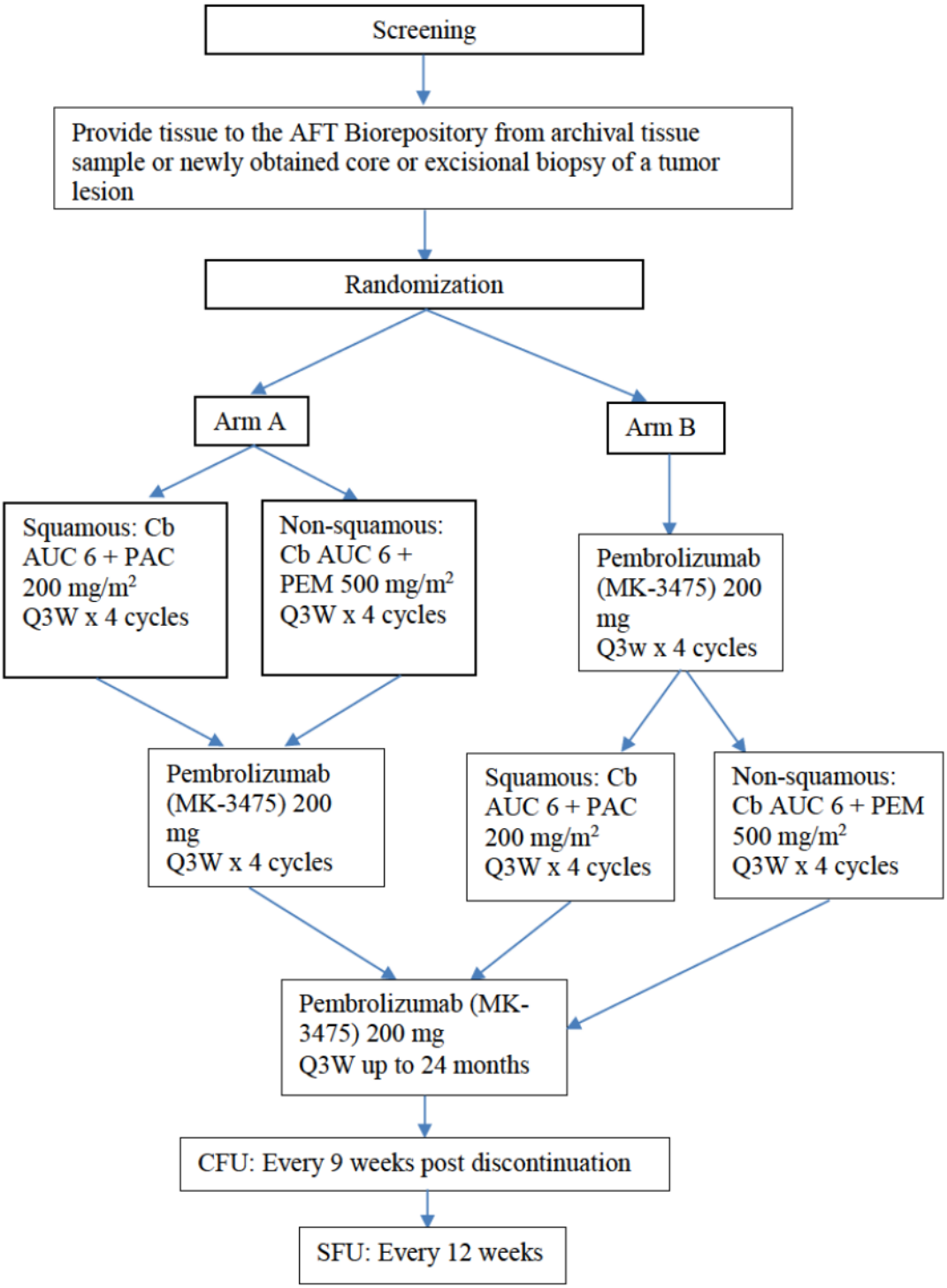
1. SYNOPSIS

1.1. STUDY SUMMARY

Abbreviated Title	Optimal Sequencing of Pembrolizumab (MK-3475) and Standard Platinum-based Chemotherapy in First-Line NSCLC
Study Phase	Randomized phase II
Clinical Indication	The treatment of patients with chemotherapy naive non-small cell lung cancer (NSCLC).
Study Type	Interventional
Type of control	Active control without placebo.
Route of administration	Intravenous
Study Blinding	Unblinded Open-label
Treatment Groups	Carboplatin and paclitaxel or pemetrexed every 3 weeks x 4 cycles followed by pembrolizumab (MK-3475) every 3 weeks for up to 24 months. Pembrolizumab (MK-3475) every 3 weeks x 4 cycles followed by carboplatin and paclitaxel or pemetrexed every 3 weeks x 4 cycles followed by pembrolizumab (MK-3475) every 3 weeks for up to 24 months. Treatment with pembrolizumab (MK-3475) may continue for up to 24 months, per investigator discretion. Treatment, visit assessments and tumor assessment shall continue on approximately the same schedule as prior cycles and may be adjusted to institutional standard of care for pembrolizumab (MK-3475) in NSCLC.
Number of study patients	Approximately 90 patients will be enrolled at an anticipated 30 sites.
Estimated duration of study	The sponsor estimates that the study will require approximately 36 months from the time of the first patient signs the informed consent until the last patient's last visit.
Duration of Participation	Each patient will participate in the study from the time the patient signs the Informed Consent Form (ICF) through the final protocol-specified contact. Eligible patients will receive assigned treatment on day 1 of each 3-week dosing cycle. Patients with complete response (CR),

	partial response (PR) or stable disease (SD), per RECIST 1.1 [1], after treatment with 4 cycles of carboplatin combined with paclitaxel or pemetrexed will continue treatment with pembrolizumab (MK-3475) until 24 months of therapy have been administered, documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the patient, patient withdraws consent, pregnancy of the patient, non-compliance with study treatment or procedure requirements, or administrative reasons. After the end of treatment, each patient will be followed for a minimum of 30 days for adverse event monitoring (serious adverse events will be collected for up to 90 days after the end of treatment). Patients will have post-treatment follow up for disease status, including initiating a non-study cancer treatment and experiencing disease progression, until death, withdrawing consent or becoming lost to follow-up.

1.2. Study Schema (Figure 1)



Cb = Carboplatin; PAC = Paclitaxel; PEM = Pemetrexed; PD = Progressive disease; CFU = Clinical follow up; SFU = Survival follow up

Patients who progress while receiving Cb AUC 6 + PAC 200 mg/m2 or PEM 500 mg/m2 may continue receiving treatment with pembrolizumab (MK-3475).

Treatment with pembrolizumab (MK-3475) may continue for up to 24 months after the initial assigned sequencing chemo/pembrolizumab (MK-3475) treatment or until disease progression on pembrolizumab (MK-3475) or an unacceptable adverse event.

Patients will be followed for at least 30 months post-randomization or until death, whichever comes first.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

2. TABLE OF CONTENTS

3. BACKGROUND

3.1. PHARMACEUTICAL AND THERAPEUTIC BACKGROUND

3.1.1. Introduction

Lung cancer continues to be the most common cause of cancer-related mortality in the United States. In 2014, approximately 224,000 patients were expected to be diagnosed with lung cancer and 160,000 patients were expected to die from this disease.[2] Most patients will be diagnosed with non-small cell histology that is regionally advanced or has spread to distant metastatic sites. In patients with stage IV non-small cell lung cancer (NSCLC) who have good performance status (ECOG level 0 or 1), treatment with a "newer" or third-generation platinum-based doublet (cisplatin or carboplatin combined with paclitaxel, docetaxel, gemcitabine, pemetrexed or vinorelbine) is most commonly recommended.[3] In the Eastern Cooperative Oncology Group (ECOG) 1594 trial, four platinum-based doublets were compared. None were superior in terms of activity or survival with an overall response rate (ORR) for the 1155 eligible patients of 19% and 1- and 2-year survival rates of 31% and 10%, respectively.[4] While there are differences in toxicity, the results of ECOG 1594 are consistent with the results of other randomized trials that have reported the relative equivalence of third-generation platinum-based doublets in the management of patients with advanced NSCLC.

In addition to performance status and toxicity, tumor histology and molecular profiling have been established as factors that can help guide regimen selection in this setting. In the landmark ECOG 4599 trial, the regimen of bevacizumab combined with carboplatin and paclitaxel was found to be superior in terms of response rate, median and one-year survival rate compared to carboplatin and paclitaxel alone in a highly selected patient population based on performance status, tumor histology, as well as lack of CNS metastatic disease, bleeding or thrombotic events.[5] In this trial, patients with squamous cell carcinoma were excluded based on a phase II trial that reported a higher rate of significant hemoptysis in patients with squamous histology.[6] In a non-inferiority, phase III trial, overall survival in 1725 patients with previously untreated NSCLC was found to be non-inferior after treatment with cisplatin and pemetrexed compared to cisplatin combined with gemcitabine (median survival 10.3 months versus 10.3 months; hazard ratio (HR), 0.94; 95% CI, 0.84 – 1.05%).[7] However, in a planned subgroup analysis, cisplatin and pemetrexed was found to be superior in patients with non-squamous NSCLC (n = 1000; HR 0.81; 95% CI, 0.7 – 0.94; p = 0.005). In contrast, patients with squamous cell histology did better with cisplatin and gemcitabine (n = 473; 10.8 months versus 9.4 months, respectively, p = 0.05). The histology effect of pemetrexed has also been reported in retrospective analysis of a second line trial comparing pemetrexed to docetaxel, as well as a phase III trial evaluating switch maintenance pemetrexed after 4 cycles of first-line platinum-based doublet chemotherapy.[8]

Molecular profiling has also been established as a strategy to select first-line chemotherapy in patients with advanced NSCLC. The presence of activating somatic mutations in the gene encoding the epidermal growth factor receptor (EGFR) has been associated with superior activity and survival outcomes after first-line treatment with an EGFR tyrosine kinase inhibitor (TKI) compared to standard platinum-based doublet chemotherapy. In the landmark Iressa Pan-Asia Study (IPASS) 1217 clinically selected patients were randomized to treatment with gefitinib compared to carboplatin and paclitaxel.[9] In the 261 patients with confirmed EGFR mutation,

gefitinib was associated with significant improvement in response rate (71% versus 47%, respectively) and progression free survival (PFS; HR, 0.48; 95% CI, 0.36 – 0.64) compared to carboplatin and paclitaxel. Four additional randomized trials have confirmed improvement in response and PFS in patients with EGFR mutations after treatment with an EGFR TKI compared to platinum-based doublet chemotherapy in both East Asian and European patient populations.[10-13] In a recent analysis of two open-label phase III trials (LUX-Lung 3 and LUX-Lung 6), the 2nd generation EGFR TKI, afatinib, was associated with superior PFS and overall survival (OS) when compared to cisplatin-based chemotherapy in patients with "common" (deletion 19 or L858R) EGFR mutations.[14] In the United States there are now two EGFR TKIs (erlotinib and afatinib) that are approved by the FDA for the first-line treatment of patients with stage IV EGFR-mutated NSCLC. In addition, based on clinical trials in molecularly selected patients, the FDA has also recently approved two anaplastic lymphoma kinase (ALK) inhibitors (crizotinib and ceritinib) for the treatment of patients with advanced NSCLC and documented ALK fusions.[15, 16]

3.1.2. PD-1 Pathway – Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades.[17] Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies.[18-22] 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. In NSCLC, recent studies have shown that tumor infiltration with CD4+ and/or CD8+ T cells is associated with better overall prognosis in patients with early stage disease.[23-25]

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4, which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2).[26, 27] The structure of murine PD-1 has been resolved.[28] PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade.[24, 26, 29, 30] The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins.[24, 31] PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells.[32, 33] Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells.[34] The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or

can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors.[34-37] Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues.[37] Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in patients with melanoma (MEL).[38] This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

PD-L1 is expressed in approximately 50% of NSCLC, including both adenocarcinoma and squamous cell carcinoma, and is associated with poor prognosis.[39-41] The expression of the PD-L1 ligand in tumors can be both innate, through constitutive oncogenic signaling, or induced in response to inflammatory signals generated by the antitumor immune response.[40] In addition, some chemotherapy agents, including paclitaxel, have been shown to increase PD-L1 expression in tumors.[40, 42]

Pembrolizumab (MK-3475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab (MK-3475)) 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.

3.1.3. Immune Checkpoint Inhibition and Lung Cancer

In clinical trials, monoclonal antibodies targeting PD-1 and PD-L1 have been associated with responses in approximately 20% of patients, many of which are durable.[43-47] Higher response rates have been reported in patients with PD-L1-positive tumors (by immunohistochemistry) compared to PD-L1-negative tumors.[44, 45, 48] However, responses after treatment with PD-1/PD-L1 inhibition in patients with PD-L1-negative tumors have been described.[46]

In a multi-center phase IB trial, 38 patients with previously treated advanced NSCLC were enrolled into an expanded cohort and treated with 10 mg/kg of pembrolizumab (MK-3475) every 21 days until disease progression.[45] The most common drug-related adverse events included rash (21%), pruritus (18%), fatigue (16%), diarrhea (13%) and arthralgia (11%). Most drug-related AE's were low grade (grade 1 or 2). One patient developed grade 2 pneumonitis and one patient developed grade 3 pulmonary edema. The ORR by irRC assessed by investigators as well as RECIST 1.1 criteria by central review was 24% and 21%, respectively. The median progression free survival (PFS) of responders was not reached at 62 weeks.[45] In a follow up report that included 194 evaluable patients with previously treated NSCLC, the ORR was 18%

and 20% by irRC and RECIST 1.1, respectively.[46] In PD-L1-positive patients (n = 159, defined as ≥ 1% tumor cells positive by IHC), the ORR was 19% by irRC and 23% by RECIST 1.1 compared to 13% and 9% in patients with PD-L1-negative tumors (n = 35). By irRC, the median PFS for patients with PD-L1-positive versus PD-L1-negative tumors was the same (16 weeks, range 10 – 18 (PD-L1-positive) and 9-28 weeks (PD-L1-negative), respectively).[46]

In a cohort of 45 treatment-naïve patients with PD-L1-positive, EGFR- and ALK-negative advanced NSCLC, the ORR by irRC and RECIST 1.1 after treatment with pembrolizumab (MK-3475) (dose 2 or 10 mg/kg q2-3 weeks) was 47% (range 32-62%) and 26% (range 14-42%), respectfully, with disease control rates of 78% (irRC) and 64% (RECIST 1.1).[47] The median PFS was 37 weeks by irRC and 27 weeks by RECIST and 90% of responders by irRC and 100% of responders by RECIST remained in response (median not reached) at the time of the report. 80% of patients experience an AE, most of which were grade I-II, including fatigue (22%), pruritis (13%), hypothyroidism (9%), dermatitis (7%), diarrhea (7%), dyspnea (7%) and rash (7%). One patient discontinued therapy after experiencing grade 3 pneumonitis and 1 patient discontinued treatment after experiencing grade 2 acute kidney injury.

3.2. STUDY DESIGN

This is a multicenter randomized phase II study to determine if the administration of standard platinum-based chemotherapy before pembrolizumab (MK-3475) in patients with stage IV non-small cell lung cancer (NSCLC) who have not previously been **treated with chemotherapy (chemotherapy naive)** will improve the overall response rate (ORR) compared to pembrolizumab (MK-3475) administered before chemotherapy. For the primary endpoint, ORR will be measured using the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1).[1] Ninety (90) eligible patients will be randomized and a "picking the winner" design will be utilized to select the most promising sequence of administration of pembrolizumab (MK-3475) and standard platinum-based chemotherapy for further investigation. Patients will be randomized in a 1:1 ratio to receive standard histology-aligned platinum-based chemotherapy (carboplatin combined with pemetrexed or paclitaxel) for 4 cycles followed by pembrolizumab (MK-3475) 200 mg every 3 weeks for 4 cycles or pembrolizumab (MK-3475) for 4 cycles followed by standard platinum-based chemotherapy for 4 cycles. Patients on both treatment arms with controlled disease (CR, PR or SD) after cycle 8 will continue to receive pembrolizumab (MK-3475) for up to 24 months.

Patients will be evaluated every 6 weeks (42 ± 7 days) with radiographic imaging to assess response to treatment. Investigators will make all treatment-based decisions using the Immune-Related Response Criteria (irRC) while on pembrolizumab (MK-3475) therapy. Patients on both treatment arms with controlled disease (CR, PR or SD) after their assigned treatment will continue pembrolizumab (MK-3475) every 3 weeks until 24 months of therapy have been administered, documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the patient, patient withdraws consent, pregnancy of the patient, non-compliance with study treatment or procedure requirements or administrative reasons. Patients receiving pembrolizumab (MK-3475) alone after cycle 8 will be evaluated with radiographic imaging every 9 weeks (63 ± 7 days). After the end of treatment, each patient will be followed for a minimum of 30 days for adverse event monitoring. Serious adverse events will be collected for up to 90 days after the end of treatment or initiation of a new antineoplastic therapy, whichever comes first and whether or not related to pembrolizumab (MK-3475). Patients will have post-treatment follow-up for disease status,

including initiating a non-study cancer treatment and experiencing disease progression, until death, withdrawing consent or becoming lost to follow-up. Treatment-related toxicities will be resolved before participants enter the clinical follow-up phase.

The primary endpoint of the study is ORR by RECIST 1.1. Secondary endpoints include ORR by irRC, progression free survival (PFS) by irRC and by RECIST 1.1, overall survival (OS) and safety as assessed by a variety of parameters of adverse events (AEs). AEs will be monitored throughout the study and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4. Pre-specified adverse events of clinical interest include: 1) Grade $\geq$ 2 diarrhea, 2) Grade $\geq$ 2 colitis, 3) Grade $\geq$ 2 pneumonitis, 4) Grade $\geq$ 3 hypo- or hyperthyroidism.

Participation in this study will be dependent on supplying tumor tissue from a previously collected or newly obtained formalin-fixed specimen from locations not radiated prior to biopsy. The specimen will be evaluated at a central laboratory facility for expression of PD-L1 by immunohistochemistry (IHC) in a prospective manor. Only patients with adequate tissue to establish PD-L1 status (strongly positive ($\geq$ 50% staining), weakly positive (1-49% staining) or negative (0% staining)) will be eligible for randomization in this study.

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 (MK-3475) 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. RATIONALE

4.1. RATIONALE FOR THE TRIAL AND SELECTED PATIENT POPULATION

While a genotype-directed strategy has been established as effective in treatment selection for patients with advanced NSCLC, only a minority of patients at this time will have a readily identifiable actionable molecular target. Furthermore, genotype-directed therapy has not been validated for patients with squamous cell carcinoma of the lung. Therefore, the majority of patients with advanced NSCLC will continue to rely on standard platinum-based doublet chemotherapy. Given the plateau in effectiveness of this approach, novel treatment strategies are clearly warranted.

Inhibition of the PD-1/PD-L1 pathway has been identified as a potential therapeutic target in patients with advanced non-small cell lung cancer (NSCLC).[40, 43, 49] The prognostic significance of PD-L1 expression in NSCLC suggests that this pathway may play an important role in immune escape and tumor progression. [39] The reported clinical activity of PD-1 and

PD-L1 inhibitors in the treatment of patients with advanced NSCLC supports continued investigation of this therapeutic strategy.

In an effort to improve the anti-tumor immune response, there has been recent interest in combining immune checkpoint inhibitors with cytotoxic chemotherapy.[40] In addition to increasing expression of PD-L1 on tumor cells, conventional chemotherapy has been shown to be capable of modulating the immune system and stimulating tumor-specific immune response, raising the possibility that combining chemotherapy with immune checkpoint inhibitors may enhance efficacy.[40] In particular, treatment with paclitaxel has been associated with several immunomodulatory effects, including enhanced T-cell activation through up-regulation of major histocompatibility complex-1 expression and dendritic cell modulation [50, 51], as well as affecting regulatory T-cells.[52]

A recent phase I trial confirmed the feasibility of combining a PD-1 inhibitor (nivolumab) with platinum-based doublets (cisplatin/gemcitabine, cisplatin/pemetrexed, and carboplatin/paclitaxel). In 56 treatment-naïve patients with stage IIIB/IV NSCLC and ECOG PS 0-1, the ORR after treatment with chemotherapy plus the PD-1 inhibitor ranged between 33 – 47% with a 1-year OS rate of 50-87%.[53] The safety profile reflected additive toxicities but no unusual safety signals were seen and there were no treatment-related deaths. Across all treatment arms, treatment-related pneumonitis occurred in 7 patients (13%), including grade 3/4 pneumonitis in 4 patients (7%). The most frequent AEs with potential immunologic etiology included skin (34% any grade/5% grade 3/4), gastrointestinal (23% any grade and 4% grade 3/4), infusion reaction (23% any grade, 2% grade 3/4), renal (14% any grade, 5% grade 3/4), and pulmonary (13% any grade, 7% grade 3/4).

The timing of administration of chemotherapy and checkpoint inhibition may be important and further investigation is warranted to define the optimal scheduling strategy. While enhanced efficacy may occur through increase in tumor-specific immunity, conventional cytotoxic chemotherapy can also decrease the immune cell population and mitigate the response to immunotherapy.[40] However, in a preclinical model of gemcitabine administered with a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor, concomitant scheduling appeared to be the most effective strategy.[54] In contrast, a randomized trial evaluating the combination of the CTLA-4 checkpoint inhibitor ipilimumab with carboplatin and paclitaxel in patients with stage IV chemotherapy-naïve NSCLC showed that phased administration of ipilimumab with chemotherapy (2 doses of placebo plus carboplatin and paclitaxel followed by 4 cycles of ipilimumab and carboplatin and paclitaxel) resulted in improved irPFS compared to chemotherapy alone (HR, 0.72; $p = 0.05$), whereas concurrent scheduling did not (HR, 0.81, $p = 0.13$).[55] Corticosteroids for paclitaxel premedication were allowed. The overall rates of grade 3/4 immune-related AEs were 15%, 20%, and 6% for phased ipilimumab, concurrent ipilimumab and control, respectively.[55]

PD-L1 expression by IHC is a promising predictive biomarker for PD-1 and PD-L1 inhibitors. However, there are at least 3 distinct PD-L1 antibodies that are being developed as companion diagnostics with varying performance characteristics and thresholds for positivity. Importantly, responses to PD-1 and PD-L1 inhibitors with prolonged disease control have been reported in patients with PD-L1-negative tumors.[40, 46] Therefore, continued investigation will be needed

to define the optimal patient population that would benefit from treatment with immune checkpoint inhibitors and enrollment of molecularly unselected patients remains justified.

4.1.1. Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab (MK-3475). The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in patients with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab (MK-3475) showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the pembrolizumab (MK-3475) program has shown that a lower dose of pembrolizumab (MK-3475) and a less frequent schedule may be sufficient for target engagement and clinical activity.

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

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

5. RATIONALE FOR ENDPOINTS

5.1. EFFICACY ENDPOINTS

5.1.1. Primary

This randomized phase II trial will utilize a selection ("pick the winner") design. Two different investigational schedules of PD-1 inhibitor administration with standard platinum-based doublet

chemotherapy will be evaluated. In this design, ORR remains an acceptable scientific endpoint to identify the best arm for further evaluation. ORR and duration of response will be assessed by both irRC, as well as by RECIST 1.1.[1] For the primary endpoint, the treatment regimen with the best ORR per RECIST 1.1 will be selected for further investigation. irRC was developed from modified WHO criteria to better capture unique responses to immune checkpoint inhibitors, including regression of index lesions in the face of new lesions and initial progression followed by tumor stabilization or regression. [55-57]

5.1.2. Secondary

PFS will be assessed by irRC and RECIST 1.1 as determined by the investigators. PFS and OS differences will be evaluated as an exploratory analysis. The treatment-related adverse events of pembrolizumab (MK-3475) and platinum-based chemotherapy will be summarized by adverse event type and grade for each treatment arm. All main analyses will be evaluated based on PD-L1 expression status, including negative (0% tumor cells positive), low expression (1-49% tumor cells positive) and high expression (50-100% tumor cells positive).

5.1.3. Molecular and Genomic Correlates of Treatment Response and Outcome

Tumor tissue, peripheral leukocytes, and blood plasma specimens at baseline and during therapy will be collected as part of this study. In addition to analysis of PD-L1 expression by IHC, collected tissue biospecimens will be further used to perform genomic, epigenomic, gene expression, and/or proteomic analyses to identify candidate biomarkers of treatment response and outcome. Serial, peripheral blood plasma biospecimens will be used to evaluate nucleic acid, proteomic, and/or metabolic biomarkers of response and outcome. All collected biospecimens will be stored in the Alliance Foundation Biorepository (AFB), until biospecimen accrual and clinical follow up is sufficiently complete to allow for the design and execution of specific correlative analyses.

6. OBJECTIVES

6.1. PRIMARY OBJECTIVE

1. To compare the ORR per RECIST 1.1 of pembrolizumab (MK-3475) in patients with chemotherapy naive advanced NSCLC after treatment with first-line carboplatin-based chemotherapy to patients treated with pembrolizumab (MK-3475) prior to first-line chemotherapy.

6.2. SECONDARY OBJECTIVES

1. To compare the progression-free survival (PFS) per RECIST 1.1 in previously chemotherapy naive with advanced NSCLC treated with first line carboplatin-based chemotherapy followed by pembrolizumab (MK-3475) to patients treated with pembrolizumab (MK-3475) prior to first-line carboplatin-based chemotherapy.
2. To characterize the adverse events related to pembrolizumab (MK-3475) by frequency, type and grade in patients with chemotherapy naive advanced NSCLC based on the sequence of administration with first-line chemotherapy.

3. To evaluate the ORR per irRC of pembrolizumab (MK-3475) administered prior to or after treatment with first-line carboplatin-based chemotherapy in patients with chemotherapy naive NSCLC.
4. To evaluate the PFS per irRC of chemotherapy naive patients with advanced NSCLC who are treated with pembrolizumab (MK-3475) administered prior to or after first-line carboplatin-based chemotherapy.
5. To evaluate the response duration of pembrolizumab (MK-3475) based on schedule of administration with standard platinum-based chemotherapy in patients with chemotherapy naive advanced NSCLC.
6. To evaluate the overall survival (OS) of patients with chemotherapy naive advanced NSCLC who received pembrolizumab (MK-3475) administered prior to or after treatment with first line carboplatin-based chemotherapy.

6.3. Correlative Objectives

1. To evaluate ORR per RECIST 1.1 and per irRC, PFS per RECIST 1.1 and per irRC, and OS after treatment with pembrolizumab (MK-3475) based on PD-L1 expression.
2. To evaluate the association between smoking status (never, previous, or current smokers) and clinical outcomes, including ORR, PFS and OS.

6.4. Future Biomedical Research

All collected biospecimens will be stored in the Alliance Foundation Biorepository (AFB), a CAP-accredited biorepository at Washington University in St. Louis, until biospecimen accrual and clinical follow-up is sufficiently complete to allow for the design and execution of specific correlative analyses using 'state-of-the-art' analytical platforms that will be available at that time.

Such biomarker research will address emergent questions not described elsewhere in this protocol and will only be conducted on specimens from appropriately consented patients. The objective of collecting specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of disease and/or their therapeutic treatments in the context of this trial. Proposals for future correlative research will undergo rigorous scientific, programmatic, and statistical review by AFT, and biospecimens will only be released to those investigators who have obtained appropriate regulatory approval and demonstrate adequate funding to successful complete proposed research aims. AFT will ensure that all collected specimens are used only for approved research protocols.

Anonymized (de-identified) data generated from biospecimens used for future correlative research, including somatic and constitutional (germline) genomic data, may be shared with other researchers or deposited in a publicly accessible or controlled-access data repositories. Correlative study results and data will never be returned to individual patients.

7. Patient Selection

For questions regarding eligibility criteria, contact the Study PI. Please note that the Study PI may not grant waivers to eligibility requirements.

7.1. Inclusion Criteria

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

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

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

3. Have a histologically or cytologically confirmed diagnosis of stage IV (M1a or M1b according to AJCC Staging Manual, 7th edition) non-small cell lung cancer (NSCLC).

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

5. Have measurable disease based on RECIST 1.1. The target lesion(s) should also have bi-dimensional measurability for irRC evaluation on study.

6. Have provided tissue from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion, that is adequate to establish PD-L1 expression status. *Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior patient enrollment.*

7. In patients with non-squamous non-small cell lung cancer, Investigators must be able to produce source documentation of the EGFR mutation status or ALK translocation status.

    i. If a patient is known to have one molecular alteration (EGFR mutation or ALK translocation), then testing for the other alteration is not required.

    ii. If a patient is known to have a mutation in KRAS, then testing for an EGFR mutation or ALK translocation will not be required.

8. Demonstrate adequate organ function as defined in Table 1.

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
Renal	
Serum creatinine **OR** GFR (Glomerular Filtration Rate)	≤1.5 X upper limit of normal (ULN) **OR** GFR ≥60 mL/min for patient with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**

	Direct bilirubin ≤ ULN for patients with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for patients with liver metastases
Albumin	≥ 2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

9. Female patient of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

10. Female patients of childbearing potential must be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (see Section 13.5). Patients of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

11. Male patients must 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.

12. **Patients with sensitizing EGFR mutation or ALK rearrangement must have progressed on an appropriate tyrosine kinase inhibitor (TKI).**

7.2. EXCLUSION CRITERIA

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

1. Has received prior treatment with chemotherapy or biologic therapy for stage IV NSCLC.

2. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.

3. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

4. Has had a prior monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

5. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

    - Note: Patients with non-squamous histology ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

    - Note: If patient received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

6. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.

7. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least two weeks prior to the first dose of trial treatment and any clinical/neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. Patients would not require follow-up MRI before starting study treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

8. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Patients with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Patients that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Patients with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study.

9. Has evidence of interstitial lung disease, or history of (non-infectious) pneumonitis that required steroids, or current pneumonitis.

10. Has an active infection requiring systemic therapy.

11. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating investigator.

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

13. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

14. 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).

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

16. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

17. Has received a live vaccine within 30 days prior to the planned first dose of study therapy.

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

18. Has a known history of active TB (Bacillus Tuberculosis)

19. Hypersensitivity to pembrolizumab (MK-3475) or any of its excipients.

8. PATIENT ENROLLMENT

8.1. SITE ENROLLMENT REQUIREMENTS

Requirements for Site Enrollment

- IRB Certification
- IRB/Regulatory Approval

Submit completed forms along with a copy of your IRB Approval, Model Informed Consent and any other required documentation to the AFT eTMF system.

8.2. PATIENT ENROLLMENT REQUIREMENTS

Informed consent: The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and enrollment.

8.3. PATIENT SCREENING, ENROLLMENT/RANDOMIZATION PROCEDURES

Patient enrollment will be facilitated using the AFT web-based IRT (interactive response technology) system.

Patients must sign informed consent and be screened prior to any study related testing, including submission of biospecimens. After written informed consent has been obtained, the study site will obtain a unique patient number or unique patient identifier which will stay the same throughout the entire study. Patients may be enrolled/randomized upon confirmation from the AFT-biorepository that tumor tissue for biomarker analysis has been received and that the patient meets all eligibility requirements for enrollment. Patients screened but not randomized for any reason have to be registered as a Screening Failure in IRT.

Prior to accessing AFT IRT, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).
- Tumor tissue will be available and can be sent to the AFT biorepository for central laboratory analysis.

The AFT IRT system will provide the site with a printable confirmation of enrollment and treatment randomization information. Please print this confirmation for your records. The site will receive instructions for drug ordering via IRT, upon randomization.

8.4. STRATIFICATION FACTORS AND TREATMENT ASSIGNMENTS

Randomization will be stratified according to:

1) **Smoking History: Never, Previous or Current**

2) **Histology: Squamous vs. Non-Squamous**

This is an open-label trial; therefore, AFT, the investigator and patient will know the treatment administered.

9. SCHEDULE OF ASSESSMENTS

Table 2. Schedule of Assessments

Trial Period:	**Treatment Cycles[1]**									**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Screening (Visit 0)	1	2	3	4	To be repeated beyond 8 cycles 5	6	7	8	Discon	Safety Follow-up[19]	Follow Up Visits[20]	Survival Follow-Up[21]
Scheduling Window (Days)[2]:	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 9 weeks post discon	Every 12 weeks
Informed Consent[3]	X												
Inclusion/Exclusion Criteria	X												
Demographics and Medical History[23]	X												
Prior and Concomitant Medication Review[4]	X	X	X	X	X	X	X	X	X	X			
NSCLC Disease Details	X												
Trial Treatment Administration[24]		X	X	X	X	X	X	X	X				
Review Adverse Events[5, 6, 22]		X	X	X	X	X	X	X	X	X	X	X	X
Full Physical Examination[17]	X									X			X
Directed Physical Examination[17]		X	X	X	X	X	X	X	X		X	X	
Vital Signs and Weight[7]	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

Trial Period:	**Treatment Cycles[1]**									**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Screening (Visit 0)	1	2	3	4	To be repeated beyond 8 cycles 5	6	7	8	Discon	Safety Follow-up[19]	Follow Up Visits[20]	Survival Follow-Up[21]
Scheduling Window (Days)[2]:	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 9 weeks post discon	Every 12 weeks
Pregnancy Test – Urine or Serum □-HCG[8, 10]	X												
PT/INR and aPTT[9, 10]	X												
CBC with Differential[10, 11]	X		X	X	X	X	X	X	X	X	X		
Comprehensive Serum Chemistry Panel[10, 11]	X		X	X	X	X	X	X	X	X	X		
Urinalysis[10, 12]	X				X				X	X			
T3, FT4 and TSH[10, 11, 13]	X		X		X		X		X	X			
ALK Translocation Testing[18]	X												
EGFR Translocation Testing[18]	X												
CT Scan (Tumor Imaging)[14, 15]	X		X		X		X		X	X		X	
Archival or Newly Obtained Tissue Collection[16]	X												
Correlative Studies Blood Collection[16A]	X				X				X				

[1]In general, assessments/procedures are to be performed on day 1 and prior to the first dose of trial treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks (21-days); however the pembrolizumab (MK-3475) treatment cycle interval may be increased due to toxicity according to the dose modification guidelines provided in Section 13. If treatment cycles are increased all procedures except imaging will be completed according to cycle number and not weeks on treatment, imaging will be performed every 6 weeks (±7 days) from the first dose of trial treatment regardless of any treatment delays during the first 8 cycles. After cycle 8, imaging will be performed every 9 weeks (63±7 days).

[2] In general, the window for each visit is ± 3 days unless otherwise specified.

[3] Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the patient signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

[4] Prior medications – record all medications taken within 30 days of visit 1 and all treatments for a prior cancer other than NSCLC even if taken greater than 30 days prior to visit 1. After the Safety Follow-up Visit record all medications taken for SAEs and ECIs as defined in Section 13.4.

[5] AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not will also be evaluated for seriousness.

[6] All AEs of unknown etiology associated with trial treatment exposure should be evaluated to determine if it is possibly an ECI.

[7] Vital signs to include: temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at visit 1 only.

[8] For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the 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. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.

[9] Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the trial for any patient receiving anticoagulant therapy.

[10] Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. See Table 3 for details regarding laboratory tests.

[11] After Cycle 1, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing.

[12] Perform urinalysis every 4 cycles.

[13] Required at baseline. Perform thyroid testing every other cycle while patients are receiving pembrolizumab (MK-3475).

[14] The initial tumor imaging will be performed within 30 days prior to the first dose of trial treatment. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 30 days prior to the first dose of trial treatment. On-study imaging during the first 8 cycles of therapy will be performed every 6 weeks (42 ± 7 days) after the first dose of trial treatment or more frequently if clinically indicated. Patients on both arms receiving pembrolizumab (MK-3475) alone after cycle 8 will be imaged every 9 weeks (63 ± 7 days) The timing for imaging studies should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab (MK-3475) cycle frequencies. The same imaging technique should be used in a patient throughout the trial. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for patient management.

[15] After first documentation of progression (if the patient is clinically stable) or response per RECIST 1.1 repeat imaging for confirmation is required. Confirmatory imaging may be performed as early as 28 days later; alternatively, the scan performed at the next scheduled time point may be used as confirmation.

[16] Tumor tissue for biomarker analysis from an archival tissue sample or newly obtained formalin fixed tumor tissue from a recent biopsy of a tumor lesion not previously radiated (required for PD-L1 determination) must be provided and received by the AFT-Biorepository before randomization.

[16A] Correlative blood samples will be collected per Section 12.1.3. At baseline, whole blood sample in EDTA tube and Streck BCT tube. At C4 and C8, Streck BCT tube only. Blood volumes, processing, storage and shipping are described in section 12.1.2.

[17] Perform a full physical examination at the screening visit, end of treatment, and every 12 weeks during survival follow up. Otherwise, perform a directed physical examination the day of the study treatment visit.

[18] Site must be able to provide documentation of the patient's tumor EGFR mutation and ALK translocation status.

[19] The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new antineoplastic treatment, whichever comes first. Patients with an AE of grade > 1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first.

[20] Patients who discontinue trial treatment for a reason other than disease progression will move into the Clinical Follow-up Phase and should be assessed every 9 weeks (63 ± 7 days) by radiologic imaging to monitor disease status. Treatment-related toxicities will be resolved before transitioning to clinical follow-up. Follow-up visit 1 should be scheduled 9 weeks after the last dose of trial treatment. Follow-up visit 2 should occur 9 weeks after Follow-up visit 1. After Follow-up visit 2, patients only need to be assessed every 9 weeks (63 ±7 days) by radiologic imaging to monitor disease status, development of drug related SAEs and ECIs/irAEs, and initiation of a new antineoplastic therapy. Unless otherwise noted in the flow chart, every effort should be made to collect patient information until the start of new antineoplastic therapy, disease progression, or death, whichever comes first.

[21] Once a patient experiences disease progression or starts a new antineoplastic therapy, the patient moves into the Survival Follow-up Phase and should be contacted by telephone every 3 months to assess for survival status, development of drug related SAEs and ECIs/irAEs and the start of new antineoplastic therapy if applicable.

[22] Record all AEs occurring within 30 days after the last dose of trial treatment or until initiation of a new antineoplastic therapy, whichever comes first. Report all SAEs (related and unrelated to trial treatment), ECIs/irAEs occurring within 90 days of the last dose of trial treatment or the initiation of a new antineoplastic therapy, whichever comes first and whether or not related to pembrolizumab (MK-3475). After this time, report only SAEs and ECIs/irAEs that are considered related to trial treatment.

[23] The study staff will complete a medical history review with the patient. This will include documentation of NSCLC Disease Details.

[24] Pembrolizumab administered beyond 12 months may be given per institutional standard for NSCLC. Treatment, visit assessments and tumor assessments shall continue on approximately the same schedule as prior cycles. Data captured beyond 12 months will be limited to SAEs, disease status and overall survival.

Table 3. 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		Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
	(CO_2 or biocarbonate)	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		
	Calcium		
	Chloride		
	Glucose		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

‡ If considered standard of care in your region.

Laboratory tests for screening 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 must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment

10. TREATMENT PLAN

10.1. TRIAL TREATMENTS

The treatment to be used in this trial is outlined below in Table 4.

Table 4. Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab (MK-3475)	200 mg	Q3W	IV infusion	Day 1 of each cycle	Experimental
Carboplatin	AUC 6	Q3W	IV infusion	Day 1 of each cycle	Standard chemotherapy
Paclitaxel	200 mg/m^2	Q3W	IV infusion	Day 1 of each cycle	Standard chemotherapy
Pemetrexed	500 mg/m^2	Q3W	IV infusion	Day 1 of each cycle	Standard chemotherapy
The pembrolizumab (MK-3475) dosing interval may be increased due to toxicity.					

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

Arm A

For Squamous Carcinoma

Carboplatin AUC = 6 IV day 1 every 21-days for up to 4 cycles.

Paclitaxel 200 mg/m^2 IV day 1 every 21-days for up to 4 cycles

Or

For Non-squamous Carcinoma

Carboplatin AUC = 6 IV day 1 every 21-days for up to 4 cycles

Pemetrexed 500 mg/m^2 IV day 1 every 21-days for up to 4 cycles.

Patients with progressive disease (PD) by RECIST 1.1 after cycle 2 or cycle 4 will be allowed to transition to pembrolizumab (MK-3475) 200 mg IV every 21-days for up to 24 months.

Patients with complete response (CR), partial response (PR) or stable disease (SD) by RECIST 1.1 criteria after cycle 4 will be treated with pembrolizumab (MK-3475) 200 mg IV every 21-days for up to 24 months.

ARM B

Pembrolizumab (MK-3475) 200 mg IV every 21-days for up to 4 cycles

Patients with CR, PR or SD by irRC will then be treated with:

For Squamous Carcinoma

Carboplatin AUC = 6 IV day 1 every 21-days for up to 4 cycles.

Paclitaxel 200 mg/m^2 IV day 1 every 21-days for up to 4 cycles

Or

For Non-squamous Carcinoma

Carboplatin AUC = 6 IV day 1 every 21-days for up to 4 cycles

Pemetrexed 500 mg/m^2 IV day 1 every 21-days for up to 4 cycles.

Patients with PD by RECIST 1.1 after cycle 6 or cycle 8 will be allowed to transition back to pembrolizumab (MK-3475) 200 mg IV every 21-days for up to 24 months, at the investigator's discretion.

Patients with complete response (CR), partial response (PR) or stable disease (SD) by RECIST 1.1 criteria after cycle 8 will then be treated with pembrolizumab (MK-3475) 200 mg IV every 21-days for up to 24 months.

10.2. Dose Selection and Preparation

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

The specific instructions for pembrolizumab (MK-3475) dose calculation, reconstitution, preparation of the infusion fluid, and administration are included in the Pharmacy Manual.

Carboplatin, pemetrexed and paclitaxel will be prepared and administered as per the approved product label.

10.2.1. 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 Schedule of Assessments (Section 9). 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.

10.2.2. Pembrolizumab (MK-3475)

Pembrolizumab (MK-3475) will be administered as an approximately 30 minute IV infusion per institutional standard (treatment cycle intervals may be increased due to toxicity). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. The specific guidance for pembrolizumab (MK-3475) dose calculation, reconstitution, preparation of the infusion fluid, and administration are included in the Pharmacy Manual.

10.2.3. Carboplatin

Calculation of Carboplatin Dose

Carboplatin Dose will be based on the Calvert Formula

Carboplatin dose (mg) = AUC of 6 x (GFR + 25)

GFR is estimated using the Cockroft-Gault formula for creatinine clearance:

$$\frac{(140\text{-patient's age}) \times (\text{patient's weight in kilograms})}{72 \times \text{patient's serum creatinine}}$$

*For females, multiply the result by 0.85

Actual body weight, not ideal body weight will be used. This value will substitute for GFR in the Calvert formula above.

Use the serum Cr value reported by the laboratory; do not apply any correction factors to the reported value.

The maximum CrCl that can be used in this calculation for both women and men is 125 mL/min.

In the case of low creatinine values resulting in high CrCl values that seem to overestimate renal function, a 24-hour urine collection for determination of CrCl is recommended.

10.2.4. Paclitaxel

For all courses where paclitaxel is to be administered, it is recommended that a preparative regimen be employed one hour prior to the treatment regimen on that day to reduce the risk associated with hypersensitivity reaction. This regimen should include a standard dose of

dexamethasone (either IV or PO), an antihistamine H1 (diphenhydramine 25 – 50 mg IV or orally, or equivalent of alternate H1 blocker), and a standard dose of anti-histamine H2 (such as cimetidine, ranitidine, or famotidine). The specific regimen used may be per institutional standard.

Paclitaxel will be infused over 3 hours. Due to risk of immediate hypersensitivity reaction, paclitaxel should be infused prior to carboplatin. Carboplatin will be administered as a 30 minute infusion following paclitaxel administration.

10.2.5. Pemetrexed

Pemetrexed premedications may be used as per institutional standard. The following guidelines may be considered.

- Folic acid: Start a low-dose oral folic acid preparation or multivitamin with folic acid at least 1 week before the first pemetrexed dose and continue for 21 days after the last dose of pemetrexed.

- Vitamin B12: vitamin B12 1000 mcg IM injection. A vitamin B12 injection must be administered at least 1 week before the initial pemetrexed dose and repeated every 3 cycles while on pemetrexed.

- Dexamethasone: Dexamethasone (4 mg orally or equivalent) should be administered BID daily the day before, day of, and the day after each dose of pemetrexed for a total of 6 doses/cycle.

11. Data And Specimen Submission, Trial Procedures

11.1. Data Collection and Submission

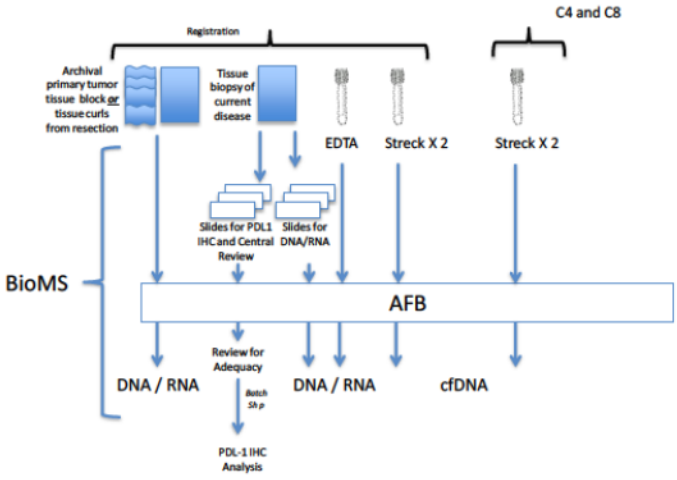
Data collection for this study will be done through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in AFT CTMS System.

12. Biospecimen collection, Shipping and processing

Tumor tissue from an archival sample or newly obtained formalin fixed biopsy of a tumor lesion not previously irradiated must be collected for integrated correlative PD-L1 biomarker analysis. A fine needle aspirate or cytologic specimen will not be accepted. Needle or excisional biopsies, or resected tissue is required. No systemic antineoplastic therapy may be administered between this biopsy and initiating study medication. Only patients with an adequate tissue biopsy submission are eligible for enrollment.

- The AFT Biorepository at Washington University is the central laboratory to receive these samples.

12.1. BIOSPECIMEN COLLECTION SCHEMA



12.1.1. Biospecimen Logging and Tracking (AFT BioMS)

Use of the AFT Biospecimen Management System (AFT.BioMS) is required for enrollment and all specimens must be logged and shipped via this system. AFT BioMS is a web-based system for logging and tracking all biospecimens collected on AFT trials. Authorized individuals may access AFT.BioMS at the following URL: https://aftbioms.wustl.edu using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the AFT.BioMS system, please refer to the 'Help' links on the AFT.BioMS webpage to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: [redacted] For assistance in using the application or questions or problems related to specific specimen logging, please contact: [redacted]

Staff members should familiarize themselves with the AFT.BioMS system and confirm that they are able to log into the system, prior to registering patients to the trial.

Please note that the AFT.BioMS system is independent from the BioMS system used for NCI-sponsored trials and requires different log on credentials.

After logging collected specimens in AFT.BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

12.1.2. Biospecimen Shipping

Biospecimen shipping kits will be available for collecting and shipping biospecimens at baseline and C4 and C8 collection time points. Biospecimen collection and shipping kits may be ordered through the AFT.BioMS system. A kit for each time point must be requested independently. Kits will be shipped to sites within 10 working days of request. Since the shipping kits contain specialized components needed for tissue and blood collection, please make certain a kit has been ordered at least 10 days prior to patient registration. Also, note that since some kit component expire, kits should not be ordered more than 90 days prior to an anticipated collection. No more than three shipping kits will be sent per request.

Although biospecimens may be shipped in batches, note that:

1. Slides of the biopsy lesion for PD-L1 biomarker analysis **MUST** be received before the patient can be registered to the therapeutic trial.
2. Whole blood collected in EDTA tubes must be shipped within 24 hours of collection.
3. Whole blood collected in BCT tubes must be shipped within 72 hours of collection.

All submitted biospecimens must be physically labeled with the AFT patient number, patient's initials and date of specimen collected. A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens. A printed, de-identified copy of the institutional surgical pathology report corresponding to the tissue / slides that are being submitted should also be included with the shipment. Please be sure to use a method of shipping that is secure and traceable. Ship specimens on Monday through Thursday only. Shipping by overnight service to assure receipt is required. Do not ship specimens on Fridays or Saturdays. All specimens should be sent to the following address:

AFT Biorepository at Washington University
c/o Siteman Cancer Center Tissue Procurement Core
425 S. Euclid Ave.
BJCIH Building, Room 5120
St. Louis, MO 63110-1005
[redacted]

Additional Resource Information:

BioMS.AFT Resource Site:
[redacted]

BioMS.AFT User manual:
[redacted]

12.1.3. Biospecimen collection

Screening/Enrollment
The following biospecimens will be collected at screening:

A. MANDATORY- Slides for PD-L1 staining. Five (5), four micron, unstained tumor tissue sections from a formalin fixed / paraffin embedded tissue block containing tumor lesion should be cut and mounted onto charged slides. Slides should be labeled with the patient study ID, institutional surgical pathology number, and serial cut number, i.e. 1-5. Please note specific instructions for slides to be cut for PD-L1 staining. Please use the slides included with the kit and follow the instructions provided for cutting and packaging these slides for shipment.

B. Slides for correlative genomic studies. If tissue is available, an additional set of five unstained, eight micron tumor tissue sections from the same formalin fixed / paraffin embedded tissue block used for PD-L1 staining should be cut and mounted onto plain slides. These slides can be cut serially after the mandatory slides (A). Slides should be labeled with the patient study ID, institutional surgical pathology number, and serial cut number.

If an institution is unable or unwilling to cut tumor slides as outlined above and it is permissible by the institution's surgical pathology department, a single representative tumor block may be submitted instead of slides. The tumor block will be cut at the AFT Biorepository for correlative science studies and returned to the institution at the conclusion of the study.

C. Original tumor tissue for correlative genomic studies. If submitting tissue from a recently recurrent or progressive lesion, and an additional tumor tissue block from the primary surgical resection is also available, a representative tumor tissue block or five unstained, eight micron tumor tissue sections mounted onto plain slides should be submitted as well. Slides should be labeled with the patient study ID, institutional surgical pathology number, and serial cut number.

D. Whole blood in EDTA tube. Collect 7 cc of whole blood by standard venous phlebotomy into the EDTA tube provided. Tube should be labeled with patient study number, patient initials, and date / time of collection. After collection invert the tube 10 times to ensure adequate mixing and anticoagulation. Store tube at room temperature until ready for shipment.

E. Whole blood in BCT (Streck) tube. Collect 8 cc of whole blood by standard venous phlebotomy into each of the two BCT (Streck) tube provided (8cc per tube). Tube should be labeled with patient study number, patient initials, and date / time of collection. After collection invert the tubes 10 times to ensure adequate mixing and preservation. Store tubes at room temperature until ready for shipment.

12.1.4. Subsequent Cycles

A. **Whole blood in BCT (Streck) tube to be collected at Cycle 4 and Cycle 8 as per Table 2.** Collect 8 cc of whole blood by standard venous phlebotomy into each of the two BCT (Streck) tubes provided (8cc per tube). Tube should be labeled with patient study number, patient initials, and date / time of collection. After collection invert the tubes 10 times to

ensure adequate mixing and preservation. Store tubes at room temperature until ready for shipment.

12.1.5. Biospecimen Processing

Upon receipt at the AFT Biorepository, biospecimens will be processed as follows:

A. MANDATORY - Slides for PD-L1 staining. One of 5 slides submitted (Slide #3) will be stained by H/E and reviewed by a qualified pathologist for percentage tumor cellularity, percentage total cellularity, percentage necrosis, and percentage lymphocytic invasion. If the submitted specimen is deemed inadequate, the site may BE REQUESTED to resubmit a new biopsy specimen. Slides from each patient will be batched shipped from the AFT biorepository to QualTex Laboratories for PD-L1 staining and central review. After staining and central review, slides will be returned to the AFT biorepository, and stored and imaged for future use.
B. Additional tissue slides from biopsy lesion and/or initial tumor diagnosis. All tissue received for secondary correlative genomic studies will be reviewed for tumor tissue cellularity. Where necessary, areas of high tumor cellularity will be macrodissected to enrich for tumor cells. Tissue sections or macrodissected tumor slides will be used for DNA and RNA isolation and stored for secondary genomic correlative studies.

C. Whole blood in EDTA tube. Following AFT Biorepository SOPs, whole blood white cells ("buffy coat") will be isolated and used to extract constitutional (white blood cell) genomic DNA, which will be stored for secondary genomic studies.

D. Whole blood in cell stabilization (Streck) tube. Following AFT Biorepository SOPs, plasma will be isolated from all BCT tubes by high speed centrifugation. Resulting plasma samples will be aliquoted and frozen in 4.5 ml aliquots, and subsequently used for cfDNA isolation and genomic studies.

12.2. TUMOR IMAGING AND CENTRAL REVIEW

12.2.1. Tumor imaging schedule

The initial tumor imaging will be performed within 30 days prior to the first dose of trial treatment. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 30 days prior to the first dose of trial treatment. On-study imaging during the first 8 cyclers of therapy will be performed every 6 weeks (42 ± 7 days) after the first dose of trial treatment or more frequently if clinically indicated. Patients on all 2 arms receiving pembrolizumab (MK-3475) alone after cycle 8 will be imaged every 9 weeks (63 ± 7 days) The timing for imaging studies should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab (MK-3475) cycle frequencies. The same imaging technique should be used in a patient throughout the trial. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for patient management.

12.2.2. Imaging core lab Central Review

Scans will be submitted to the Imaging Core Lab (ICL) at Ohio State University for central review within3 days of imaging acquisition.

The complete CT scans will be submitted to the Imaging Core Laboratory in digital DICOM format; **BMP files, JPG files, or hard copies (films) are not acceptable.**

The entire imaging data in DICOM format must be submitted to the ICL within no more than **30 business days** once the image acquisition is completed at site.

De-identify the patient data using institutional procedures to remove patient name and medical record number while preserving the **patient ID number** and **protocol number** of the AFT trial. The de-identified digital images may be burned to a CD or transferred to a PC based system for further electronic data transfer purposes.

Data can be electronically transferred to the Imaging Core Lab by **1) Web Transfer; 2) FTP transfer**:

1. Web Transfer:

Any PCs with internet access and web browser (e.g., Internet Explorer, Mozilla Firefox) can be used to transfer DICOM images and other required files to the ICL through website upload.imagingcorelab.com. The standard Web Transfer information will be provided separately through the specific trial e-mail, per the request by participating sites before their first data submission.

2. FTP Transfer:

Any FTP software can be used to initiate access to the secure FTP Server of the ICL. The standard FTP access information will be provided separately through the specific trial e-mail, per the request by participating sites before their first data submission.

Send an e-mail notification to inform the Imaging Core Lab at the specific trial email of the data submission **once the data transfer is completed**.

3. Shipment/Mail (not preferred but accepted):

If the above electronic data transfers cannot be achieved, the de-identified images in DICOM format can be burned to a CD, labeled with info of patient ID, study date, baseline/follow-ups on the CD cover, and mailed to the ICL at:

Imaging Core Lab
Department of Radiology
The Ohio State University Medical Center
[redacted]

Any questions or problems about the data transfer to the Imaging Core Lab, email the ICL at the specific trial email AFT09@ImagingCoreLab.com, or call the ICL IT group at [redacted] for help.

13. Dose and Treatment Modifications, Concomitant Medications, Supportive Care

13.1. Dose Modification

13.1.1. Chemotherapy

General guidelines

If more than one of the dose modifications applies, use the most stringent (i.e., the greatest dose reduction).

The dose levels outlined in the table below are used for dose modifications. If dose reduction below level -2 is required, discontinue the drug causing the toxicity and continue the other drug (s). If both drugs require discontinuation due to toxicity, patients may be allowed to transition to or return to treatment with pembrolizumab upon discussion with study chair/AFT.

Table 5. Dose modification guidelines for drug-related adverse events (chemotherapy).

Dose Level	Pemetrexed	Carboplatin	Paclitaxel
0	500 mg/m^2	100%	200 mg/m^2
-1	375 mg/m^2	75%	150 mg/m^2
-2	250 mg/m^2	50%	100 mg/m^2

Hematologic Toxicity

For ANC < 1500 or platelets < 100,000 on day 1, delay treatment with carboplatin and pemetrexed or paclitaxel until ANC ≥ 1500 and platelets ≥ 100,000, then resume at the previous doses. If treatment is delayed for ≥ 3 weeks, discontinue protocol therapy.

For platelets < 25,000, decrease carboplatin and pemetrexed or paclitaxel by one dose level for all subsequent doses.

For febrile neutropenia occurring at any time during a cycle, decrease carboplatin and pemetrexed or paclitaxel by one dose level for all subsequent doses.

For a second episode of thrombocytopenia < 25,000 or febrile neutropenia, decrease carboplatin and pemetrexed or paclitaxel by one dose level for all subsequent doses.

Gastrointestinal Toxicity

Mucositis

For grade 3 or 4 mucositis despite prophylactic vitamin supplementation, delay carboplatin and pemetrexed until toxicity resolves to ≤ grade 2. When mucositis resolves to ≤ grade 2,

resume carboplatin at the previous dose and pemetrexed with one level dose reduction for all subsequent cycles. If treatment is delayed ≥ 3 weeks, discontinue protocol therapy.

Diarrhea

See Section 13.4 for supportive care guidelines if the patient is also receiving concurrent pembrolizumab (MK-3475). For grade 3 or 4 diarrhea despite antidiarrheal medication and prophylactic vitamin supplementation, delay carboplatin and pemetrexed or paclitaxel. Once diarrhea resolves to ≤ grade 2, resume therapy with carboplatin at the previous dose and one dose level reduction of pemetrexed or paclitaxel for all subsequent cycles. If treatment is delayed for ≥ 3 weeks, discontinue all protocol therapy.

Nephrotoxicity

If creatinine clearance is < 45 ml/min, delay carboplatin and pemetrexed. When CrCl improves to ≥ 45 ml/min, resume carboplatin and pemetrexed at the previous doses. If treatment is delayed/interrupted for ≥ 3 weeks, discontinue treatment with chemotherapy.

Skin Toxicity

See Section Section 13.4 for supportive care guidelines if the patient is also receiving concurrent pembrolizumab (MK-3475).

Grade 3: Hold carboplatin and pemetrexed or paclitaxel until toxicity improves to ≤ grade 1, then resume carboplatin at the previous dose level and pemetrexed or paclitaxel with one dose level reduction. If chemotherapy is held for skin toxicity for > 3 weeks, discontinue protocol therapy.

Pulmonary Toxicity

See Section 13.4 for supportive care guidelines if the patient is also receiving concurrent pembrolizumab (MK-3475).

If a patient is receiving chemotherapy alone (arm A or arm B): Pemetrexed and paclitaxel may rarely cause pulmonary toxicity characterized by dyspnea and interstitial pneumonitis. The pneumonitis will usually respond to steroids. Other causes of dyspnea should be excluded (i.e. anemia, cardiac, COPD exacerbation, etc) before concluding that pulmonary toxicity is chemotherapy related.

For grade 2 pulmonary toxicity due to paclitaxel or pemetrexed, hold protocol treatment. Patients may be retreated with a two level dose reduction in pemetrexed or paclitaxel on the next and all subsequent cycles at the physician's discretion if pulmonary symptoms improve to grade 0-1 within 3 weeks.

For grade 3 or 4 pulmonary toxicity, discontinue chemotherapy.

Hypersensitivity Reactions

See Section 13.4 for supportive care guidelines if the patient is also receiving concurrent pembrolizumab (MK-3475).

For grade 3 allergic or anaphylaxis reactions thought to be due to carboplatin or paclitaxel, discontinue treatment with chemotherapy.

Other Non-Hematologic

Grade 3 toxicity (not described above). Delay all drugs until toxicity improves to ≤ grade 2, then resume treatment with one dose level reduction for each agent. If treatment is delayed for > 3 weeks, discontinue chemotherapy.

Grade 4 toxicity (not described above). Discontinue all chemotherapy.

13.2. PEMBROLIZUMAB (MK-3475)

Adverse events (both non-serious and serious) associated with pembrolizumab (MK-3475) 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 (MK-3475) must be withheld for drug-related toxicities and severe or life-threatening AEs as per Tables 6 and 7 below. See Section 13.4 for supportive care guidelines, including use of corticosteroids.

Pembrolizumab (MK-3475) will be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per Tables 6 and 7 below.

Table 6. Dose modification guidelines for drug-related hematologic adverse events (pembrolizumab (MK-3475)).

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Patient (after consultation with Sponsor)
Hematological Toxicity	1, 2	No	N/A	N/A	N/A
	3* *Excluding Grade 3 neutropenia, anemia, and thrombocytopenia	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
	4	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week	

Table 7. Dose modification guidelines for drug-related adverse events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab (MK-3475) for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab (MK-3475) when patients are clinically and metabolically stable.
Hypophysitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism	2-4	Therapy with pembrolizumab (MK-3475) can be continued while treatment for the thyroid disorder is instituted	Therapy with pembrolizumab (MK-3475) can be continued while treatment for the thyroid disorder is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[2]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.
[1] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.
[2] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued after consultation with the Study PI. With investigator and Study PI agreement, patients with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled.

Patients who experience a recurrence of the same severe or life-threatening event at the same grade or greater with re-challenge of pembrolizumab (MK-3475) should be discontinued from trial treatment.

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

13.3. 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 Study Chair. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient's primary physician. For patients receiving standard chemotherapy regimens, sites may follow local investigator discretion for the administration of pre-medications. However, the decision to continue the patient on trial therapy or vaccination schedule requires the mutual agreement of the Investigator, the Sponsor, and the patient.

13.3.1. Acceptable concomitant medications

All treatments that the investigator considers necessary for a patient'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.

13.3.2. Prohibited concomitant medications

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

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab (MK-3475)
- Radiation therapy
  - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology **or** as a supportive care medication if the patient is receiving concurrent chemotherapy (arm C). Inhaled corticosteroids are allowed. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

  Patients 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. Patients 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.

13.4. RESCUE MEDICATIONS AND SUPPORTIVE CARE

13.4.1. Supportive Care Guidelines for Pembrolizumab (MK-3475)

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

- Diarrhea: Patients should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.
  - In patients with severe enterocolitis (Grade 3), pembrolizumab (MK-3475) will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of

prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.

- In patients with moderate enterocolitis (Grade 2), pembrolizumab (MK-3475) should be withheld and anti-diarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.

- All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.

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

- Immune-related adverse events: Please see Section 13.4.3 below regarding diagnosis and management of adverse experiences of a potential immunologic etiology.

- Management of Infusion Reactions: Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting.

Table 8 below shows treatment guidelines for patients who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 8. 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 patient is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the patient 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 patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Patient may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Patient is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

13.4.2. Supportive care guidelines for Pneumonitis

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

Table 9. Recommended Approach to Handling Pneumonitis

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

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

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

13.4.3. Supportive care guidelines for events of Clinical interest/immune-related adverse events (IRAEs)

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

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE. Patients who develop a Grade 2 or higher irAE should be discussed immediately with the Study PI.

Recommendations to managing irAEs not detailed elsewhere in the protocol are detailed in Table 9.

Table 10. General Approach to Handling irAEs

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

13.5. OTHER CONSIDERATIONS

13.5.1. Contraception

Pembrolizumab (MK-3475) may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab (MK-3475) has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. patient 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).

Patients 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 15.2.4-Reporting of Pregnancy and Lactation to AFT. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

13.5.2. Use in pregnancy

If a patient inadvertently becomes pregnant while on treatment with pembrolizumab (MK-3475), the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the AFT without delay and within 24 hours 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 AFT. If a male patient impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to AFT and followed as described above. AFT will report pregnancy outcomes to Merck.

13.5.3. Use in Nursing Women

It is unknown whether pembrolizumab (MK-3475) 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.

14. MEASUREMENT OF EFFECT

RECIST version 1.1 will be used for assessment of tumor response for assessment of the primary endpoint. Immune related response criteria will be utilized to make patient management decisions during the trial.

14.1. SCHEDULE OF EVALUATIONS:

The initial tumor imaging will be performed within 30 days prior to the first dose of trial treatment. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 30 days prior to the first dose of trial treatment. On study imaging for the first 8 cycles on all 2 arms will be performed every 6 weeks (42 ± 7 days) after the first dose of trial treatment or more frequently if clinically indicated. CT timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab (MK-3475) cycle frequencies. On study imaging while patients are receiving pembrolizumab (MK-3475) alone after cycle 8 will be performed every 9 weeks (63 ± 7 days).

After the first documentation of response per irRC, confirmatory scans may be performed as early as 28 days later; alternatively, the scan performed at the next scheduled time point (e.g. every 42 ± 7 days) may be used as confirmation for response. After the first documentation of progression (if the patient is clinically stable) per irRC, confirmatory scans will be performed between 4 and 6 weeks from then.

After the first documentation of progression while receiving pembrolizumab (MK-3475) alone it is at the discretion of the investigator to keep a clinically stable patient on trial treatment or to stop trial treatment until repeat imaging performed 4-6 weeks later confirms progression. Clinical stability is defined as:

- Absence of symptoms and signs indicating clinically significant progression of disease (including worsening laboratory values).
- NO decline in ECOG performance status.
- Absence of rapid progression of disease or progressive tumor at critical anatomical sites (e.g. cord compression) requiring urgent alternative medical intervention.

Patients that are deemed clinically unstable are not required to have repeat imaging for confirmation. If progression is confirmed, then the patient will be discontinued from trial treatment. If progression is not confirmed, then the patient should resume/continue trial treatment and have their next scan according to the every 6-week (42 ± 7 days) schedule from the first dose of study treatment. When feasible, patients should not be discontinued until progression is confirmed.

Imaging during the follow-up period is to be repeated every 9 weeks (63 ± 7 days) for patients who discontinue trial treatment for reasons other than disease progression until the patient experiences confirmed disease progression or starts a new antineoplastic therapy.

Trial eligibility will be according to RECIST 1.1 criteria; however disease response on trial will be assessed using irRC by investigators.

The same imaging technique should be used in a patient throughout the trial.

14.2. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) 1.1 CRITERIA FOR EVALUATING RESPONSE IN SOLID TUMORS

RECIST version 1.1* will be used in this study for assessment of tumor response.

* As published in the European Journal of Cancer:

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

14.2.1. Definitions of Measurable and Non-Measurable Disease

Measurable Disease

A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan,

A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Non-Measurable Disease

All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥ 1.0 to < 1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT), are considered as non-measurable as well.

Note: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis < 1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

14.2.2. Guidelines for Evaluation of Measurable Disease

Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

Acceptable Modalities for Measurable Disease:

Conventional CT: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness be at least 2.5 mm but no greater than 5 mm.

Measurement at Follow-up Evaluation:

- A subsequent scan must be obtained *not less than 4* weeks following initial documentation of an objective status of either complete response (CR) or partial response (PR).
- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of *not less than 6* weeks.
- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met

criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

Measurement of Treatment/Intervention Effect
Target Lesions & Target Lymph Nodes

- Measurable lesions up to a maximum of 5 lesions representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

  Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- **Baseline Sum of Dimensions (BSD):** A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- **Post-Baseline Sum of the Dimensions (PBSD):** A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.
- **The minimum sum of the dimensions (MSD)** is the minimum of the BSD and the PBSD.

Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed.

14.2.3. Response Criteria

All target lesions and target lymph nodes followed by CT must be measured on re-evaluation at evaluation times specified in Section 14.2.1 & 14.2.2. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

Evaluation of Target Lesions

- **Complete Response (CR):** All of the following must be true:
  a. Disappearance of all target lesions.
  b. Each target lymph node must have reduction in short axis to < 1.0 cm.
- **Partial Response (PR):** At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD.
- **Progression (PD):** At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
  b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD. In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- **Complete Response (CR):** All of the following must be true:
  a. Disappearance of all non-target lesions.
  b. Each non-target lymph node must have a reduction in short axis to <1.0 cm
- **Non-CR/Non-PD:** Persistence of one or more non-target lesions or non-target lymph nodes.
- **Progression (PD):** At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

For Patients with Measurable Disease

Table 11. Target and Non-Target Lesions

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated	Yes	PD

Symptomatic Deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration.

Definitions of analysis variables

Formal definitions of variables used in analyses can be found in the Statistical Considerations section of the protocol.

14.3. IMMUNE RELATED RESPONSE CRITERIA

For all patients who experience disease progression on study, the date noted of disease progression is the time of the scan where it is originally detected, and not the following date of the confirmatory scan.

Definitions of measurable and non-measurable disease.

Measurable disease: Neoplastic masses that can be precisely measured in 2 in-plane perpendicular diameters. Both its longest diameter and its longest perpendicular must be greater than or equal to 10 mm or 2 times the axial slide thickness if axial slice thickness is greater than 5 mm. Lymph nodes must have a short-axis line-length of ≥ 15 mm. Malignant lymph nodes must be measurable in 2 perpendicular diameters. Both its longest diameter and its longest perpendicular must be greater than or equal to 15 mm. The quantitative endpoint will be defined as the product of the longest diameter with its longest perpendicular.

Non-measurable disease: Non-measurable lesions are those that are not suitable for quantitative assessment over time. These include:

- Neoplastic masses which are too small to measure, because their longest uninterrupted diameter or longest perpendicular are less than 10 mm.

- Neoplastic masses whose boundaries cannot be distinguished. This includes masses that cannot be demarcated from surrounding tissue because of inadequate contrast, masses with overly complex morphology, or those with highly heterogeneous tissue composition.

- Other types of lesions that are confidently felt to be represent neoplastic tissue, but difficult to quantify in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic disease, cystic lesions, ill-defined abdominal masses, etc.

For irRC, only target lesions selected at baseline and measurable new lesions are taken into account.

At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated.

At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥ x 5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total time-point tumor burden.

Overall response using irRC:

- **Complete Response (irCR):** Complete disappearance of all tumor lesions (whether measurable or not, and no new lesions). CR must be confirmed by repeated consecutive assessments made no less than 4 weeks from the date first documented.

- **Partial Response (irPR):** Decrease in SPD of 50% or greater by a consecutive assessment at least 4 weeks after first documentation.

- **Stable Disease (irSD):** Failure to meet criteria for irCR or irPR, in absence of irPD.

- **Progressive Disease (irPD):** at least 25% increase in SPD relative to nadir (minimum recorded tumor burden). Confirmation by a repeat, consecutive assessment no less than 4 weeks from the data first documented.

Please note other key differences between irRC and the original WHO criteria:

- New measurable lesions will be incorporated into the SPD.

- New non measurable lesions do not define progression but preclude irCR.

- Non-index lesions contribute to defining irCR (complete disappearance required).

IrRC for the current protocol is adopted from the following reference:

Wolchok, JD, Hoos, A, O'Day S, et al., Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. Clinical Cancer Research, 2009 Dec 1; 15 (23): 7412-20. Epub 2009 Nov 24.

15. END OF TREATMENT/INTERVENTION

15.1. DURATION OF TREATMENT

15.1.1. CR, PR, or SD

Patients who are in CR, PR or SD will continue on therapy per the study calendar. After treatment is discontinued, patients will be followed per the study calendar.

15.1.2. Disease Progression

Remove from protocol therapy any patient with disease progression by irRC while receiving pembrolizumab (MK-3475) document details, including tumor measurements, on data forms. After disease progression, patients should be followed for survival per the study calendar (Section 9).

15.1.3. Discontinuation of study agent

If the patient discontinues pembrolizumab (MK-3475) patients should be followed for survival per the study calendar (Section 9).

15.2. PATIENT WITHDRAWAL/DISCONTINUATION CRITERIA

15.2.1. Patient Withdrawal

Patients 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 patient may be

withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued.

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

- The patient or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression by irRC while receiving pembrolizumab (MK-3475)

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

- Unacceptable adverse experiences (see Section 15)
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the patient
- The patient has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The patient is lost to follow-up
- Completed 24 months of treatment with pembrolizumab (MK-3475)
    - *Note: 24 months of study medication is calculated from the end of 8 cycles of sequencing chemo/pembrolizumab (MK-3475)*
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 9. After the end of treatment, each patient will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment). Patients 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. Treatment-related toxicities will be resolved before participants enter the clinical follow-up phase. After documented disease progression each patient will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

15.3. DEFINITIONS AND FOLLOW-UP REQUIREMENTS

Definition of ineligible patients: A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible. Patients who are deemed ineligible

may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient were to continue protocol treatment. Notification of the local IRB may be necessary per local IRB policies.

Definition of clinical follow-up: The follow-up period where the study participant is no longer receiving treatment, but is still following the study calendar for tests, exams, and correlative endpoints (e.g., specimen collection, quality of life, disease assessments as required by the study).

Definition of survival only follow-up: The follow-up period where the study participant is monitored for long-term endpoints, is no longer receiving study treatment, and is not required to follow the study calendar for tests, exams, and correlative endpoints (e.g. specimen collection, quality of life, disease assessments as required by the study). In this follow-up period, there is a schedule in which case report forms should be submitted, but the physician visits are based on the standard of care.

15.4. Follow-up for Ineligible Patients

Study participants who are registered to the trial and receive any protocol treatment but deemed ineligible must follow the schedule of assessments detailed in Section 9.

15.5. Follow-up for Patients Never Receiving Protocol Intervention

Study participants who are enrolled into the trial but who never go on to receive study intervention must still complete follow-up requirements as specified below.

Screening, on-study, endpoint (e.g., relapse or progression), and survival data submission required.

16. Adverse Events

An adverse event (AE) 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 pembrolizumab (MK-3475) 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 onset of menses or menopause occurring at a physiologically appropriate time.

Adverse events may occur during the course of the use of pembrolizumab (MK-3475) during this study or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

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

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. The CTCAE is available at ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms, using the codes provided.

16.1. Routine Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs will be recorded as part of medical history during Screening. Any new AEs or increase of a documented AE from screening/history will be recorded from the time of the first study related procedure through 30 days following cessation of treatment. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 9. All adverse events are entered into the eCRF in Rave.

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

16.2. Expedited Adverse Event Reporting

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Investigators are required to notify the AFT and their Institutional Review Board if a patient has a reportable serious adverse event. **The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 will be utilized for AE reporting.** The CTCAE is identified and located on the CTEP website at: ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE. SAEs/IARs must be entered into the eCRF and into the Novella Argus Safety Management System, as applicable within 24 hours of learning of the event. These will be entered into the Argus system within 24 hours of learning of the event. This will allow the safety monitor and monitor to review the information and assess the safety of the patient.

Note: All deaths on study require both routine reporting and reporting via the Argus Safety Reporting System, regardless of causality. Attribution to treatment or other cause should be provided.

16.2.1. Serious Adverse Event (SAE)

Serious adverse events will be recorded from the time of the first study related procedure through 90 days following cessation of treatment or initiation of a new antineoplastic therapy, whichever comes first and whether or not related to pembrolizumab (MK-3475).

Table 12. Serious Adverse Event Reporting Requirements

REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS

NOTE: Investigators **MUST** immediately report to the sponsor (AFT) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
7) Or is a new cancer (that is not a condition of the study).
8) Or is associated with an overdose.

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the AFT via the Argus Safety Reporting System within the timeframes detailed in the table below. The events will also require reporting into Argus Safety Reporting System. AFT will send SAE reports to Merck Global Safety within 2 working days.

Hospitalization	**Grade 1 Timeframes**	**Grade 2 Timeframes**	**Grade 3 Timeframes**	**Grade 4 & 5 Timeframes**
Resulting in Hospitalization > 24 hrs	Enter into ARGUS Safety Reporting System within 24 hours of the sites awareness of the event			
Not resulting in Hospitalization ≥ 24 hrs	Not required to enter into Argus Safety Reporting System		Enter into Argus Safety Reporting System within 24 hours of the sites awareness of the event	

Expedited AE reporting timelines are defined as:

- "All Grade 3, 4 and 5 AEs: 24-Hour; 4 Calendar Days" - The AE must initially be reported via Argus Safety Reporting System ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ **4** calendar days of the initial 24-hour report.

  o "All Grade 1 and 2 AEs resulting in hospitalization or prolonged hospitalization: 24-Hour; 10 Calendar Days" - The AE must initially be reported via Argus Safety Reporting System ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ **10** calendar days of the initial 24-hour report.

- .

All serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention, through 90 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the pembrolizumab (MK-3475), require reporting into Argus Safety Reporting System within 24 hours of awareness of the event.

NOTE: Deaths occurring outside of the serious adverse event reporting period that are clearly due to progressive disease should **NOT** be reported via Argus Safety Reporting System, but rather should be reported via routine reporting methods in the Rave data capture system. Deaths occurring within the reporting window, even if considered to be related to disease progression as the cause of death should be reported within ARGUS Safety Reporting System with death noted as the outcome of the event.

16.2.2. Events of Clinical Interest and Immune Related Adverse Events

Selected non-serious and serious adverse events are also known as (ECI) and/or Immune Related Adverse Events (irAEs) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours within ARGUS Safety Reporting System. ECIs/irAEs and all SAEs, that occur in any patient from the date of first study related procedure through 90 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the pembrolizumab (MK-3475), must be reported within ARGUS Safety Reporting System within 24 hours and AFT will report to Merck Global Safety within 2 working days.

ECIs/ir AEs for this trial include:

1. An overdose of pembrolizumab (MK-3475), as defined in Section 16.2.3. Definition of an Overdose for This Protocol and Reporting of Overdose to AFT, 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.

3. In the event a patient develops any of the following AEs, a detailed narrative of the event should be reported as an ECI/irAE within ARGUS Safety Reporting System within 24 hours and AFT will report to Merck Global Safety within 2 working days of the event:

a. Grade ≥ 3 diarrhea
b. Grade ≥ 3 colitis
c. Grade ≥ 2 pneumonitis
d. Grade ≥ 3 hypo- or hyperthyroidism

Section 13.4.3 above provides guidance regarding identification, evaluation and management of ECIs and irAEs. Additional ECIs are identified in this section and also need to be reported within the ARGUS Safety Reporting System within 24 hours and AFT will report to Merck Global Safety within 2 working days of the event.

Patients should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and patients should be asked for signs and symptoms suggestive of an immune-related event.

Patients who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

16.2.3. Definition of an Overdose for this Protocol and Reporting of Overdose to AFT

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

If a dose of pembrolizumab (MK-3475) meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

16.2.4. Reporting of Pregnancy and Lactation

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 patient (spontaneously reported to them), including the pregnancy of a male patient's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the patient initiates new anticancer therapy, whichever is earlier. All patients and female partners of male patients who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

16.3. EVALUATING ADVERSE EVENTS

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

All adverse events regardless of CTCAE grade must also be evaluated for seriousness. See Table 13 below for additional guidance.

Table 13. Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events.

V4.0 CTCAE Grading	**Grade 1**	Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.
	Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
	Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.
	Grade 4	Life threatening consequences; urgent intervention indicated.
	Grade 5	Death related to AE
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Pembrolizumab (MK-3475) that:	
	†Results in death; or	
	†Is life threatening; or places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or	
	†Results in or prolongs an existing inpatient hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†Is a congenital anomaly/birth defect (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new cancer; (that is not a condition of the study) or	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Pembrolizumab (MK-3475) to be discontinued?	

Relationship to test drug	Did the Pembrolizumab (MK-3475) cause the adverse event? The determination of the likelihood that the Pembrolizumab (MK-3475) 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 Pembrolizumab (MK-3475) and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Pembrolizumab (MK-3475) caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Pembrolizumab (MK-3475) 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 Pembrolizumab (MK-3475)? 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 Pembrolizumab (MK-3475) (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Pembrolizumab (MK-3475) discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Pembrolizumab (MK-3475); or (3) the trial is a single-dose drug trial); or (4) Pembrolizumab (MK-3475)(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Pembrolizumab (MK-3475) 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) Pembrolizumab (MK-3475) 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 PEMBROLIZUMAB (MK-3475), OR IF REEXPOSURE TO THE PEMBROLIZUMAB (MK-3475) 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 Pembrolizumab (MK-3475) 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 Pembrolizumab (MK-3475) relationship).**	
Yes, there is a reasonable possibility of Pembrolizumab (MK-3475) relationship.	There is evidence of exposure to the Pembrolizumab (MK-3475). The temporal sequence of the AE onset relative to the administration of the Pembrolizumab (MK-3475) is reasonable. The AE is more likely explained by the Pembrolizumab (MK-3475) than by another cause.	
No, there is not a reasonable possibility Pembrolizumab (MK-3475) relationship	Subject did not receive the Pembrolizumab (MK-3475) OR temporal sequence of the AE onset relative to administration of the Pembrolizumab (MK-3475) is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)	

17. DRUG INFORMATION

17.1. 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 14.

Table 14. Product Descriptions

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

17.2. PACKAGING AND LABELING INFORMATION

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

17.3. CLINICAL SUPPLIES DISCLOSURE

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

17.4. 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.

17.5. 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 patients 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.

18. STATISTICAL CONSIDERATIONS

The primary objective of this randomized phase II trial is to determine the overall response rate (ORR per RECIST 1.1) in chemotherapy naive patients with stage IV NSCLC after the administration of standard platinum-based chemotherapy before pembrolizumab (MK-3475) (arm A) and administration of pembrolizumab (MK-3475) administered before standard platinum-based chemotherapy (arm B).

For our ultimate goal to select the most promising one from the two experimental regimens to investigate it further in a larger comparative phase II/III trial, we will use "picking the winner" design.[58] In the "picking the winner" design, we will select the treatment regimen with the best ORR per RECIST 1.1 for further investigation with no restriction on the minimal magnitude of observed ORR differences and the minimal number of responders. The minimal difference in the numbers of responses of the two arms is 1. To be selected as the "winner", one treatment arm must have at least 1 more response than the other. A total of 90 eligible patients will be randomized with 1:1 ratio to the two arms with stratification on smoking history (never, previous or current smoker) and histology (squamous vs. non-squamous).

18.1. SAMPLE SIZE JUSTIFICATION

When pembrolizumab (MK-3475) was given as single agent for advanced NSCLC, the overall response rates (ORRs) assessed by the immune-related response criteria and by RECIST 1.1 criteria were 24% and 21%, respectively. We expect when standard chemotherapy is combined with pembrolizumab (MK-3475), the ORR will be at least 30% for an unselected chemotherapy naive NSCLC population. For the purpose of sample size justification, we assume the ORR for arm A and arm B are 45% and 30%, respectively. Under this assumption the study with 45 patients treated on each arm will choose the most promising arm with at least 91% probability based on the observed ORRs, the least promising arm with at most 6% probability and make an inconclusive decision with approximately 3% probability. The table below displays the performance of this trial when the ORRs of the two arms are slightly different from the scenario we assume. The probability of inconclusive is the probability that the numbers of responses of two treatments are the same. In addition, with 45 patients on each arm, the study will produce a two-sided 90% confidence interval with a width equal to 0.260 (0.242) when the observed ORR is 0.45 (0.30).[59]

ORR for A	ORR for B	Prob. Choosing A	Prob. Choosing B	Prob. Inconclusive
0.3	0.3	0.454	0.4542	0.09161
0.3	0.2	0.837	0.10987	0.05314
0.45	0.35	0.807	0.13977	0.05346
0.45	0.3	0.915	0.05556	0.02904
0.45	0.2	0.994	0.00331	0.00314

18.2. ACCRUAL AND FOLLOW UP

Assuming a 5% cancellation and ineligibility rate, the study will register a total of 95 patients. In a similar patient population, CALGB 9730 and CALGB 30801 accrued approximately 15 patients per month. At an enrollment rate of 8 patients per month, the trial will reach its accrual target in approximately 12 months. All randomized patients will be followed for response, progression free survival and overall survival for 30 months after the last enrollment.

18.3. ADVERSE EVENTS MONITORING

If 5 or more of the first 20 patients in any of the two arms experience grade 4/5 non-hematologic adverse events that are probably, possibly, or definitely related to study treatment, OR if the rate of treatment-related deaths within the first 60 days exceeds 4 or more in an arm among the first 20 patients at any time, accrual to the study will be suspended to allow for investigation. After consideration by the study team, a decision will be made as to whether accrual can be resumed, potentially with modifications to entry criteria and/or study conduct.

18.4. STATISTICAL ANALYSIS PLAN

All randomized patients will be included in the primary analysis. Tumor response due to protocol treatments will be determined by RECIST 1.1. For each treatment arm ORR per RECIST 1.1 due to each type of treatment agent will be estimated and the exact 95% confidence interval will be provided. The combined ORR due to carboplatin-based - chemotherapy and pembrolizumab (MK-3475) up to the first 8 cycles will be estimated and their exact 95% confidence intervals will be given. For exploratory purpose, the difference of ORR per RECIST 1.1 between PD-L1 expression levels (positive vs. negative) will also be examined. Multivariate logistic regression will be used to evaluate the effects of treatment arm and PD-L1 levels on ORR while adjusting for other risk factors. The response duration of pembrolizumab (MK-3475) as well as its 95% confidence interval will be estimated separately for each arm. Response duration is defined as time from the first assessment of CR/PR until the first occurrence of PD, or until the date of death (if occurred within 1 year). The ORR per irRC will be defined and analyzed with the same approach as ORR per RECIST 1.1.

For each treatment phase (arm A: Cb+Pac/Pem 4 cycles, pembrolizumab (MK-3475) 4 cycles, pembrolizumab (MK-3475) up to 1 year; arm B: pembrolizumab (MK-3475) 4 cycles, Cb+Pac/Pem 4 cycles, pembrolizumab (MK-3475) up to 1 year, the cumulative response rate (RR) based on RECIST 1.1 and irRC will be calculated as well as their 95% CIs. The baseline measurement for irRC will be reset at the beginning of each pembrolizumab (MK-3475) phase, while the baseline measure for RECIST 1.1 will not be reset for each treatment phase.

Progression-free survival (PFS) will be defined with disease progression determined per RECIST 1.1 criteria. The median progression free survival (mPFS) and its 95% confidence interval will be estimated for each arm. Log rank test will be used to test the survival difference for descriptive purpose. The difference of PFS per RECIST 1.1 between PD-L1 expression levels (positive vs. negative) will also be characterized. Multivariable Cox regression will be used to evaluate the effect of treatment arms and PD-L1 expression levels on PFS while adjusting for other risk factors. Progression-free survival will also be defined according to the irRC criteria. PFS per irRC will be analyzed with the same approach of PFS per RECIST 1.1. Similar analyses will be conducted for overall survival (OS).

The analysis for PFS and OS will be conducted after about 67% patients experienced the corresponding events. All patients will be followed for both endpoints for at least 24 months and it will provide sufficient time length to observe the required numbers of events.

The association between PD-L1 expression and clinical outcomes, including ORR, PFS and OS will be evaluated using multivariable regression models with PD-L1 as independent variables while adjusting for treatment arm and other prognostic factors.

The association between smoking status (never, former/light, current smokers) and clinical outcomes, including ORR, PFS and OS will be evaluated in multivariable regression models while adjusting for treatment arm and other prognostic factors.

The frequencies and percentages of treatment related adverse events of pembrolizumab (MK-3475) and platinum-based chemotherapy will be summarized by adverse event type and grade for each treatment arm.

The sample size of this randomized phase II trial is determined for a pick-the-winner design with RECIST ORR as the primary endpoint. The recommendation about which treatment arm will be investigated in future trials will be decided based on a totality of evidence from each treatment arm regarding of cumulative response rates based on RECIST and irRC, progression free survival, overall survival and treatment related adverse events.

19. General Regulatory and Other considerations

19.1. Compliance with Trial Enrollment and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow patients 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.

19.2. REGULATORY AND ETHICAL COMPLIANCE

This study will be conducted in compliance with the study protocol, subsequent amendment(s) and with the study-specific manuals/guidelines, if applicable. These documents ensure that the ICH E6 guideline for Good Clinical Practice is maintained as well as compliance with the principles of the Declaration of Helsinki (World Medical Association), or the laws and regulations of the country in which the research is conducted, whichever afford the greater protection to the individual.

Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulation and applicable local, state and federal laws.

19.3. INFORMED CONSENT

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable by local regulations), to obtain written Informed Consent from each patient participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. This information must be provided to the patient prior to undertaking any study-related procedure which is not part of the routine clinical management of the patient (i.e. would not be indicated outside the study). The proposed Informed Consent Form and consenting process must comply with the GCP guidelines, regulatory requirements and be consistent with IRB/institutional policies.

19.4. RESPONSIBILITIES OF THE INVESTIGATOR/IRB/IEC/REB

The regulatory requirements for the Investigator can be found in Subpart D of 21CFR312 (21CFR 312.60: General Responsibilities of Investigators) and in ICH E6 Section 4.

Additional requirements are also outlined in the Statement of Investigator Responsibilities (Form FDA 1572) and the Site Services Agreement. Alliance Foundation Trials, LLC (AFT) will supply the protocol and subsequent amendments.

The investigator is responsible for overall study compliance, execution, oversight and management of the study at their site, and satellite sites if applicable.

As specified in 21CFR 312.62(Investigator Record Keeping and Record Retention) and ICH E6 Sections 4.9 and 8, the Investigator is responsible for ensuring that their study staff maintains and retains all study related documentation, including but not limited to: signed Informed Consent forms, source documents, protocol documents, Institutional Review Board (IRB) approvals, relevant IRB and Sponsor correspondence, and assorted regulatory documents. The Investigator

is responsible for retaining and keeping safe all patient related documentation. In order to do this, the site staff will complete electronic case report forms (eCRFs) in a timely manner.

19.5. Financial Disclosure

Investigators will provide AFT with adequate and accurate financial information in accordance with local regulations and laws in order to allow AFT to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing updated information on financial interests during the course of the study as well as for 1 year after completion of the study.

19.6. Protocol Deviations

The investigator is responsible to document and explain any deviations from the approved protocol. The investigator should promptly report any deviations that might impact patient safety and data integrity to AFT and if locally applicable, to the respective IRB in accordance with local IRB policies and procedures.

A deviation is a departure from the protocol. If deviations are discovered by the monitor or data manager, other member of study staff or otherwise, they will be discussed with the Investigator and study staff. AFT does not provide waivers for protocol deviations.

19.7. Protocol Amendments

Any modifications to the protocol or the Informed Consent Form which may impact on the conduct of the study, potential benefit of the study, or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be released by AFT, agreed by the investigator(s) and approved by relevant IRBs prior to implementation. A signed and dated statement that the protocol, any subsequent relevant amended documents and the Informed Consent Form have been approved by relevant IRBs must be provided to AFT before the study is initiated. Because administrative processing of amendments may take time which could impact study conduct, AFT may release operational memos to allow such changes to the protocol conduct to occur prior to the formal amendment review without being considered a protocol deviation. This is particularly true for changes which impact patient safety. Such memos should be processed per local IRB/ institutional standard.

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be released by the AFT, agreed by the investigator(s) and notified to the IRB as per institutional guidelines.

19.8. Retention of Records

Any records and documents relating to the conduct of this study and the distribution of investigational drug, must be retained by the study chair until notification by AFT, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations. No records may be

disposed of without the written approval of AFT. Written notification should be provided to AFT prior to transferring any records to another party or moving them to another location.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (eg. retirement, relocation), AFT should be prospectively notified. The study records must be transferred to a designee acceptable to AFT, such as another investigator, another institution, or to AFT itself.

19.9. DATA CONFIDENTIALITY

Patient medical information both, associated with biologic specimens, is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) which has been signed by the patient, unless permitted or required by law. Data derived from biologic specimen analysis on individual patients will not be provided to study investigators unless a request for research use is granted. The overall results of any research conducted using biologic specimens will be available in accordance with the effective AFT policy on study data publication.

Data collected during this study may be used to support the development, registration or marketing of an investigational product. All data collected during the study will be controlled by the Sponsor, AFT. AFT will abide by all relevant data protection laws. After a patient has consented to take part in the study, their medical records and the data collected during the study may be reviewed by representatives of the Sponsor to confirm that the data collected are accurate and for the purpose of analyzing the results. These records and data may be additionally reviewed by auditors or by regulatory authorities.

19.10. DATABASE MANAGEMENT AND QUALITY CONTROL

Rave EDC will be used for this study. The study data will be entered by study-site personnel from the source documents onto an eCRF in RAVE EDC.
eCRFs will be completed in a timely manner.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto eCRFs.
At study completion, when the database has been declared to be complete and accurate, the database will be locked.

If new pembrolizumab (MK-3475) safety information results in significant changes in the risk/benefit assessment, the Informed Consent Form should be reviewed and updated if necessary. All patients who may be directly affected (including those already being treated) should be informed of the new information, given a revised form and give their consent to continue in the study.

19.11. SITE MONITORING

Monitoring visits will be conducted by representatives of the Alliance Foundation according to the US CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6).

19.12. DATA AND SAFETY MONITORING BOARD (DSMB)

The Alliance Foundation Trials Data Safety Monitoring Board will be monitoring this study to ensure objectivity and the safety of participants. The DSMB will meet twice a year either at a face-to-face meeting or by teleconference. At each meeting, the study will be reviewed for safety and progress toward completion. When appropriate, the DSMB will also review formal interim analyses of the outcome data. If necessary, the DSMB will recommend study closure or modifications. Any DSMB recommendations for changes to the study will be circulated to investigators in the form of an addendum to this protocol document.
The DSMB will include accrual data, adverse events, and results of interim analyses when available. In determining whether the study should be continued, the DSMB will consider the results of each interim analysis, as described above. The DSMB will also consider the evidence regarding safety, i.e. adverse events and the feasibility of completing the study, i.e., the accrual rate. Weighing the adverse events and the feasibility of study completion is complex and therefore no particular cut-offs of these measurements are provided in advance. The DSMB will use its discretion in weighing these measurements.

19.13. REGULATORY REPORTING

Serious adverse events will be forwarded to FDA by the IND Sponsor, AFT, according to 21 CFR 312.32.

It is the responsibility of the investigator and the research team to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices (GCP), the protocol guidelines, AFT's guidelines, and Institutional Review Board (IRB) policy.

19.14. AUDITS AND INSPECTIONS

To enable evaluations and/or audits from health authorities or AFT, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., eCRFs and hospital records), all original signed informed consent forms, copies of all eCRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports).In the event that the investigator or other site personnel are notified of a Health Authority's intent to inspect the site(s), notification will be sent to compliance@alliancefoundationtrials.org immediately upon awareness. Investigator sites will be audited by AFT under the AFT site audit program. Sites will be audited within eighteen (18) months of first patient in (FPI) on any AFT

sponsored study. Affiliate and satellite sites are subject to audit by AFT but in most cases will be centrally audited at the main member site.

19.15. 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.

19.16. Publication of Study Protocol and Results

Alliance Foundation Trials, LLC prioritizes the timely presentation and publication of study results. Publications and any kind of presentations of results from the study shall be in accordance with accepted scientific practice, academic standards and customs and must be approved in writing by AFT as the sponsor of this study. No investigator may present or publish any portion of this study without written approval from AFT.

20. LIST OF REFERENCES

1. Eisenhauer, E.A., et al., *New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).* Eur J Cancer, 2009. **45**(2): p. 228-47.
2. Siegel, R., et al., *Cancer statistics, 2014.* CA Cancer J Clin, 2014. **64**(1): p. 9-29.
3. Socinski, M.A., et al., *Treatment of stage IV non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines.* Chest, 2013. **143**(5 Suppl): p. e341S-68S.
4. Schiller, J.H., et al., *Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer.* N Engl J Med, 2002. **346**(2): p. 92-8.
5. Sandler, A., et al., *Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer.* N Engl J Med, 2006. **355**(24): p. 2542-50.
6. Johnson, D.H., et al., *Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer.* J Clin Oncol, 2004. **22**(11): p. 2184-91.
7. Scagliotti, G.V., et al., *Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer.* J Clin Oncol, 2008. **26**(21): p. 3543-51.
8. Scagliotti, G., et al., *Treatment-by-histology interaction analyses in three phase III trials show superiority of pemetrexed in nonsquamous non-small cell lung cancer.* J Thorac Oncol, 2011. **6**(1): p. 64-70.
9. Mok, T.S., et al., *Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma.* N Engl J Med, 2009. **361**(10): p. 947-57.
10. Maemondo, M., et al., *Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR.* N Engl J Med, 2010. **362**(25): p. 2380-8.
11. Mitsudomi, T., et al., *Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial.* Lancet Oncol, 2010. **11**(2): p. 121-8.
12. Zhou, C., et al., *Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study.* Lancet Oncol, 2011. **12**(8): p. 735-42.
13. Rosell, R., et al., *Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial.* Lancet Oncol, 2012. **13**(3): p. 239-46.
14. Yang, J.C., et al., *Overall Survival in Patients with Advanced Non-small Cell Lung Cancer Harboring Common (Del 19/L858R) Epidermal Growth Factor Receptor Mutations: Pooled Analysis of Two Large Open-label Phase III Studies Comparing Afatinib with Chemotherapy.* J Clin Oncol, 2014. **32:5s**((suppl; abstr 8004)).
15. Shaw, A.T., et al., *Crizotinib versus chemotherapy in advanced ALK-positive lung cancer.* N Engl J Med, 2013. **368**(25): p. 2385-94.

16. Shaw, A.T., et al., *Ceritinib in ALK-rearranged non-small-cell lung cancer.* N Engl J Med, 2014. **370**(13): p. 1189-97.
17. Disis, M.L., *Immune regulation of cancer.* J Clin Oncol, 2010. **28**(29): p. 4531-8.
18. Dong, H., et al., *Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion.* Nat Med, 2002. **8**(8): p. 793-800.
19. Sharpe, A.H. and G.J. Freeman, *The B7-CD28 superfamily.* Nat Rev Immunol, 2002. **2**(2): p. 116-26.
20. Brown, J.A., et al., *Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production.* J Immunol, 2003. **170**(3): p. 1257-66.
21. Francisco, L.M., P.T. Sage, and A.H. Sharpe, *The PD-1 pathway in tolerance and autoimmunity.* Immunol Rev, 2010. **236**: p. 219-42.
22. Thompson, R.H., et al., *PD-1 is expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma.* Clin Cancer Res, 2007. **13**(6): p. 1757-61.
23. Shepherd, F.A., J.Y. Douillard, and G.R. Blumenschein, Jr., *Immunotherapy for non-small cell lung cancer: novel approaches to improve patient outcome.* J Thorac Oncol, 2011. **6**(10): p. 1763-73.
24. Hiraoka, K., et al., *Concurrent infiltration by CD8+ T cells and CD4+ T cells is a favourable prognostic factor in non-small-cell lung carcinoma.* Br J Cancer, 2006. **94**(2): p. 275-80.
25. Zhuang, X., et al., *A high number of CD8+ T cells infiltrated in NSCLC tissues is associated with a favorable prognosis.* Appl Immunohistochem Mol Morphol, 2010. **18**(1): p. 24-8.
26. Talmadge, J.E., M. Donkor, and E. Scholar, *Inflammatory cell infiltration of tumors: Jekyll or Hyde.* Cancer Metastasis Rev, 2007. **26**(3-4): p. 373-400.
27. Usubutun, A., et al., *Prognostic factors in renal cell carcinoma.* J Exp Clin Cancer Res, 1998. **17**(1): p. 77-81.
28. Al-Shibli, K.I., et al., *Prognostic effect of epithelial and stromal lymphocyte infiltration in non-small cell lung cancer.* Clin Cancer Res, 2008. **14**(16): p. 5220-7.
29. Deschoolmeester, V., et al., *Tumor infiltrating lymphocytes: an intriguing player in the survival of colorectal cancer patients.* BMC Immunol, 2010. **11**: p. 19.
30. Galon, J., et al., *Type, density, and location of immune cells within human colorectal tumors predict clinical outcome.* Science, 2006. **313**(5795): p. 1960-4.
31. Nobili, C., et al., *Prolonged survival of a patient affected by pancreatic adenocarcinoma with massive lymphocyte and dendritic cell infiltration after interleukin-2 immunotherapy. Report of a case.* Tumori, 2008. **94**(3): p. 426-30.
32. Hodi, F.S. and G. Dranoff, *The biologic importance of tumor-infiltrating lymphocytes.* J Cutan Pathol, 2010. **37 Suppl 1**: p. 48-53.
33. Kloor, M., *Lymphocyte infiltration and prognosis in colorectal cancer.* Lancet Oncol, 2009. **10**(9): p. 840-1.
34. Lee, H.E., et al., *Prognostic implications of type and density of tumour-infiltrating lymphocytes in gastric cancer.* Br J Cancer, 2008. **99**(10): p. 1704-11.
35. Leffers, N., et al., *Prognostic significance of tumor-infiltrating T-lymphocytes in primary and metastatic lesions of advanced stage ovarian cancer.* Cancer Immunol Immunother, 2009. **58**(3): p. 449-59.

36. Nishimura, H., T. Honjo, and N. Minato, *Facilitation of beta selection and modification of positive selection in the thymus of PD-1-deficient mice.* J Exp Med, 2000. **191**(5): p. 891-8.
37. Hiraoka, N., *Tumor-infiltrating lymphocytes and hepatocellular carcinoma: molecular biology.* Int J Clin Oncol, 2010. **15**(6): p. 544-51.
38. Liotta, F., et al., *Frequency of regulatory T cells in peripheral blood and in tumour-infiltrating lymphocytes correlates with poor prognosis in renal cell carcinoma.* BJU Int, 2011. **107**(9): p. 1500-6.
39. Mu, C.Y., et al., *High expression of PD-L1 in lung cancer may contribute to poor prognosis and tumor cells immune escape through suppressing tumor infiltrating dendritic cells maturation.* Med Oncol, 2011. **28**(3): p. 682-8.
40. Champiat, S., et al., *Incorporating immune-checkpoint inhibitors into systemic therapy of NSCLC.* J Thorac Oncol, 2014. **9**(2): p. 144-53.
41. Chen, Y.B., C.Y. Mu, and J.A. Huang, *Clinical significance of programmed death-1 ligand-1 expression in patients with non-small cell lung cancer: a 5-year-follow-up study.* Tumori, 2012. **98**(6): p. 751-5.
42. Zhang, P., et al., *Chemopreventive agents induce programmed death-1-ligand 1 (PD-L1) surface expression in breast cancer cells and promote PD-L1-mediated T cell apoptosis.* Mol Immunol, 2008. **45**(5): p. 1470-6.
43. Brahmer, J.R., et al., *Safety and activity of anti-PD-L1 antibody in patients with advanced cancer.* N Engl J Med, 2012. **366**(26): p. 2455-65.
44. Spigel, D., et al., *Clinical activity, safety, and biomarkers of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastic non-small cell lung cancer.* J Clin Oncol, 2013. **31**(Suppl; abstr 8008).
45. Garon, E., et al., *Abstract A20: MK-3475 monotherapy for previously treated non-small cell lung cancer: Preliminary safety and clinical activity.* . Clin Cancer Res, 2014. **20**: p. A20.
46. Garon, E., et al., *Safety and Clinical Activity of MK-3475 in Previously Treated Patients with Non-small Cell Lung CAncer.* J Clin Oncol, 2014. **32:5S**((suppl;abstr 8020)).
47. Rizvi, N., et al., *Safety and Clinical Activity of MK-3475 as Initial Therapy in Patients with Advanced Non-small Cell Lung Cancer.* J Clin Oncol, 2014. **32:5s**((suppl; abstr 8007)).
48. Gettinger, S.N., et al., *First-line Nivolumab Monotherapy in Advanced NSCLC: Safety, Efficacy, and Correlation with PD-L1 Status.* . J Clin Oncol, 2014. **325s**((suppl; abstr 8024)).
49. Brahmer, J., et al., *Survival and long-term follow up of phase I trial of nivolumab (Anti-PD-1; BMS-936558, ONO-4538) in patients with previously treated advanced non-small cell lung cancer.* J Clin Oncol, 2013. **31**(suppl; abstr 8030).
50. Liu, W.M., et al., *Pre-treatment with chemotherapy can enhance the antigenicity and immunogenicity of tumours by promoting adaptive immune responses.* Br J Cancer, 2010. **102**(1): p. 115-23.
51. John, J., et al., *Differential effects of Paclitaxel on dendritic cell function.* BMC Immunol, 2010. **11**: p. 14.
52. Zhang, L., et al., *Differential impairment of regulatory T cells rather than effector T cells by paclitaxel-based chemotherapy.* Clin Immunol, 2008. **129**(2): p. 219-29.

53. Antonia, S.J., et al., *Nivolumab (anti-PD-1; BMS-936558, ONO-4538) in combination with platinum-based doublet chemotherapy in advanced non-small cell lung cancer.* J Clin Oncol, 2014. **32:5s**((suppl; abstr 8113)).
54. Lesterhuis, W.J., et al., *Synergistic effect of CTLA-4 blockade and cancer chemotherapy in the induction of anti-tumor immunity.* PLoS One, 2013. **8**(4): p. e61895.
55. Lynch, T.J., et al., *Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study.* J Clin Oncol, 2012. **30**(17): p. 2046-54.
56. Johnson, D.B., M.J. Rioth, and L. Horn, *Immune Checkpoint Inhibitors in NSCLC.* Curr Treat Options Oncol, 2014.
57. Wolchok, J.D., et al., *Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria.* Clin Cancer Res, 2009. **15**(23): p. 7412-20.
58. Simon, R., R.E. Wittes, and S.S. Ellenberg, *Randomized phase II clinical trials.* Cancer Treat Rep, 1985. **69**(12): p. 1375-81.
59. Fleiss, J., L. B, and M. Paik, *Statistical Methods for Rates and Proportions*, J.W. Sons, Editor. 2003: New York.

21. APPENDICES

21.1. APPENDIX I: 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.
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