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TITLE: Pembrolizumab, **R**adi**o**therapy, and **C**hemotherapy in N**e**oadjuvant Treatment of Malignant **E**sophago-gastric **D**iseases. (**PROCEED**)

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Principal Investigator: Manisha Palta, MD
Assistant Professor

Department of Radiation Oncology
Duke University Box 3085
Durham, NC 27710

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GLOSSARY OF ABBREVIATIONS

EGC	esophago-gastric cancers
pCR	pathologic complete response
3D	3-dimensional
IMRT	intensity modulated radiotherapy
PET	positron emission tomography
CT	computed tomography
CTCAE	common terminology criteria for adverse events
AUC	area under curve
CRT	chemoradiotherapy
TTLR	time to local recurrence
TTDR	time to distant recurrence
PFS	progression free survival
OS	overall survival
T regs	regulatory T-cells
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
PD-1	programmed death 1
CD 28	cluster of differentiation 28
Ig	immunoglobulin
IgV-type	Ig Variable–type
CS	Correlative science
TE	Tumor microenvironment
PMBCs	Peripheral blood mononuclear cells
DIPC	Duke Immune Profiling Core
Treg	T cell
m-MDSC	monocytic myeloid-derived suppressor cells

1.0 TRIAL SUMMARY

Abbreviated Title	**P**embrolizumab, **R**adi**o**therapy, and **C**hemotherapy in **N**eoadjuvant T**r**eatment of Malignant **E**sophago-gastric **D**iseases. (**PROCEED**)
Trial Phase	Phase II trial
Clinical Indication	Resectable, non-metastatic locally advanced esophagus, gastroesophageal junction and gastric cancers
Trial Type	Single arm with initial safety-run-in
Type of control	n/a
Route of administration	Intravenous
Trial Blinding	n/a
Treatment Group	1) Neoadjuvant pembrolizumab (3 cycles) with concurrent chemoradiotherapy with carboplatin/paclitaxel, followed by surgical resection and 3 cycles of adjuvant pembrolizumab
Primary Objective	1) To investigate whether neoadjuvant chemoradiotherapy combined with pembrolizumab improves pathologic complete response compared to historical control with chemoradiotherapy.
Number of trial subjects	30-38
Estimated enrollment period	May 1, 2017 – May 31, 2019
Estimated duration of trial	3 years (2.5 years for enrollment + 6 months follow-up) All patients will be followed from enrollment until the study end date, which will occur when the last patient has been followed for 6 months, based on an estimated 2.5 year recruitment period.
Duration of Participation	1 year
Estimated average length of treatment per patient	5 months

2.0 TRIAL DESIGN

2.1 Trial Design

This is a single-institution, prospective phase II trial with an initial safety run-in to evaluate the efficacy and safety of neoadjuvant pembrolizumab combined with chemoradiotherapy and adjuvant pembrolizumab in patients with locally advanced esophageal and gastric cancers (EGC). Chemoradiation therapy (45Gy in 25 fractions with concurrent, weekly carboplatin [AUC 2] and paclitaxel [50mg/m2 of BSA]) with three cycles of pembrolizumab will be administered as neoadjuvant therapy. These patients will also receive three cycles of adjuvant pembrolizumab after surgical resection (1).

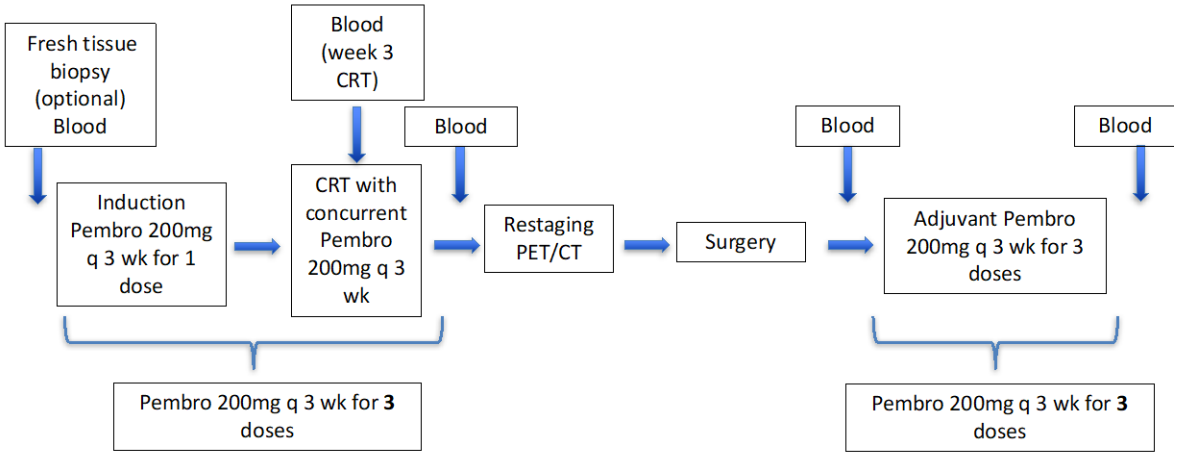
An initial safety run-in of 5 patients will be performed to evaluate safety of concurrent pembrolizumab and chemoradiotherapy for EGC. If no more than 1 grade 3+ toxicity is definitely related to concurrent pembrolizumab and observed within 30 days of the last dose of neoadjuvant pembrolizumab (i.e. cycle 3) for the fifth patient, then the study will

continue to accrue. In the event that more than 1 of the first 5 patients has a grade 3+ toxicity definitely related to concurrent pembrolizumab, then an additional five patients (total 10 patients) will be enrolled with close toxicity assessment.

Enrolled patients will receive three doses of neoadjuvant pembrolizumab (200 mg administered as an intravenous infusion over 30 minutes every 3 weeks). The first dose of pembrolizumab will be administered approximately 14 days prior to initiating radiotherapy. The second dose will be administered three weeks later (week 1 +/- 1 week of chemoradiation). The third dose will be administered 3 weeks later (week 4 +/- 1 week of chemoradiotherapy). Pembrolizumab will be given every 3 weeks and may be given at the same time as systemic therapy. All patients will receive radiation treatment (45Gy in 25 fractions at 1.8 Gy/fraction) using image-guided radiation therapy with concurrent, weekly carboplatin (AUC 2) and paclitaxel (50mg/m2 of BSA). Restaging will be performed per standard of care approximately 4-8 weeks after completing chemoradiotherapy. Resection will be performed approximately 6-16 weeks after completing chemoradiotherapy per standard of care. Postoperatively, three additional cycles of pembrolizumab (200 mg every 3 weeks) will be administered as adjuvant therapy. Timing will be at the discretion of the treating physician based on patient healing and recovery from any postoperative complications.

Patients will be evaluated at least weekly during radiation treatment, every 3-6 months for the first 2 years after treatment, and every 6-12 months in years 3 to 5. PET/CT or CT chest/abdomen/pelvis (C/A/P) will be performed at the time of these scheduled follow up visits to evaluate for local or distant tumor recurrence. Additional imaging will be performed if clinically indicated. Adverse events will be recorded and graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (2).

2.2 Trial Diagram



CRT: Chemoradiation 45Gy IMRT or 3D with image guidance and concurrent carboplatin (AUC 2)/paclitaxel (50mg/m^2)

Primary endpoint: pCR
Secondary endpoints: Toxicity
Exploratory: immune correlates, disease endpoints

3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objectives & Hypotheses

(1) **Objective:** To investigate whether neoadjuvant chemoradiotherapy combined with pembrolizumab followed by resection improves pathologic complete response (pCR) compared to historical control with standard of care neoadjuvant chemoradiotherapy followed by resection (23%).(3)

Hypothesis: Neoadjuvant chemoradiotherapy combined with pembrolizumab followed by resection will improve pCR compared to standard of care neoadjuvant radiotherapy followed by resection.

3.1.1 Secondary Objectives & Hypotheses

(1) **Objective:** To assess the safety of neoadjuvant pembrolizumab administered with conventionally fractionated chemoradiotherapy in EGC.

Hypothesis: Neoadjuvant chemoradiotherapy combined with pembrolizumab will be associated with an acceptable toxicity profile.

3.2 Exploratory Objectives

(1) **Objective:** To identify immune related biomarkers as predictors of clinical response to pembrolizumab and chemoradiotherapy

(2) **Objective:** To estimate the distribution of time to local recurrence (TTLR), time to distant recurrence (TTDR), progression free survival (PFS), and overall survival (OS)

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact functions of 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 ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor. It is also approved in the treatment of metastatic non-small cell lung cancer and recurrent or metastatic head and neck cancers.

4.1.2 Preclinical and Clinical Trial Data

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

EGC is the fourth most common cancer with incidence of 1 million people worldwide.(4) In the United States nearly 42,000 patients are diagnosed with esophageal or gastric malignancies.(5) For the individuals who present with locally advanced, resectable, non-metastatic disease the mainstay of treatment involves a combination of neoadjuvant chemoradiation followed by surgery. With neoadjuvant treatment the current pCR is approximately 30%. Long term survival in patients receiving neoadjuvant chemoradiation with carboplatin/paclitaxel and surgery is median 49.4 months and corresponding 5 year survival of 47% (1) Data suggests that long term outcomes in patients who achieve a pCR is significantly higher than non-responders. (6) We hypothesize that concurrent administration of pembrolizumab with chemoradiation for locally advanced EGC will enhance local tumor response and activate the immune system to eliminate occult micrometastatic disease.

Antibodies targeting immune checkpoints, including the anti-PD-1 antibody pembrolizumab, have induced durable responses in patients with metastatic cancers of many types (7-19). Furthermore, anti-PD-1 antibodies are generally well tolerated, with therapies targeting the PD-1 pathway associated with less toxicity than anti-CTLA-4 antibodies. Experience with immune checkpoint blockade in EGC is limited. At the 2014 European Society of Medical Oncology meeting recent data from Japan evaluated patients with recurrent or metastatic esophago-gastric adenocarcinomas for PD-1 expression, and if positive, enrollment on a Phase 1b study with pembrolizumab. Statistically significant

associations between PD-1 expression and progression free survival (PFS, p=0.032) and objective response rate (ORR, P=0.071) were seen. These results were achieved with most common adverse events being fatigue and hypothyroidism.(20) In light of these data, Phase II and III studies for advanced gastric cancer are ongoing.

To date, no clinical trials have examined combined anti-PD-1 therapy and chemoradiation treatment for EGC. Data from a phase I clinical trial in metastatic melanoma and several preclinical studies in various tumor models indicate that radiotherapy enhances the therapeutic effect of immune checkpoint inhibitors (21-25). Radiation therapy may augment the anti-tumor immune response by inducing exposure of new tumor antigens through cross presentation, upregulating MHC-I expression, stimulating chemokines that recruit cytotoxic T-cells, and upregulating death receptors which promote cytotoxic T-cell activity (26). Furthermore, isolated case reports of the abscopal effect, in which localized radiation treatment triggers distant tumor regression through a systemic immune-mediated response, suggest a synergistic interplay between radiotherapy and the immune system (27, 28).

When immune checkpoint inhibitors are administered in the absence of radiation therapy, tumor mutational load correlates with the efficacy of immunotherapy (15, 29, 30). We hypothesize that immune stimulation by radiotherapy will trigger a response to immune checkpoint blockade that will enhance local tumor response and eradicate micro-metastases.

4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) NCT01295827 is being conducted to evaluate the safety and clinical activity of single agent MK-3475 (Pembrolizumab). 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 (Pembrolizumab) showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No 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 (Pembrolizumab) and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475(Pembrolizumab) administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and 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 (Pembrolizumab) were found to be dependent on body weight.

The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 (Pembrolizumab) has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 (Pembrolizumab) in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 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.

4.2.2.1 Efficacy Endpoints

pCR will be the primary study endpoint and safety will be the secondary endpoint. The rationale is that combined pembrolizumab and chemoradiotherapy will stimulate an anti-tumor immune response, leading to enhanced local tumor effect and be well tolerated. With neoadjuvant treatment the pCR is approximately 23% in patients with adenocarcinoma histology. (1) Data suggests that long term outcomes in patients who achieve a pCR is significantly better than non-responders. (6)

4.2.2.2 Biomarker Research

See section 8.0.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Patients with potentially resectable, locally advanced esophagus or gastric adenocarcinoma are eligible for entry into the trial.

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 for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Has a pathologic diagnosis of invasive esophageal, gastroesophageal or gastric adenocarcinoma.
4. Staging CT CAP or PET/CT shows no evidence of metastatic disease.
5. Have a performance status of 0-2 on the ECOG Performance Scale.
6. Plan for neoadjuvant chemoradiation.
7. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 14 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 or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

8. Female subject of childbearing potential should have a negative serum pregnancy within 48 hours prior to receiving the first dose of study medication.

9. Female and male subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in the Duke Contraception Policy.

5.1.3 Subject Exclusion Criteria

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

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.

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

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

4. Hypersensitivity to pembrolizumab or any of its excipients.

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

6. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy for the current diagnosis of EGC.

7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer. (all patients with prior radiotherapy must be reviewed by the PI to determine if patient is eligible).

8. Has known metastatic disease. Staging CT C/A/P or PET/CT will be mandatory no more than 45 days prior to enrollment to evaluate for the presence of metastatic disease.

9. Has unresectable disease or is medically inoperable.

10. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with chronic use of disease modifying agents, corticosteroids or

immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

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

12. Has an active infection requiring systemic therapy.

13. Has a history or current evidence of physical or physiological contraindication to participation in this study, at the discretion of the treating investigator.

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

15. 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.

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

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

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

19. 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.

20. Has a diagnosis of scleroderma.

21. Has a known history of allogenic stem cell transplant

22. Has received a solid organ transplant.

5.2 Trial Treatment: Pembrolizumab

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

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
Carboplatin	AUC 2	QW	IV infusion	Weekly during radiation (min 4	SOC

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
				cycles)	
Paclitaxel	50mg/m^2 of BSA	QW	IV infusion	Weekly during radiation (min 4 cycles)	SOC

Radiotherapy will be initiated within 14 days after the first dose of pembrolizumab. Radiation treatment will be administered at a dose of 1.8Gy/fraction to a total dose of 45Gy. Radiotherapy will be given with concurrent, weekly carboplatin (AUC 2) and paclitaxel (50mg/m2 of BSA) as per standard of care. Three cycles of pembrolizumab will be administered prior to surgical resection. Pembrolizumab will be given every 3 weeks and may be given at the same time as systemic therapy. Three cycles of adjuvant pembrolizumab will be administered after surgery. Given the possibility of post-operative complications after neoadjuvant chemoradiotherapy and surgery for EGC, we anticipate variation in timing of adjuvant pembrolizumab based on physician judgment.

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 Merck Prescribing Information.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

AEs associated with pembrolizumab exposure, including coadministration with additional compounds, may represent an immunologic aetiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab/combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab/combination treatment, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab/combination treatment are provided in Table 4.

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

5.2.1.3 Dose Modification Guidelines for Drug-Related Adverse Events

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last study intervention treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If study intervention has been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT Elevation or Increased	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Bilirubin			prednisone or equivalent) followed by taper	value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

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, and/or

holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the PI. The reason for interruption should be documented in the patient's study record.

5.2.2 Timing of Dose Administration

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

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

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

5.2.3 Trial Blinding/Masking

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

5.3 Trial Treatment: Radiation Therapy (Below are recommendations but at the discretion of the treating physician.).

Image-guided radiation treatment (IGRT) is recommended for this study.

5.3.1 Dose Specifications

5.3.1.1 Neoadjuvant Chemotherapy

Carboplatin (AUC 2) and paclitaxel (50mg/m2 of BSA) will be given concurrent, weekly with radiation with plan for at least 4 total doses neoadjuvantly per treating medical oncologist. Administration will be as per standard of care.

5.3.1.2 Preoperative IGRT

Either 3D conformal radiotherapy (3D-CRT) or intensity modulated radiation therapy (IMRT)/volumetric arc therapy (VMAT) may be utilized. Recommendations for dose volume histogram (DVH) constraints for critical normal structures are at the discretion of the treating physician but Section 5.35 provides recommended metrics.

A prescription dose of 45Gy in 25 daily fractions will be prescribed with recommendation to cover 95% of the PTV.

5.3.2 Technical Factors

Megavoltage photon beams produced by linear accelerators with energies of ≥ 4 MV are permitted.

Image guidance may be achieved using any one or more of the following techniques:

- Orthogonal 2D kilovoltage (KV) and MV electronic images, e.g., ExacTrac;
- Linear-accelerator mounted kV and MV conebeam CT images;
- Linear-accelerator mounted MV CT images (e.g., Tomotherapy);

Any questions regarding IGRT technology should be directed to the PI.

5.3.3 Localization, Simulation, and Immobilization

Patients should be immobilized in stable and comfortable positions to allow accurate repositioning from treatment to treatment and to prevent movement during treatments. A variety of immobilization devises may be utilized, including Alpha Cradle, indexed wingboard and vac-lock. Radiotherapy treatment plans will be generated after CT simulation. Ideally PET/CT simulation will be performed for radiation treatment planning. Respiratory motion assessment is recommended and if motion is greater than 1.5cm respiratory motion management is advised but at the discretion of the treating physician.

5.3.4 Treatment Planning/Target Volumes

The definition of volumes will be in accordance with the ICRU Report #62: Prescribing, recording and Reporting Photon Beam Therapy (supplement to ICRU Report #50).

Gross Tumor Volume (GTV): Gross tumor defined as the primary tumor in the esophagus/stomach and grossly involved regional lymph nodes.

Clinical Target Volume (CTV): The CTV is defined as a 2-4cm superior and inferior expansion along the length of the esophagus and stomach and a 1-1.5cm radial expansion for the primary and nodal GTV. The superior and inferior expansion should follow the contour of the esophagus and stomach. The intent is to extend the margin along the length of the esophagus and stomach to provide a margin for coverage of the submucosal extension of tumor. The celiac axis may be covered for tumors of the distal esophagus, GE junction or stomach. The internal target volumes (ITV) as assessed on the 4D-CT will be included in the CTV. Elective nodal coverage is at the discretion of the treating physician.

Planning Target Volume (PTV): Include CTV and set up uncertainty. Typically PTV includes CTV plus 0.5-1cm in all directions.

Boost PTV: Defined as the GTV with expansion of 1-1.5cm.

5.3.5 Critical Structures

Radiation dose to normal tissues should be kept within the accepted normal tissue tolerances when using standard 1.8Gy fractionation schedules. The following are suggested normal tissue parameters:

Normal Tissue	Description		
Lung	Lung-PTV	V20	≤25%
Heart	Heart & pericardium	Mean V40	≤25% ≤40%
Kidney	Combined kidneys	V20	≤30%
Spinal Cord	Spinal cord	Max	50Gy
Liver	Liver	V30 Mean	≤33% 21Gy

5.3.6 Compliance Criteria

Treatment interruptions should be minimized. Radiation treatment breaks longer than 5 days will be documented. If radiation treatment break is longer than 5 days there will be discussion with PI to consider taking the patient off study. If chemotherapy is held at the discretion of the treating medical oncologist, it will be documented but not counted as a treatment break

5.3.7 Chemoradiation Therapy Adverse Events

5.3.7.1 Acute Adverse Events

Common chemoradiation adverse events include: anorexia/weight loss, constipation, diarrhea, esophagitis, fatigue, nausea/vomiting, dermatitis, hair thinning/alopecia, nerve damage, and reduction in blood counts.

5.3.7.2 Long-term Adverse Events

Possible long-term treatment adverse events include esophageal stenosis/stricture, difficulty maintaining weight, depressed blood counts, pneumonitis, increased risk of cardiovascular disease, myelopathy, renal dysfunction necessitating dialysis, and bowel obstruction, perforation or bleeding.

5.3.8 Trial Treatment: Surgery

5.3.8 Surgical Evaluation

A surgeon, radiation oncologist and medical oncologist must see any eligible patient prior to instituting preoperative therapy.

Resection of the EGC will occur following combined preoperative chemoradiation and pembrolizumab after restaging imaging has confirmed no evidence of metastatic disease and patient is medically fit for surgery as per standard of care.

5.3.9 Postoperative Management

Post-operative management is at the discretion of the surgical team per standard of care.

5.3.10 Surgical Adverse Events

Major wound complications, such as secondary operations, re-admissions, and/or invasive procedures will be collected based on retrospective review of the patient's electronic medical record.Constitution symptoms related to surgical recovery such as weight loss, nausea and vomiting, fatigue, post-operative pain, constipation caused by narcotic medication prescribed for pain management both during and after discharge from hospital, will not be captured. Anticipated surgical complications specifically, anastomic leak, fistula, chylothorax, pneumonia and pericardial effusion will be captured.

5.4 Treatment Arm

An initial safety run-in of 5 patients will be performed to evaluate safety of concurrent pembrolizumab and chemoradiotherapy for EGC. If no more than 1 grade 3 or higher toxicity is definitely related to concurrent pembrolizumab and observed within 30 days of the last dose of neoadjuvant pembrolizumab (i.e. cycle 3) for the fifth patient, then the study will continue to accrue. In the event that more than 1 of the first 5 patients has a grade 3 or higher toxicity definitely related to concurrent pembrolizumab, then an additional five patients (total 10 patients) will be enrolled with close toxicity assessment. If more than 2 grade 3 or higher toxicities definitely related to concurrent pembrolizumab and chemoradiotherapy are observed in the 10 patients, then the PI will consider that the safety cohort be repeated using a lower dose of radiation with close toxicity assessment.

Cohort	Number Patients	Pembrolizumab	# Grade 3+ toxicities permitted
1	5-10	200 mg every 3 weeks	1 (if more than 1 Grade 3+ toxicity then additional 5 patients accrued)
Expansion	28-33	200 mg every 3 weeks	

Accrual: 38 patients with intent to have 30 evaluable patients (patients who complete neoadjuvant treatment and undergo resection) for the primary endpoint.

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.

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:

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

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 section describes other medications that are prohibited in this trial.

Biological therapy or immunotherapy will remain prohibited beyond the treatment phase unless the patient develops metastatic disease. There are no additional prohibited therapies during the post-treatment follow-up phase.

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines for Pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these

guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

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

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

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

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

    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea despite anti-diarrheals, 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 and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. TSH will be performed at baseline and prior to administration of subsequent cycles of pembrolizumab as per institutional policy.

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

- **Hepatic**:
    - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
        - Treat with IV or oral corticosteroids
    - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.

- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

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

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

Table 3 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. 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.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 4: Life-threatening; pressor or ventilatory support indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.6.2 Supportive Care Guidelines for Chemoradiation

- Corticosteroids will be administered as per standard of care for systemic therapy administration. Subjects will be pre-medicated with dexamethasone 8mg po the night before, the morning prior to each chemotherapy, and for 2 days after each chemotherapy. If a patient is allergic to dexamethasone, a steroid equivalent may be used at the discretion of the treating physician.

Efforts will be made to minimize the use of corticosteroids during chemoradiation for symptomatic or supportive management.

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. The Duke Contraception policy will be followed.

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 as per Duke policy. 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 PI should any untoward effect occur. In addition, a subject may be withdrawn by the PI 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 withdraws consent.
- 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 progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by review of electronic medical record until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.9 Subject Replacement Strategy

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**		**Treatment Cycles/Radiotherapy/Surgery**						**Post-Treatment**		
Treatment Cycle/Title:	Pre-Screening (Visit 1)	Main Study Screening (Visit 2)	C1	XRT[a] (5-6 wk) + C2/C3	Surg.	C4*	C5*	C6*	Safety Follow-up	Follow Up Visits	Survival Follow-Up
Timing (Weeks)		-4 to -1	Wk 0	Wk 1 – 6	6–20 wk post-C3/XRT	4-12 wk postop	3 wk post-C4	3 wk post-C5	30 days post-C6	Per treating MD discretion	Every 52 wk
Scheduling Window (Days):		-28 to -1	± 3	± 3	± 21	± 3	± 3	± 3	± 7		
Informed Consent		X									
Inclusion/Exclusion Criteria	X	X									
Demographics and Medical History	X	X									
Study Drug Administration[b]			X	X		X	X	X			
Chemotherapy Administration[c]				X							
Radiotherapy Administration[d]				X							
Surgical Resection of Primary Tumor					X[h]						
Post-study anticancer therapy status										X	
Survival Status										X	X
Review Adverse Events			X	X	X	X	X	X	X	X	
Full Physical Examination	X								X		
Focused Physical Examination			X	X		X	X	X		X	
Vital Signs and Weight	X	X	X	X	X		X	X	X	X	
ECOG Performance Status	X	X	X	X		X	X	X	X	X	
Pregnancy Test – Serum β-HCG (if appropriate)		X									
PT/INR and aPTT		X[i]			X						
CBC with Differential		X[i]	X	X	X	X	X	X			
Comprehensive Serum Chemistry Panel		X[i]	X	X	X	X	X	X			

Trial Period:	**Screening Phase**		**Treatment Cycles/Radiotherapy/Surgery**						**Post-Treatment**		
Treatment Cycle/Title:	Pre-Screening (Visit 1)	Main Study Screening (Visit 2)	C1	XRT[a] (5-6 wk) + C2/C3	Surg.	C4*	C5*	C6*	Safety Follow-up	Follow Up Visits	Survival Follow-Up
Timing (Weeks)		-4 to -1	Wk 0	Wk 1 – 6	6–20 wk post-C3/XRT	4-12 wk postop	3 wk post-C4	3 wk post-C5	30 days post-C6	Per treating MD discretion	Every 52 wk
Scheduling Window (Days):		-28 to -1	± 3	± 3	± 21	± 3	± 3	± 3	± 7		
Urinalysis		X									
TSH		X		X		X	X	X			
T3, FT4		X									
ACTH,		X									
Cortisol		X									
LH/FSH		X									
Testosterone		X									
EKG		X									
EUS	[g]X										
CT CAP or PET/CT for staging	X				X[e]					X	
Archival or Newly Obtained Tissue Collection		X[f]				X					
Correlative Studies Blood Collection	X			X	X preop	X			X		

[a]Patients will be evaluated at least weekly during radiation treatment including assessment for adverse events.
[b]Study drug is pembrolizumab
[c] Chemotherapy is weekly Carboplatin/Paclitaxel as per standard of care
[d]Radiotherapy will be administered daily (Monday through Friday) for five-five and a half weeks (25-28 total treatments)
[e]Restaging will be performed prior to surgical resection, and may be repeated at the discretion of the treating physician
[f]PDL-1 assay testing will be performed on archived or fresh tissue from biopsy
[g]EUS for local tumor staging (if ultrasound probe able to traverse tumor). Not required if EUS probe cannot traverse the lesion.
[h] Surgical resection will occur 6-20 weeks after chemoradiotherapy. Surgical resection >20 weeks after chemoradiotherapy may be allowed at the surgeon's discretion.

[i] Screening labs will be performed within 14 days of treatment initiation

- *adjuvant systemic therapy is preferred as outlined in the study calendar but timing and administration is at the discretion of the treating medical oncologist

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.1 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 and Registration Process

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial. After obtaining Informed Consent, eligible patients will be enrolled on this trial. Subjects will be issued a subject unique identifying numbers for eligible participants. An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each subject treated with the investigational product in the study or registered to the study.

While all study evaluations must be performed by the Investigator as described in Section 9.0, Study Evaluations and Study Calendar (Section 6.1). This study will use a web based data entry system, REDCAP, for data collection.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature 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 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 the trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB 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. Details regarding the disease for which the subject has enrolled in this study will be recorded separately.

7.1.1.4 Concomitant Medications Review

7.1.1.4.1 Concomitant Medications

The investigator or qualified designee will record steroid and endocrine related medications, including topical steroids, if any, taken by the subject during the trial. All medications related to reportable SAEs 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.

7.1.2 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 have performed a complete physical exam during the prescreening period.

7.1.2.3 Focused 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 focused physical exam as clinically indicated prior to trial treatment administration.

7.1.2.4 Vital Signs

Vital signs will be taken 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

Staging CT C/A/P or PET/CT will be performed prior to and after completion of neoadjuvant radiotherapy, may be repeated at the discretion of the treating physician prior to definitive surgical resection.

7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

Fresh tissue collection will be performed prior to treatment initiation (optional endoscopic procedure) and at the time of surgery. Blood collection will be performed at 5 predefined time points as detailed in the trial flow chart.

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	Total triiodothyronine (T3)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Free thyroxine (T4)
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Thyroid stimulating hormone (TSH)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Adrenocorticotropic Hormone (ACTH)
Absolute Lymphocyte Count	*(CO_2 or bicarbonate)*		Cortisol
	Uric Acid		
	Calcium		Luteinizing hormone (LH)- in women
	Chloride		Follicle stimulating hormone (FSH) – in women
	Glucose		Testosterone- males
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		Blood for correlative studies
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

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. After discontinuing treatment following assessment of CR, these subjects should return to the site for a safety follow-up visit (described in Section 7.1.5.3.1) and then proceed to the follow-up period of the study (described in Section 7.1.5.4).

7.1.4.2 Blinding/Unblinding

This is an open-label trial. Blinding will not be performed.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - trial flow chart. Specific procedure-related details are provided above in Section 7.1 - trial procedures.

7.1.5.1 Screening

7.1.5.1.1 Screening Period

7.1.5.2 Treatment Period

Patients will be evaluated by the treating radiation oncologist at least once per week while undergoing neoadjuvant, concurrent chemoradiation treatment. During the neoadjuvant and adjuvant pembrolizumab therapy, patients will be evaluated at least every three weeks by the treating medical oncologist with labs performed as per study flow chart.

7.1.5.3 Post-Treatment Visits

After completion of the final cycle of pembrolizumab, patients will be evaluated by the treating medical oncologist, radiation oncologist, or surgical oncologist every 3-6 months for the first two years, then every 6-12 months for years three to five as per standard of care.

7.1.5.3.1 Safety Follow-Up Visit

The mandatory safety follow-up visit will be required for subjects who have completed 6 cycles of pembrolizumab and should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the safety follow-up visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever

occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded by review of the medical chart.

7.1.5.4 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the follow-up phase and should be assessed as per discretion of treating oncologist. 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. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

7.1.5.4.1 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject associated with administered of a pharmaceutical product and/or use of a medical procedure, 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, 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.

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

All adverse events that occur after the consent form is signed but before treatment 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, or a procedure.

From the time of treatment 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 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 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before intervention allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention allocation/randomization through 30 days following cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation/randomization through 90 days following cessation of study intervention or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of intervention allocation/randomization through 120 days following cessation of study intervention, or 30 days following cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to Merck if the event is considered drug-related.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify Merck.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to Merck within the time frames as indicated in the table below :

Table: Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period:** **Consent to Randomization/ Allocation**	**Reporting Time Period:** **Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period:** **After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Merck:**
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 2 business days but no longer than 3 calendar days of learning of event
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 2 business days but no longer than 3 calendar days of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 2 business days but no longer than 3 calendar days of learning of event

7.2.2 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 5 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.3 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 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

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

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

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

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

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

SAE reports and any other relevant safety information are to be forwarded on a MedWatch form (FDA 3500) to the Merck Global Safety facsimile number: +1-215-661-6229

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.

7.2.4.2 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 5 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, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 5 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 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 5 days 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.

7.2.4.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Section 7.2.3. (Immediate Reporting of Adverse Events to the Sponsor and to Merck), unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to Merck Global Safety within 5 working days either by electronic or paper media.

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

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Merck Global Safety as a SAE within 5 working days of determination that the event is not progression of the cancer under study

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

7.2.5 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. Intensity of all adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events v 4.0 (CTCAE) on a five-point scale (grades 1 to 5, Table 6) and reported in detail on the CRF. 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.)

7.2.6 Sponsor Responsibility for Reporting Adverse Events

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

8.0 CORRELATIVE/SPECIAL STUDIES

We will perform immunohistochemistry and flow cytometric analysis in order to find markers that correlate with or predict response to neoadjuvant treatment. Whole exome sequencing, RNA expression analysis, and T-cell receptor sequencing may also be considered to explore expression profiles of tumor neo-antigens, immune modulators, and T cell repertoires. Immunohistochemistry and immunofluorescence will be performed on optional pretreatment biopsy and surgical resection specimens using standard methodology and an automated analyzer. Imaging analysis will be used for quantification. Flow cytometric analysis will be performed on peripheral blood samples and tumor specimens to characterize the peripheral blood immunophenotype and tumor immune cell infiltrate in patients receiving chemoradiotherapy and pembrolizumab. We will use CD3, CD4, CD8, B220, Foxp3, PD-1, Eomes, Ki67, and Granzyme B staining to analyze the tumor lymphocyte population, including quantification of the immunoinhibitory Treg population and characterization of exhausted versus reinvigorated effector T cells. We will utilize CIBERSORT to characterize the tumor immune cell composition. CIBERSORT is a computational method that analyzes RNA expression data within complex tissues to quantify estimated fraction of leukocyte subsets, including naïve and memory B cells, CD8+ T cells, resting and activated memory CD4+ T cells, natural killer cells, monocytes, macrophage subtypes, resting and activated dendritic cells, and neutrophils (31). Flow cytometry, immunohistochemistry, and/or immunofluorescence will be employed to assess cell surface expression of MHC-I, PD-1, PD-L1, PD-L2, and CTLA-4 in pre-treatment biopsy and surgical resection specimens. Given that tumor mutational load correlates with clinical response to anti-PD-1 therapy administered in the absence of radiation therapy (15, 30), whole exome sequencing may be performed to correlate mutational load with outcomes. Finally, next-generation deep sequencing may be used to assess diversity of the T cell receptor repertoire and heterogeneity

8.1 Collection, Handling, and Shipping of Specimens

Additional blood and tumor samples will be collected for research purposes only. Some of these research studies are mandatory for study participation and some are optional. The optional studies will be performed only on patients who have provided informed consent for each individual study. Samples will be transported in compliance with current regulatory guidelines for transport of biological specimens.

8.1.1 Tumor Samples (optional)

Paraffin-embedded samples from initial tumor biopsy will be assessed for PDL-1 expresssion using an house testing platform. Fresh tumor biopsies via endoscopic procedure at study

entry are optional for patients who have provided written consent for this separate procedure. Fresh tissue from surgical resection specimen will be processed and stored in the Duke biorepository.

8.1.2 Blood Samples

Blood samples will be analyzed via flow cytometry for the presence of PD-1 expressing T cells as well as for the proportion of circulating regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). Other immune cell populations may also be explored. Plasma may also be analyzed for cytokines and genetic alterations in cell free DNA related to tumor immunology and cancer biology. Please see Table below for complete blood sample collection schedule. Three acid citrate dexatrose (ACD) and 2 ethylenediamine tetraacetic acid (EDTA) will be obtained at the following time points:

Time points for blood sample collections	
Pre-treatment	After consent is signed, prior to first study drug administration
On-treatment	Week 3 of chemoradiation +pembrolizumab
On-treatment	Post- Cycle 3, prior to surgical resection
On-treatment	After surgery, Pre-Cycle 4
Post-treatment	30 days post-Cycle 6

8.2 Correlative Studies

The following correlative studies will be performed using PBMCs and tumor tissues collected from the patients included in the study:

The planned Correlative Science (CS) studies for this Phase II clinical trial will focus on comprehensive immune profiling of the pre- and post-treatment tumor microenvironment (TE) as well as baseline and longitudinal Peripheral blood mononuclear cells (PBMCs) samples in an attempt to identify both baseline signatures that predict which patients might benefit from neoadjuvant pembrolizumab plus concurrent chemoradiotherapy as well as pharmacodynamic signatures that could provide mechanistic insights regarding therapeutic responses. Given the past difficulties in the identification of anti-PD-1 signatures in the peripheral circulation (i.e. PBMC), special emphasis will be placed on immune profiling the TE. The principal profiling platform to be used in these studies will be highly standardized, polychromatic flow cytometry assays that have been developed by the Duke Immune Profiling Core (DIPC) specifically for monitoring immune signatures in the context of immune checkpoint blockade trials.

The 3 proposed immune profiling panels for this trial are depicted below, and include: 1) a 12-color 'Exhaustion Panel', 2) a 12-color 'Tumor Reactive T Cell Panel', and 3) a 14-color regulatory T cell (Treg) and monocytic myeloid-derived suppressor cells (m-MDSC) panel.

Panels	Marker	Purpose	Fluorophore	Clone	Manufacturer
Exhaustion (12-color)	Fixable Live/Dead Stain	Dead cell exclusion	*TBD*		*TBD*
	CD3	T cells	BUV395	SK7	BD Biosciences
	CD4	CD4+ (helper) T cells	BUV805	SK3	BD Biosciences
	CD8	CD8+ (cytotoxic) T cells	BV510	SK1	BD Biosciences
	CD279 (PD1, MIH4))	Activation/Inhibition	PE	EH12.2H7	BioLegend
	CD28	Co-stimulation	PerCP-Cy5.5	CD28.8	eBiosciences
	Ki67	Proliferation	*TBD*	*TBD*	*TBD*
	CD223 (Lag3)	Activation/Inhibition	PE-Cy7	3DS223H	eBiosciences
	CD366 (TIM3)	Activation/Inhibition	BB515	7D3	BD Biosciences
	CD274 (PD-L1)	Activation/Cross-inhibition	*TBD*	*TBD*	*TBD*
	CD273 (PD-L2)	Activation/Cross-inhibition	APC-R700	MIH18	BD Biosciences
	CD276 (B7H3)	Activation/Cross-inhibition	BV421	7-517	BD Biosciences
Tumor Reactive T cells (12-color)	Fixable Live/Dead Stain	Dead cell exclusion	*TBD*		*TBD*
	CD3	T cells	BUV395	SK7	BD Biosciences
	CD4	CD4+ (helper) T cells	BUV805	SK3	BD Biosciences
	CD8	CD8+ (cytotoxic) T cells	BV510	SK1	BD Biosciences
	CD279 (PD1, MIH4))	Activation/Exhaustion	PE	EH12.2H7	BioLegend
	CD28	Co-stimulation	PerCP-Cy5.5	CD28.8	eBiosciences
	CD38	Activation	APC-R700	HB7	BD Biosciences
	CD197 (CCR7; 150503)	Maturation	PE-Dazzle594	GO43H7	BioLegend
	CD45RA	Maturation	APC	HI100	BioLegend
	CD152 (CTLA4)	Regulation	BV786	BNI3	BD Biosciences
	Ki67	Proliferation	Ax488	Ki-67	BioLegend
	CD278 (ICOS)	Activation	BV650	DX29	BD Biosciences
Treg & MDSC (14-color, 15-marker)	Fixable Live/Dead Stain	Dead cell exclusion	*TBD*		*TBD*
	CD3	T cells	BUV395	SK7	BD Biosciences
	CD4	CD4+ (helper) T cells	BUV805	SK3	BD Biosciences
	CD16	NK cells, Non-classical monocytes	APC	3G8	BioLegend
	CD56	NK cells	APC	HCD56	BioLegend
	CD19	B cell exclusion	*TBD*	*TBD*	*TBD*
	CD20	B cell exclusion	*TBD*	*TBD*	*TBD*
	CD39 (eBioA1)	Regulation	PE-Cy7		eBiosciences
	CD152 (CTLA4)	Regulation	BV786	BNI3	BD Biosciences
	CD194 (CCR4)	Regulation	PE	*TBD*	*TBD*
	CD14	Classical monocytes	PerCP-Cy5.5	45-0149-42	eBiosciences
	HLA-DR	Activated T cells, APC's	BV605	G46-6	BD Biosciences
	Ki67	Proliferation	Ax488	Ki-67	BioLegend
	CD25	Activation	APC-R700	2A3	BD Biosciences
	CD127	Regulation	PE-Dazzle594	A019D5	BioLegend

Each of these established panels can also serve as a base for inclusion of additional phenotypic markers of interest. Instrumentation within DIPC includes a 4-laser BD SORP LSRII analyzer (19-parameter capacity), a 5-laser BD SORP LSRFortessa analyzer (21-parameter capacity), and a 5-laser BD SORP LSRFortessa X50 analyzer (46-parameter capacity). This later instrument with 5 high powered lasers, each serving a decagon composed of 10 tunable detectors, is capable of highly efficient high dimension profiling, and includes a 'microfluidics console' that is ideally suited for comprehensive analyses of samples with limited cellular content such as occasional TE specimens. 'Reportables' for all the immune profiling analyses will include single parameter frequencies (62 for the 'exhaustion' panel; 54 for the 'tumor reactive' panel; and 73 for the 'Treg and MDSC' panel) in addition to frequencies of selected co-expression markers.

In addition to the 3 proposed phenotyping panels above, a fourth 'Intracellular Cytokine Staining' (ICS) panel will be included to measure the frequency and relative polyfunctionality of T cell reactivities against highly conserved tumor associated antigens (TAA). Based on the expression of TAA by the individual patient's pre-treatment tumor, PBMC and TE samples will be stimulated with TAA peptide pools consisting of 15-mers with 11 amino acid overlaps in the presence of a transport inhibitor. The antigen-driven T cell response will be assessed by determining the frequencies of CD4+ and CD8+ T cells staining positive for intracellular IFN-γ, IL-2, TNF-α, granzyme B, and expression of CD107a. Using Boolean gating, the relative polyfunctionality of the anti-TAA responses can be delineated.

The proposed Correlative Science studies for this Phase II protocol will test the following hypotheses:

1) Neoadjuvant pembrolizumab with concurrent chemoradiotherapy and adjuvant pembrolizumab will produce higher frequencies of activated T cells in PBMC and TE than standard of care chemoradiotherapy alone.
2) Enrolled patients with an immunologically activated ('hot') tumor microenvironment (TE) at baseline will derive greater therapeutic benefit from neoadjuvant pembrolizumab therapy than those with a non-activated ('cold') TE.
    - Baseline TE containing >20% CD8+ cells co-expressing CTLA-4 and PD-1 will constitute an immunologically activated TE
3) Enrolled patients with PDL-1+ tumors will derive greater therapeutic benefit than patients with PDL-1- tumors.
4) Clinical Response(s) to therapy will be accompanied by an increase in the frequency and polyfunctionality of anti-TAA T cell responses in PBMC and TE.

9.0 STUDY EVALUATIONS AND STUDY CALENDAR

9.1 Screening Studies

The following procedures will be performed during the screening period:

- Informed consent
- History/demographics updated within 2 weeks prior to patient enrollment
- Documentation of cancer
- CBC with differential
- Comprehensive Serum Chemistry Panel
- T3, FT4, and TSH
- Urinalysis
- Serum β–HCG or urine pregnancy test for women of childbearing potential
- Blood for research studies (PBMCs) will be collected (pre-treatment) after study consent is signed
- Optional Tumor Biopsy (pre-treatment) after study consent is signed

- Staging imaging (CT CAP or PET/CT) to confirm no evidence of metastatic disease
- EUS for local tumor staging (if ultrasound probe able to traverse tumor). Not required if EUS probe cannot traverse the lesion.

- EKG within 30 days prior to first study drug administration.

The screening period can be up to 30 days prior to first study drug administration (Day 1 Cycle 1). Laboratory baseline evaluations are to be conducted within 14 days prior to first administration of study drug. Radiologic imaging must be done within 45 days prior to first study drug administration.

9.2 On Study Evaluations

Visits will occur with the treating medical oncologist at each pembrolizumab treatment visit (i.e. every 3 weeks during Cycles 1 – 3 and Cycles 4 – 6) from study initiation. The following procedures will be performed during the pembrolizumab treatment period:

- Physical exam, including weight, vital signs, ECOG performance status
- Administration of study drug
- Recording of adverse events
- Relevant laboratory evaluations, WBC, Hgb, Plt, ANC, Cr, K, Ca, ALT, AST, Total Bilirubin, alkaline phosphatase, TSH
- Blood for research studies (PBMCs) will be collected at week 3 of chemoradiation, prior to surgery, and prior to cycle 4 and at safety follow up visit
- Disease assessments will be performed at after completion of neoadjuvant chemoradiation and then at the treating physicians discretion

Visits will occur with the treating radiation oncologist once weekly during the five week radiation treatment period. The following procedures will be performed during the radiation treatment period:

- Physical exam, including weight, vital signs, ECOG performance status
- Recording of adverse events

A visit with the operating surgeon will typically occur within four-eight weeks of completing chemoradiotherapy to assess treatment-induced toxicity and determine optimal timing for surgical resection. Additional postoperative visits by the surgeon will occur as per treating physician's discretion.

Subsequent follow-up visits will occur approximately every 3-6 months for the first two years after treatment, every 6-12 months during years three to five as per discretion of treating physicians. These visits may alternate among the medical oncologist, radiation oncologist, and surgeon. The following will be performed during this post-treatment period:

- Physical exam, including weight, vital signs, ECOG performance status
- Recording of adverse events (up to 90 days after last dose of pembrolizumab)
- CT CAP or PET/CT

9.3 Off Study Evaluation

Final visit is to be performed at the time (or within 30 days +/- 14 days) of removal from the study if adjuvant therapy is administered. Off study evaluations will include:

- Physical exam: height, weight vital signs, ECOG performance status
- Recording of adverse events (for unresolved adverse events, patients should be monitored for 30 days following the last dose of study drug)

Patients who complete study treatment should be followed for local recurrence, distant recurrence, progression free and overall survival every 6 months by retrospective review of the patient's chart or by phone call.

10.0STATISTICAL ANALYSIS PLAN

10.1 Statistical Analysis Plan

The primary objective of this one-arm Phase II trial is to test whether neoadjuvant chemoradiotherapy combined with Pembrolizumab followed by surgical resection has a pathologic complete response (pCR) rate that is significantly larger than the historical control pCR rate observed with standard of care (neoadjuvant radiotherapy followed by surgical resection). A historical pCR rate of 0.23 (van Hagen, 2012) was observed in 161 patients. An accrual rate of about 12 patients per year is expected in this trial. While the planned statistical design requires no more than 30 patients (30 months of accrual), the trial could accrue as many as 38 patients (36 months of accrual) in order to replace patients who withdraw before surgery. Thus, the length of the trial could be as long as 41 months (i.e., 36 months of accrual plus 5 months for the last patient to be evaluated for response).

A two-stage design will be used to test the null hypothesis that the true pCR rate is ≤ 0.30 against the alternative hypothesis that the true pCR rate is ≥ 0.50. This design will allow the trial to stop early to accept the null hypothesis. If there are no more than 4 responders (27%) in the first 15 evaluable patients, the trial will stop to accept the null. Otherwise, an additional 15 evaluable patients will be accrued. The null will be rejected only if at least 13 (43%) or more of the 30 patients respond. The significance level and power of this design are 0.08 and 0.81, respectively. The probability of early termination under the null and alternative hypotheses is 0.56 and 0.06, respectively. The observed pCR rate will be estimated with its exact 80% confidence interval.

Secondary Objective 1 is to estimate the safety of the study treatment. Toxicity by type and grade will be tabulated. Toxicity rates of interest will be calculated with their 80% confidence intervals. Only 2 Grade+3 toxicities of any type will be tolerated in the first ten accrued patients. If and when a third Grade 3+ toxicity is observed in the first ten patients, a dose reduction in radiation will be considered.

Exploratory Objective 1 is to estimate the association between pCR rate and selected predictors of response. Using categorical predictors of clinical interest, pCR rates with their 80% confidence intervals will be presented according to the level of the predictors.

Exploratory Objective 2 is to estimate the distribution of time to local recurrence (TTLR), time to distant recurrence (TTDR), progression free survival (PFS), and overall survival (OS). Local recurrence will be defined as the time from enrollment to local recurrence; distant recurrences will be ignored and deaths will be censored. TTDR will be defined analogously. PFS will be defined as the time from enrollment to local recurrence, distant recurrence, or death due to any cause, whichever comes first. OS is defined as the time from enrollment to death due to any cause. The Kaplan Meier method will be used to estimate these four distributions.

10.1.1 Interim Analysis to Monitor Safety

After the first 5 eligible patients have been accrued to the study, an analysis will be performed to assess acute treatment-related toxicity. If more than 1, grade 3 or greater toxicities is definitely related to concurrent pembrolizumab and chemoradiotherapy are observed, then an additional five patients will be added to this treatment arm. If no issues concerning for safety are observed within 30 days of the last dose of neoadjuvant pembrolizumab (cycle 3) for the fifth patient, then the study will continue to accrue. Patients accrued prior to the interim analysis will be evaluated for the primary endpoint.

11.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

11.1 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

11.2 Packaging and Labeling Information

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

11.3 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.

11.4 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.

11.5 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.

12.0 ADMINISTRATIVE AND REGULATORY DETAILS

12.1 Confidentiality

All patient data will be captured and maintained in a study specific database with password protected access. Data is entered using an assigned patient identification number. The data provided to those reviewing the results, for example the study statistician will include the patient identification numbers, but will not include patient identifiable data. The research samples obtained in this study will only be sent using the patient identification number which can only be linked to the patient at a given institution by the treating physician. All documentation that contains personal health information that may include patient identifiable information will be maintained at the site to preserve patient confidentiality.

12.2 Compliance with Financial Disclosure Requirements

By signing this protocol, the investigator agrees to provide to the Sponsor accurate financial information to allow the Sponsor to submit complete and accurate certification and disclosure statements as required by U.S. Food and Drug Administration regulations (21 CFR Part 54).

The investigator further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. This requirement also extends to sub investigators. The investigator also consents to the transmission of this information to Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

12.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; 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 study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations Sponsored by Merck is attached. The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review, and regulatory agency inspection of trial-related documents and procedures and provide for direct access to all study-related source data and documents.

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

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

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

International Conference of Harmonization Good Clinical Practice guidelines (Section 4.3.3) recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

According to European legislation, a Sponsor must designate a principal or coordinating investigator (CI) to review the report (summarizing the study results) and confirm that to the best of his/her knowledge the report accurately describes conduct and results of the study.

The Sponsor may consider one or more factors in the selection of the individual to serve as the CI (e.g., thorough understanding of clinical trial methods, appropriate enrollment of subject/patient cohort, timely achievement of study milestones, availability of the CI during the anticipated review process).

The investigator will promptly inform the Sponsor of any regulatory agency inspection conducted for this study.

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

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

12.4 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.

12.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written SOPs to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

12.6 Data Management

All patient data will be captured and maintained in a study-specific database with password-protected access (REDCAP). Data is entered using an assigned patient identification number. The data provided to those reviewing the results, for example the study statistician, will include the patient identification numbers, but will not include patient identifiable data.

The research samples obtained in this study will only be sent using the patient identification number, which can only be linked to the patient by the study team. All documentation that contains personal health information that may include patient identifiable information will be maintained at the site to preserve patient confidentiality.

Access to the password-protected study website will be limited to individuals involved in the clinical trial: overall Study PI, research nurses, and data managers responsible for this trial. Adverse Events reporting will be performed as outlined in Section 7.

This clinical research study will be monitored both internally by the PI and institutionally by the Duke Cancer Institute (DCI). In terms of internal review the PI will continuously monitor and tabulate adverse events. Appropriate reporting to the Duke University Medical Center IRB will be made. If an unexpected frequency of Grade III or IV events occur, depending on their nature, action appropriate to the nature and frequency of these adverse events will be taken. This may require a protocol amendment, dose de-escalation, or potentially closure of the study. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

Interim analyses occur as scheduled;

Stopping rules for toxicity and/or response are met;

Risk/benefit ratio is not altered to the detriment of the subjects;

Appropriate internal monitoring of AEs and outcomes is done;

Over-accrual does not occur;

Under-accrual is addressed with appropriate amendments or actions;

Data are being appropriately collected in a reasonably timely manner.

DCI review and monitoring of this protocol occurs in accordance with the NCI-approved Data and Safety Monitoring Plan. Briefly, protocol review begins with an initial review by the Cancer Protocol Committee (CPC), which assesses the ethics and safety of the protocol. Documentation of these assessments will be maintained. Formal, independent monitoring will be conducted by the DCI Monitoring Team after the first 3 subjects are enrolled, followed by annual monitoring of 1-3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk. DCI Monitoring Team reports and additional data/safety/toxicity reports submitted by the PI will be reviewed by the Safety Oversight Committee (SOC) on an annual basis. Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns. Monitoring visits may also be initiated upon request by DUHS and DCI Leadership, CPC, SOC, a sponsor, an investigator, or the IRB.

The Duke School of Medicine Office of Audit, Risk and Compliance (OARC) office may conduct confidential audits to evaluate compliance with the protocol and the principles of

GCP. The PI agrees to allow the OARC auditor(s) direct access to all relevant documents and to allocate his/her time and the time of the study team to the OARC auditor(s) in order to discuss findings and any relevant issues.

OARC audits are designed to protect the rights and well-being of human research subjects. OARC audits may be routine or directed (for cause). Routine audits are selected based upon risk metrics generally geared towards high subject enrollment, studies with limited oversight or monitoring, Investigator initiated Investigational Drugs or Devices, federally-funded studies, high degree of risk (based upon adverse events, type of study, or vulnerable populations), Phase I studies, or studies that involve Medicare populations. Directed audits occur at the directive of the IRB or an authorized Institutional Official.

OARC audits examine research studies/clinical trials methodology, processes and systems to assess whether the research is conducted according to the protocol approved by the DUHS IRB. The primary purpose of the audit/review is to verify that the standards for safety of human subjects in clinical trials and the quality of data produced by the clinical trial research are met. The audit/review will serve as a quality assurance measure, internal to the institution. Additional goals of such audits are to detect both random and systemic errors occurring during the conduct of clinical research and to emphasize “best practices” in the research/clinical trials environment.

12.6.1.1 Database Access

This study uses REDCAP, a web-based data entry system for electronic data capture (EDC). All patient registrations and Case Report Forms (CRFs) will be entered electronically via the study website.

12.6.1.1 Enrolling a Patient

A signed informed consent document(s) will be obtained prior to entry into the study. Patients who consent and are being evaluated for eligibility should be tracked on the site screening log. Following consent and verification of eligibility, patients will be registered in the study database. Please note that only patients who meet all eligibility criteria will be registered in the study database.

Each enrolled patient will automatically be assigned a unique patient identification number following registration in the study database.

12.6.1.1 Data Entry

Required eCRFs should be submitted electronically within 10 working days of the required visit. Serious Adverse Events (SAEs) should be entered into the database as soon as possible and no later than 5D days after site PI was initially informed of the SAE.

13.0 APPENDICES

13.1 ECOG Performance Status

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

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

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

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

Adverse events not listed on the CTCAE should be graded as follows:

CTC Grade	Equivalent To:	Definition
Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity
Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the patient
Grade 3	Severe	Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the patient at direct risk.
Grade 4	Life threatening or disabling	An immediate threat to life or leading to a permanent mental or physical conditions that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival.
Grade 5	Death	AE resulting in death

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