

TITLE: A Phase II trial of Preoperative chemoradiotherapy and MK-3475 for Esophageal Squamous Cell Carcinoma

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1.0 TRIAL SUMMARY

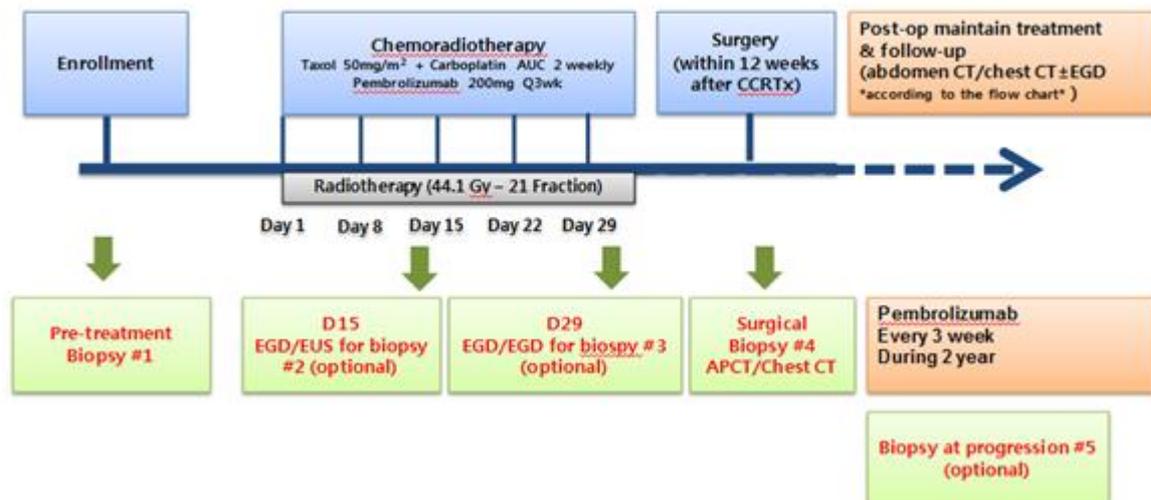
Abbreviated Title	A Phase II trial of Preoperative chemoradiotherapy and MK-3475 for Esophageal Squamous Cell Carcinoma
Trial Phase	Single arm phase II trial
Clinical Indication	Stage Ib-III esophageal squamous cell carcinoma
Trial Type	Interventional
Type of control	Single arm
Route of administration	IV
Treatment Groups	
Number of trial subjects	28
Estimated enrollment period	May 2016 – May 2018
Estimated duration of trial	May 2016 – May 2022
Duration of Participation	May 2016 – May 2022
Estimated average length of treatment per patient	1 year

2.0 TRIAL DESIGN

2.1 Trial Design

Single arm phase II

2.2 Trial Diagram



3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** To evaluate antitumor efficacy of pembrolizumab in combination with chemoradiotherapy : pathologic complete response (pCR) rate

Hypothesis: Pembrolizumab in combination with chemoradiotherapy is tolerable and synergistic for esophageal squamous cell carcinoma

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective:**

1) To evaluate antitumor efficacy

- Disease free survival, overall survival, pathologic response rate, and clinical response

2) Safety

Hypothesis: Pembrolizumab in combination with chemoradiotherapy is tolerable and synergistic for esophageal squamous cell carcinoma

3.3 Exploratory Objective

Objective:

- To identify the potential immune dynamics after pembrolizumab using serial biopsied fresh tumor.
- To explore the predictive biomarkers of pembrolizumab using exome sequencing and RNA sequencing

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8⁺ T-cells and the ratio of CD8⁺

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 ζ , PKC θ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4⁺ and CD8⁺ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United States for the treatment of patients with unresectable or metastatic melanoma and metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 as determined by an FDA-approved test with disease progression on or after platinum-containing chemotherapy and, if EGFR or ALK genomic tumor aberrations positive, should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA.

4.1.2 Preclinical and Clinical Trial Data

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

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Esophageal cancer (EC) is the eighth most common cancer worldwide. It is a highly lethal disease, causing more than 400,000 deaths per year. Despite adequate preoperative staging, 25% of patients treated with primary surgery have microscopically positive resection margins (R1), and the 5-year survival rate rarely exceeds 40%. Therefore, neoadjuvant chemoradiotherapy has been studied for better oncologic outcome.

The role of neoadjuvant chemoradiotherapy has been debated for several decades. Recent randomized, controlled, phase 3 study compared neoadjuvant chemoradiotherapy followed by surgery with surgery alone in patients with potentially curable esophageal or esophagogastricjunction carcinoma(1). Overall survival was significantly better in the chemoradiotherapy–surgery group (hazard ratio, 0.657; 95% confidence interval, 0.495 to 0.871; $P = 0.003$). Median overall survival was 49.4 months in the chemoradiotherapy–surgery group versus 24.0 months in the surgery group and adverse-event was acceptable. Especially, in the subgroup analysis, squamous cell histology demonstrated better trend with preoperative chemoradiotherapy (figure 1). Therefore, preoperative chemoradiotherapy is safe and leads to a significant increase in overall survival for ESCC.

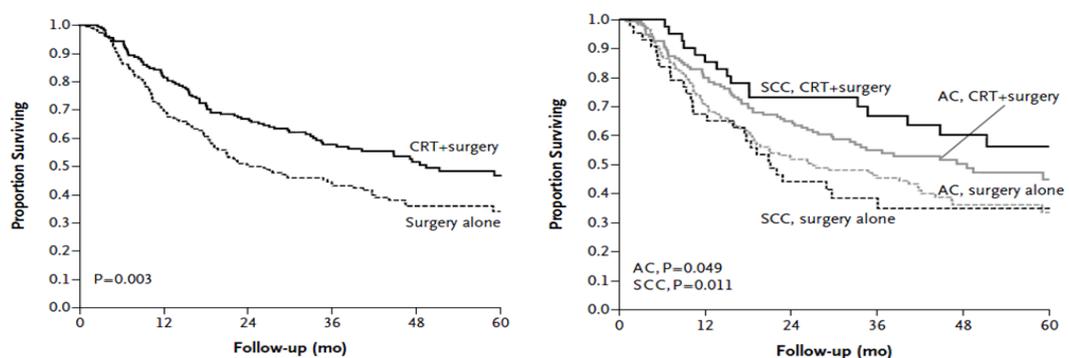


Figure 1. Survival According to Treatment Group (ACC: adenocarcinoma SCC: squamous cell carcinoma)

EC consists of two major histologic subtypes; esophageal squamous cell carcinoma (ESCC) and adenocarcinoma (EAC). Both histologic subtypes have different risk factors and epidemiology. ESCC continues to be the major subtype of EC in Asia, and the main risk factors include smoking and alcohol abuse. Given widely different epidemiological and clinical features, EAC and ESCC may represent distinct disease entities which may benefit from different therapeutic approaches. Therefore, further neoadjuvant clinical trial with homogenous ESCC cohort is strongly warranted.

4.2.2 Rationale for the Chemoradiotherapy in Combination with Pembrolizumab

Pembrolizumab (MK3475) is a humanized IgG4 monoclonal antibody to human programmed cell death-1 (PD-1). PD-1 is a receptor of the CD28 family, which is expressed on activated lymphocytes (T cells, B cells and NKT cells) and myeloid cells. PD-1 binds to PD-1 ligands (PD-L1 and PD-L2), which are expressed on antigen-presenting cells, and transmits regulatory stimuli to lymphocytes to down-modulate the activation of lymphocytes. PD-1 ligand is also expressed in various human cancer tissues other than antigen presentation cells. Regarding the radiotherapy, irradiated tumor cells are known to release antigens that help immune system against tumor. Treatment with anti-PD-L1 antibodies also synergizes with radiation, and appears to exert benefit through reduction in the accumulation in irradiated tumor.(2, 3) In mice, inhibiting PD-L1 restored both T cell function and tumor response to radiation therapy and anti-CTLA4, increase overall survival. PD-L1 on tumor cells is known as dominant resistance mechanism to radiation therapy. Therefore, combination treatment of pembrolizumab with chemoradiotherapy is ongoing for head/neck cancer, renal cell carcinoma, melanoma, and non-small cell lung cancer (NCT02318771) and pancreatic cancer (NCT02305186). Combining pembrolizumab with neoadjuvant chemoradiotherapy is a promising strategy to improve clinical outcome in ESCC. Using serial biopsied fresh tissue and the novel/high-throughput RNA sequencing technologies, we suggest a study to identify predictive biomarkers of pembrolizumab in ESCC patients with neoadjuvant chemoradiotherapy.

4.2.3 Rationale for Dose Selection/Regimen/Modification

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

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

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to

have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

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

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

4.2.4 Rationale for Endpoints

4.2.4.1 Efficacy Endpoints

The primary endpoint of phase II study is to assess complete pathologic response rate. Definition of complete pathologic response is “no cancer cell, including lymph nodes” which corresponds with tumor regression score 0. Definition of pathologic response is as follows. Tumor regression score Grade 0 and 1 will be defined as “responder” and 2 and 3 will be considered as “non-responders”

Tumor regression score *	Ryan et al. description
0 (Complete response)	No cancer cell, including lymph nodes

1 (Moderate response)	Single cells or small groups of cancer cells
2 (Minimal response)	Residual cancer cells outgrown by fibrosis
3 (Poor response)	Minimum or no treatment effect: extensive residual cancer

*NCCN 2015

4.2.4.2 Biomarker Research

1) Exome sequencing (tumor/normal pairs) of fresh-frozen tumor tissues at pre-treatment and at recurrence to identify potential immune epitope and mechanisms of acquired resistance.

2) RNA sequencing or nanostring nCounter of fresh-frozen tumor tissues at pre-treatment, on-treatment and to identify potential immune-related gene signatures

3) T cell function and phenotype analysis in tumor microenvironment [CD4/CD8+ T cell, FoxP3+ Treg cell, immune checkpoint expression (PD1,PDL1, LAG3, TIM3, CTLA4)]

4) Analysis of immune marker using FACS

-Examine the phenotypic characteristics of CD4 and CD8 T cells in terms of various immune check points (PD-1, CTLA4, TIM3, LAG3) and memory markers in fresh tissue and PBMC by FACS on pre-treatment, after 3 weeks and post- treatment.

-Examine the tumor infiltrating immune cells including Treg cells and MDSCs on pre-treatment, after 3 weeks and post- treatment.

-Blood cytokine analysis will be performed at the time points with multi cytokine bead analysis on pre-treatment, after 3 weeks and post- treatment.

5) Analysis of T cell function using ex vivo stimulation

-Stimulate T cell with Dynabeads Human T-activator CD3/CD28 in ex vivo and measure the IFN-r by ELISA.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Histologically confirmed stage T1N1-2 or T2-4aN0-2 (AJCC 7 TNM classification) esophageal squamous cell carcinoma (ESCC)

5.1.2 Subject Inclusion Criteria

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

1. Histologically confirmed ESCC

2. Clinical stage T1N1-2 or T2-4aN0-2 (AJCC 7 TNM classification)
3. No evidence of metastasis
4. Be willing and able to provide written informed consent/assent for the trial.
5. Be ≥ 20 years of age on day of signing informed consent.
6. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion through repeated biopsies. *Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1. Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the Sponsor.*
7. Have a performance status of 0 or 1 on the ECOG Performance Scale.
8. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

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

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

10. Female subjects of childbearing potential (Section 5.7.2) must be willing to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, for the course of the study through 120 days after the last dose of study medication.

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

11. Male subjects of childbearing potential (Section 5.7.1) must agree to use an adequate method of contraception as outlined in Section 5.7.1- Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

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

5.1.3 Subject Exclusion Criteria

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

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
3. Has a known history of active TB (Bacillus Tuberculosis)
4. Hypersensitivity to pembrolizumab or any of its excipients.
5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., \leq Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
6. 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., \leq Grade 1 or at baseline) from adverse events due to a previously administered agent.
 - Note: Subjects with \leq Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
 - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
7. Has another malignancy within the last 5 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative surgery, or in situ cervical cancer.

8. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
9. Has known history of, or any evidence of active, non-infectious pneumonitis.
10. Has an active infection requiring systemic therapy.
11. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
12. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
13. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
14. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
15. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
16. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
17. Has received a live vaccine within 30 days of planned start 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.

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2. The treatment consisted of 3 phases – neo-adjuvant chemoradiotherapy, surgery, and post-operative adjuvant treatment.

Table 2 Trial Treatment

	Neo-adjuvant chemoradiation (about 5 weeks)		Post op maintain treatment (within 8 weeks after surgery)			
Drug	Dose/Potency	Dose Frequency	Dose/Potency	Dose Frequency	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg	Day 1 and 22	200 mg	Every 3 weeks until recurrence During 2yrs	5 weeks +	Experimental

Drug	Neo-adjuvant chemoradiation (about 5 weeks)		Post op maintain treatment (within 8 weeks after surgery)		Regimen/ Treatment Period	Use
	Dose/Potency	Dose Frequency	Dose/Potency	Dose Frequency		
Taxol	50 mg/m ²	Day 1,8,15,22,29			2 years	Standard
Carboplatin	AUC 2mg/ml*min	Day 1,8,15,22,29				Standard

5.2.1 Treatment procedure

5.2.1.1 Neo-adjuvant chemoradiation period

The treatment consisted of taxol, carboplatin, pembrolizumab, and radiation. The radiation treatment comprises 44.1Gy (2.1Gy/Fr, total 21Fr) and that will be about 5 weeks period. The investigator should make an effort to delivery enough amount of radiation to the patients. Intensity modulated RT (IMRT) or 3D CRT (three-dimensional conformal radiotherapy) will be allowed. The maximum chemotherapy dosing will be 5.

5.2.1.2 Surgery

Before surgery, abdomen/chest CT scan and gastroscopy with biopsy will be done with other laboratory tests. Surgery should be done within 12 weeks after last neo-adjuvant treatment (recommend within 4-8 weeks after last treatment). The operational method will depend on the best clinical judgement of investigators or responsible surgeon.

5.2.1.3 Adjuvant period

Adjuvant treatment should be performed within 8 weeks after surgery (recommended period : 3-6 weeks after surgery). Pembrolizumab 200mg will be administered every 3 week until 2 years, disease recurrence, death, unacceptable toxicity or consent withdrawal which comes first. A Abdomen/chest CT scan will be performed every 12 weeks (3 months) after surgery, and an optional gastroscopy may be performed every 24 weeks (6 months).

5.2.2 Dose Selection/Modification

5.2.2.1 Dose Selection

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

Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Medication package insert.

5.2.2.2 Dose Modification (Escalation/Titration/Other)

Reduction or holding of one agent and not the other agents is appropriate if, in the opinion of the Investigator, the toxicity is clearly related to one of the study drugs. If, in

the opinion of the Investigator, the toxicity is related to the combination of two agents, both drugs should be reduced or held according to recommended dose modifications. If the toxicity is related to the combination of three agents, all three agents should be reduced or held according to the recommended dose modifications. If one or more study agent(s) are held for toxicity, the schedule for restarting the agent(s) should correspond with the next treatment cycle once the toxicity has resolved according to the recommended guidelines.

If any of the individual study drugs must be delayed for a day or more, all agents should be delayed for the same timeframe. If a patient requires a dose delay of taxol/carboplatin components of study treatment for > 2 weeks due to toxicity, the treatment regimen will be permanently discontinued for unacceptable toxicity.

5.2.2.2.1 Dose Modification of pembrolizumab

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

Table 3

Dose Modification Guidelines for 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 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below) ^a	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.
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 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		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	

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Myocarditis	1-2	Toxicity resolves to Grade 0	
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity ^c	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)			In case of signs or symptoms of SJS or TEN, withhold administration and refer the patient to specialized care for evaluation and treatment. Permanently discontinue if SJS or TEN is confirmed.
Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event. ^a 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. ^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 – Infusion Treatment Guidelines for further management details. ^c Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.			

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

5.2.2.2.2 Dose Modification of taxol/carboplatin

Table 4. Dose modifications for hematologic toxicity

Event		Action
Grade 1-3	1 st occurrence	Hold until recovery to \leq grade 1 or baseline. Resume without reduction Consider G-CSF support
	2 nd occurrence	Reduce by 1 dose level (DL). Consider G-CSF support

	3 rd occurrence	Reduce by 2DL Consider G-CSF support
Grade 3 Febrile neutropenia	1 st occurrence	Hold until recovery to \leq grade 1 or baseline. Reduce by 1DL Consider G-CSF support
	2 nd occurrence	Reduce by 2DL Consider G-CSF support
	3 rd occurrence	Discontinue
Grade 4 Febrile neutropenia	1 st occurrence	Reduce by 2DL Consider G-CSF support
	2 nd occurrence	Discontinue

If AE is considered independently related to a specific drug, reduction or holding one agent and not the other agents is permitted based on the investigator's opinion. The first dose reduction is a 25% reduction in both drugs, and the second dose reduction is a 50% reduction.

Table 5. Dose modifications for non-hematologic toxicity

Event		Action
Grade 3-4 non- hematologic toxicities	1 st occurrence	Hold until recovery to \leq grade 1 or baseline. Reduce by 1 DL
	2 nd occurrence	Reduce by 2 DL.
	3 rd occurrence	Discontinue

Grade 4 Laboratory Adverse Events	1 st occurrence	Hold until recovery to \leq grade 1 or baseline. Reduce by 1DL
	2 nd occurrence	Reduce by 2DL

If AE is considered independently related to a specific drug, reduction or holding one agent and not the other agents is permitted based on the investigator's opinion.

5.2.2.2.3 Dose Modification of radiation

Regarding toxicity associated with radiation, every adverse events should be recorded according to NCI CTCAE version 4.0. Radiation treatment will be omitted or delayed based on the physician's judgement.

5.2.3 Timing of Dose Administration

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

All trial treatments will be administered on an outpatient basis.

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

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution. Paclitaxel 50mg/m² via intravenous infusion over 1 hour, followed by carboplatin dose targeted to achieve an AUC 2 mg/mL*min over 30 minutes on day 1,8,15,22, and 29 in neo-adjuvant period.

5.2.4 Trial Blinding/Masking

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

5.3 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other

medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.3.1 Acceptable Concomitant Medications

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

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

5.3.2 Prohibited Concomitant Medications

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

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

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

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

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

5.4 Rescue Medications & Supportive Care

5.4.1 Supportive Care Guidelines for Pembrolizumab

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

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

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

- **Pneumonitis:**

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

- **Diarrhea/Colitis:**

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

- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2 diarrhea/colitis**, administer oral corticosteroids.

- For **Grade 3 or 4 diarrhea/colitis**, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or \geq Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
 - For **T1DM or Grade 3-4 Hyperglycemia**
 - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
 - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

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

- **Hyperthyroidism or Hypothyroidism:**

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

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

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

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

- **Myocarditis**
 - For Grade 1-4 events, administer corticosteroids based on the severity of the events.
 - Perform appropriate evaluation to confirm the cause and/or exclude other causes.

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

Table 2 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 2 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
<u>Grade 1</u> Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
<u>Grade 2</u> Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	Stop Infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.	
<u>Grades 3 or 4</u> Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	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. Subject is permanently discontinued from further trial treatment administration.	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.4.2 Supportive Care Guidelines for Paclitaxel (lung cancer protocol)

Paclitaxel: Paclitaxel 50 mg/m² will be administered as an IV infusion on day 1, 8, 15, 22, 29 every cycle and should precede infusion with carboplatin.

All subjects receiving the above chemotherapy should be pre-medicated with oral or injectable steroids according to the approved product label and/or standard practice.

Additional pre-medications should be administered as per standard practice.

For additional details, refer to approved product labels for details regarding dose calculation,

reconstitution, preparation of the infusion fluid, and administration for each of the standard

of care chemotherapies.

5.4.3 Supportive Care Guidelines for Carboplatin

Carboplatin: Carboplatin AUC 2 will be administered as an IV infusion over 30 minutes day 1, 8, 15, 22, 29 of every week cycle following paclitaxel infusions.

5.4.4 Supportive Care Guidelines for Radiotherapy

Treatment interruptions should be avoided as much as possible. However, if esophagitis of CTCAE Grade 4 has occurred, interruption of radiation therapy up to Grade 2 is permitted. Treatment should resume as soon as esophagitis has reduced to grade 3 or less. Patients whose radiotherapy interruption exceeds 4 weeks will not be given further doses of the study drug.

5.5 Diet/Activity/Other Considerations

5.5.1 Diet

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

5.5.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

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

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

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

OR

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

OR

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

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

(1) practice abstinence[†] from heterosexual activity;

OR

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

Acceptable methods of contraception are[†]:

Single method (one of the following is acceptable):

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

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

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a

subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.5.3 Use in Pregnancy

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

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

5.5.4 Use in Nursing Women

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

5.6 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4 – Other Procedures.

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic recurrence
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements

- The subject is lost to follow-up
- Completed 2 years of uninterrupted treatment with pembrolizumab or 35 administrations of study medication post-operation, whichever is later.

Note: 2 years of study medication is calculated from the date of first dose after surgery. Subjects (This criterion is studied, permanently discontinued, but does not qualify as a dropout)

- For the patient who progresses during neoadjuvant period or is not candidate for the surgery or does not achieve R0 resection, study medication will be stopped and the patient will be managed by investigator's judgement.
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than recurrence will have post-treatment follow-up for disease status until recurrence, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented recurrence each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.6.1 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared.

5.7 Subject Replacement Strategy

5.8 Clinical Criteria for Early Trial Termination

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

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

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

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	Screening Phase	Neo-adjuvant Treatment Cycles and Radiotherapy					Operation	Post op maintain - Treatment	Completion of Maintain treatment or Discontinuation of Treatment	1st Follow Up Visit After Completion of Maintain treatment or Discontinuation of Treatment	Follow Up Visits after 1st Follow Up Visit
		1 D1	2 D8	3 D15	4 D22	5 D29					
Treatment Cycle/Title:	Main Study Screening (Visit 2)						Esophagectomy	Maintain treatment Every 3 week until recurrence During 2yrs	Completion of Maintain treatment During 2yrs or Discontinuation of Treatment	30 days After last administration	Every 4m for 1yr Every 6m for 3yr Then annually Follow-Up
Scheduling Window (Days):	-28 to -1	± 3	± 3	± 3	± 3	± 3		± 3	± 7	± 7	± 14
Administrative Procedures											
Informed Consent	x										
Inclusion/Exclusion Criteria	x										
Demographics and Medical History	x										
Prior and Concomitant Medication Review	x										
Trial Treatment Administration <u>Weekly taxol (50 mg/m2)/carbo (AUC2)</u>		x	x	x	x	x					
Trial Treatment Administration <u>Pembrolizumab 200mg IV</u>		x			x			x			
Radiation Therapy ¹		x	x	x	x	x					
Survival Status											x ²
Clinical Procedures/Assessments											
Review Adverse Events	x	x	x	x	x	x		x	x	x	
Full Physical Examination	x	x	x	x	x	x		x	x	x	
Vital Signs and Weight	x	x	x	x	x	x		x	x	x	
ECOG Performance Status	x	x	x	x	x	x		x	x	x	
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory											

Pregnancy Test – Urine or Serum β -HCG	x								x	x	
PT/INR and aPTT	x								x	x	
CBC with Differential	x	x		x		x		x	x	x	
Comprehensive Serum Chemistry Panel	x	x		x		x		x	x	x	
Urinalysis	x					x		x	x	x	
T3, FT4 and TSH	x					x			x	x	
ECG	x	x				x					
Efficacy Measurements											
Tumor Imaging (Abdominal CT, chest CT)	x					x ⁹	x ⁹	X ³	x ⁴		x ⁵
Upper GI endoscopy	x			x (optional)		X (optional)		X ⁶	x ⁷		x ⁸
EUS (endoscopic ultrasound)	x			x (optional)		x (optional)					
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood											
Archival or Newly Obtained Fresh Tissue Collection	x			x (optional)		x (optional)	x		x (optional)		
Correlative Studies Blood Collection	x			x (optional)		x (optional)	x		x		x (optional)

1. Radiation therapy consists of 21 treatments during 5 weeks.

2. All subjects who complete trial treatments and those who discontinue for any reason will be checked for survival on a schedule.3. Imaging is performed every 12 weeks (3 months) during maintain treatment.
4. If maintain treatment is completed, imaging will be performed according to the originally planned schedule; if discontinued due to AE, imaging will be required if no imaging has been performed within 4 months.
5. Imaging (optional: gastrointestinal endoscopy) will be performed every 4 months for subjects who have completed trial treatments.
6. During maintain treatment, an optional gastroscopy will be performed every 24 weeks (6 months) to check for recurrence.
7. If maintain treatment is completed, it will proceed according to the originally planned schedule, and in case of discontinuation due to AE, imaging will be required if no examination has been performed within 4 months.
8. Imaging (optional: gastrointestinal endoscopy) will be performed every 4 months for subjects who have completed trial treatments.
- 9 Tumor imaging (chest CT, abdominal CT) should be performed at any time between D29 and preoperative (within 12 weeks of last treatment, preferably within 4-8 weeks).

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Medical History

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

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

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

7.1.1.4.2 Concomitant Medications

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

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

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

7.1.1.5.2 Prior Treatment Details

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

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

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

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

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

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

7.1.2.2 Full Physical Exam

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

7.1.2.3 Directed Physical Exam

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

7.1.2.4 Vital Signs

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

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

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

7.1.2.6 Tumor Imaging and Assessment of Disease

Lesion assessment method and timing, evaluation of disease, determining DFS will be conducted according to RECIST version 1.1. Disease assessment modalities include imaging (e.g., CT, MRI, bone scan, plain radiography), physical examination (as indicated for palpable/superficial lesions) and upper gastrointestinal endoscopy. Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays.

To meet screening criteria, baseline tumor imaging must be performed within 28 days prior to the first dose of pembrolizumab. Repeat radiographic assessment will be performed on Day 29 of concurrent chemoradiotherapy. To ensure comparability between the baseline and subsequent assessments, the same method of assessment and the same technique should be used when assessing response.

7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

Every effort should be made to collect tumor specimens if they are accessible and can be easily sampled. These biopsies and blood samples will be taken in subjects who have signed the corresponding section of the ICF.

For tissues, tumor and normal tissues will be paired, and the time points will be baseline, Day 15 and Day 29 (post-dose), surgery, and disease progression. At baseline and at surgery, this will be mandatory; otherwise, it will be optional. Blood will be collected at baseline, surgery, completion of maintain treatment, or discontinuation of treatment, and will be optional at other times.

Sample volumes will be as follows.

Tissue	
Time points	Volume
Baseline (mandatory)	10 slides or 1 core each of tumor/normal tissue (approximately ~3 mm ³)
Day 15 (post-dose) (optional)	10 slides or 1 core each of tumor/normal tissue (approximately ~3 mm ³)
Day 29 (post-dose) (optional)	10 slides or 1 core each of tumor/normal tissue (approximately ~3 mm ³)
Surgery (mandatory)	10 slides or 1 core each of tumor/normal tissue (approximately ~3 mm ³)
Disease progression (optional)	10 slides or 1 core each of tumor/normal tissue (approximately ~3 mm ³)

Blood sample	
Time points	Volume
Baseline (mandatory)	19ml (mandatory)
Day 15 (post-dose) (optional)	19ml (optional)

Day 29 (post-dose) (optional)	19ml (optional)
Surgery (mandatory)	19ml (mandatory)
Completion of Maintain treatment or Discontinuation of Treatment (mandatory)	19ml (mandatory)
Follow Up visit or Discontinuation of Treatment (optional)	19ml (optional)

Collateral research aims include the followings:

1. Exome sequencing (tumor/normal pairs) of fresh-frozen tumor tissues at pretreatment and at recurrence to identify potential immune epitope and mechanisms of acquired resistance.

2. RNA sequencing or nanostring nCounter of fresh-frozen tumor tissues at pre-treatment, on-treatment and to identify potential immune-related gene signature

3. T cell function and phenotype analysis in tumor microenvironment [CD4/CD8+ T cell, FoxP3+ Treg cell, immune checkpoint expression (PD1,PDL1, LAG3, TIM3, CTLA4)]

4. Analysis of immune marker using FACS

- Examine the phenotypic characteristics of CD4 and CD8 T cells in terms of various immune check points (PD-1, CTLA4, TIM3, LAG3) and memory markers in fresh tissue and PBMC by FACS on pre-treatment, after 3 weeks and post- treatment.
- Examine the tumor infiltrating immune cells including Treg cells and MDSCs on pre-treatment, after 3 weeks and post- treatment.
- Blood cytokine analysis will be performed at the time points with multi cytokine bead analysis on pre-treatment, after 3 weeks and post- treatment.

5. Analysis of T cell function using ex vivo stimulation

- Stimulate T cell with Dynabeads Human T-activator CD3/CD28 in *ex vivo* and measure the IFN- γ by ELISA.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5.

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β -human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β -hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam (<i>If abnormal</i>)	Total triiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count	(<i>CO₂ or bicarbonate</i>)	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin (<i>If total bilirubin is elevated above the upper limit of normal</i>)		
	Total protein		
	Blood Urea Nitrogen		

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

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

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

7.1.5 Visit Requirements

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

7.1.5.1 Screening

7.1.5.1.1 Screening Period

A signed, written ICF must be obtained from the subject prior to any study-specific procedures or assessments. Screening assessments and procedures will be performed as indicated in the 6.1. Study Flow Chart 6.1.

7.1.5.2 Treatment Period

Treatment will begin after screening procedure is performed, and visit requirements are outlined in Section 6.0 – Trial Flow Chart.

7.1.5.3 Post-Treatment Visits

7.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

7.1.5.4 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than recurrence will move into the Follow-Up Phase and should be assessed every 6 weeks (42 ± 7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 9 weeks (± 7 days). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, recurrence, death, end of the study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

7.1.5.4.1 Survival Follow-up

Once a subject experiences confirmed recurrence or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.2 Assessing and Recording Adverse Events

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

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

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

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

Recurrence of the cancer under study is not considered an adverse event.

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

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

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

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck

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

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

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

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

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

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor and to Merck

7.2.3.1 Serious Adverse Events

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

- Results in death;
 - Is life threatening;
 - Results in persistent or significant disability/incapacity;
 - Results in or prolongs an existing inpatient hospitalization;
 - Is a congenital anomaly/birth defect;
 - Is an other important medical event
- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
- Is a new cancer (that is not a condition of the study);
 - Is associated with an overdose.

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

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than recurrence of the cancer under study (reference Section 7.2.3.3 for additional details) that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than recurrence of the cancer under study (reference Section 7.2.3.3 for additional details). whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

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

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

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

7.2.3.2 Events of Clinical Interest

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

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

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

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

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

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

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

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

7.2.4 Evaluating Adverse Events

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

which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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

Table 6 Evaluating Adverse Events

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

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

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

For sample size calculation, the current trial originally used a two-stage, Minimax design to evaluate the null hypothesis that the true pathologic complete response (pCR) rate will be 10% and the alternative hypothesis that the pCR rate \geq 30%, with type I error (α) level of 10% and type II error (β) of 0.10. If 1 or more successes are observed in the first 16 patients, accrual for that stratum will be continued until a total of 25 patients. If, of these 25 patients, 5 or more pathologic complete responses, additional investigation is warranted. Allowing for a follow-up loss rate of 10 %, the total sample size is expected as 28 patients.

8.2 Statistical Analysis Plan

Analyses of pRR and DFS will be performed on the ITT population. The Kaplan-Meier approach will be used to estimate median OS with 95% CI. The efficacy variables in this study are DFS and OS.

Disease-free survival is defined as the time between the day of first cycle and the date of first documentation of recurrence or date of death, whichever occurs first. Documentation of recurrence will be defined as per RECIST v1.1 criteria based on investigator assessment. Patients without documented recurrence or death will be censored at the date of last tumor assessment (or, if no tumor assessments are performed after the baseline visit).

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

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

Table 7 Product Descriptions

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

Regarding, taxol and carboplatin, where permitted by regulations, sites will obtain and use commercially available drugs. For further details, see the local prescribing information for each agent.

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

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

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

Only the subject number and subject initials will be recorded in the case report form. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of the institutional review board (IRB), or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with the Korean Medical Service Act. The investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified. In this multicenter trial, in order to facilitate contact between investigators, the PI may share an investigator's name and contact information with other participating investigators upon request.

10.2 Compliance with Financial Disclosure Requirements

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

10.3 Compliance with Law, Audit and Debarment

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

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

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal,

state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the PI as required by this protocol. Trial documentation will be promptly and fully disclosed to the PI by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by regulatory authorities as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. It is anticipated that the retention period can be up to 15 years after protocol database lock.

10.4 Compliance with Trial Registration and Results Posting Requirements

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

10.5 Quality Management System

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

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data.

Product: MK-3475
Protocol/Amendment No.:

11.0 APPENDICES

11.1 ECOG Performance Status

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

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

11.2 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

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

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

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

* As published in the European Journal of Cancer:

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

11.4 References

1. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol* 2011;**12**: 681–92.
2. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-84.
3. Deng L, Liang H, Burnette B, Beckett M, Darga T, Weichselbaum RR, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. *J Clin Invest* 2014;124:687-95.
4. Zeng J, See AP, Phallen J, Jackson CM, Belcaid Z, Ruzevick J, et al. Anti-PD-1 blockade and stereotactic radiation produce long-term survival in mice with intracranial gliomas. *Int J Radiat Oncol Biol Phys* 2013;86:343-9.