TITLE: A single-arm phase II study of chemoradiotherapy plus pembrolizumab as adjuvant therapy for locally advanced esophageal squamous cell carcinoma patients at high risk of recurrence following preoperative chemoradiotherapy plus surgery

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1.0 TRIAL SUMMARY

Abbreviated Title	Adjuvant cisplatin-chemoradiotherapy (CRT) followed by pembrolizumab in esophageal squamous cell carcinoma (ESCC) after preoperative CRT and surgery
Trial Phase	II
Clinical Indication	Locally advanced ESCC patients receiving preoperative chemoradiotherapy at high risk of recurrence (closed or involved resection margin or extranodal invasion of involved lymph nodes or ypN2-3)
Trial Type	Interventional
Type of control	N/A
Route of administration	Intravenous (IV)
Trial Blinding	Unblind
Treatment Groups	Cisplatin-CRT followed by Pembrolizumab
Number of trial subjects	Approximately 26 subjects will be enrolled
Estimated enrollment period	24 months
Estimated duration of trial	The trial will require approximately 60 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	• Subjects need to sign the informed consent form to be enrolled into this trial. • After a screening phase up to 28 days, each subject will receive adjuvant weekly cisplatin –CRT (cisplatin, 30mg/m^2/week x 2; radiotherapy, 180-200 cGy/fraction x 10-13) followed by pembrolizumab (200mg/3 weeks x 18) (approx. a total of 56 weeks). • Treatment will continue until the completion of the planned cisplatin-CRT plus 18 cycles of pembrolizumab, or until recurrent disease, unacceptable adverse events, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdrawal of consent, pregnancy of the subject, noncompliance with trial treatment, or administrative reasons requiring cessation of treatment. • To detect the tumor recurrence, all patients will be evaluated by pertinent evaluation and imaging studies every 4 cycles of pembrolizumab during treatment phase, then every 3 months for post-treatment year-1 to year-2, and every 6 months for post-treatment year-3 and year-4. • Subjects who discontinue for reasons other than recurrent disease will have post-treatment follow-up visits for monitoring disease status as if they were still on treatment until recurrent disease, initiating a non-study cancer treatment, withdrawing consent from study participation, or becoming lost to follow-up. • All subjects will be followed (e.g., by telephone or visit) for overall survival until death, withdrawal of consent from study participation, or the end of the study, whichever comes first. After the end of study 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 or for 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier.
Estimated average length of treatment per patient	56 weeks

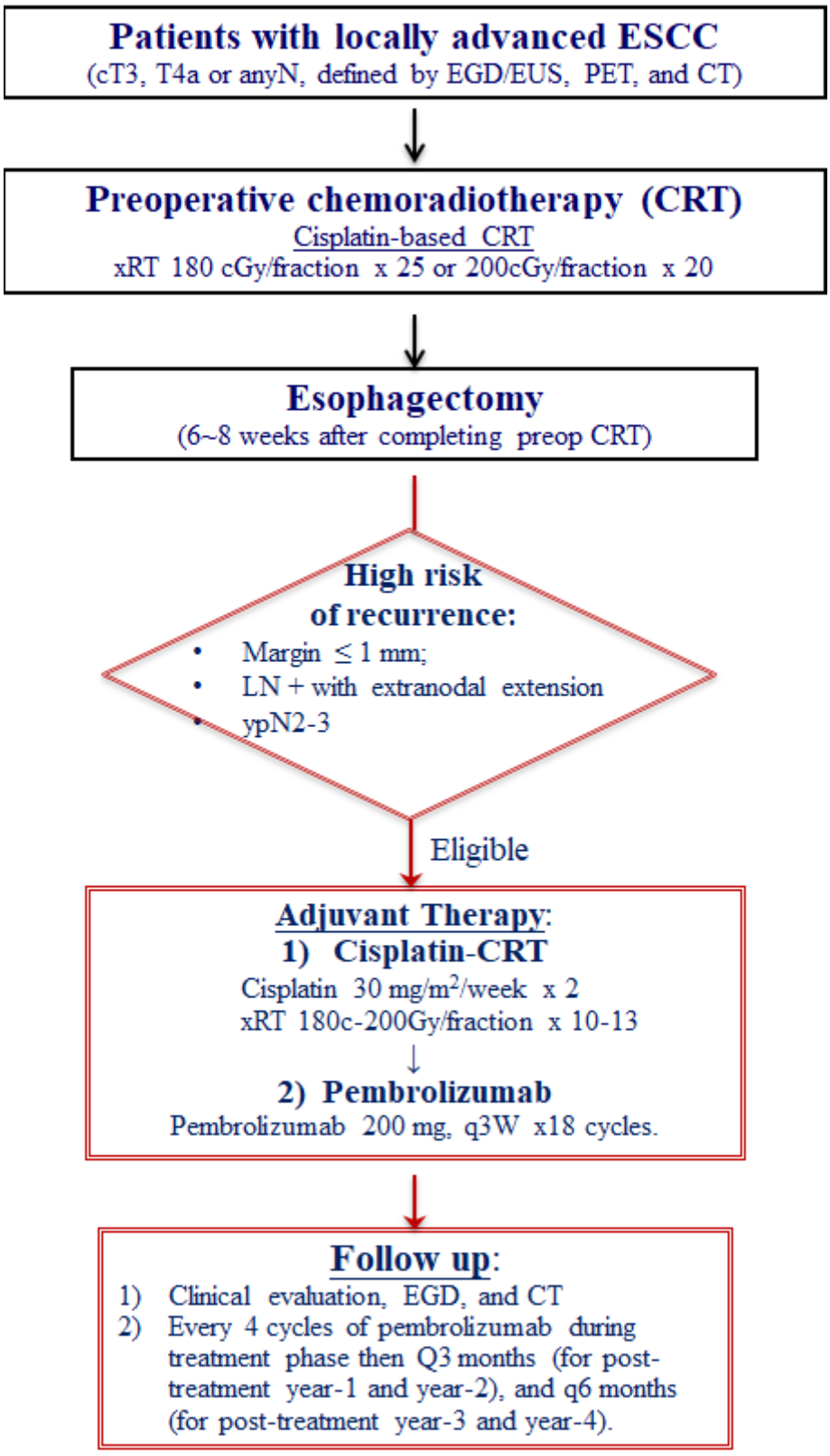
2.0 TRIAL DESIGN

2.1 Trial Design

It is a single-arm phase II trial. The target population is patients with histologically diagnosed locally advanced ESCC patients (clinically staged at least T3 and/or any N and M0 by endoscopic ultrasonography [EUS] and fludeoxyglucose-positron emission tomography [FDG-PET]) who have received preoperative cisplatin-based chemoradiotherapy (CRT) followed by surgery, and exhibit high risk of tumor recurrence. Eligible patients will receive adjuvant cisplatin-based CRT followed by pembrolizumab for 18 cycles.

The study hypothesizes that adjuvant cisplatin-based CRT followed by pembrolizumab will improve the 1-year relapse-free survival rate for these high-risk ESCC patients from 32% to 60%. With the two-sided type 1 error probability of 0.05 and type 2 error probability of 0.2, the study needs to enroll a total of 26 patients, taking another 10% of dropout rate. The duration of patient accrual is expected as 24 months. To detect the mature overall survival data, additional follow-up period of 36 months is needed.

2.2 Trial Diagram



3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

In locally advanced ESCC patients who have high risk of recurrence following preoperative CRT and esophagectomy, the study will explore the efficacy of adjuvant pembrolizumab in improving their outcomes.

(1) **Objective:**

a. To improve the 1-year relapse-free survival (RFS) rate, compared with historical control.

(2) **Hypothesis:**

a. The addition of pembrolizumab to adjuvant cisplatin- CRT would reduce the recurrent rate of locally advanced ESCC patients who have high risk of recurrence following preoperative CRT and esophagectomy.

3.2 Secondary Objective(s) & Hypothesis(es)

The study will also explore other efficacy endpoints and safety of adjuvant pembrolizumab in locally advanced ESCC patients who have high risk of recurrence following preoperative CRT and esophagectomy.

(1) Objective:

a. To improve the median RFS, compared with historical control.
b. To improve the 3-year RFS rate, compared with historical control
c. To improve the 3-year overall survival (OS) rate, compared with historical control.
d. To improve the median OS, compared with historical control.
e. To determine the toxicity and safety.

(2) Hypothesis:

a. In addition to improving the 1-year RFS rate, the addition of pembrolizumab to adjuvant cisplatin- CRT would improve median RFS in locally advanced ESCC patients who have high risk of recurrence following preoperative CRT and esophagectomy.
b. In addition to improving the 1-year RFS rate and the median RFS, the addition of pembrolizumab to adjuvant cisplatin- CRT would also improve the 3-yar RFS rate in locally advanced ESCC patients who have high risk of recurrence following preoperative CRT and esophagectomy.

c. The addition of pembrolizumab to adjuvant cisplatin- CRT would improve the OS, through reducing the recurrence rates, of locally advanced ESCC patients who have high risk of recurrence following preoperative CRT and esophagectomy.

d. In addition to improving 3-year OS rate, the addition of pembrolizumab to adjuvant cisplatin- CRT would also improve the median OS in locally advanced ESCC patients who have high risk of recurrence following preoperative CRT and esophagectomy.

e. The addition of pembrolizumab to adjuvant cisplatin- CRT is safe and does not result in significant toxicities in locally advanced ESCC patients who have high risk of recurrence following preoperative CRT and esophagectomy.

3.3 Exploratory Objective

The study will also explore potential biomarkers in predicting the outcomes of locally advanced ESCC patients who have high risk of recurrence following preoperative CRT and esophagectomy, and are treated with adjuvant cisplatin-CRT and pembrolizumab.

(1) **Objective:**

a. To explore the ESCC tissue-based biomarkers associated with tumor recurrence.

b. To explore the blood-based biomarkers associated with tumor recurrence

(2) Hypothesis:

a. Certain immune biomarkers in tumor microenvironment of esophagectomy tissues following preoperative CRT would associate with the outcomes of locally advanced ESCC patients following preoperative CRT and esophagectomy at high risk of recurrence. These tissue-based biomarkers can be explored as prognostic or predictive biomarkers for locally advanced ESCC patients in the future.

- Immunohistochemistry (IHC) of PD-L1 expression in tumor cells and in tumor-infiltrating immune cells. IHC for different lineages of tumor-infiltrating immune cells (phenotype), including activated CD8+ T cells, regulatory T cells, natural killer cells, suppressor CD4+ T cells, tumor-associated macrophages and myeloid derived suppressor cells.
- Immune related gene expression profile (GEP) by NanoString technology
- Immune repertoire of tumor (deep sequencing for CDR3 region of T-cell receptor [TCR]).
- Mutation analysis of tumor (targeted genes sequencing or whole exome sequencing [WES])

b. Certain biomarkers in peripheral blood wound associate with the outcomes of locally advanced ESCC patients following preoperative CRT and esophagectomy at high risk of recurrence. These blood-based biomarkers can be explored as prognostic or predictive biomarkers for locally advanced ESCC patients in the future.

- Critical cytokines (such as interleukin (IL)-2, IL-6, IL-8, IL-9, IL-10, IL-17, IL-21, interferon-gamma, transforming growth factor-beta, etc).
- PD-L1 (enzyme-linked immunoassay for PD-L1 in serum).
- Immune repertoire of peripheral blood (deep sequencing for CDR3 region of TCR) for correlation with tumor part.
- Circulating cell-free DNA (targeted sequencing of genomic alterations of interest) for correlation with the mutation analysis of tumor.

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 CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The

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

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

4.1.2 Preclinical and Clinical Trial Data

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 is a significant malignant disease worldwide. In 2012, more than 450,000 patients were diagnosed with esophageal cancer and more than 400,000 patients died of esophageal cancer worldwide [1]. Esophageal cancer is an even more significant cancer type in Asia than other parts of the world because more than 80% of esophageal cancer patients are diagnosed from Asian countries. Squamous cell carcinoma (SCC) is the predominant histology, and accounts for >90% of esophageal cancer diagnosed in Asian countries [1,2]. In Taiwan, there were 2,372 newly diagnosed esophageal cancer patients in 2012 and the number is increasing; among them, more than 90% were squamous cell carcinoma in histology [3].

Multimodality therapy for locoregional esophageal cancer

Locoregional esophageal cancer is a potentially curable disease. In the past, patients with locoregional esophageal cancer were typically treated with either surgery or definitive chemoradiotherapy (CRT); however, only 15% to 25% of them experience long-term, disease-free survival [4–6]. Since 1990s, multimodality therapy has been actively investigated in esophageal cancer. Among different strategies to combine various types of

treatment modality, preoperative CRT followed by surgery has been most investigated by multiple randomized control trials. A meta-analysis compiling 12 randomized trials, the majority of which used cisplatin/5-FU-based CRT, found that the survival effect of preoperative CRT for resectable esophageal cancer showed the pooled hazard ratio (HR) was 0.78 (95% CI 0·70 –088) , corresponding to an absolute survival benefit at 2 years of 8.7% [7].

The most convincing data favoring preoperative CRT for locoregional esophageal cancer thus far is disclosed in the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS). The trial randomized 368 patients with resectable esophageal and esophago-gastric junctional (EGJ) cancer for the treatment of preoperative paclitaxel and carboplatin-CRT or surgery alone. The data demonstrated an unequivocal survival benefit of preoperative CRT in locoregional esophageal cancer and EGJ cancer: median survivals were 49.4 months in the preoperative CRT group and 24.0 months in the surgery alone (HR, 0.657; 95% CI, 0.495 to 0.871; $P = 0.003$) [8]. The survival benefit of preoperative CRT holds true in both SCC and adenocarcinoma subtypes.

Preoperative CRT followed by surgery has thus become one of the standard-of-cares for loco-regional esophageal cancer in many centers around the world including our center, the National Taiwan University Hospital, Taipei, Taiwan. Between 2000 and 2012, we conducted three prospective phase II clinical studies investigating paclitaxel and cisplatin-based regimen as preoperative CRT in patients with locally advanced esophageal cancer at National Taiwan University Hospital, Taipei, Taiwan [9–11]. The pooled analysis of 140 locally advanced ESCC patients enrolled in the 3 phase II trials showed that the median overall survival of them was 30.9 months (95% CI 21.4–40.4) and the 3-year-OS rate of them was 45.6% (95% CI 37.2–54.0) [12].

Overall, after intensive multimodality therapy such as preoperative CRT plus surgery, 40 to 50% of patients diagnosed with locally advanced esophageal cancer can enjoy long-term disease-free. On the other hand, the rest 50-60% of the locally advanced esophageal cancer patients would succumbed to recurrence and metastasis of esophageal cancer.

Prognostic factors for locoregional ESCC patents treated with preoperative CRT

Several poor prognostic factors have been identified for patients with esophageal cancer receiving definitive locoregional therapy. Closed or involved resection margin (R1 resection) has been recognized as a poor prognostic factor for patients with ESCC received preoperative CRT followed by surgery [13,14]. Most treatment guidelines, including the National Comprehensive Cancer Network guidelines, suggest adjuvant radiotherapy for esophageal cancer patients having R1 resection following esophagectomy [15].

Lymph node metastasis identified in post-CRT surgical specimens has also been identified as a poor prognostic factor for locoregional cancer patients receiving preoperative CRT [16–18]. Our own analysis based on 140 ESCC patients receiving preoperative CRT also found that lymph node metastasis, especially ypN2-3, in post-CRT pathological staging was associated with inferior progression-free survival (PFS) and OS [12]. Further, we identified that extranodal invasion (ENI) of involved lymph nodes is an independent prognostic factor

associating with inferior PFS [12], a finding corroborating other reports of esophageal cancer patients who receive surgery alone [19,20].

Overall, these observations in ESCC are in line with those in head and neck squamous cell carcinoma (HNSCC), a disease which shares very similar risk factors with ESCC. The close/involved resection margin and ENI have been recognized as the most significant prognostic factors for HNSCC. Hence, HNSCC patients with these poor prognostic factors are now routinely treated with postoperative CRT [21,22].

Based on the afore-mentioned data, the local guidelines at our center thus recommend adjuvant CRT for locoregional esophageal cancer patients who have either close/involved margin or ENI of involved lymph nodes following preoperative CRT plus surgery. Nevertheless, our recent analysis indicated that despite of adjuvant CRT, the prognosis of these patients with high risk of recurrence, i.e., involved margin, positive LN with ENI, and ypN2-3, remains very poor. Their median recurrence-free survival (RFS) was 6.7 months and their 1-year RFS rate was 32.3% (subgroup analysis for [12]).

Immune checkpoint blockade holds promise as a promising therapy for ESCC

Recently, blockade of immune checkpoints, including cytotoxic T lymphocyte antigen 4 (CTLA-4) and PD-1/PD-L1, has demonstrated promising clinical activities in multiple cancer types. The clinical activity against multiple cancer types have been generally moderate, with objective tumor response rates in the range of 15~ 30%. Mutational load and neoantigen have been identified as one of the potential biomarkers for immune checkpoints blockade [23,24]. With the advance of sequencing techniques, large-scale genomic sequencing in increasing number of patients has been conducted in multiple cancer types, including ESCC. The mutational load of ESCC is more than median in many cancer types [25–29].

The expression of PD-L1/PD-L2, another one potential biomarker for PD-1/PD-L1 blockade, was found in 42% and 48%, respectively of ESCC tumors [30]. Intratumoral abundance of CD4 and CD8 T cells has also been reported as a prognostic factor in ESCC patients [31]. The preliminary anti-tumor activity of PD-1/PD-L1 immune checkpoint blockers as a single agent in advanced esophageal cancer patients who have progressed on standard systemic chemotherapy has been recently reported. The objective tumor response of pembrolizumab in ESCC patients with positive PD-L1 expression was 29% [32]. Another study using another anti-PD-1 monoclonal antibody in a group of ESCC patients (N = 65) reported a response rate of 16% [33].

Potential synergism in antitumor effect of immune checkpoint blockade and CRT

Synergism between chemotherapeutic agents and PD-1/PD-L1 immune checkpoint blockers was reported in preclinical models of various cancers. Recently, the “abscopal effect”, which refers to a rare phenomenon of tumor regression at a site distant from the primary site of radiotherapy, was reported in patients treated with radiotherapy and immune-checkpoint inhibitors [34–36].

Collectively, the combination of PD-1/PD-L1 immune checkpoint inhibitor with CRT, which is of strong rationales to be highly synergistic in antitumor effects, is a potential strategy to

improve the outcome of locally advanced ESCC patients following preoperative CRT plus surgery at high risk of recurrence.

4.2.2 Rationale for Dose Selection/Regimen of adjuvant CRT

The dose of adjuvant radiotherapy will be 18-26 Gy given in 10-13 fractions dependent on the dose of preoperative radiotherapy. The study will enroll subjects who have been treated with preoperative CRT with radiation dose of 40-45 Gy given in 20-25 fractions per our institutional treatment standards. As a result, this radiation dose has been selected to assure that cumulated radiation dose at the loco-regional area not exceeding 66Gy, a dose range which is generally accepted as a safe and definitive RT for locoregional esophageal cancer.

The chemotherapy to be administered is weekly cisplatin (30 mg/m^2) given concurrently with radiation. The rationales of using weekly cisplatin include: (1) cisplatin-based CRT has been established as a standard postoperative adjuvant therapy for patients with high-risk head and neck squamous cell carcinoma (HNSCC) [37-39], a disease that shares very similar risk factors and genetic alterations with ESCC; (2) although high-dose (100 mg/m^2), once-every-3-weeks cisplatin-CRT is the standard approach, it results in severe acute toxicity in more than three quarters of HNSCC patients; (3) weekly cisplatin at the dose of 30 to 40 mg/m^2 has been widely accepted as general clinical practice due to multiple advantages including easy administration, lesser requirement of supportive care, and lower toxicity [40]; (4) ESCC patients who have been treated with preoperative CRT followed by radical surgery are generally fragile and not fit for intensive chemotherapy such as high-dose once-every-3-weeks cisplatin.

4.2.3 Rationale for Dose Selection/Regimen/Modification of Pembrolizumab

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

1. The primary endpoint is the 1-year RFS rate.

2. The secondary endpoints include median RFS, 3-year OS rate, median OS time, 3-year RFS rate, safety and toxicity.

4.2.4.2 Biomarker Research

1. Tumor tissue part:

   a. Pre-treatment tumor tissue (i.e., esophagectomy tissue following preoperative cisplatin-based CRT) is mandatory for biomarker study accompanying with the clinical trial. The biomarker study will evaluate the following immune biomarkers in tumor microenvironment:

      - IHC of PD-L1 expression in tumor cells and in tumor-infiltrating immune cells. IHC for different lineages of tumor-infiltrating immune cells (phenotype), including activated CD8+ T cells, regulatory T cells, natural killer cells, suppressor CD4+ T cells, tumor-associated macrophages and myeloid derived suppressor cells.
      - Immune related GEP by NanoString technology
      - Immune repertoire of tumor (deep sequencing for CDR3 region of TCR)
      - Mutation analysis of tumor (targeted genes sequencing or WES)

   b. The potential biomarkers will be correlated with patients' RFS and OS.

   c. If recurrent disease is noted, the recurrent tumor tissues will be procured for biomarker study in comparison with the corresponding pre-treatment tumor tissues (optional).

2. Peripheral blood part:

   a. Blood sample collection is optional for biomarker study accompanying with the clinical trial. The biomarker study will evaluate the following immune biomarkers in peripheral blood:

      - Critical cytokines (such as IL-2, IL-6, IL-8, IL-9, IL-10, IL-17, IL-21, interferon-gamma, transforming growth factor-beta, et al).
      - PD-L1 (enzyme-linked immunoassay for PD-L1 in serum).
      - Immune repertoire of peripheral blood (deep sequencing for CDR3 region of TCR) for correlation with tumor part.
      - Circulating cell-free DNA (targeted sequencing of genomic alterations of interest) for correlation with the mutation analysis of tumor.

   b. The potential biomarkers in peripheral blood will be correlated with patients' RFS and OS.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

1. Histologically proven squamous cell carcinoma of esophagus.

5.1.2 Subject Inclusion Criteria

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

1. Be willing and able to provide written informed consent/assent for the trial.
2. Be ≥ 20 years of age on day of signing informed consent.
3. Be a diagnosed by pathology or cytology with a locally advanced ESCC, which is clinically stage according to the TNM system of the American Joint Committee on Cancer (AJCC) Cancer Staging System (8th edition), fulfilling one of the following criteria as determined by endoscopic ultrasound, computed tomography, bronchoscopy and positron emission tomography:
   a. T3, N0, M0;
   b. T4a, N0, M0;
   c. T1–4a, N1-3, M0.
4. Have been treated with preoperative cisplatin-based CRT followed by esophagectomy with lymph node dissection for the locally advanced ESCC (defined by above criteria).
5. Have a performance status of 0 or 1 on the ECOG Performance Scale.
6. Exhibit at least one risk factor of tumor recurrence in the post-CRT surgical tissues:
   a. Close (≤1mm) or involved margin;
   b. Residual tumor cells in lymph nodes with ENI.
   c. ypN2-3
7. Demonstrate adequate organ function as defined in
8. 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)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL 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
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]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 diagnosed with adenocarcinoma of esophagus or gastroesophageal junction.

2. Has synchronously diagnosed with a squamous cell carcinoma of aero-digestive way, other than esophageal cancer.

3. Has prior malignancy, except for: (a) adequately treated basal cell or squamous cell skin cancer; (b) in-situ cervical cancer; (c) previously diagnosed malignancy which have been adequately treated and shown no evidence of recurrence for more than 5 years.

4. 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.

5. 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.

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

7. Hypersensitivity to pembrolizumab or any of its excipients.

8. Has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

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

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

9. 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.

10. Has known history of, or any evidence of active, non-infectious pneumonitis.

11. Has an active infection requiring systemic therapy.

12. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the 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.

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

14. 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.

15. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

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

17. Hepatitis B virus positive subjects (defined as HBsAg positive and/or detectable HBV DNA).

    - Participants who are HBsAg positive are eligible if they have received HBV antiviral therapy for at least 4 weeks and have undetectable HBV viral load prior to enrollment.

    - Participants should remain on anti-viral therapy throughout study intervention and follow local guidelines for HBV anti-viral therapy post completion of study intervention.

18. Hepatitis C virus positive subjects (defined as anti-HCV Ab positive and detectable HCV RNA).

    - Participants with history of HCV infection are eligible if HCV viral load is undetectable at screening.

    - Participants must have completed curative anti-viral therapy at least 4 weeks prior to randomization.

19. Concurrent active Hepatitis B (defined as HBsAg positive and/or detectable HBV DNA) and active Hepatitis C virus (defined as anti-HCV Ab positive and detectable HCV RNA) infection.

20. 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.

21. Has received organ transplantation.

5.2 Trial Treatments

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

Table 2 Trial Treatment

Drug or radiotherapy	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Cisplatin	30 mg/m^2	QW	IV infusion	Day 1 of each week for 2 weeks, starting within 8 weeks after esophagectomy.	Adjuvant CRT
Radiotherapy	180-200 cGy	QD (Monday to Friday)		Total 10-13 fractions	Adjuvant CRT
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle for 18 cycles, starting within 4 weeks after completing adjuvant cisplatin-CRT	Experimental

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

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

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

5.2.1.2 Dose Modification (Escalation/Titration/Other)

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 3 below. See Section 5.6 for supportive care guidelines, including use of corticosteroids.

Table 3.1 Dose Modification Guidelines for Pembrolizumab-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

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
AST, ALT, or Increased Bilirubin	2 (AST/ALT: 3-5 x upper limit of normal [ULN]; bilirubin: 1.5-3 x ULN)	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
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
Hyper-thyroidism	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
Hypo-thyroidism		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[a]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 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 or recurrent grade 2	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	3-4	Permanently discontinue	Permanently discontinue
Skin or suspicious Steven-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	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

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Skin	4	Permanently discontinue	Permanently discontinue
Confirmed SJS	3-4	Permanently discontinue	Permanently discontinue
Confirmed TEN	4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[b]	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
	Persistent 2 or 3 except endocrine dysfunction under endocrine supplement with good control; 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		Permanently discontinue
	Recurrent 3	Permanently discontinue	Permanently discontinue
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

[a] 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 4– Infusion Treatment Guidelines for further management details.

[b] 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.

Table 3.2 Dose Modification Guidelines for Cisplatin-CRT-Related Adverse Events

Toxicities experienced at the day of starting a new cycle	Recommended Cisplatin-CRT Protocol Treatment	
	xRT	Cisplatin(30 mg/m^2/wk)
When ANC <2,000 – 1,500//µl, or Platelet <100K – 75K//µl	Continue	30 mg/m^2/wk
When ANC <1,500 – 1,000//µl, or Platelet <75K – 50K//µl	Continue	25 mg/m^2/wk

When ANC <1,000 – 500//µl, or Platelet <50K – 25K//µl	Continue	Hold
When ANC <500/µl, or Platelet <25K/µl, or febrile neutropenia, or active infection, or other life-threatening conditions	Hold	Hold
Serum creatinine >2 x ULN	Continue	Hold
Persistent ≥ Gr. 3 toxicities, such as nausea or vomiting, despite of adequate supportive care	Continue	Hold

5.2.2 Timing of Dose Administration

5.2.2.1 Cisplatin-CRT:

a. Cisplatin-CRT is to be started within 8-12 weeks after esophagectomy, when the patient recovers well from the operation.

b. Cisplatin 30 mg/m^2, IV infusion for 60~ 120 min, weekly, for 2 weeks.

   i. Sufficient hydration will be given at the discretion of the investigator.

   ii. Anti-emetics such as 5-HT3 antagonists, aprepitant, steroid, and metoclopramide will be given at the discretion of the investigator.

c. Radiotherapy: (intensity modulated radiotherapy) 180-200 cGy/fraction, once daily, 5 days a week, for a total of 10-13 fractions.

   i. Radiotherapy will be administered by megavoltage linear accelerators (≥ 6 MV photon) using multiple fields (≥ 2) technique.

   ii. Planning CT (CT simulation) must be done for isodose distribution and evaluation of dose-volume histogram.

   iii. The target volumes of radiation should encompass the tumor volume (both primary esophageal tumor and metastatic lymphadenopathy) with adequate margins covering subclinical disease (including submucosal, mediastinal, and/or supraclavicular or celiac lymphatics) and treatment variability (including setup errors, breathing, and organ motion). Gross tumor volume (GTV) is defined as the volume of all visible esophageal tumor and involved lymphadenopathy using all available imaging studies including CT scan, EUS, and 18F-FDG-PET scan. The clinical target volume (CTV) is defined as the

GTV plus areas considered at significant risk of microscopic disease including a 0.5-1.0cm circumferential margin and 3-4 cm longitudinal margin.

iv. Radiation will be delivered with intensity modulated radiotherapy technique, with a daily fraction size of 180-200 cGy, 5 days a week.

5.2.2.2 Pembrolizumab:

a. Pembrolizumab is to be started within 4 weeks after completing last dose of CRT, when the patient recovers well from the CRT.

b. Pembrolizumab 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.

c. Pembrolizumab will be administered on an outpatient basis.

d. Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. 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).

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

5.2.2.3 Visits during adjuvant therapy (also listed in 7.1.5.2):

a. During the period of adjuvant cisplatin-CRT:

i. The patient will be seen on a weekly basis until 2 weeks after completing CRT.

ii. The patient will be evaluated for clinical symptoms and signs, hemogram, and biochemistry panel including bilirubin, AST, ALT, BUN, creatinine, Na, K, Ca, Mg, and other abnormalities found at screening check.

b. During the period of adjuvant pembrolizumab therapy:

i. The patient will be seen on a 3-weekly basis for a total of 54 weeks.

ii. The patient will be evaluated for clinical symptoms and signs, hemogram, and biochemistry panels including bilirubin, AST, ALT, ALP, gamma-GT, LDH, albumin, BUN, creatinine, Na, Cl, K, Ca, Mg, glucose, and endocrine function (every 2 cycles) including TSH, T3, fT4, ACTH and cortisol.

iii. Pregnancy Test – Urine or Serum beta-HCG (for woman only), coagulation

test with PT/INR and aPTT, and urinalysis will be checked every 2 cycles.

5.2.3 Trial Blinding/Masking

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

5.3 Randomization or Treatment Allocation

This is a single-arm study.

5.4 Stratification

No stratification will be done

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

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

5.5.1 Acceptable Concomitant Medications

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

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

5.5.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic biological therapy not specified in this protocol
- Immunotherapy not specified in this protocol

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

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

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

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

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

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

- **Hyperthyroidism or Hypothyroidism**:

  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment,

and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

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

- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

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

Table 4 Infusion Reaction Treatment Guidelines

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

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
<u>Grades 3 or 4</u> Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., 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.		

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

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

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

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

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

OR

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

OR

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

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

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

OR

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

Acceptable methods of contraception are[‡]:

Single method (one of the following is acceptable):

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

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

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)

- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

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

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

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

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the 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.

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the 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 disease 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
- 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 recurrent disease will have post-treatment follow-up for disease status until disease recurrence, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease 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.

5.9 Subject Replacement Strategy

No subject replacement strategy will be arranged.

5.10 Clinical Criteria for Early Trial Termination

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

1. Quality or quantity of data recording is inaccurate or incomplete

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

4. Plans to modify or discontinue the development of the study drug

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

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	**Screening Phase**		**Adjuvant Cisplatin-CRT**		**Pembrolizumab**				**End of Treatment**	**Post-Treatment**		
					To be repeated beyond 4 cycles							
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1	2	1	2	3	4	Discon	Safety Follow-up	Year-1 & Year-2	Year-3 & Year-4
Scheduling Window (Days):		-28 to -1	± 3	± 3		± 3	± 3	± 3	At time of Discon	30 days post discon	Every 3 months	Every 6 months
Pre-screening Consent	V											
Informed Consent		V										
Inclusion/Exclusion Criteria	V	V										
Demographics and Medical History		V										
Prior and Concomitant Medication Review		V										
Trial Treatment Administration[a]			V	V	V	V	V	V				
Survival Status[b]			V	V	V	V	V	V	V	V	V	V
Review Adverse Events[c]				V	V	V	V	V	V	V		
Full Physical Examination		V			V				V	V	V	V
Directed Physical Examination			V	V		V	V	V				
Vital Signs and Weight	V	V	V	V	V	V	V	V	V	V	V	V
ECOG Performance Status	V	V	V	V	V	V	V	V	V	V	V	V
Pregnancy Test – Urine or Serum β-HCG		V			V		V		V			
PT/INR and aPTT		V			V		V		V	V		
CBC with Differential		V	V	V	V	V	V	V	V	V	V	V
Comprehensive Serum Chemistry Panel[d]		V	V	V	V	V	V	V	V	V	V	V
Urinalysis		V			V		V		V	V		

Trial Period:	**Screening Phase**		**Adjuvant Cisplatin-CRT**		**Pembrolizumab**				**End of Treatment**	**Post-Treatment**		
					To be repeated beyond 4 cycles							
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1	2	1	2	3	4	Discon	Safety Follow-up	Year-1 & Year-2	Year-3 & Year-4
Scheduling Window (Days):		-28 to -1	± 3	± 3		± 3	± 3	± 3	At time of Discon	30 days post discon	Every 3 months	Every 6 months
T3, FT4 and TSH		V			V		V		V	V	V	V
ACTH, Cortisol		V			V		V		V	V	V	V
Tumor Imaging[e]		V						V			V	V
Archival or Newly Obtained Tissue Collection[f]		V			V (optional)							
Correlative Studies Blood Collection (optional)[g]		V		V	V (every 4 cycles and recurrence)					V (Year-1 and 2: every 3 months until recurrence)		

[a]Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

[b]Once a subject experiences confirmed disease 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.

[c]SAEs will be followed through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier.

[d]Check bilirubin, AST, ALT, BUN, creatinine, Na, K, Ca, Mg, and other abnormalities found at screening check during adjuvant cisplatin-CRT phase; check bilirubin, AST, ALT, ALP, gamma-GT, LDH, albumin, BUN, creatinine, Na, Cl, K, Ca, Mg, P, glucose during pembrolizumab phase and post-treatment Year-1 to Year-4.

[e]Tumor imaging includes CT scan with/without contrast (if renal function is acceptable) for neck, chest, abdomen and symptomatic regions and esophagoscopy.

[f]Tissue proof for recurrent lesion if feasible.

[g]Blood samples for biomarker study. The collection will be performed until disease recurrence (last blood sample collection).

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 days Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects. Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

7.1.1.7 Assignment of Treatment Number

All eligible subjects will receive a treatment number. The treatment number identifies the subject for all procedures occurring after treatment allocation/randomization. Once a treatment number is assigned to a subject, it can never be re-assigned to another subject. A single subject cannot be assigned more than 1 treatment number.

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

Interruptions from the protocol-specified treatment plan for greater than 12 weeks between doses for non–drug-related or administrative reasons require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management. The total volume of study treatment infused will be compared to the total volume prepared to determine compliance with each dose administered. The instructions for preparing and administering study treatment are provided in the Pharmacy Manual. Administration of trial treatment will be witnessed by the investigator and/or trial staff or qualified designee per institutional guidelines and procedures.

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

The schedules of tumor imaging and assessment of tumor status are detailed in 7.1.5.4.

7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

Please see 4.2.3.2 biomarker research about the detail for tumor tissue collection and correlative studies blood sampling. The time points about samples collection are summarized in 6.0 Study Flowchart.

7.1.3 Laboratory Procedures/Assessments

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

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

Table 5 Laboratory Tests

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

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.3.1 Blood Collection

(1) On every occasion of collecting blood for exploratory biomarker research, 10 ml of blood will be collected through sodium citrate-containing tubes.

(2) The blood samples will be sent to Lab for further processing within 30 minutes.

(3) 10 ml blood for collection of plasma (in aliquots) and peripheral blood mononuclear cells (PBMCs) through Ficoll-Hypaque centrifugation. The PBMCs will be separated into two equal pellets: one to be freshly frozen; the other kept in RNAZol.

The time points for blood sampling (Correlative Studies Blood Collection) are described in Section 6.0 – Trial Flow Chart.

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.

7.1.4.2 Blinding/Unblinding

Not applicable.

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

Approximately 28 days prior to treatment, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated.

a. The candidate patient will be screened according to the 5.1 Entry Criteria.

b. Laboratory tests performed according to Table 5 and Flow Chart 6.1.

c. Tumor imaging performed according to Flow Chart 6.1.

7.1.5.2 Treatment Period (also detailed in 6.1 Study Flow Chart):

a. During the period of adjuvant cisplatin-CRT:

   i. The patient will be seen on a weekly basis until 2 weeks after completing CRT.

   ii. The patient will be evaluated for clinical symptoms and signs, hemogram, and biochemistry panel including bilirubin, AST, ALT, BUN, creatinine, Na, K, Ca, Mg, and other abnormalities found at screening check.

b. During the period of adjuvant pembrolizumab therapy:

   i. The patient will be seen on a 3-weekly basis for a total of 54 weeks.

   ii. The patient will be evaluated for clinical symptoms and signs, hemogram, biochemistry panels including bilirubin, AST, ALT, ALP, gamma-GT, LDH, albumin, BUN, creatinine, Na, Cl, K, Ca, Mg, P, and glucose, and endocrine function (every 2 cycles) including TSH, T3, fT4, ACTH and cortisol.

   iii. Pregnancy Test – Urine or Serum beta-HCG (for woman only), coagulation test with PT/INR and aPTT, and urinalysis will be checked every 2 cycles.

   iv. Tumor imaging includes CT scan (of neck, chest, and abdomen) and esophagoscopy every 4 cycles of pembrolizumab.

7.1.5.3 Post-Treatment Visits

a. Safety Follow-UP Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment (pembrolizumab) 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. Subjects who are eligible for retreatment with pembrolizumab (as described in Section 7.1.5.5) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

7.1.5.4 Assessment of Tumor Status (also detailed in 6.1 Study Flow Chart):

a. During the post-treatment year-1, and post-treatment year-2:

   i. Clinical evaluation, including physical examination;

   ii. Hemogram, and biochemistry panels including bilirubin, AST, ALT, ALP, gamma-GT, LDH, albumin, BUN, creatinine, Na, Cl, K, Ca, Mg, P, glucose, TSH, T3, fT4, ACTH and cortisol.

   iii. CT scan (of neck, chest, and abdomen) and esophagoscopy;

   iv. Repeated every 3 months.

b. During the 4^{th} and 5^{th} years after esophagectomy (i.e., the post-treatment year-3, and post-treatment year-4):

   i. Clinical evaluation, including physical examination;

   ii. Hemogram, and biochemistry panels including bilirubin, AST, ALT, ALP, gamma-GT, LDH, albumin, BUN, creatinine, Na, Cl, K, Ca, Mg, P, TSH, T3, fT4, TSH, ACTH and cortisol.

   iii. CT scan (of neck, chest, and abdomen) and esophagoscopy;

   iv. Repeated every 6 months.

7.1.5.5 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Section 7.1.5.5. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

7.1.5.5.1 Survival Follow-up

Once a subject experiences confirmed disease 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.

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 day 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 another 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 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 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.

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 mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the 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

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

The target sample size of this prospective, single-arm, phase 2 study is 26 patients. The estimated time for patient accrual is 2 years. It takes a minimum of additional 3 years to complete the follow up of the last accrued patient. The total study period is planned to be 5 years.

The primary objective of the study is to improve the 1-year RFS rate for locally advanced ESCC patients who have received preoperative cisplatin-based CRT followed by surgery, and exhibit high risk of tumor recurrence. The secondary objectives of the study included the median recurrence-free survival, overall survival and overall survival rate, and safety and toxicity. According to the subgroup analysis of our previous study [12], the median RFS for locally advanced ESCC patients who have received preoperative cisplatin-based CRT followed by surgery, and exhibit high risk of tumor recurrence (defined as closed or involved margin [≤ 1mm] or ENI or ypN2-3) is 6.7 months, equivalent to a 1-year RFS rate of 32.3%.

8.2 Statistical Analysis Plan

8.2.1 Sample Size Determination

According to the subgroup analysis of our previous study [12], the median RFS for locally advanced ESCC patients who have received preoperative cisplatin-based CRT followed by surgery, and exhibit high risk of tumor recurrence (defined as closed or involved margin [≤ 1mm] or ENI or ypN2-3) is 6.7 months, equivalent to a 1-year RFS rate of 32.3%. It would need a sample size of 24 patients to detect a difference of the 1-year RFS rate from 32% to 60% by calculated using an exact binomial test with a power of 80% and a 5% significance level. Having taken an additional 10% of early drop-out rate into consideration, the total enrolled patient number will be 26 for this study. We estimate an enrollment rate of 12 patients per year at my center. Therefore, total study period will be 5 years, including 2 years of patient enrollment and 3 years of patient follow-up.

8.2.2 Definition of Variables

8.2.2.1 Recurrence-free survival is the time from enrollment to disease recurrence or the last follow-up (censored). Recurrence is defined by suspicious lesion noted by tumor imaging according to RECIST 1.1. Tissue proof for suspicious lesion is recommended if it is feasible.

8.2.2.2 Overall survival is the time from enrollment to death of any cause or the last follow-up (censored).

8.2.2.3 Evaluation of Toxicity: The incidence and severity of toxicity will be summarized according to the NCI Common Toxicity Criteria Version 4.0.

8.2.3 General Statistical Consideration

8.2.3.1 All statistical analyses will be performed for intent-to-treatment population.

8.2.3.2 The survival estimates will be derived from Kaplan and Meier curves.

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

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 of data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

10.2 Compliance with Financial Disclosure Requirements

Following the regulations of NTUH

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.

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

Following the regulations of NTUH

10.6 Data Management

All available data will be displayed. Listings of patients with premature termination will be provided with the dates and reasons for termination. Missing data will not be replaced by any estimated or imputed values.

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)

REFERENCE

1. http://globocan.iarc.fr/Default.aspx (assessed on Feb. 22, 2016)
2. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol* 2006;24:2137–50.
3. Cancer statistics of Taiwan in year 2003, Cancer Registry. Department of Health, Taiwan, ROC. (Accessed at http://www.doh.gov.tw/statistic/index.htm in May 2005).
4. Herskovic A, Martz K, al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med 1992;326:1593–1598.
5. Mariette C, Piessen G, Triboulet JP. Therapeutic strategies in oesophageal carcinoma: role of surgery and other modalities. Lancet Oncol 2007;8:545–553.
6. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. Lancet

2013;381:400–412.
7. Sjoquist KM, Burmeister BH, Smithers BM, et al.; Australasian Gastro-Intestinal Trials Group. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol 2011;12:681–692.
8. van Hagen P, Hulshof MC, van Lanschot JJ, et al.; CROSS Group. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074–2084.
9. Lin CC, Hsu CH, Cheng JC, et al. Concurrent chemoradiotherapy with twice weekly paclitaxel and cisplatin followed by esophagectomy for locally advanced esophageal cancer. Ann Oncol 2007;18: 93–98.
10. Lin CC, Hsu CH, Cheng JC, et al. Concurrent chemoradiotherapy with cetuximab plus twice-weekly paclitaxel and cisplatin followed by esophagectomy for locally advanced esophageal squamous cell carcinoma. J Clin Oncol 2013;31 (suppl; abstr 4099).
11. Lin CC, Hsu CH, Tzen KY, et al. Fluorodeoxyglucose positron emission tomography for evaluating early response during neoadjuvant chemoradiotherapy in patients with locally advanced esophageal squamous cell carcinoma. J Clin Oncol 2012;30 (suppl; abstr e14576).
12. Guo JC, Huang TC, Lin CC, et al: Postchemoradiotherapy pathologic stage classified by the American Joint Committee on the cancer staging system predicts the prognosis of patients with locally advanced esophageal squamous cell carcinoma. J Thorac Oncol 2015;10:1481–9.
13. Chao YK, Yeh CJ, Chang HK, et al: Impact of circumferential resection margin distance on locoregional recurrence and survival after chemoradiotherapy in esophageal squamous cell carcinoma. Ann Surg Oncol 2011;18:529–34.
14. Liu CY, Wang BY, Lee MY, et al: The prognostic value of circumferential resection margin in esophageal squamous cell carcinoma after concurrent chemoradiation therapy and surgery. J Chin Med Assoc 2013;76:570–5.
15. https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf
16. Reynolds JV, Muldoon C, Hollywood D, et al. Long-term outcomes following neoadjuvant chemoradiotherapy for esophageal cancer. Ann Surg 2007;245:707–716.
17. Akutsu Y, Shuto K, Kono T, et al. The number of pathologic lymph nodes involved is still a significant prognostic factor even after neoadjuvant chemoradiotherapy in esophageal squamous cell carcinoma. J Surg Oncol 2012;105:756–760.
18. Okumura H, Uchikado Y, Matsumoto M, et al. Prognostic factors in esophageal squamous cell carcinoma patients treated with neoadjuvant chemoradiation therapy. Int J Clin Oncol 2013;18:329–334.
19. Metzger R, Drebber U, Baldus SE, et al: Extracapsular lymph node involvement differs between squamous cell and adenocarcinoma of the esophagus. Ann Surg Oncol 2009;16:447–453.
20. Sakai M, Suzuki S, Sano A, et al: Significance of lymph node capsular invasion in esophageal squamous cell carcinoma. Ann Surg Oncol 2012;19:1911–7.
21. Cooper JS, Pajak TF, Forastiere AA, et al: Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous cell carcinoma of the head and neck. N Engl J Med 2004;350:1937–44.
22. Bernier J, Domenge C, Ozsahin M, et al: Postoperative irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945–52.
23. Rizvi NA, Hellmann MD, Snyder A, et al: Mutational landscape determines sensitivity to PD-1 blockade in non – small cell lung cancer. Science 2015;348:124–8.

24. Snyder A, Makarov V, Merghoub T, et al: Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma. N Engl J Med. 2014;371:2189–99.
25. Agrawal N, Jiao Y, Betteqowda C, et al: Comparative genomic analysis of esophageal adenocarcinoma and squamous cell carcinoma. Cancer Discov 2012;2:899–905.
26. Lin DC, Hao JJ, Nagata Y, et al: Genomic and molecular characterization of esophageal squamous cell carcinoma. Nat Genet 2014;46:467–73.
27. Song Y, LI L, Ou Y, et al: Identification of genomic alterations in oesophageal squamous cell cancer. Nature 2014;509:91–5.
28. Gao YB, Chen ZL, Li JG, et al: Genetic landscape of esophageal squamous cell carcinoma. Nat Genet 2014;46:1097–102.
29. Zhang L, Zhou Y, Cheng C, et al: Genomic analyses reveal mutational signatures and frequently altered genes in esophageal squamous cell carcinoma. Am J Hum Genet 2015;96:597–611.
30. Ohigashi Y, Sho M, Yamada Y, et al: Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer. Clin Cancer Res 2005;11:2947–53.
31. Cho Y, Miyamoto M, Kato K, et al. CD4+ and CD8+ T cells cooperate to improved prognosis of patients with esophageal squamous cell carcinoma. Cancer Res 2003;63:1555–9.
32. Doi T, Piha-Paul SA, Jalal SI, et al: Pembrolizumab (MK-3475) for patients (pts) with advanced esophageal carcinoma: Preliminary results from KEYNOTE-028. J Clin Oncol 2015;33 (suppl; abstr 4010).
33. Takashi U, Muro K, Hara H, et al: Phase 2 study of Nivolumab (Anti-PD-1; ONO-4538) in Patients with Esophageal Cancer: Preliminary Report. ESMO 2015 Abs #2301.
34. Postow MA, Callahan MK, Barker CA, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. N Engl J Med 2012,366:925–31.
35. Grimaldi AM, Simeone E, Giannarelli D, et al. Abscopal effects of radiotherapy on advanced melanoma patients who progressed after ipilimumab immunotherapy. Oncoimmunotherapy 2014;3:e28780.
36. Twyman-Saint Victor C, Rech AJ, Maity A, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature 2015;520:373–7.
37. Cooper JS, Pajak TF, Forastiere AA, et al; Radiation Therapy Oncology Group 9501/Intergroup. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med. 2004;350:1937-44.
38. Bernier J, Domenge C, Ozsahin M, et al; European Organization for Research and Treatment of Cancer Trial 22931. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med. 2004;350:1945-52.
39. Bachaud JM, Cohen-Jonathan E, Alzieu C, et al. Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: final report of a randomized trial. Int J Radiat Oncol Biol Phys. 1996;36:999-1004.
40. Noronha V, Joshi A, Patil VM, et al. Once-a-Week Versus Once-Every-3-Weeks Cisplatin Chemoradiation for Locally Advanced Head and Neck Cancer: A Phase III Randomized Noninferiority Trial. J Clin Oncol. 2017 [Epub ahead of print].