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A Randomized Phase II Study Evaluating Pembrolizumab vs Topotecan in the Second-line Treatment of Patients with Small Cell Lung Cancer
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Study Resources

Adverse Event Reporting via Medidata Rave® iMedidata Portal 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

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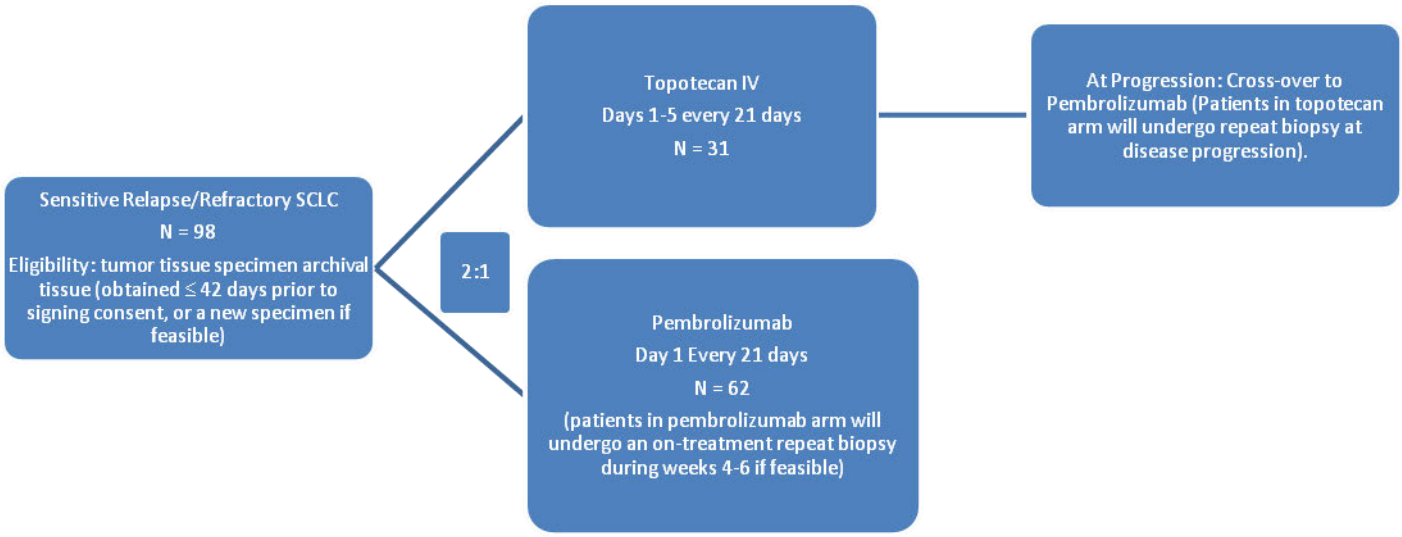
1. SYNOPSIS

1.1. STUDY SUMMARY

Abbreviated Title	Pembrolizumab vs Topotecan in the Second-line Treatment of Patients with Small Cell Lung Cancer
Study Phase	Randomized Phase II
Clinical Indication	Small cell lung cancer (SCLC) patients in need of second-line therapy after standard platinum/etoposide chemotherapy.
Study Type	Interventional
Type of Control	Active control without placebo
Route of Administration	Intravenous
Study Blinding	Unblinded open-label
Treatment Groups	Topotecan every 3 weeks until progression of disease; at which point, patients can cross over to the pembrolizumab arm. Pembrolizumab 200mg every 3 weeks until progression of disease or up to 24 months, whichever occurs first.
Number of Study Patients	Approximately 98 patients will be enrolled at an anticipated 10 sites.
Estimated Duration of Study	Approximately 19 to 23 months to accrue and enroll the patients, with an additional 6 months of follow-up to observe events for the primary endpoint of progression free survival after the last patient is started on study; we have included an additional 6 months to allow patients responding on study drug to remain on protocol.
Subject Eligibility	Patients with sensitive or refractory disease will be eligible for the study; where sensitive disease will be defined as those patients with disease progression after treatment with standard first-line etoposide/platinum ≥60 days from completing chemotherapy, and refractory disease will be defined as patients with disease progression < 60 days from completing chemotherapy. Patients with treated brain metastases will be eligible. Patients with underlying or previous paraneoplastic syndromes are not eligible.
Study Objectives	The primary endpoint is to determine if there is an improvement in progression free survival for SCLC patients treated with pembrolizumab compared to topotecan. RECIST 1.1 will be used for this analysis. Secondary endpoints will include safety, objective response rate by RECIST 1.1, and overall survival. Exploratory endpoints based on correlative studies will be assessed.
Study Design	This is a multi-institutional, randomized, open-label phase II study of pembrolizumab compared to topotecan, administered to patients with SCLC who have progressed or relapsed after first-line treatment with etoposide and platinum. Patients will be randomized in a 2:1 fashion to receive pembrolizumab or topotecan. Participants in the topotecan arm that progress will be allowed to cross-over to the pembrolizumab arm.
Study Treatment Plan	Pembrolizumab Arm: Pembrolizumab will be administered via IV infusion at 200 mg every 3 weeks, and treatment continued for up to 24 months, until documented disease progression, unacceptable side effects or intercurrent illness that prevents further administration of treatment, investigators' decision to

	withdraw the subject, subject withdraws consent, pregnancy of the patient, noncompliance of the patient, or for administrative reasons. Topotecan Arm: Topotecan will be administered via IV infusion at 1.25 mg/m^2 on days 1 to 5 of a 3-week cycle. Pegfilgrastim may be given on day 6, 7, or 8 to offset neutropenia. Patients who progress in the topotecan arm will be allowed to cross-over to the pembrolizumab arm.
Efficacy Assessments	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 RECIST 1.1.
Safety Assessments	Patients will be evaluated clinically by physical exam and with routine blood work every 21 days. Adverse events 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.
Laboratory/Correlative Study Assessments	Tumor samples will be required at study entry. Although subjects will be enrolled regardless of PD-L1 status, subjects will be required to provide tissue of a tumor lesion (either archived tissue if sample was obtained no more than 42 days prior to signing consent or a new biopsy before initiating therapy). Patients in the pembrolizumab arm will undergo a repeat biopsy while on treatment, if clinically feasible, during weeks four to six after initiating treatment. Those patients on the topotecan arm that progress and cross-over to receive pembrolizumab will undergo a biopsy, if clinically feasible, before initiating the new treatment. Tissue-based correlative studies will be performed, including and not limited to, immunohistochemistry to evaluate expression of PD-L1 and immune cell markers, whole exome sequencing for evaluation of mutational burden and the neoantigen landscape, and transcriptome analyses of the tumor and immune microenvironment. Peripheral blood cell/serum plasma samples for correlatives will be collected for all patients at screening, at week 4-6 biopsy, at imaging during all cycles, and at progression/cross-overfor characterization of T-cell phenotypes to understand how changes may correlate with clinical response.
Study Follow-Up	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 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. Subjects who discontinue treatment for reasons other than disease progression will have post-treatment follow-up every 6 weeks for disease status until progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone contact every 12 weeks for overall survival until death or withdrawal of consent.

1.2. STUDY SCHEMA (FIGURE 1)



*:With allowance of 5% ineligible, cancelling and unevaluable, the study plans to register 98 patients, and randomize 93.

Patients who progress on the topotecan arm may cross-over to receive treatment with pembrolizumab.

Treatment is to continue for up to 24 months post-randomization or until disease progression on pembrolizumab or an unacceptable adverse event.

Patients will be followed until death.

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. SMALL CELL LUNG CANCER

Small cell lung cancer (SCLC) remains a worldwide public health problem. In the United States, the decrease in prevalence of tobacco use has resulted in a gradual decrease in SCLC incidence over the past decade; nonetheless, SCLC remains a major cause of cancer mortality, currently accounting for 14% of all lung cancers, or approximately 30,000 patients annually. [1,2] Tobacco exposure is strongly associated with the development of SCLC, with only 2 to 3% of patients being never-smokers. [3,4]

Compared to non-small cell lung cancer (NSCLC), SCLC has a unique natural history with a shorter doubling time, higher growth fraction, earlier development of widespread metastases, and uniform initial response to chemotherapy and radiation. Outcomes for SCLC have not changed dramatically as the majority of patients, including those with limited-stage disease and those initially responsive to chemotherapy and radiation, develop chemoresistance. As a result, overall five year survival rates are a dismal 6%. [1,2]

First line treatment for SCLC involves combination chemotherapy with cisplatin or carboplatin plus etoposide (with the addition of radiation therapy in limited stage), which results in a 60-80% overall response rate. However, all patients with extensive stage SCLC, and the majority of patients with limited SCLC, suffer relapse within months of completing initial therapy. The strongest predictor of outcome for patients with relapsed disease is the duration of response. Patients who maintain an appropriate response to initial therapy for 3 months or more are deemed “sensitive”. These patients have a higher likelihood of response to second-line chemotherapy, though at best it is half that expected in the first-line setting, and their survival averages around 6 months. Patients with “refractory” disease either had no response to initial therapy, or progressed within 3 months after completing treatment. Their chance of response to second-line therapy is less than 10%, and survival is 3 to 4 months.[5]

Single agent topotecan or CAV (cyclophosphamide, doxorubicin and vincristine) are appropriate treatment regimens for patients with sensitive relapse. A randomized trial comparing topotecan to CAV showed a response rate of 24% for topotecan and 18% for CAV, which was not statistically significant, with median survival of 6 months for both.[6] In this study, sensitive disease was defined as relapse more than 60 days (or 2 months) after the completion of first line chemotherapy. This study led to the U.S. Food and Drug Administration’s approval of intravenous topotecan with an indication for sensitive relapsed SCLC (> 60 days from completion of first line treatment).

In three single arm phase II studies, topotecan was studied in patients with recurrent or progressive SCLC after treatment with first line chemotherapy. The three studies stratified patients for sensitive disease (response to initial therapy for $\geq$ 90 days) or refractory disease (no response to initial therapy, or progression within 90 days after completing treatment) and included patients with stable brain metastases.[7-9] The European Organization for Research and Treatment of Cancer study reported a 21.7% overall response rate (37.8% among sensitive patients, 6.4% among refractory patients) and a 33-week median duration of response.[7] Depierre et al. showed a 14% response rate (median survival, 25.7 weeks) in sensitive patients and a 2% response

rate (median survival, 16.3 weeks) in refractory patients.[9] In the third study, the response rates were similar - 19% (median survival, 26.6 weeks) and 3% (median survival, 20.4 weeks) for patients with sensitive and refractory disease, respectively.[8] A pooled analysis of the sensitive patients treated with second-line topotecan in these three SCLC studies reported an 18% response rate.[10]

Oral topotecan was compared to intravenous topotecan in a randomized phase III trial and was found to have similar activity in patients with chemotherapy sensitive disease[45] beneficial in both sensitive and refractory disease patients, In a phase III trial oral topotecan was compared to best supportive care in patients with both chemotherapy sensitive and refractory disease, and with a partial response of 7% and prolonged overall survival at 26 weeks was observed with topotecan compared to overall survival of 14 weeks with best supportive care. Currently, intravenous and oral topotecan remain the only drug approved for second-line treatment of SCLC.
Although the initial studied dose of intravenous topotecan is 1.5 mg/m^2, the agent has been evaluated at a lower dose of 1.25 mg/m^2 on days 1 to 5 of an every 21-day cycle.[12,13]

The prognosis for patients with recurrent SCLC is poor, especially for those with refractory disease. As few options exist, there is a clear need for new therapeutic agents.

3.2. PD1 PATHWAY: PHARMACEUTICAL AND THERAPEUTIC BACKGROUND

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades.[14] Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies.[15-18] Additionally, 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. Notably, effector T cells are significantly higher in the peripheral blood of patients with limited stage SCLC compared to those with extensive stage SCLC and in long term disease-free survivors relative to those with recurrent disease. [19]

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. [20] 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.[20] 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).[21] The structure of murine PD-1 has been resolved.[22] 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).[21] 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. [23-25] The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from CTLA-4 as both molecules regulate an

overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells.[20] Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells.

The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors.[16,26] 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.[16] 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.[16] PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor.[20,26] PD-1 has been suggested to regulate tumor-specific T-cell expansion in patients with melanoma. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab recently has been approved in the United States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor,[27] as well as in previously treated patients with metastatic squamous and nonsquamous non-small cell lung cancer (NSCLC) whose tumors expressed ≥50% PD-L1.[28]

3.3. STUDY DESIGN AND INTERVENTION

3.3.1. Study Design and Intervention

This is a multi-institutional, randomized, phase II study of pembrolizumab compared to topotecan, administered to patients with SCLC who have progressed or relapsed after first-line treatment with etoposide and platinum (cisplatin or carboplatin). This study will be conducted to determine if there is an improvement in progression free survival for SCLC patients treated with pembrolizumab compared to the standard therapy of topotecan. RECIST 1.1 will be used for this analysis.[29]

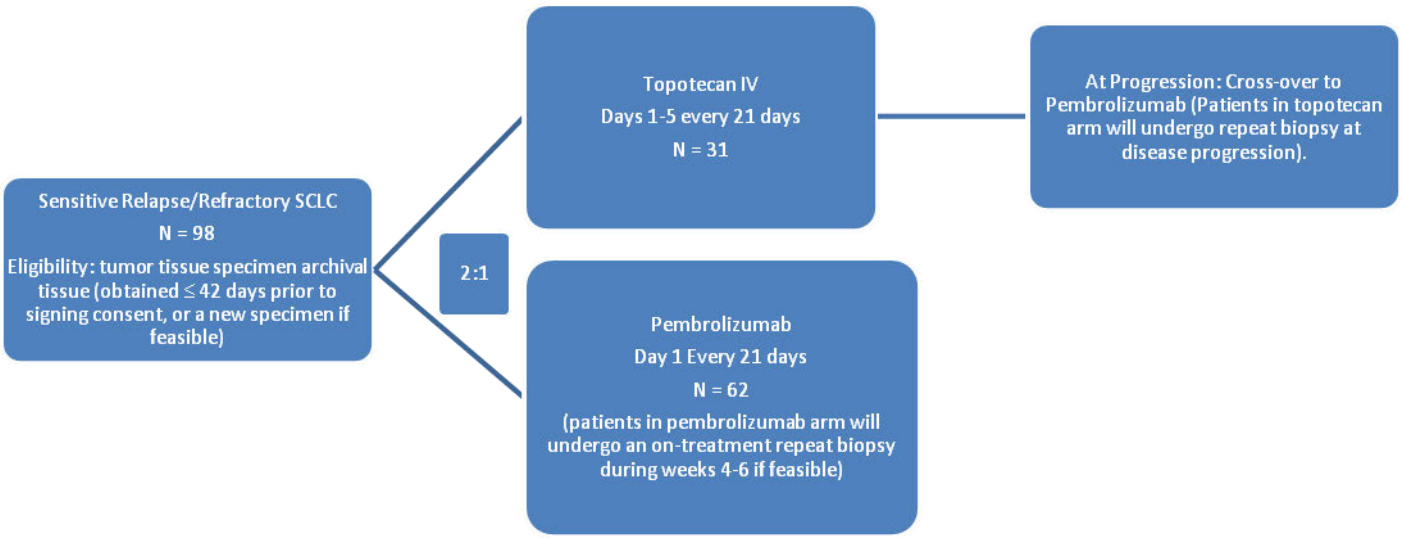
Patients with sensitive or refractory disease will be eligible for the study; where sensitive disease will be defined as those patients who relapse >60 days after the completion of the first-line of chemotherapy.[30] Patients with treated brain metastases will be eligible. Those patients with underlying or previous paraneoplastic syndromes are not eligible.

Ninety-three patients will be randomized in a 2:1 fashion to pembrolizumab or topotecan. Patients will be stratified based on disease type (sensitive vs.

refractory). Patients who progress in the topotecan arm will be allowed to cross-over to the pembrolizumab arm. Tumor samples will be required before initiating new therapy (preferably a new specimen) and a repeat biopsy will be performed, if clinically feasible, on-treatment (during weeks 4 to 6) for those in the pembrolizumab arm and at the time of disease progression for those in the topotecan arm. Scans will be reviewed by the investigator or designee.

Secondary endpoints will include safety, objective response rate by RECIST 1.1 and overall survival. Correlatives, including analyses of tissue and blood, will be assessed as well, as described below.

Figure 2. Study Design



*:With allowance of 5% ineligible, cancelling and unevaluable, the study plans to register 98 patients, and randomize 93.

3.3.2. Intervention

Patients who meet the eligibility criteria and are randomized to one of the treatment arms, will receive either topotecan alone intravenously at 1.25 mg/m^2 on days 1 to 5 of a 21-day cycle or pembrolizumab alone administered intravenously at 200mg every 21 days.

During the study period, patients will be evaluated clinically by physical exam and with routine blood work every 21 days. Adverse events 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 ≥ 2 diarrhea, 2) Grade ≥ 2 colitis, 3) Grade ≥ 2 pneumonitis, 4) Grade ≥ 2 hepatitis 5) Grade ≥ 3 hypo- or hyperthyroidism.

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 RECIST 1.1. Patients will continue to receive topotecan or pembrolizumab every three weeks until documented disease progression, unacceptable side effects, 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 on the topotecan arm who progress on study will be allowed to cross-over to the pembrolizumab arm.

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 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. Immune related serious adverse events will be followed for 90 days after end of treatment. Subjects who discontinue treatment for reasons other than disease progression will have posttreatment follow-up every 6 weeks for disease status until progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone contact every 3 months for overall survival until death or withdrawal of consent.

Although subjects will be enrolled regardless of PD-L1 status, subjects will be required to provide tissue of a tumor lesion (either archived tissue or a new biopsy before initiating therapy). Tumor samples will be required before initiating therapy (preferably a new specimen) and a repeat biopsy will be performed, if clinically feasible, on-treatment (during weeks 4 to 6) for those in the pembrolizumab arm and at the time of disease progression for those in the topotecan arm. PD-L1 expression status by immunohistochemistry will be determined on tumors at baseline, on treatment and at the time of topotecan progression. Numerous other correlative studies also will be performed, as outlined below. Peripheral blood mononuclear cell samples will be collected at screening, at day 1 of cycles 1, 2 and 3, and at the time of each imaging study (while on study), for characterization of T-cell phenotypes to understand how changes may correlate with clinical response.

4. RATIONALE

4.1. RATIONALE FOR THE STUDY AND SELECTED PATIENT POPULATION

4.1.1. The Immune System in Small Cell Lung Cancer and Immune Checkpoint Blockade

Several lines of evidence demonstrate the immunogenic nature of SCLC and highlight the potential efficacy of PD-1 blockade in this disease. SCLC is occasionally associated with paraneoplastic auto-antibodies and these patients are characterized by improved survival, [31] suggesting these auto-antibodies may be indicative of tumor-specific immune responses. By contrast, loss of MHC expression is found in some SCLCs, implying that downregulation of tumor-specific or tumor-associated antigen presentation represents an important mechanism to escape immune surveillance. [32,33] Effector T cells are significantly higher in the peripheral blood of patients with limited stage SCLC compared to those with extensive stage SCLC and in long term disease-free survivors relative to those with recurrent disease. [19] Most recently, the PD-1 and PD-L1 pathway has been interrogated in SCLC by immunohistochemistry and gene expression analysis. [34] Although PD-L1 is low on SCLC tumor cells, it is highly expressed on tumor infiltrating macrophages, [34] suggesting that PD-1 blockade may be effective in this disease.

Anti-CTLA-4 blockade has been combined with cytotoxic chemotherapy in patients with extensive stage SCLC, demonstrating early feasibility and safety of administering immunotherapy in this disease. [35,36]

The Phase IB Multicohort Study of Pembrolizumab for PD-L1 Positive Advanced Solid Tumors (Keynote-028, NCT02054806) included a cohort of SCLC patients with extensive stage disease who had progressed after receiving first-line chemotherapy. To be eligible for treatment with pembrolizumab, an archived pre-treatment sample or newly obtained core evaluated for the PD-L1 expression was necessary. One-hundred forty seven samples were evaluable for PD-L1, of which 42 (29%) displayed ≥1% PD-L1 positivity in tumor, inflammatory cells or stroma. Subsequently, 24 patients were treated according to protocol. Only one patient incurred a treatment related death secondary to colitis. The objective response rate was 29% (95% CI, 12.6-51), with a median duration of response of 29 weeks (range, 0.1 to 29.1). While the median progression free survival was 1.8 months (95% CI, 1.6-8.5), the 6-month rate PFS was 33%, indicating durable responses. Notably, there was no relationship between the extent of PD-L1 positivity and the frequency of responses. [37]

4.1.2. Complex Molecular Landscape of Small Cell Lung Cancer and Opportunity for Immunotherapy

SCLC results from chronic exposure to tobacco carcinogens, leading to a high burden of genomic alterations, including mutations, insertions, deletions, large

scale copy number alterations, and gross inter- and intra-chromosomal rearrangements.[38] [39-41] The only other malignancy with a higher mutational burden than SCLC is melanoma, caused by ultraviolet light, another potent carcinogen. [40-42] Most of the mutations observed in SCLC tumors are passengers, that is, those that do not meaningfully contribute to growth, progression or invasion of disease. *TP53* and *RB1* inactivation are almost universal and unlike lung adenocarcinoma, the genomic landscape of SCLC is not broadly characterized by targetable driver oncogenes involved in activation of kinase signaling. Rather, other processes such as transcriptional deregulation, histone modification, and dysregulation of the cytoskeleton are implicated. [38,40,41] Based on emerging data from the group at MSKCC, demonstrating the link between increased mutational burden and responsiveness to T cell checkpoint inhibitors in melanoma and NSCLCs, [43,44] we believe the nearly universally deranged SCLC genomes intimate that these tumors may be particularly sensitive to immunotherapies.

4.1.3. Rationale for Use of Pembrolizumab in Small Cell Lung Cancer in the Second Line Setting

Therapeutic options remain limited in SCLC, and more effective therapies are critically needed.

As SCLC is characterized by immunogenic effects and an exceptionally high degree of genomic alterations due to tobacco carcinogens, immune checkpoint blockade utilizing pembrolizumab warrants further exploration in this disease. Evaluating pembrolizumab in the second line setting is appropriate given the early data available demonstrating its activity in SCLC.

4.2. RATIONALE FOR DOSE SELECTION/REGIMEN/MODIFICATION

4.2.1. Pembrolizumab and rationale for its Dose Selection

Pembrolizumab will be provided by Merck. Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks.

An open-label Phase I trial (KEYNOTE 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 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 every 2 weeks). No maximum tolerated dose has been identified to date. Recent data from other clinical studies within the pembrolizumab (MK-3475) program has shown that a lower dose of the agent and a less frequent schedule may be sufficient for target engagement and clinical activity.

Pharmacokinetic (PK) data analysis of pembrolizumab (MK-3475) administered every 2 weeks and every 3 weeks showed slow systemic clearance, limited

volume of distribution, and a long half-life (refer to Investigator's Brochure, 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 evaluating both an every 2 week and every 3 week 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 every 3 weeks 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 every 3 weeks vs. the proposed dose regimen of 2 mg/kg every 3 weeks (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

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

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

4.2.2. Topotecan and Rationale for its dose selection

Topotecan is manufactured by GlaxoSmithKline and is commercially available. Topotecan will be administered intravenously at 1.25 mg/m^2 on days 1 to 5 of each 3 week (21-day) cycle. This dose has been selected to mitigate the hematologic toxicities associated with topotecan at the initially studied dose of 1.5 mg/m^2, while preserving its efficacy.[12,13]

This 1.25 mg/m^2 dose was evaluated in a prospective multicenter trial to determine whether it could improve safety in patients with relapsed/ refractory small cell lung cancer without loss of efficacy.[12,13] In this study, patients

received topotecan intravenously on days 1–5, every 21 days, for up to six courses. For those patients who did not incur toxicities, topotecan was increased to 1.5mg/m^2; yet in those with severe side effects, the dose was reduced to 1.0 mg/m^2. Severe toxicities were considered grade 4 neutropenia lasting greater than 7 days; grade 4 thrombocytopenia or platelet count < 100,000/mm^3 and neutrophils < 1500/mm^3; or any grade 3 or 4 non-hematologic toxicity besides alopecia, nausea and emesis. A total of 514 topotecan courses were received by 164 patients; in 72.6% of those courses, the dose remained at 1.25 mg/m^2; in 9.1% it was reduced and in 18.3% it increased. Toxicities seemed to be less for the patients treated at the 1.25 mg/m^2 dose when compared to historical data, as grade 4 neutropenia and thrombocytopenia occurred in 7% and 5% of courses, with mild non-hematologic toxicities. Efficacy was maintained as the overall response rate for all patients (sensitive and refractory) was 14.1% and median survival was 23.4 weeks. Therefore, topotecan at a dose of 1.25 mg/m^2 was found to be as effective as the dose of 1.5 mg/m^2, but with reduced toxicity. As such, we have chosen this dosing schedule for this study.

5. RATIONALE FOR ENDPOINTS

5.1. EFFICACY ENDPOINTS

5.1.1. Primary

This randomized phase II study will assess progression free survival (PFS) as the primary endpoint based on RECIST 1.1. Given the cross-over design, PFS as opposed to overall survival was considered to be an acceptable scientific endpoint to identify the best treatment for SCLC patients in need of second-line therapy. According to the findings from the phase III study studying topotecan vs CAV[6] in the second-line treatment of SCLC patients and the phase III trial comparing oral and intravenous topotecan,[45] we expect only a median PFS of 12 weeks for the control arm. Further, it is anticipated that the SCLC patients responding to pembrolizumab will have a longer duration of response, which will be assessed by RECIST 1.1.[29] The PFS rate at 6 and 9 months in each group will be assessed and compared.

5.1.2. Secondary

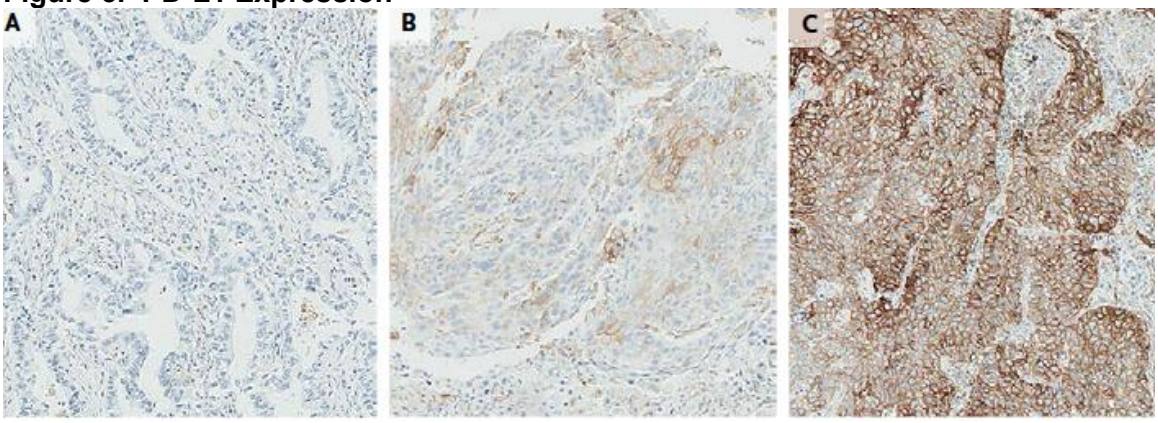
The objective response rate (ORR) will be determined in each arm of the study by RECIST 1.1. Notably, topotecan leads to a differential response in SCLC patients with sensitive vs refractory disease, which we do not anticipate in those receiving pembrolizumab. With the cross-over design, we will be able to determine the ORR for pembrolizumab in the second- and third-line setting. Overall survival of patients in each arm of the study will be analyzed. The treatment-related toxicity of pembrolizumab and topotecan will be summarized by toxicity type and grade for each treatment arm.

5.2. EXPLORATORY ENDPOINTS; BIOMARKERS OF RESPONSE TO IMMUNE CHECKPOINT INHIBITORS

5.2.1. PD-L1 Tumor Expression

Tumor PD-L1 expression levels extensively have been evaluated to determine potential associations with response to pembrolizumab. In Keynote-001, 449 patients with previously treated non-small cell lung cancer patients (NSCLC) received pembrolizumab at 2mg/kg (N = 55) and at 10 mg/kg (N = 394).[46] The anti-PD-L1 antibody clone 22C3 (Merck) and a prototype immunohistochemical assay was used to determine PD-L1 status. PD-L1 positivity was defined as membranous staining in at least 1% of cells (neoplastic and intercalated mononuclear inflammatory cells) within tumor nests or a distinctive staining pattern caused by the infiltration of mononuclear inflammatory cells in the stroma that formed a banding pattern adjacent to tumor nests. A tumor proportion score (TPS) was assigned to each sample based on the percentage of tumor cells with membranous PD-L1 staining.[28,46]

Figure 3. PD-L1 Expression



TPS < 1% **TPS ≥ 1 – 49%** **TPS ≥ 50%**

Response rates significantly were higher in patients whose samples demonstrated a TPS ≥ 50%. Further, patients with higher PD-L1 expression seemed to have a faster time to response. Median overall survival was 15.5 months (95% CI, 10 – NR) in patients with TPS ≥ 50% compared to 11.3 months (95% CI, 8.8 – 14.0) in all patients.

In Keynote-028, PD-L1 expression was necessary for SCLC patients to be eligible, as described above. One-hundred forty seven samples were evaluable for PD-L1, of which 42 (29%) displayed ≥1% PD-L1 positivity in tumor, inflammatory cells or stroma. Subsequently, 24 patients were treated according to protocol who had received one or more prior lines of therapy for SCLC. Notably, there was no relationship between the extent of PD-L1 positivity and the frequency of responses. [37]

5.2.2. Smoking Status, Smoking-Related Genotoxicity, and Mutation Burden

We and others have shown that smokers with lung cancers are most likely to benefit from PD-1 blockade. [47] In 495 patients with NSCLCs treated with pembrolizumab, the response rate was 22.5% in smokers compared to 10.3% in never smokers.[28] We hypothesize this differential response is related to the increased mutational burden found in smoking-related cancers. To examine this hypothesis, we have performed whole exome sequencing of 34 NSCLC patients treated with pembrolizumab; higher mutational burden was associated with a more durable response to pembrolizumab and an improvement in progression-free survival (PFS) compared to those with lower mutation burden.[44] We also applied a molecular classifier of smoking-related genotoxicity, which distinguishes genomes characteristic of lung cancers in smokers (defined by a predominance of C>T transversions, termed "transversion-high" or TH, smoking signature) from the genomic alterations characteristic of lung cancers in never smokers (transversion low, TL, non-smoking signature). TH-tumors were highly associated with response and improved PFS to pembrolizumab. Moreover, TH-tumors were highly associated with mutation burden, suggesting that the molecular smoking signature may be able to identify those patients with the greatest mutation burden and most likely to benefit from pembrolizumab.[44] The association between response to pembrolizumab, mutation burden, and molecular smoking history is highly applicable to SCLC as this disease is nearly entirely related to smoking and characterized by an elevated mutation burden.

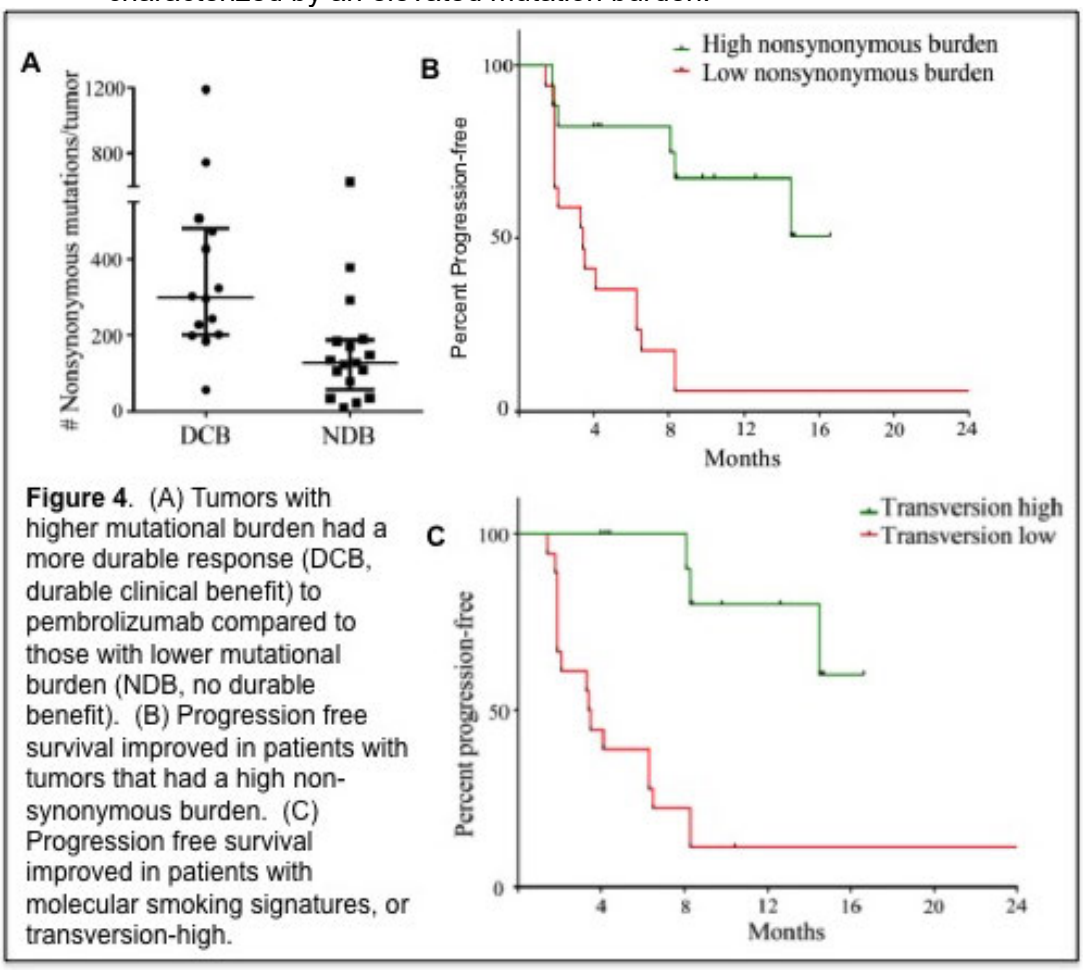


Figure 4. (A) Tumors with higher mutational burden had a more durable response (DCB, durable clinical benefit) to pembrolizumab compared to those with lower mutational burden (NDB, no durable benefit). (B) Progression free survival improved in patients with tumors that had a high non-synonymous burden. (C) Progression free survival improved in patients with molecular smoking signatures, or transversion-high.

The critical link in understanding the association between mutation burden and response to T cell checkpoint inhibitors may be neoantigens. Neoantigens are cancer-specific novel immunogenic peptides resulting from somatic, non-synonymous mutations in tumor cells, which when presented by class I or II MHC molecules, can be targets for T-cell recognition and effector responses.[48-52] Whole exome sequencing and computational neoantigen prediction also have been performed on a series of melanomas from patients treated with ipilimumab.[43] Responders to ipilimumab were characterized by an elevated mutation burden and neoantigen-specific T cell responses were identified in the peripheral blood of three long-term responders to ipilimumab. We also have begun to explore the neoantigen landscape associated with response to pembrolizumab in NSCLC: responders have a greater absolute burden of neoantigens. Additionally, in one patient with a near complete response to pembrolizumab, we identified a neoantigen-specific T cell response in the peripheral blood that corresponded with clinical response to anti-PD-1 therapy.[44] This case is suggestive that responses to anti-PD-1 therapy may be mediated by expansion of neoantigen-specific T cell clones and that neoantigen-based peripheral blood monitoring may provide an opportunity to examine and monitor response to PD-1 therapy.

6. OBJECTIVES

6.1. PRIMARY OBJECTIVE

To demonstrate an improvement in progression free survival (PFS) in patients with relapsed sensitive or refractory SCLC receiving pembrolizumab compared to topotecan, utilizing RECIST 1.1.

6.2. SECONDARY OBJECTIVES

i. Determine the objective response rate (ORR) in each arm of the study by RECIST 1.1.

ii. Determine the overall survival (OS) of patients in each arm of the study.

iii. Determine the ORR, and OS of pembrolizumab and topotecan, in the following patient groups:
    a. Sensitive disease vs. Refractory disease

iv. Determine the safety and tolerability of pembrolizumab in patients with SCLC.

6.3. EXPLORATORY OBJECTIVES

i. To describe the immunophenotype of SCLCs, assessed by immunohistochemistry and the associations with ORR, PFS and OS to each of the treatment arms.
    a. For those patients treated in the pembrolizumab arm, pre-treatment samples also will be compared to on-treatment biopsy samples to identify the immunophenotype of response.

ii. To describe the temporal change in T cell immunophenotypes in peripheral blood mononuclear cell samples and correlate with clinical response.

iii. To explore the relationship between mutational burden and response to pembrolizumab therapy.

iv. To identify candidate neoantigens and explore their associations with response to pembrolizumab therapy.

v. To examine the changes in tumors that are associated with either response or resistance to study therapy by performing comparative analyses on matched specimens.

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 study. 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

7.1. INCLUSION CRITERIA

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

1. Have histologically or cytologically confirmed small cell lung cancer. Confirmation will be done at each participating site.

2. Have relapsed or progressed after only one prior chemotherapy regimen, which must have been an etoposide-platinum doublet. Eligible patients will be defined as follows:

   "Sensitive" Disease: Patients who had one previous line of chemotherapy and relapsed after ≥ 60 days of completion of treatment.

   "Refractory" Disease: Patients with no response to first-line chemotherapy or progression <60 days after completing treatment.

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

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

5. Have a performance status of ≤ 1 on the ECOG Performance Scale.

6. Have measurable disease based on RECIST 1.1.
7. Have a tumor tissue specimen available from either a core or excisional biopsy. The tumor specimen should be of adequate size and tumor cellularity to perform whole exome sequencing and immunohistochemistry. In subjects for whom newly obtained samples cannot be obtained (e.g. tumor inaccessible or safety concern), archived tissue may be submitted, if it otherwise satisfies all specimen criteria. Archival samples must have been obtained within 42 days prior to signing consent (please refer to section 12.1 of protocol).

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	≥8 g/dL (without transfusion)
Renal	
Serum creatinine **OR** Glomerular Filtration Rate (GFR)	≤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
*GFR should be calculated per institutional standards.	

9. Female patients of childbearing potential should have a negative urine or serum pregnancy within 72 hours of starting treatment. 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 an adequate method of contraception as outlined in Section 14.4.1 – Contraception for the course of the study through 120 days after the last dose of study medication (see Section 13.4.1). Patients of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

11. Male patients must agree to use an adequate method of contraception as outlined in Section 14.4.1 – Contraception - starting with the first dose of study therapy through 120 days after the last dose of study therapy. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

7.2. EXCLUSION CRITERIA

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

1. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 14 days of the first dose of treatment.

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

3. 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 14 days earlier.

4. 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 ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion and may qualify for the study.

5. Has undergone major surgery, he/she 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.

7. Has known active central nervous system (CNS) metastases. Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of study treatment and any 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 study treatment.

8. Has known carcinomatous meningitis.

9. Has an active autoimmune disease requiring systemic treatment in the past 2 years 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.

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

11. Has an active infection requiring systemic therapy.

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

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

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

15. Has received prior therapy with an anti-PD-1, anti-PD-L1, 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).

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

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

18. 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.

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

20. Hypersensitivity to pembrolizumab or any of its excipients.

21. Patients with underlying or previous paraneoplastic syndromes

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 be screened and sign informed consent 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 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 time frames.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).
- Adequate tumor tissue will be available and can be sent to the AFT biorepository for central laboratory analysis within 14 days of randomization.

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) **Sensitive Disease vs Refractory Disease:** sensitive disease will be defined as those patients with disease progression who relapse after treatment with standard first-line etoposide/platinum ≥60 days from completing chemotherapy, and refractory disease will be defined as patients with disease progression < 60 days from completing chemotherapy.

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

9. SCHEDULE OF ASSESSMENTS

9.1. SCHEDULE OF ASSESSMENTS

Table 2. Schedule of Assessments

Study Period:	**Treatment Cycles[1]**									**End of Treatment[§]**	**Post-Treatment Evaluations**		
Treatment Cycle/Title:	Screening (Visit 0)	1	2	3	4	To be repeated beyond 8 cycles				At time of treatment discontinuation	Safety Follow-up[19]	Follow Up Visits[20]	Survival Follow-Up[21]
						5	6	7	8				
Scheduling Window (Days)[2]:	-14 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of treatment discontinuation	30 days	Every 6 weeks	Every 12 weeks
Informed Consent[3]	X												
Inclusion/Exclusion Criteria[3]	X												
Demographics	X												
Medical History[4]	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Medication Review[5]	X	X	X	X	X	X	X	X	X	X			
SCLC Disease Details[6]	X												
Study Treatment Administration		X	X	X	X	X	X	X	X				
Review Adverse Events[7, 8, 22]		X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X	X		X	X	
Vital Signs and Weight[9]	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
Pregnancy Test – Urine or Serum β-HCG[10, 12]	X	X											
PT/INR and aPTT[11, 12]	X												
CBC with Differential[12, 13]	X		X	X	X	X	X	X	X	X	X		
Comprehensive Serum Chemistry Panel[12, 13]	X		X	X	X	X	X	X	X	X	X		
Urinalysis[12, 14]	X				X				X	X			

Study Period:	**Treatment Cycles[1]**									**End of Treatment[§]**	**Post-Treatment Evaluations**		
Treatment Cycle/Title:	Screening (Visit 0)	1	2	3	4	To be repeated beyond 8 cycles 5	6	7	8	At time of treatment discontinuation	Safety Follow-up[19]	Follow Up Visits[20]	Survival Follow-Up[21]
Scheduling Window (Days)[2]:	-14 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of treatment discontinuation	30 days	Every 6 weeks	Every 12 weeks
T3, FT4 and TSH[12, 13, 15]	X		X		X		X		X	X			
EKG	X												
Tumor Imaging (CT Scan/MRI)[16, 17]	X		X		X		X		X	X		X	
Archival or Newly Obtained Tissue Collection[18]	X												
Newly Obtained Tissue Collection	X[23]		X[24]							X[25]			
Correlative Studies Blood Collection[26]	X		X		X		X		X				

[1] In general, assessments/procedures are to be performed on day 1 and prior to the first dose of study treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks (21-days); however the 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 study treatment regardless of any treatment delays during the first 8 cycles.

[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. Informed consent and assessment of eligibility criteria can be obtained 21 days prior to the start of treatment.

[4] Medical history should be completed by study staff and include all comorbidities, as well as a detailed assessment of smoking history: number of years of tobacco smoke, packs of cigarettes smoked, ongoing tobacco smoke or time since quitting smoking. This will also include documentation of SCLC disease status.

[5] Prior medications – record all medications taken within 14 days of visit 1 and all treatments for a prior cancer other than SCLC. After the Safety Follow-up Visit record all medications taken for SAEs and ECIs as defined in Section 17.

[6] Disease details are to be collected, including: sites of disease; first-line chemotherapy (cisplatin vs carboplatin); number of cycles of first-line chemotherapy; administration of prophylactic cranial irradiation, consolidative mediastinal radiation or palliative radiation to an osseous site; best response to prior therapy (stable disease, partial response, complete response, progression of disease); time to relapse (sensitive disease vs resistant disease).

[7] 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.

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

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

[10] For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first dose of study 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.

[11] Coagulation factors (PT/INR and aPTT) should be performed if clinically indicated and monitored closely throughout the study for any patient receiving anticoagulant therapy.

[12] Laboratory tests for screening are to be performed within 14 days prior to the first dose of study treatment. See Table 3 for details regarding laboratory tests.

[13] After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing.

[14] Perform urinalysis every 4 cycles.

[15] Required at baseline. Perform thyroid testing every other cycle while patients are receiving pembrolizumab.

[16] Baseline tumor imaging will include the following: CT chest and abdomen with contrast OR CT chest without contrast and MRI abdomen with/without gadolinium and imaging of other known sites of disease; and brain imaging with MRI with/without contrast (or CT with contrast if the patient cannot tolerate an MRI). Imaging of the pelvis should be performed as clinically indicated or if there is known metastases in the pelvis. The initial tumor imaging will be performed within 14 days prior to the first dose of study 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 14 days prior to the first dose of study treatment. On-study imaging will be performed every 6 weeks (42 ± 7 days) after the first dose of study treatment or more frequently if clinically indicated. **The timing for imaging studies should follow calendar days and should not be adjusted for delays in cycle starts or extension of topotecan or pembrolizumab cycle frequencies**. The same imaging technique should be used in a patient throughout the study. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for patient management.

[17] 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.

[18] Tumor tissue for biomarker analysis from an archival tissue sample (not more than 42 days prior to signing consent) or newly obtained tumor tissue from a recent biopsy of a tumor lesion not previously radiated. Please see AFT 17 Correlative Science Manual for specimen collection instructions. If a NEW biopsy is performed, the investigator should ensure that adequate tissue is collected.

[19] Patients who discontinue study treatment for a disease progression, will undergo a mandatory Safety Follow-up Visit approximately 30 days after the last dose of study 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 study treatment for a reason other than disease progression will move into the Follow-up Phase and should be assessed every 6 weeks (42 ± 7 days) by radiologic imaging to monitor disease status, development of drug related SAEs and ECIs/irAEs, and initiation of a new antineoplastic therapy. Follow-up visit 1 should be scheduled 6 weeks after the last dose of study treatment. 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 study treatment or until initiation of a new antineoplastic therapy, whichever comes first. Report all SAEs (related and unrelated to study treatment) occurring within 90 days of the last dose of study treatment or the start of new anti-cancer treatment, whichever comes first. All ECIs/irAEs occurring within 90 days of the last dose of study treatment should be reported regardless of initiating new anticancer therapy. After this time, report only SAEs and ECIs/irAEs that are considered related to study treatment.

[23] If archival sample is not available, fresh tissue samples will be collected for correlative studies.

[24]Those patients receiving pembrolizumab will undergo a biopsy obtained during week 4 to 6 of treatment for biomarker analysis, if clinically feasible and safe. A tumor lesion not previously radiated (required for PD-L1 determination) should be biopsied. The tumor sample must be sent to the AFT-Biorepository. See AFT 1 Correlative Science Manual for additional details.

[25] Patients on the topotecan arm who progress and are to cross-over to the pembrolizumab arm, will undergo a biopsy just before initiating experimental treatment, if clinically feasible and safe. A tumor lesion not previously radiated (required for PD-L1 determination) should be biopsied. The tumor sample must be sent to the AFT-Biorepository.

[26] Whole blood samples for genomic analyses, and peripheral blood cell/serum plasma samples for correlatives will be collected for all patients at screening, at week 4-6 biopsy, at imaging during all cycles, and at progression/cross-over. Samples will be collected per Section 12. Note that each time point requires differing types of blood collection. Please refer to the lab manual for detailed instructions on sample collection. [§] For patients who cross-over from the topotecan arm to the pembrolizumab arm, they will undergo the same assessments and procedures from study start, except that a repeat tumor biopsy will not be performed during weeks 4 to 6.

Table 3. Laboratory Tests

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

Laboratory tests for screening should be performed within 14 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 study treatment. At cross-over, laboratory tests can be performed up to 72 hours prior to dosing of pembrolizumab.

9.2. TUMOR IMAGING SCHEDULE

The initial tumor imaging will be performed within 14 days prior to the first dose of study 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 14 days prior to the first dose of study treatment.

On-study imaging will be performed every 6 weeks (42 ± 7 days) after the first dose of study treatment, or more frequently if clinically indicated. 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) or topotecan cycle frequencies. The same imaging technique should be used in a patient throughout the study. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for patient management.

10. TREATMENT PLAN

10.1. STUDY TREATMENTS

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

Table 4. Study Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg	Every 3 weeks	IV Infusion	Day 1 of each 3 week cycle	Experimental
Topotecan	1.25 mg/m^2 Days 1 to 5	Every 3 weeks	IV Infusion	Days 1-5 of each 3 week cycle	Standard/ Control
The pembrolizumab (MK-3475) dosing interval may be increased due to toxicity.					

Study treatment should begin on the day of randomization and no later than 48 hours from the date on which treatment is allocated/assigned (or 72 hours if randomization occurs on a Friday).

Experimental Arm

Pembrolizumab: 200 mg IV every 21-days until progression of disease or unacceptable toxicities.

Control Arm

Topotecan at 1.25mg/m^2 on days 1 to 5 every 21-days until progression of disease or unacceptable toxicities. Pegfilgrastim can be administered on day 6, 7 or 8 of every cycle as determined by the investigator.

Patients with progression of disease by RECIST 1.1 will be allowed cross over to receive **pembrolizumab** 200 mg IV every 21-days for up to 1 year until progression of disease or unacceptable toxicities.

10.2. DOSE SELECTION AND PREPARATION

The rationale for selection of doses to be used in this study is provided in Sections 4.2.1 and 4.2.2.

The specific instructions for pembrolizumab (MK-3475) preparation and administration are included in the Pharmacy Manual.

Topotecan will be prepared and administered as per the approved product label or institutional standard practice.

10.2.1. Timing of Dose Administration

Study 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). Study treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All study treatments will be administered on an outpatient basis.

10.2.2. Pembrolizumab

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

10.2.3. Topotecan

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

Antiemetics will be administered prior to each dose of topotecan as per institutional standards.

Pegfilgrastim can be given on day 6, 7 or 8 of every cycle, as determined necessary by the investigator.

11. DATA AND SPECIMEN SUBMISSION, STUDY 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 study in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in AFT CTMS System.

12. BIOSPECIMEN COLLECTION

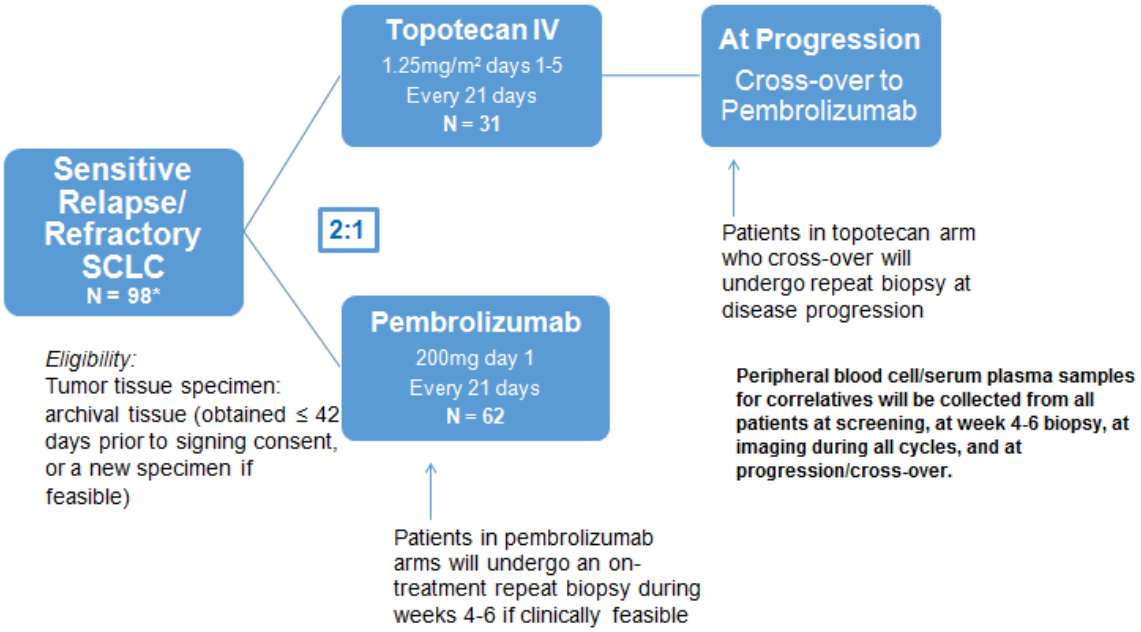
In order to be eligible for the study, all subjects with progressive or recurrent SCLC must provide a tumor tissue specimen. A newly acquired specimen will be preferred, although a recently-obtained (≤ 42 days prior to consent) archived sample can be used if available. Patients in the pembrolizumab (MK-3475) arm will undergo a repeat biopsy while on treatment (during weeks 4 to 6 (days 29 to 42), if clinically feasible. Patients in the topotecan arm will undergo a repeat biopsy at the time of disease progression just before the cross-over to pembrolizumab, if clinically feasible.

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

Fine needle aspirates or cytologic specimens will not be accepted. Core needle or excisional biopsies, or resected tissue is required at each time point. Importantly, the specimen should not be from a previously irradiated lesion.

In addition, whole blood and peripheral blood mononuclear cell (PBMC) samples will be collected at baseline and at specified times throughout the study. Please see the biospecimen collection schema in Section 11.1 below for specific time points. Detailed information regarding the collection, processing and shipping of samples collected for screening and during the study are included in the AFT 17 Correlative Science Manual.

12.1. BIOSPECIMEN COLLECTION SCHEMA



13. CORRELATIVE STUDIES

13.1. IMMUNOHISTOCHEMISTRY EVALUATION

Expression of phenotypic and functional immune cell markers on tumor infiltrating cells, as well as immune signaling markers on the surface of tumor cells will be evaluated by multispectral immunohistochemistry. FFPE tumor tissue collected from pre-treatment and on-treatment biopsy will be utilized. Immunohistochemical markers may include, but not be limited to PDL-1, PD-L2, PD-1, CD3, CD4, CD8, FoxP3, CD68, MHC I and II, GITR, OX40, LAG-3 and TIM-3.

We will correlate expression of these markers to response, PFS and OS. For those patients treated in the pembrolizumab arm, pre-treatment samples also will be compared to on-treatment biopsy samples to identify the immunophenotype of response.

13.2. WHOLE EXOME SEQUENCING OF TUMOR AND MATCHED NORMAL FOR EVALUATION OF MUTATIONAL BURDEN AND NEOANTIGEN LANDSCAPE

Tumor DNA and matched normal DNA will be extracted for whole exome analyses. Once DNA has been obtained and extracted, we will perform massively parallel sequencing of the tumor tissue and the available matched normal tissue. Genomic DNA will be captured via solution based hybrid selection and sequenced on the Illumina HiSeq platform. Matched normal DNA also will be collected from whole blood and sequenced in conjunction with somatic tumor DNA. This is necessary to make the variant calls in next-generation sequencing assays. It is not the intent of this analysis to utilize these samples to identify germline susceptibility mutations. However, in the course of investigating somatic sequence variations, germline susceptibility variants may be suggested by comparative germline sequencing. In addition, some somatic mutations are themselves directly suggestive of a germline predisposition (e.g. *BRCA1*). See Appendix II for plan should a potentially actionable incidental finding is identified during the course of this research.

Assessment of total somatic mutational burden:
The somatic sequencing data will be analyzed for base mutations, insertions, fusions, deletions, copy number alterations and in all target genes. Total nonsynonymous mutation burden per tumor sample will be determined and correlated to radiographic response. Other analysis may include differential impact of individual genomic alterations and response to study therapy.

***Assessment of the neoantigen landscape*:**
Utilizing whole exome sequencing, we will identify candidate neoantigenics in SCLCs and explore their associations with response to pembrolizumab therapy.

Neoantigens are modeled in silico by examining the components of antigen presentation on MHC (*antigenicity*).[53] Expressed somatic missence mutations

are translated into pairs of short peptide strings: one including the mutation and one corresponding to the wild type sequence. *In silico* analysis is performed (for example using NetMHC (http://www.cbs.dtu.dk/services/NetMHC-3.2/ [54,55] or similar algorithm to predict the binding affinity of a given peptide for patient specific MHC I and II. Candidate neoantigens of particular interest will be identified by having a predicted class I or II MHC binding affinity to patient-specific HLA alleles of at least 500nM.

HLA typing may be inferred using ATHLATES or determined directly using normal DNA.

13.3. TRANSCRIPTOME ANALYSES

Gene expression profiling of the immunologic composition of the tumor microenvinroment is assessed by RNAseq. This may be performed on pre-treatment tumor, on-treatment tumor samples, as well as serially collected peripheral blood lymphocytes. RNA is extracted, quality controlled and mRNA is isolated, fragmented, purified, and undergoes whole transcriptome library preparation per protocol.

We will utilize gene expression data to evaluate changes in the tumor and tumor microenvironment between pre- and matched on-treatment (for the pembrolizumab arm) or post-treatment (for the topotecan arm) specimens that are associated with either response or resistance to study therapy.

13.4. PERIPHERAL BLOOD BASED STUDIES

Multiparametric flow cytometry will be performed at baseline and during treatment to assess baseline and changes in composition/activation status of lymphocyte subsets present in peripheral blood mononuclear cell preparations (PBMCs). Lymphocyte subsets to be assayed may include, but are not limited to CD3+, CD8+ and CD4+ T-cell subsets (activated; effector/memory; regulatory) and populations of those cells as defined by the expression of activation, exhaustion, or signaling markers such as, but not limited to, FoxP3, Ki67, ICOS, CTLA-4, PD-1, LAG-3, and Tim-3.

Serially collected PBMCs may also be used to screen for autologous neoantigen-specific T cell responses in the peripheral blood. Methods for doing so include combinatorial coding with peptide-MHC multimers,[51,56] which permits high-throughput detection of antigen-specific T-cells to multiple potential antigens in parallel. Briefly, using synthesized peptides from candidate neoantigens as described above, large quantities of fluorochome-labeled peptide-MHC complexes are generated such that each neoantigen is coded by a unique fluorochrome combination. Then, using conditional MHC ligands that are cleaved upon exposure to UV-light, empty, peptide-reactive MHC molecules are then exposed to autologous T-cells and reactivity of TILs to peptide-MHC complexes will be assessed and quantified by flow cytometry.

Neoantigen-specific T-cells will be isolated and may be expanded and used for future experiments.

As improvements in technology and scalability permit, alternative strategies for identifying neoantigen-specific T cells in treated patients may be explored.

13.5. T CELL RECEPTOR SEQUENCING

Using serial RNA samples extracted from PBMC and tumor samples, we will comprehensively characterize their T cell receptor repertoire. We will compare their diversity and dynamics in responders versus non-responder and also assess their correlation with changes in mutational/neoantigen burden during treatment.

In order to examine all possible variable (V), diversity (D), and joining (J) segments of the T cell receptor combinations, we will first apply the 5'RACE (5' rapid amplification of cDNA end) method using a SMART (Switching Mechanism At 5' end of RNA Transcript) library construction kit (Clontech). We will perform PCR amplification of T cell receptor α (TCRA) and T cell receptor β (TCRB) gene products with adapter-conjugated primer sets in order to prepare amplicon libraries compatible with Illumina NGS platform. The template library will then be amplified by Nextera XT index kit (Illumina) that allows barcode tagging and pooling of up to 16 samples. Subsequently, the prepared library will be analyzed using MiSeq Reagent 600-cycle kit v3 and MiSeq system (Illumina) that will generate 3-6 million T cell receptor reads per sample. The final data will be analyzed using Tcrip software or MiTCR.

In addition, we will perform similar comprehensive T cell receptor analyses for clones of neoantigen-specific T cells isolated from PBMCs and/or TILs in section 12.4 above.

14. DOSE AND TREATMENT MODIFICATIONS (ESCALATION/TITRATION/OTHER), CONCOMITANT MEDICATIONS, SUPPORTIVE CARE

14.1. DOSE MODIFICATION

14.1.1. Pembrolizumab (MK-3475) Dose Modification

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 dosing may continue in the event of an unrelated or grade 1 adverse event. Pembrolizumab (MK-3475) must be withheld for drug-related toxicities and severe or life-threatening adverse events, as per Table 5 below. Drug-related toxicities are managed by dose delay or interruption rather than dose reduction. See Section 14.3.1 for supportive care guidelines, including use of corticosteroids.

Table 5. Dose Modification Guidelines for Pembrolizumab Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 6 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 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 for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when patients are clinically and metabolically stable, yet discontinue treatment if patients are not improved within 6 weeks of last dose
Hypophysitis	2-4	Toxicity resolves to Grade 0-1 Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 6 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 6 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
			prednisone or equivalent per day within 6 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 6 weeks
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity, excluding hematologic toxicity[2]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 6 weeks
	4	Permanently discontinue	Permanently discontinue
Hematologic Toxicity			
Thrombocytopenia associated with bleeding	3	Toxicity resolves to Grade 0-1 or baseline May increase the dosing interval by 1 week	Toxicity does not resolve within 6 weeks of last dose Permanently discontinue if associated with severe or life threatening bleeding event
Neutropenia, anemia, or thrombocytopenia	4	Toxicity resolves to Grade 0-1 or baseline May increase the dosing interval by 1 week	Toxicity does not resolve within 6 weeks of last dose Permanently discontinue if associated with any severe or life threatening event

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[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose: Refer to Table 8 Infusion Treatment Guidelines for further management details.

[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 6 weeks of the last dose.

If toxicity does not resolve to Grade 0-1 within 6 weeks after last infusion, study treatment should be discontinued after consultation with the Study PI. With Study Chair and AFT agreement, patients with a laboratory adverse event still at Grade 2 after 6 weeks may continue treatment in the study 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 study 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). Patients should be placed back on study therapy within 1 week of the scheduled interruption, unless otherwise discussed with the Study Chair and AFT. The reason for interruption should be documented in the patient's study record.

14.1.2. Topotecan Dose Modification

Should toxicity develop, treatment should be modified rather than discontinued. Patients will be allowed to have no more than two separate dose reductions. All dose reductions are permanent.

Patients will be evaluated on Day 1 of each 21-day cycle. In the setting of grade 1 or greater toxicity, treatment will be adjusted according to the tables below. If there is an indication for treatment to be held, re-evaluation will occur 7 days later. If treatment can be resumed on day 8, there will be at least one decrease in dose level as noted below for topotecan. If treatment must be held again at day 8, there will be a decrease by two dose levels whenever treatment resumes. If treatment must be held for 22 days or more (≥ 6 weeks since initiation of last cycle), the patient will be withdrawn from study.

Table 6. Dose Reduction Guidelines for Topotecan

Dose level	Topotecan Dose	Schedule
-1	Decrease by 0.25 mg/m^2 (To 1.0 mg/m^2)	Days 1-5
-2	Decrease by 0.5 mg/m^2 from baseline (To 0.75 mg/m^2)	Days 1-5

Table 7. Dose Modification Guidelines for Topotecan Drug-Related Adverse Events

Adverse Event	Parameters on day of treatment	CTCAE v4.0 Grade	Topotecan
Hematologic			
ANC	1000 – 1499 /mm^3	Grade 2	Hold, then decrease by one dose level
	< 1000 /mm^3	Grade 3 – 4	Hold, then decrease by one dose level
Hemoglobin	8.0 – 9.9 g/dL	Grade 2	No change
	< 8.0 g/dL	Grade 3 – 4	Hold, then decrease by one dose level
Platelets	75,000 – 99,000 /mm^3	---	Hold
	50,000 – 74,000 /mm^3	Grade 2	Hold, then decrease by one dose level
	< 50,000 /mm^3	Grade 3 – 4	Hold, then decrease by one dose level
Neutropenic Fever	---	Grade 3 – 4	Off study
Infection (Documented clinically) with Grade 3 / 4 ANC	Local intervention	Grade 2	Hold, then decrease by one dose level
	IV antibiotics indicated	Grade 3 – 4	Off study
Non-Hematologic, Non-Neurologic			
Creatinine Clearance Cockcroft-Gault	≥ 60 ml/min	---	No change

(non CTCAE)	40-59 ml/min	---	Hold, then decrease by one dose level
	20-39 ml/min	---	Hold, then decrease by two dose levels
	< 20 ml/min	---	Off study
AST or ALT[1]	2.6 – 5.0 x ULN	Grade 2	Hold
	> 5.0 x ULN	Grade 3 – 4	Hold, then decrease by one dose level
Total Bilirubin	1.6 – 3.0 x ULN	Grade 2	Hold
	> 3.0 x ULN	Grade 3 - 4	Hold, then decrease by one dose level
Alkaline phosphatase	2.6 – 5.0 x ULN	Grade 2	Hold
	> 5.0 x ULN	Grade 3 – 4	Hold, then decrease by one dose level
Other Non-Hematologic[2]	---	Grade 2	No Change
	---	Grade 3	Hold, then decrease by one dose level
	---	Grade 4	Hold, then decrease by one dose level

[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] Excludes: alopecia, cough, dehydration, dry mouth, dry skin, dysphagia, edema, flatulence, flushing, heartburn, hemorrhoids, hiccoughs, hyper- or hypopigmentation, insomnia, nail changes, patient odor, or sweating.

14.2. CONCOMITANT MEDICATIONS/VACCINATIONS (ALLOWED & PROHIBITED)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the study, discontinuation from study therapy 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. However, the decision to continue the patient on study therapy or vaccination schedule requires the mutual agreement of the Study Chair, AFT, and the patient.

14.2.1. 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 study

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 study treatment and 30 days after the last dose of study treatment should be recorded. Concomitant medications administered after 30 days after the last dose of study treatment should be recorded if administered due to a severe adverse event (SAE) or SAEs and/or event of clinical interest, as defined in Section 17.2.2.

14.2.2. Prohibited Concomitant Medications

Patients are prohibited from receiving the following therapies during the screening and treatment Phase of this study:

- 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, non-target solitary lesion or to the brain may be allowed after consultation with the Study PI and Sponsor
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. 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.
- Immunosuppressive medications including, but not limited to systemic corticosteroids (>10 mg/day prednisone or equivalent), methotrexate, azathioprine, and tumor necrosis factor alpha (TNF-α) blockers. Use of immunosuppressive medications for the management of investigational product-related AEs and in subjects with contrast allergies. The use of physiologic steroid replacement may be approved after consultation with the investigator and Study PI. In addition, use of inhaled and intranasal corticosteroids is permitted. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
- Systemic glucocorticosteroids for any other purpose other than to modulate symptoms from an event of clinical interest or for use as a pre-medication prior to a CT scan for subjects with contrast allergy or

for use for COPD exacerbation requiring steroid for recovery. Replacement doses of steroids (for example, prednisone 5-7.5 mg daily) are permitted while on study. Inhaled corticosteroids are allowed.

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 study.

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

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

14.3. RESCUE MEDICATIONS AND SUPPORTIVE CARE

14.3.1. Supportive Care Guidelines for Pembrolizumab

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.

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

- 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 one month.

- In patients with severe enterocolitis (Grade 3), pembrolizumab (MK-3475) will be permanently discontinued and treatment with systemic corticosteroids should be initiated (1 to 2 mg/kg/day of prednisone or equivalent). Prophylactic antibiotics should be initiated for opportunistic infections. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continue over at least 1 month.

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 13.3.1.3. 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 subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop the infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: ▪ IV fluids ▪ Antihistamines ▪ NSAIDS ▪ Acetaminophen ▪ Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	Patient may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: ▪ Diphenhydramine 50 mg po (or equivalent dose of antihistamine). ▪ Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
	If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment administration.**	
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: ▪ IV fluids ▪ Antihistamines ▪ NSAIDS ▪ Acetaminophen ▪ Narcotics ▪ Oxygen ▪ Pressors ▪ Corticosteroids ▪ Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Patient is permanently discontinued from further study 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		

14.3.2. Supportive Care Guidelines for Pneumonitis

Patients with symptomatic pneumonitis should immediately stop receiving pembrolizumab 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 6 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 Events of Clinical Interest and Immune-related Adverse Event Guidelines in Section 13.3.3 below for additional recommendations.

For Grade 2 pneumonitis that improves to ≤ Grade 1 within 6 weeks, the following rules should apply:

- For the first episode of pneumonitis
  - May increase dosing interval by one week in subsequent cycles

- For the second episode of pneumonitis
  - Permanently discontinue pembrolizumab if upon rechallenge, the patient develops pneumonitis ≥ Grade 2

14.3.3. 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 10.

Table 10. General Approach to Treating IRAEs

IRAE	Withhold/Discontinue Pembrolizumab?	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 6 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment, utilizing 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.

14.3.4. Supportive Care Guidelines for Events of Clinical Interest/Immune Related Adverse Events (IRAEs)

Patient 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. Patients can receive aggressive anti-diarrheal agents, including and not limited to: loperamide and atropine/diphenoxylate.

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

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.

Bone Marrow Support: Pegfilgrastim can be administered on day 6, 7 or 8 of every cycle at the discretion of the investigator. Pegfilgrastim can be initiated at cycle 1 or after neutropenia is observed. There are no contraindications to blood transfusions.

14.4. OTHER CONSIDERATIONS

14.4.1. Contraception

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

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

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

OR

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

OR

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

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

(1) Practice abstinence* from heterosexual activity;

OR

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

The following are considered acceptable barrier methods of contraception:

Single method (one of the following is acceptable):

- Intrauterine device (IUD)
- Vasectomy of a female subject's male partner
- Contraceptive rod implanted into the skin

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

- Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- Cervical cap with spermicide (nulliparous women only)
- Contraceptive sponge (multiparous women only)
- Male condom or female condom (cannot be used together)
- Hormonal contraceptive: oral contraceptive pill (estrogen/progestin – only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection)

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

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

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 patients of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of study therapy. If there is any question that a patient of childbearing potential will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

14.4.2. Use in Pregnancy

If a patient inadvertently becomes pregnant while on treatment with pembrolizumab (MK-3475), the subject will immediately be removed from the study. The site will contact the patient at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to AFT without delay and within 24 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.

14.4.3. Use in Nursing Women

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

15. MEASUREMENT OF EFFECT

This randomized phase II study will evaluate PFS as the primary endpoint based on RECIST 1.1,[29] which will be used for assessment of tumor response.

15.1. SCHEDULE OF EVALUATIONS

The initial tumor imaging will be performed within 14 days prior to the first dose of study 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 14 days prior to the first dose of study treatment. On-study imaging will be performed every 6 weeks (42 ± 7 days) after the first dose of study treatment or more frequently if clinically indicated. The timing for imaging studies should **follow calendar days** and should not be adjusted for delays in cycle starts or extension of topotecan or pembrolizumab (MK-3475) cycle frequencies. The same imaging technique should be used in a patient throughout the study.

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 study treatment or to stop study treatment until repeat imaging performed 4-6 weeks later confirms progression.

Clinical stability in a patient whose disease displays radiographic progression 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. Upon repeat imaging, if progression is confirmed, then the patient will be discontinued from study treatment. As the primary endpoint is PFS, the date of the first scan that documented progression should be used. If progression is not confirmed, then the patient should resume/continue study treatment and have the 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.

For patients who discontinue study treatment for reasons other than disease progression, imaging should continue according to the same schedule (every 6 weeks/ 42 ± 7 days) until the patient experiences confirmed disease progression or starts a new antineoplastic therapy.

Study eligibility will be according to RECIST 1.1 criteria.

15.1.1. Response for 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 for tumor response.

*As published in the European Journal of Cancer

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

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).

Lesions that are previously irradiated must show clear evidence of progression to be considered as measurable disease.

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.

15.1.3. 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. <u>These lesions can be non-nodal or nodal</u> 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.

15.1.4. Response Criteria

All target lesions and target lymph nodes followed by CT must be measured on re evaluation at evaluation times specified in Section 15.2.1 & 15.2.3. 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

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
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.

16. End of Treatment/Intervention

16.1. Duration of Treatment

16.1.1. 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

16.1.2. 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).

16.1.3. Discontinuation of Study Agent

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

16.2. Patient Withdrawal/Discontinuation Criteria

16.2.1. Patient Withdrawal

In the absence of serious toxicity or complications, all patients will continue treatment until evidence of disease progression, or for up to 24 months, whichever is first.

Patients may withdraw consent at any time for any reason or be dropped from the study 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 study is inappropriate, the study 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 study for any of the following reasons:

- The patient or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression while receiving pembrolizumab as per RECIST 1.1.
  Note: A patient may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, per the investigator's discretion, given the potential of tumor flare.
- Unacceptable adverse experiences
- 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 study treatment or procedure requirements
- The patient is lost to follow-up
- 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 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 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. Patients who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status every 6 weeks until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each patient will be followed by telephone every 12 weeks for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

16.3. DEFINITIONS AND FOLLOW-UP REQUIREMENTS

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

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.

16.4. FOLLOW UP FOR INELIGIBLE PATIENTS

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

16.5. FOLLOW-UP FOR PATIENTS NEVER RECEIVING PROTOCOL INTERVENTION

Study participants who are enrolled into the study 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.

17. 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 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 (or topotecan) during this study, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of small cell lung cancer 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.

17.1. ROUTINE ADVERSE EVENT REPORTING

Adverse event data collection and reporting, which are required as part of every clinical study 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. All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the study, or are the result of a protocol specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Any new AEs or increase of a documented AE from screening/history will be recorded from the time of the first treatment allocation/randomization 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. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Adverse events will not be collected for patients during the pre-screening period 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.

17.2. 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 SAEs/Infusion Associated Reactions (IARs) must be entered into the eCRF via Rave EDC 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 reporting via Rave EDC, regardless of causality. Attribution to treatment or other cause should be provided.

17.2.1. Serious Adverse Event (SAE)

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event due to any cause other than progression of the cancer under study that occurs to any subject must be reported within the timelines listed in Table 12 below if it causes the patient to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

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

Note: 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. In addition to the above criteria, although not serious per ICF definition, are reportable to AFT in the same timeframe as SAEs to meet certain local requirements. Therefore these events are considered serious by AFT for collection purposes:

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

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the AFT via the Rave Electronic Data Capture (EDC) system within the timeframes detailed in the table below. 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 Rave EDC within 24 hours of the sites awareness of the event			
Not resulting in Hospitalization ≥ 24 hrs	Not required to enter into Rave EDC as an SAE.		Enter into Rave EDC as an SAE 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 Rave EDC ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ **4** calendar days of the initial 24-hour report.
- "All Grade 1 and 2 AEs resulting in hospitalization or prolonged hospitalization: 24-Hour; 10 Calendar Days" - The AE must initially be reported via Rave EDC ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ **10** calendar days of the initial 24-hour report.

Serious adverse events will be recorded from the time of treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the patient initiates a new antineoplastic therapy, whichever comes first. Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study whether or not related to pembrolizumab (MK-3475) must be reported into Rave EDC within 24 hours of awareness of the event.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to pembrolizumab (MK-3475) that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph must also be reported immediately to AFT.

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

NOTE: Deaths occurring outside of the serious adverse event reporting period that are clearly due to progressive disease 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 Rave EDC with death noted as the outcome of the event.

17.2.2. 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 reported within 24 hours within Rave EDC system.

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

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to pembrolizumab (MK-3475), must be reported within via Rave EDC within 24 hours and AFT will report to Merck Global Safety within 2 days

ECIs/ir AEs for this study include:

1. An overdose of pembrolizumab, as defined in Section 16.3 - 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.

17.2.3. Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to AFT as described in Section 16.2.1 – Table 12, unless there is evidence suggesting a causal relationship between pembrolizumab and the event. Any such event will be submitted to AFT via Rave EDC within 24 hours and AFT will report to Merck Global safety within 2 working days.

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

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

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

17.2.4. Definition of an overdose for this protocol and reporting of overdose to AFT

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

If a dose of pembrolizumab 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."

17.2.5. 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) that occurs during the study. Sites may use the pregnancy form in Rave EDC to report pregnancies.

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

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

17.3. 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 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 to treat a preexisting condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of pembrolizumab and is documented in the patient's medical history); or	
	†Is a congenital anomaly/birth defect (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new cancer; (that is not a condition of the study) (although serious per ICH definition, is reportable to AFT within 24 hours and AFT will report to Merck Global Safety within 2 working days).	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	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 Pembrolizumab to be discontinued?	

Relationship to study drug	Did Pembrolizumab cause the adverse event? The determination of the likelihood that Pembrolizumab 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 Pembrolizumab and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Pembrolizumab caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to Pembrolizumab 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 Pembrolizumab? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies 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 (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was Pembrolizumab 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 Pembrolizumab; or (3) Pembrolizumab(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to Pembrolizumab 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) Pembrolizumab(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY PEMBROLIZUMAB, OR IF REEXPOSURE TO PEMBROLIZUMAB 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 Study Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Pembrolizumab 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 relationship).**	
Yes, there is a reasonable possibility of Pembrolizumab relationship.	There is evidence of exposure to Pembrolizumab. The temporal sequence of the AE onset relative to the administration of Pembrolizumab is reasonable. The AE is more likely explained by Pembrolizumab than by another cause.	
No, there is not a reasonable possibility Pembrolizumab relationship	Patient did not receive Pembrolizumab OR temporal sequence of the AE onset relative to administration of Pembrolizumab is not reasonable OR the AE is more likely explained by another cause than pembrolizumab.. (Also entered for a subject with overdose without an associated AE.)	

18. DRUG INFORMATION

18.1. 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 100 mg/ 4mL	Solution for Injection

18.2. PACKAGING AND LABELING INFORMATION

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

18.3. CLINICAL SUPPLIES DISCLOSURE

This study is open-label; therefore, the patient, the study 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.

18.4. 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 study medication must be recorded by an authorized person at the study site.

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

18.5. 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 study.

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.

19. STATISTICAL CONSIDERATIONS

This phase II study will determine if there is a benefit in progression free survival (PFS) for SCLC patients receiving pembrolizumab (Experimental arm, E) as compared to topotecan (Control arm, C) in the second-line setting. The primary endpoint will be PFS, defined as the time between randomization and disease progression or death of all causes, whichever comes first.

A total of 98 patients will be registered to this study. Taking into account 5% rate of ineligibility and cancellation, a total of 93 eligible patients will be randomized 2:1 allocation to arm E and arm C. Randomization will be implemented with dynamic allocation algorithm with the stratification factor for disease type (sensitive vs. refractory). All patients will be followed for a minimum of 6 months after the last enrollment of the study.

19.1. SAMPLE SIZE JUSTIFICATION

According to the findings from the phase III study studying topotecan vs CAV[6] in the second-line treatment of SCLC patients and the phase III study comparing oral and intravenous topotecan,[45] we expect a median PFS of 12 weeks for the control arm (C) and 20 weeks (a 67% increase) for the experimental therapy (E) in the pooled patient population with relapsed sensitive or refractory SCLC. Under the assumption of exponential survival time, it corresponds to a hazard ratio λ_E/λ_C = 0.60. Assuming an accrual rate of 4 randomized patients per month, it will take approximately 23 months to enroll 93 randomized patients (62 arm E and 31 arm C). With additional follow-up of 26 weeks (approximately 6 months) after the enrollment of the last patient, or approximately 86 events (59 arm E, 27 arm C), the study has approximately 82% power to reject the null hypothesis $\lambda_E/\lambda_C = 1$ and accept the alternative hypothesis $\lambda_E/\lambda_C < 1$ when the true $\lambda_E/\lambda_C = 0.60$ using a stratified log rank test at a 1-sided significance level of 0.10.

Per above, eligible patients will be randomized with 2:1 allocation to two arms (E and C). The patients on arm C are allowed to receive pembrolizumab after progression. The final analysis is expected to take place 6 months after the last enrolled patient has been treated.

In the primary analysis, a stratified log rank test with equal weights over time will be used to test the PFS difference between two arms. As late treatment effect is often observed for immunotherapy, a weighted log rank test with Fleming-Harrington weights[58] also will be used as a supplementary analysis to maximize the test efficiency for late treatment effect. More details can be found in the Analytic Method section.

Objective response rate (ORR) is a secondary endpoint. The sample size of the study is not determined by having adequate power to test ORR. With 62/31 patients on arm E/C, the study has approximately 82% power to differentiate ORR<12% versus ORR>32% at one-sided significance level of 0.10

19.2. ACCRUAL AND FOLLOW-UP

With allowance of 5% ineligible, cancelling and unevaluable, the study plans to register 98 patients. We estimate to enroll and randomize 4 patients per month and anticipate approximately 23 months to achieve the target accrual. A minimum of 6 months of follow-up is needed to evaluate the primary objective if the accrual rate is at the expected range.

19.3. 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.

20. STATISTICAL ANALYSIS PLAN

The primary analysis will include all randomized patients but exclude ineligible patients or patients who cancel this study before receiving any protocol treatment.

The primary efficacy endpoint is PFS, which is defined as the time from the date of randomization to the date of earliest radiographic disease progression or death. If the subject does not experience radiographic disease progression or death, then the data will be censored at the date of the last disease assessment. PFS will be analyzed by Kaplan Meier methodology and compared between arm E and arm C, using a log-rank test stratified by disease type (sensitive vs refractory). A two-sided, stratified log-rank test P value will be provided. Median PFS time will be calculated and 95% confidence interval for median PFS will be presented. Overall survival (OS) will be analyzed in a similar manner as PFS.

Late treatment effect is often expected for immunotherapy. For this reason, a weighted log rank test with Harrington-Fleming weights that optimize the expected late treatment effect will be conducted as a supplementary analysis for both PFS and OS. In particular, the following three parameter settings will be used: (1) $\rho = 0$ and $\gamma = 0.5$; (2) $\rho = 0$ and $\gamma = 1$; and (3) $\rho = 0$ and $\gamma = 2$ (39).

The proportion of subjects with objective response as assessed by the investigator using RECIST version 1.1 will be evaluated for randomized subjects. The objective response rate will be estimated and compared between arm E and arm C, using a Cochran-Mantel-Haenszel (CMH) test stratified by tumor volume. A two-sided, stratified CMH test P value will be provided. In addition, a 95% confidence interval will be constructed for the estimated proportions. Similar analysis will be conducted for disease control rate (DCR), which is defined as the proportion of patients achieving complete, partial and stable disease after the protocol treatment.

All subjects who receive at least one dose of the study drug will be included in safety analysis. Treatment-related toxicity will be summarized by grade, type and system organ

class. Comparisons of the percentages of subjects experiencing an adverse event between arm E and arm C will be performed using Fisher's exact test.

The association between candidate biomarkers in tumor samples, including, but not limited to, CD3, CD4, CD8, FoxP3, PD-1, CD68, MHC class I and II, and PD-L1, with response will be evaluated using Wilcoxon rank sum test. The association of these biomarkers with PFS and OS will be evaluated using single-predictor Cox models.

The correlation between T-cell immunophenotypes in peripheral blood mononuclear cell samples and clinical response will be evaluated with Chi-square test.

The correlation between mutational burden in tumor specimens and objective response will be evaluated using Wilcoxon rank sum test separately for patients treated by pembrolizumab and topotecan.

The difference in neoantigen signature between SCLC tumors responding to PD-1 inhibition and those not responding to therapy will be evaluated.

21. GENERAL REGULATORY CONSIDERATIONS

21.1. COMPLIANCE WITH STUDY 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 study is solely responsible for determining whether the study 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 studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

21.2. REGULATORY AND ETHICAL COMPLIANCE

By signing the Protocol the investigator agrees to treat all of the information that is provided with the strictest confidentiality and to require the same of his personnel as well as the IRB. Study documents (protocols, investigator`s brochures, eCRFs, etc.) provided by the AFT will be stored in an appropriate manner in order to ensure confidentiality. The information provided to the investigator by AFT must not be made available to other parties without a direct written authorization by the aforesaid parties, with the exception of the extent to which disclosure is necessary in order to obtain informed consent from the patients who wish to participate in the study.

21.3. ETHICS AND GOOD CLINICAL PRACTICE

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.

The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

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.

By signing the study protocol the investigator agrees to comply with the instructions and procedures described therein and thus to adhere to the principles of good clinical practice, which these instructions and procedures reflect.

21.4. CONFIDENTIALITY

Patient medical information both, associated with biologic specimens or not, 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 in generally 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.

21.5. 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.

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.

21.6. 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).

For patients not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the patients and his/her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the patient and representative have orally consented to participation in the study, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. The Investigator or designee must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

Furthermore, it is the investigator's responsibility to obtain the signed Informed Consent Form, and a signature from the person conducting the informed consent discussion, prior to undertaking any study-related procedure. The proposed Informed Consent Form must accomplish with the ICH GCP guideline and regulatory requirements.

If new pembrolizumab 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.

21.7. MONITORING AND REMOTE MONITORING

The Investigator is responsible for being available during sponsor monitoring visits. Study staff should be available to answer questions and address any issues or data clarifications. Prior to these visits, the monitor will send a confirmation letter to the Investigator outlining the data that they would need access to. The site should have this readily available prior to the visit. This includes ICFs, source records as needed, medical/electronic medical records, safety, drug accountability and the ISF. The first site monitoring visit will occur approximately four weeks after the first AFT-17 patient is enrolled.

It is expected that the data is entered into the eCRF in a timely manner after the first information is collected, preferably within 3-5 days after the study procedure has been performed. The monitor will also be able to review this data remotely. In this case, the monitor will request de identified source data to be sent to them for cross references.

21.8. 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.

21.9. 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 grant protocol deviation waivers.

21.10. RETENTION OF RECORDS

Any records and documents relating to the conduct of this study and the distribution of investigational drug, including ICFs, eCRFs, PRO data, laboratory test results, and medication inventory records, 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.

21.11. CLINICAL CRITERIA FOR EARLY STUDY ADMINISTRATION

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

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

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

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23. APPENDICES

Appendix I: ECOG Performance Status
Appendix II: Plan to be Utilized Should a Potentially Actionable Incidental Finding be Identified in Course of Research Conducted on Samples Collected Under this Protocol

23.1. APPENDIX I: ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

23.2. APPENDIX II: PLAN TO BE UTILIZED SHOULD A POTENTIALLY ACTIONABLE INCIDENTAL FINDING BE IDENTIFIED IN THE COURSE OF RESEARCH CONDUCTED ON SAMPLES COLLECTED UNDER THIS PROTOCOL

In the event an investigator's research identifies a finding that he or she believes should be communicated to the subject (and/or family designee), the investigator shall communicate this to the institutional IRB, should it be a requirement. The finding will be reviewed by a group convened by the institutional IRB to determine whether the incidental finding should be discussed with the subject. In the event that group convened by the institutional IRB determines that the finding should be discussed with the subject, and the subject has consented to be re-contacted, then the treating/consenting physician shall be contacted by the institutional IRB representative and asked to refer the subject to the Clinical Genetics Service of the institution for further discussion of the research finding. After appropriate counseling and consent, the Clinical Genetics Service of the institution will request permission to confirm the result in a New York Department of Health-approved laboratory prior to communication of the specific result. If the patient is not available (e.g. deceased), then the surrogate designated on the consent will be contacted and the above will occur.

Germline BAM files will not be separately analyzed in the future without additional informed consent, anonymization, and/or human subjects review by the institutional IRB.

24. APPROVAL SIGNATURES

APPROVAL SIGNATURES

Printed	Signature	Title	Date
Suzanne George, M.D.			
Xiaofei Wang, Ph.D.			
Thomas Stinchcombe, MD			