CUMC IRB#: AAAQ9871
Version Date: Version 1.9; 10 AUG 2021

TITLE: A Phase II study of chemotherapy and immune checkpoint blockade with Pembrolizumab in the perioperative and maintenance treatment of locoregional gastric or GE junction adenocarcinoma.

SPONSOR: Gulam Manji, MD., PhD.,
Columbia University Medical Center

Coordinating Center: **Columbia University Medical Center/ NewYork-Presbyterian**

Principal Investigator: Gulam Manji, MD., PhD.
161 Fort Washington Ave
New York, NY 10032
Telephone: (212) 305-7115
Email address: gam2140@cumc.columbia.edu

Collaborating Institution **Weill Cornell Medical College/ NewYork-Presbyterian**

Co-Principal Investigator: Manish A. Shah, MD
1305 York Avenue, Room Y1247
New York, NY 10021
Telephone: 646-962-2547
Fax: 646-962-1607
Email address: mas9313@med.cornell.edu

Collaborating Institution **Washington University in St. Louis**

Co-Investigator: Haeseong Park, MD
660 S. Euclid Ave., Room 8056
St. Louis, MO 63110
Telephone: 314-362-5740
Fax: 314-362-7086
Email address: haeseongpark@wustl.edu

Collaborating Institution **Rhode Island Hospital/Lifespan Cancer Institute**

Co-Investigator: Alexander Raufi, MD
164 Summit Ave. Fain building 3rd floor
Providence, RI 02906
Telephone: 401-793-2920
Fax: 401-793-7603
Email address: ARaufi2@Lifespan.org

IND NUMBER: [redacted]

TABLE OF CONTENTS

LIST OF TABLES

1.0 TRIAL SUMMARY

Abbreviated Title	Perioperative chemotherapy and pembrolizumab in locally advanced gastric cancer
Trial Phase	Phase II
Clinical Indication	Gastric or Gastroesophageal Junction Adenocarcinoma
Trial Type	Interventional
Type of control	No Treatment Control (historical control)
Route of administration	Intravenous
Trial Blinding	Unblinded Open-Label
Treatment Groups	Single Cohort: Standard of care combination peri-operative chemotherapy plus Pembrolizumab with Pembrolizumab maintenance.
Number of trial subjects	28 evaluable
Estimated enrollment period	18 months
Estimated duration of trial	We estimate that the trial will require 36 months from the time the first subject signs informed consent until the last subject completes the final treatment. It will take an estimated 18 months to complete enrollment of all subjects.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through final contact. After a screening phase, eligible subjects will be enrolled on the trial and will begin chemotherapy and pembrolizumab on Cycle 1 Day 1. Treatment will continue for 12 weeks and then be paused for surgical planning and surgical resection. Subjects will resume therapy with Cycle 5 Day 1 following surgical recovery which is estimated to be between 6-10 weeks following surgery. Once subjects resume on Cycle 5 Day 1, they will continue pembrolizumab treatment every 3 weeks for 17 cycles total. Treatment will continue unless there is documented disease progression or recurrence following surgery, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, Investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, subject receives 17 cycles of study medication, or administrative reasons requiring cessation of treatment. 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 or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier). All subjects will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study.
Estimated average length of treatment per patient	16 months

1.1 PROTOCOL SYNOPSIS

Title	Phase II study of combination chemotherapy and immune checkpoint blockade with Pembrolizumab in the perioperative and maintenance treatment of locoregional gastric or GE junction adenocarcinoma.
Short Title	Perioperative chemotherapy and pembrolizumab in locally advanced gastric cancer (Merck Internal Reference: MISP 52339)
Protocol Number	AAAQ9871
Phase	Phase II
Methodology	Single arm, multi-center, Phase II study with interim safety analysis
Study Duration	30 months (for efficacy results)
Study Centers	Columbia University Medical Center, New York; Weill Cornell Medical Center, New York; Washington University in St. Louis, St. Louis; Rhode Island Hospital/Lifespan Cancer Institute, Providence, Rhode Island
Objectives	Primary Objective: 1. To evaluate the efficacy of combination therapy with immune checkpoint blockade and chemotherapy as determined by the pathologic complete response rate (pCR). Pathological complete response is defined as no invasive disease within an entirely submitted and evaluated gross lesion, and histologically negative nodes. Secondary Objectives: 2. To determine the efficacy of combination therapy with immune checkpoint blockade and chemotherapy by overall response rate (ORR), and used in the perioperative period in eradicating micrometastatic disease as measured by disease free survival (DFS) and overall survival. 3. To compare paired tissue and serum samples (pre-treatment and post-treatment) from individually treated patients to explore the immune effects of combination therapy and predictors of response as determined by IHC, flow cytometry, and genomic analysis of tumor and immune cells Exploratory Objective: 1. To determine if pathologic complete response (pCR) rate correlates with recurrence free survival (RFS)

Number of Subjects	There will be an estimated 38 patients enrolled in this protocol. We estimate that at least 28 subjects will proceed to surgery and be evaluable for the primary outcome of pCR. All subjects will be available for the secondary analysis of ORR, DFS, and OS.
Diagnosis and Main Inclusion Criteria	Locoregional gastric or GE junction adenocarcinoma Primary Inclusion Criteria: - T2 or greater disease or N1 - Patient suitable for surgical resection - ECOG 0-1 Primary Exclusion Criteria: - Metastatic disease (Stage 4 disease) - Previous treatment for gastric cancer - Active infection - Active autoimmune disease
Study Product, Dose, Route, Regimen	Pembrolizumab dosed IV at 200mg every 21 days per cycle. Doublet or Triplet chemotherapy with Capecitabine, oxaliplatin, and epirubicin (optional) (21 day cycle). Epirubicin can be excluded at the discretion of the treating physician.
Duration of administration	21 day cycles of combination chemotherapy and pembrolizumab: Perioperative Treatment: 3 cycles prior to surgery and 3 cycles following surgery. Subjects will receive an additional cycle of pembrolizumab alone prior to surgery (4^{th} cycle). Maintenance Treatment: Subjects will receive an additional maintenance period following surgery which consists of up to 17 additional cycles of single agent pembrolizumab following completion of combination therapy.
Reference therapy	Not applicable- single arm.

Statistical Methodology	The **primary hypothesis** of this study is that combination therapy including immunotherapy and chemotherapy will result in increased efficacy compared to chemotherapy alone. This will be evaluated based on the **primary outcome** of pathologic complete response (pCR), which is defined as no invasive disease within an entirely submitted and evaluated gross lesion, and histologically negative nodes as determined by an independent pathologist at Columbia University (T0N0). We will enroll an estimated 38 subjects to allow for at least 28 evaluable subjects. This Phase II study will have 80% power to detect an increase in pCR rate from 3% to 15% with a one-sided alpha of 0.05. A key **secondary efficacy outcome** is disease free survival (DFS).

2.0 TRIAL DESIGN

2.1 Trial Design

This is a non-randomized, multi-site, open-label trial of pembrolizumab and chemotherapy in subjects with gastric or gastroesophageal junction adenocarcinoma. Up to 38 subjects may be enrolled in a single cohort, for a sample of 28 evaluable subjects, to assess the efficacy of combination therapy with standard peri-operative chemotherapy in resectable gastric or GE junction adenocarcinoma. The trial was initiated at 2 sites and two additional sites were subsequently added to increase enrollment.

All study subjects will receive standard of care chemotherapy for 3 cycles prior to and 3 cycles following surgery in combination with Pembrolizumab with an additional cycle of Pembrolizumab (4 total) in the pre-operative period. Additionally, subjects will complete 12 months of maintenance Pembrolizumab (14 additional doses to complete 17 post-operative cycles) following completion of post-operative chemotherapy. The primary efficacy endpoint will be pathologic complete response (pCR) rate among all enrolled subjects. Recurrence or disease progression will be determined based on RECIST 1.1 and investigator assessment.

Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlines in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.(As referened in Appendix 13.2)

After the end of treatment, each subject will be followed for 30 days for adverse event monitoring. Serious adverse events and Events of Clinical Interest (ECI) will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. Subjects who discontinue treatment for reasons other than disease recurrence will have post-treatment follow-up for disease status until disease recurrence, withdrawing consent, or becoming lost to follow-up. All subjects will be contacted by telephone for overall survival until death, withdrawal of consent or the end of the study, whichever comes first.

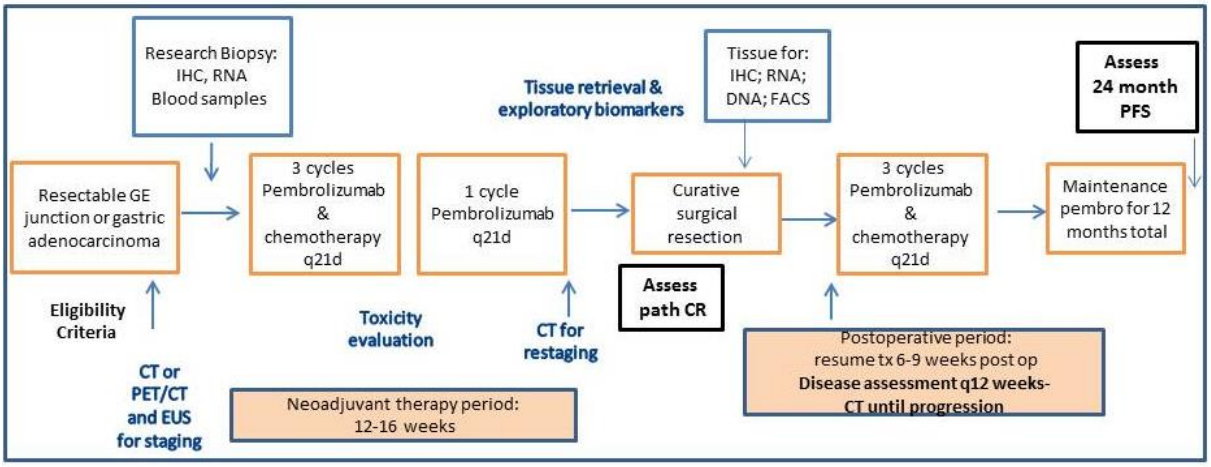
The primary objectives of the trial are to determine the efficacy of addition of pembrolizumab (200mg fixed dose Q3W) to standard of care peri-operative therapy and as maintenance therapy as measured by pathological complete response (pCR) at the time of resection. Secondary objectives include assessment of disease free survival,, overall survival (OS), response rate (ORR), safety and tolerability of combination and maintenance therapy in this clinical setting. Additional secondary objectives include overall survival (OS), and duration of response (DOR) in all subjects and those with PD-L1 positive tumors. Exploratory objectives are planned to assess the relationship between candidate efficacy/resistance biomarkers and anti-tumor activity of pembrolizumab and by comparing baseline tissue measurements as well as biological response measures.

All subjects will be required to provide adequate tumor tissue from baseline for evaluation of PD-L1 expression and additional immunological profiling. In addition, all subjects will be required to submit adequate tumor tissue at the time of resection (unless they achieve pathological or near pathological complete response). A biopsy is also requested at the time of recurrence, but will not be required.

This study will be conducted in conformance with Good Clinical Practices.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outline in the Trial Flow Chart – Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram



3.0 OBJECTIVES AND HYPOTHESES

3.1 Primary Objective & Hypothesis

1. Objective: To determine the efficacy of combination therapy with immune checkpoint blockade and chemotherapy in subjects with resectable gastric adenocarcinoma as determined by the pathologic complete response rate (pCR)..

Hypothesis: We hypothesize that PD-1 blockade will lead to immune activation and enhance the efficacy of chemotherapy in patients with locally advanced gastric cancer. This will lead to an improved pathological response (as assessed by complete pathologic response rate).

3.2 Secondary Objectives & Hypotheses

1. Objective: To determine the impact of combination immune therapy and chemotherapy on disease free survival (DFS), overall survival (OS),immune activation, and tumor response in gastric adenocarcinoma as measured by changes in tumor immune profile following neo-adjuvant therapy.

Hypothesis: We hypothesize that combination chemotherapy and pembrolizumab will improve ORR, DFS, OS, and enhance immune activation and lead to increased immune infiltration and tumor death in the peri-operative period.

2. Objective: To assess the safety of combination chemotherapy and immune therapy including maintenance immune therapy following surgery in gastric adenocarcinoma.

Hypothesis: We hypothesize that maintenance therapy with pembrolizumab will be safe and feasible following surgical resection and will control growth of micrometastasis and delay recurrence of gastric cancer.

3.3 Exploratory Objectives & Hypotheses

Objective: To identify tumor and patient characteristics that predict response and correlate with long term outcomes following treatment with combination Pembrolizumab and chemotherapy.

Hypothesis: We hypothesize that baseline markers of immune activation such as Tumor Infiltrating Lymphocytes and CD8+ lymphocytes will correlate with response to pembrolizumab and that responders to pembrolizumab will have distinct tumor immune phenotype as determined by immunohistochemistry compared to non-responders.

4.0 BACKGROUND & RATIONALE

4.1 Background

In addition to the rationale outlined in the subsequent sections, refer to the Investigator's Brochure (IB)/approved labeling for more detailed background information on MK-3475 (pembrolizumab).

4.1.1 Pharmaceutical and Therapeutic Background

4.1.1.1 Gastric and GE junction Adenocarcinoma

Gastric cancer is one of the most common cancers worldwide with high incidence in China, Japan, and Korea. Although relatively less common in North America, it is estimated to cause 11,000 deaths in the United States in 2014[1]. Surgical resection is the primary treatment for gastric cancer but most patients present with locally advanced disease and recurrence is common after surgery. Systemic chemotherapy has been shown to reduce the rates of recurrence and prolong survival in surgically resected patients. Because of the high risk of recurrence with surgical resection alone, the current standard of care is to treat with combination therapy incorporating chemotherapy in addition to surgery. On the basis of the pivotal MAGIC trial[2], one commonly utilized standard of care incorporates perioperative chemotherapy with 3 cycles of chemotherapy prior to surgery and 3 cycles following resection. Despite improvement in survival with chemotherapy, the majority of patients are not cured of their cancer using this approach and long term survival (5 years) following surgery and chemotherapy remains below 50%. New therapies are needed to produce improved and durable responses.

4.1.1.2 Neoadjuvant chemotherapy and outcomes in gastric cancer:

The use of neoadjuvant therapy prior to planned surgical resection may increase the likelihood of achieving a complete resection (R0), improve surgical outcomes and enable the delivery of systemic chemotherapy prior to complete surgical recovery. This approach is the current standard of care for the treatment of resectable gastric cancer. The tumor response to neoadjuvant therapy is predictive of improved outcomes[3] and pathologic complete response (pCR) is a predictor of improved survival for gastric and GE junction adenocarcinoma.[4] Despite this, the current regimen of systemic chemotherapy for 9-12 weeks prior to surgery rarely results in pathologic complete response. Unlike other studies using radiotherapy in which pCR is seen at higher levels (predominantly in GE junction and esophageal tumors), in chemotherapy trials there are low rates of pCR. In the pivotal MAGIC trial there were no reported pCR[2] and in the large multicenter FNLCC/FFCD trial (12 weeks of pre-op chemo) the pCR rate was only 3%[5].

4.1.1.3 Immune checkpoint therapy:

In the last few years it has become clear that cancers are recognized by the immune system, which can suppress and even eliminate malignant clones, resulting in substantial patient benefit, and, in some cases, long term response. Anti-tumor immunity can be enhanced by antibody-mediated blockade of coinhibitory molecules such as CTLA-4 or PD1. These checkpoint-blocking antibodies have shown significant clinical activity in a variety of tumor types including, melanoma, RCC and NSCLC[6].

The most promising agents are the antibodies targeting the PD1 or its ligand, PD-L1. PD1 is expressed on broad subsets of immune cells and is upregulated by activated T lymphocytes in the tumor microenvironment.[7] PD1 has two known ligands, PD-L1 and PD-L2. PD-L1 and to a lesser extent PD-L2 are expressed on human gastric cancer[8], and in many malignancies

expression of PD-L1 has been correlated with prognosis. Thus interrupting the PD-1/PD-L1 interaction could be an effective anticancer therapy by blunting inhibition of immune responses, thereby facilitating cytotoxic T cell responses against the tumor. Pembrolizumab is an anti-PD-1 antibody that received initial FDA approval in September 2014[9]. We propose utilizing this novel antibody in combination with chemotherapy in the perioperative treatment of locoregional gastric cancer.

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades[10]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies[11-14]. 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)[15]. 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[16]. 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[17-19]. 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.

4.1.2 Preclinical and Clinical Trial Data

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a mono-therapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a mono-therapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-ɣ, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo[20,21]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a mono-therapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the Investigator's Brochure [IB]).

Clinical trials have demonstrated efficacy in patients with advanced melanoma, non –small cell lung cancer, head and neck cancer, bladder cancer and gastric adenocarcinoma.

4.1.3 Ongoing Clinical Trials

Preliminary interim data is available from a cohort of gastric adenocarcinoma patients studied in trial KN012. KEYNOTE-012 trial is a multi-cohort phase 1b study of which one cohort enrolled subjects with recurrent or metastatic gastric or GEJ adenocarcinoma that expressed PD-L1 (≥1% by immunohistochemistry). This cohort enrolled 39 patients (19 from Asia and 20 outside Asia), 67% of whom had received 2 or more prior chemotherapy lines. The primary efficacy endpoint was objective response rate (ORR). Despite the heavily pre-treated patient population, Pembrolizumab monotherapy demonstrated an interim ORR of 33% by RECIST v.1.1 per investigator review (95% confidence interval (CI) (19.1%, 50.2%); all partial responses). The interim disease control rate (DCR) was 41% (95% CI (25.6%, 57.9%). ORR was similar in patients from Asia and outside of Asia, while the DCR was numerically higher in Asia. Responses were observed across all lines of treatment. It should be noted that in the non-Asia group, patients had less prior therapy relative to the Asian patients, and that ORR in later line patients (≥3L) was higher in the Asian group (1 PR/7 patients in the non-Asia group, 4 PR/13 patients in the Asia group). As of the data cutoff date of 14 Nov 2014, the median duration of response was 24 weeks (6 months). Based on preliminary data there appears to be a correlation between response and degree of PD -L1positivity[22].

In these gastric cancer patients in KN012, single agent pembrolizumab at 10 mg/kg Q2W was generally well tolerated, with the type, severity and frequency of adverse events similar to that observed in other indications (see the IB for information about adverse events in other indications). There was 1 death reported in the gastric cancer cohort. This patient had adverse events of tracheomalacia (Grade 3) and hypoxia (Grade 5). The investigator considered the Grade 5 hypoxia to be related to study treatment.

Early Data from the FLOT4-AIO Trial:

The results of the phase 2 part of the open-label, randomized phase 2/3 FLOT4-AIO trial demonstrated an increase in pathologic complete regression (response) with the combination of neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin (FLOT) as compared to epirubicin, cisplatin, and fluorouracil or capecitabine ECF/ECX[23]. The primary endpoint for the phase 2 part of the study was proportion of patients with pathological complete regression which was defined as the proportion of patients with pathological complete regression over the total number of patients evaluated centrally by the study pathologist. Pathologic complete regression was defined according to the Becker regression criteria which estimates the percentage of vital tumor cells in relation to the macroscopically identifiable tumor bed. **Pathologic complete regression is defined as no residual tumor cells**. This study reported, a significantly higher proportion of patients achieving a pathological complete regression in patients receiving FLOT compared to those receiving ECF/ECX (20 [16%; 95% CI 10.3–23.0] of 128 patients in the FLOT group vs 8 [6%; 2.8–11.3] of 137 patients in the ECF/ECX group; p=0.02)

FLOT + Pembro Trial:

The KEYNOTE-585 (NCT03221426) is a global, multicenter, randomized, double-blind, Phase III study comparing perioperative chemotherapy (cisplatin plus 5-fluorouracil or cisplatin plus capecitabine or 5-flurouracil plus docetaxel plus oxaliplatin [FLOT]) with pembrolizumab to chemotherapy with placebo. The planned sample size is approximately 800 patients and the primary endpoints are overall survival (OS), event-free survival (EFS) and pathologic complete response (pCR). PathCR rate is defined as the percentage of participants having a pathCR. **PathCR is defined as no invasive disease within an entirely submitted and evaluated gross lesion, and histologically negative nodes.**

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

This is a Phase 2 study of combination standard of care chemotherapy plus pembrolizumab with the addition of maintenance pembrolizumab in subjects with resectable gastric or gastroesophageal junction adenocarcinoma. It will be conducted in a single cohort at multiple sites and will include subjects who are appropriate for peri-operative chemotherapy and surgical resection. Despite aggressive therapy and extensive surgery, the majority of these

subjects will have recurrence of disease. Many subjects (35%) will have early recurrence within 6-9 months of surgery indicating the need for more aggressive upfront therapy in these subjects. In addition, the majority of patients will ultimately have recurrence and 5 year survival rates are 35-40% despite aggressive therapy.

Attempts at increasing the dose or duration of chemotherapy are limited due to increasing toxicity. The ability to combine immunotherapy with pembrolizumab gives the potential to increase therapeutic options while continuing standard of care chemotherapy. The particular use of maintenance therapy may delay or eliminate the growth of residual micrometastatic disease and lead to durable disease control. Additionally, this study provides the foundation for substantial correlative work to define tumor and patient characteristics that may predict for response to pembrolizumab in gastric cancer. This study will enroll all appropriate subjects regardless of PD-L1 status, but this will be checked in the baseline and surgical specimens of all subjects. In addition, we will analyze blood and tumor biomarkers including emerging immunological profiling, whole genome and protein analysis to identify changes within a specific tumor and predictors of response. Additionally, in gastric cancers PD-L1 and PD-L2 overexpression have recently been associated with EBV- positive tumors[24] and we will assess whether this correlates with response in the current study.

4.2.2 Rationale for Dose Selection/Regimen/Modification

The underlying rationale for this study is to combine standard of care chemotherapy in the dose and schedule that would normally be used and to assess the addition of pembrolizumab for both efficacy and safety.

GE junction and gastric cardia adenocarcinomas in which the treating physician plans to utilize neo-adjuvant chemoradiotherapy regimens will not be eligible for this study.

4.2.2.1 Rationale for Pembrolizumab Dosing

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

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

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

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

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

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

4.2.2.2 Rationale for Chemotherapy Dosing and Modifications

For combination chemotherapy dosing we will employ standard of care chemotherapy regimens without deviation from routine regimens. The two large randomized studies demonstrating benefit of peri-operative chemotherapy utilized different regimens. The most common regimens are based on the MAGIC trial which utilized a 3 drug regimen of Epirubicin, Cisplatin, and 5-FU. This regimen has proved difficult to tolerate and subsequent Phase 3 studies have demonstrated the non-inferiority of utilizing Oxaliplatin or Capecitabine in a similar 3 drug regimen[25]. The FFCD trial utilized a 2 drug regimen of cisplatin and infusional 5-FU. Current guidelines and practice consider several 2 drug options as long as they utilize a

platinum agent with a 5-FU agent, though some centers continue to utilize 3 drug combinations.

For this study, the objective is to test the addition of pembrolizumab to standard of care therapy and thus it will be up to the investor's choice to determine the optimal starting regimen as long as this is a standard regimen containing at least a platinum and 5-FU agent (with guidance from NCCN guidelines). Epirubicin will be allowed if cardiac function is adequate as defined in this study.

4.2.2.3 Rationale for Combination Chemotherapy and Pembrolizumab

One of the objectives of this study is to assess the benefit of combination therapy in improving efficacy in gastric cancer. Based on current knowledge about toxicity profiles and multiple ongoing completed clinical trials, it is expected that there will be limited overlapping toxicities between these two modalities. However, the safety and tolerability of this combination and impact on surgical outcomes will be closely monitored in this study.

Preclinical data in various animal models has identified a potential role for chemotherapy in modulating the immune microenvironment and potentiating the effect of immune checkpoint blockade therapy. In this regard, oxaliplatin has shown particular impact on increasing CD8+ T cell infiltration[26] and in a colon cancer animal model, oxaliplatin was effective than other chemotherapies in inducing tumor regression with checkpoint blockade[27]. We will test this provocative hypothesis with the use of this agent in the current protocol.

4.2.3 Rationale for Endpoints

Rational for Primary Endpoint of Complete Pathological Response

As cancer therapies improve, robust and durable clinical responses are becoming more common. Neoadjuvant chemotherapy, given prior to surgical resection, is utilized more frequently and has become a standard of care for patients with resectable gastric cancer. To account for this, the 8th edition of American Joint Committee on Cancer (AJCC) gastric cancer TNM staging system has incorporated ypTNM so that the extent of downstaging may be quantified. Pathological complete response (pCR), defined as the absence of invasive/in situ cancer after treatment, had been an uncommon occurrence in solid tumors until recently. There is strong data in breast, rectal and bladder cancer, showing that achieving pCR after neoadjuvant chemotherapy confers a better overall and disease-free survival[28-31]. In 2014, the FDA released guidelines on the use of pCR as an endpoint in neoadjuvant treatment of high-risk early-stage breast cancer. The use of pCR as a surrogate endpoint in gastric cancer has also garnered support. In the early 2000's several studies were able to demonstrate that histologic tumor regression grades correlated with patient prognosis after neoadjuvant chemotherapy. For example Becker et al showed in thirty-six patients with gastric carcinoma treated with the combination of etoposide, doxorubicin, and cisplatin that tumor regression correlated significantly with survival ($P = 0.01$)[32]. Several more recent retrospective reviews and meta-analyses have also shown a correlation between pCR and survival after neoadjuvant chemotherapy in gastric and gastroesophageal junction cancer[33-36]. **Pathological complete**

response (pCR) for this study is defined as no invasive disease within an entirely submitted and evaluated gross lesion, and histologically negative nodes (T0N0). The submitted specimens will be reviewed by an independent designated pathologist at Columbia University. For samples for which a consensus is not reached, the sample will be sent for independent review to either Washington University or Brown University for review and the results discussed for a final determination.

Efficacy Endpoints

The primary efficacy objective of this study is to evaluate anti-tumor activity of pembrolizumab in combination with chemotherapy in down staging disease as determined by the pathologic complete response rate (pCR), the rate of pathologic complete response at the time of surgery following 12 weeks of initial therapy.

Additional efficacy endpoints will be assessed, most notably the ability of this combination to eradicate micro-metastatic disease and prevent recurrence following complete resection of localized gastric or GE junction adenocarcinoma. This will be assessed by measuring time to disease recurrence or death (recurrence free survival) as measured from the time of trial initiation. Safety Endpoints

The primary safety objective of this trial is to characterize the safety and tolerability of pembrolizumab in combination with chemotherapy in subjects with resectable gastric cancer. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE 4.0 criteria Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab, including serious adverse events (SAEs) and events of clinical interest (ECIs).

Safety will be assessed by reported adverse experiences using CTCAE, Version 4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific immune –related adverse events (irAEs) will be collected and designated as immune-related events of clinical interest (ECIs) as described in Section 7.3.3.2.

Biomarker Research and Exploratory Endpoints

As an exploratory clinical endpoint, analysis will be performed to determine if pathologic complete response (pCR) rate correlates with recurrence free survival (RFS).

Additional biomarker research to identify factors important for pembrolizumab therapy may also be pursued. For example, tumor and blood samples (including serum and plasma) from this study may undergo proteomic, genomic, metabolomics, and transcriptional analyses.
This research may evaluate factors important for predicting responsiveness or resistance to pembrolizumab therapy and other immunologic targets.

Assays may include but are not be limited to the following:

Immunohistochemistry
PD-L1 expression in tumor tissue will be characterized by immunohistochemistry to explore the relationship between PD-L1 expression and response to treatment with pembrolizumab (this is a secondary objective of the trial). Other exploratory biomarkers (e.g. PD-1 expression, markers of T-cell phenotype) may also be evaluated.

Transcriptional Analyses
As potential exploratory analysis messenger RNA (mRNA) expression profiling in archival material (biopsy specimens, peripheral blood) will be completed to assess expression of approximately 500 genes and attempt to define a gene set critical for clinical response to pembrolizumab. The hypothesis to be tested is that pembrolizumab induces responses in tumors that reflect an inflamed/ immune phenotype based on gene expression signatures capturing PD -L1 & interferon gamma transcriptional programs. Global profiling will also be pursued. Expression of individual genes related to the immune system may also be evaluated such as immune signatures and critical cytokines (e.g., IL-10). MicroRNA profiling may also be pursued in serum samples.

Proteomic analysis
In addition to expression on the tumor tissue, PD-L1 can be shed from tumor and released into the blood. Enzyme-linked immunoassay can measure PD-L1 in serum and correlate this expression with response to pembrolizumab therapy, as well as levels of PD-L1 IHC or protein in the tumor. Blood would be a less invasive component from which to measure PDL1 protein biomarker. In addition to this specific protein biomarker, both tissue and blood derivatives can be subjected to proteomic profiling studies using a variety of platforms that could include but are not limited to immunoassay, Liquid Chromatography/Mass Spectrometry. This approach could identify novel protein biomarker that could aid in subject selection for pembrolizumab therapy.

Gene Analyses
The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to define certain tumor types at the genetic level as being 'hypermutated' or can detect the presence of specific T-cell clones within the tumor microenvironment or in the peripheral blood. There is a potential that the hypermutated state and/or increased T-cell clonality may correlate with response to pembrolizumab therapy, and/or that the converse, 'hypomutated' state or lack of dominant T-cell clones may correlate with non-response.

In addition, understanding genetic determinants of drug response is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the subject population.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with gastric or gastroesophageal junction adenocarcinoma of at least 18 years of age will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

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

1. Have previously untreated localized gastric or GE junction adenocarcinoma as defined by T2 or greater primary lesion or the presence of any positive nodes- N+(clinical nodes) without evidence of metastatic disease.

2. Plan to proceed to surgery following peri-operative chemotherapy based on standard staging studies per local practice.

3. Be willing and able to provide written informed consent/assent for the trial. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research. In cases of partial impairment, impairment that fluctuates over time, or complete impairment due to dementia, stroke, traumatic brain injury, developmental disorders (including mentally disabled persons), serious mental illness, and delirium, a subject may be enrolled if the subject's legally authorized representative consents on the subject's behalf.

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

5. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. *Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1.*

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

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**	≤1.5 X upper limit of normal (ULN) **OR**

Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≥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 **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

8. Have a 2D Echocardiogram with left ventricular ejection fraction ≥ 45% in order to receive epirubicin, if epirubicin is planned. Subjects with inadequate EF or other contraindication can proceed on study without the use of Epirubicin.

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

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

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

11. Male subjects of childbearing potential (Section 5.7.2) must agree to use an adequate method of contraception as outlined in Section 5.7.2- Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

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

5.1.3 Subject Exclusion Criteria

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

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

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids (prednisone 10 mf or equivalent) may be approved after consultation with the Sponsor.

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

4. Hypersensitivity to pembrolizumab or any of its excipients.

5. Has had any prior chemotherapy, targeted small molecule therapy, or radiation therapy for their current diagnosis.

6. Has a known additional malignancy that is progressing or requires active treatment within 3 years from registration. 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. Subjects with a history of prior malignancy diagnosed and treated greater than 3 years form registration may be considered with consultation of the primary investigator.

7. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

8. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

9. Has known history of prior pneumonitis requiring treatment with steroids, or any evidence of active, non-infectious pneumonitis.

10. Has an active infection requiring systemic therapy which is not expected to have resolved by Cycle 1 Day 1 dosing.

11. Has a history or current evidence of any condition (e.g. known deficiency of the enzyme dihydropyrimidine dehydrogenase [DPD]), therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

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

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

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

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

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

17. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor-investigator staff directly involved with this trial, unless prospective IRB approval (by chair or designee) is given allowing exception to this criterion for a specific subject.

18. Has received a live vaccine within 30 days of planned start of study therapy.

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

5.2 Trial Treatments

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

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
Oxaliplatin	130 mg/m2	Q3W	IV infusion	Day 1 of each 3 week chemo cycle	Combination agent
Capecitabine (Xeloda)	625mg/m2	BID, day 1-21	PO administration	Day 1-21 of each 3 week chemo cycle	Combination agent
Epirubicin	50mg/m2	Q3W	IV infusion	Day 1 of each 3 week chemo cycle	Combination agent

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

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

Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Pharmacy Manual. Preparation and administration of the chemotherapy agents used in Cohort 2 should be completed as per the approved product label. See Sections 5.2.2.2 –5.2.2.4 for general recommendations for administration.

Body surface area (BSA) in m^2 should be calculated per local guidance.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

The Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0) must be used to grade the severity of adverse events.
If appropriate, the Investigator may attribute each toxicity event to any of the individual chemotherapy agents used or pembrolizumab alone in the combination arms and use stepwise dose modifications according to Table 3. Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be interrupted or discontinued due to toxicity.

If a dose level reduction for toxicity occurs with any agent, the dose may not be re-escalated. Dose modifications are always based on the previous cycle.

Subjects may have up to 2 dose level reductions per chemotherapy agent throughout the course of the study, as described in Table 3 with the exception of Epirubicin. If further toxicity occurs or the criteria for resuming treatment are not met, the subject must be discontinued from chemotherapy treatment. Of note, in the event a subject is discontinued from chemotherapy treatment, the subject may still be eligible for continued treatment with pembrolizumab (Dose Level -3 in Table 3). Refer to Table 4, and Table 5 for dose modification guidelines for adverse events for pembrolizumab; other chemotherapy will be modified per institutional standards and package labeling. If a subject experiences several toxicities and there are conflicting recommendations, follow the most conservative dose adjustment recommended (dose reduction appropriate to the most severe toxicity).

Reduction or with-holding of one chemotherapy agent and not the other agent is appropriate if, in the opinion of the Investigator, the toxicity is definitely related to one of the study treatments. If, in the opinion of the Investigator, the toxicity is related to the combination of two chemotherapy agents, both treatments should be reduced (if applicable), interrupted or discontinued according to recommended dose modifications. If the toxicity is related to the combination of three agents, all three agents should be reduced or held according to the recommended dose modifications.

Exceptional circumstances to following the dose modification tables below may be considered after consultation with the Sponsor Investigator.

Table 3 Dose modifications for Trial Medications

Drug	Starting Dose	Dose Level - 1	Dose Level - 2	Dose Level -3

Pembrolizumab	200 mg fixed dose	Dose reductions are not permitted	Dose reductions are not permitted	Dose reductions are not permitted
Oxaliplatin	130 mg/m2	110 mg/m2	90 mg/m2	Discontinue
Capecitabine (Xeloda)	625mg/m2 BID	500 mg/m2 BID	375 mg/m2 BID	Discontinue
Epirubicin	50mg/m2	40 mg/m2	discontinue	N/A

Capecitabine treatment may be shortened to 14 days at any currently treated dose level at the discretion of the treating physician based on toxicity assessment. Epirubicin may be excluded from the initial treatment regimen at the discretion of the treating physician, or the starting dose may be reduced to 40 mg/m2 (dose level -1), at the discretion of the treating physician.

If a toxicity is not otherwise specified, investigators should refer to the label or local standard of care for dose adjustments. At the Investigator's discretion, dose modification according to Table 3 is allowed for intolerable Grade 2-3 toxicities that are not specified in the tables below. These dose modification decisions must be documented in the subject's study records.

5.2.1.2.1 Dose Modification for Pembrolizumab

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 4 below. Pembrolizumab will be permanently discontinued for any severe or Grade 3 (grade 2 for pneumonitis) drug-related AE that recurs or any life-threatening event. See Section 5.6 for supportive care guidelines, including use of corticosteroids.

Table 4 Dose Modification Guidelines for Drug-Related Adverse Events for Pembrolizumab

Toxicity	**Hold Treatment For Grade**	**Timing for Restarting Treatment**	**Treatment Discontinuation**
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when patients are clinically and metabolically stable

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

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

[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer to Table 5 Infusion Reaction Treatment Guidelines **Error! Reference source not found.**for further management details.

[c] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

5.2.1.2.2 Dose Modifications for Chemotherapy

Standard of care chemotherapy will be utilized in this protocol and modifications are allowed based on guidance detailed in Table 3 at the discretion of the treating investigator and per standard package instructions. Permanent discontinuation of any agent should be considered for any severe or life-threatening event.

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

5.2.2 Timing of Dose Administration

All trial treatments should be administered in the order presented below on an outpatient basis.

Cycle 1 Day 1:

Study treatment with pembrolizumab must be administered on Day 1 Cycle 1, after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0), followed by oxaliplatin and capecitabine. Chemotherapy may be administered up to 3 days after the scheduled Day 1 of each cycle due to administrative reasons.

Cycle 2 Onwards:

Study treatment with pembrolizumab, followed by oxaliplatin and capecitabine, may be administered up to 3 days before or after the scheduled Day 1 of each cycle for administrative reasons. It is not required that pembrolizumab is given on the same day as IV chemotherapy, but it must be administered before IV chemotherapy is administered in each cycle.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study treatment (e.g., elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects may restart study treatment as soon as clinically appropriate at the Investigator discretion, and not exceeding 3 weeks from the interrupted dosing. Discussion with the Sponsor-Investigator must occur if the Investigator determines a subject cannot restart study medication within 3 weeks. The reason for interruption must be documented in the subject's study record.
Surgical Resection
Should occur 4-6 weeks following the last chemotherapy dose. Tissue will be collected for correlative studies.

Post-operative therapy
Should begin 6-10 weeks following resection. The dose of chemotherapy can be adjusted down 1 level or omitted at the treating physician's discretion. Pembrolizumab may be administered without chemotherapy in the post-operative setting.

5.2.2.1 Pembrolizumab

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

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

5.2.2.2 Chemotherapy Administration

All sites will administer pembrolizumab in combination with epirubicin (when appropriate), oxaliplatin and capecitabine as the combination chemotherapy regimen. Administration of oxaliplatin and epirubicin (when appropriate) should begin on Day 1 of each three week cycle,

as detailed in Table 3 and the Trial Flow Chart (Section 6.0). Administration of capecitabine should begin on Day 1 of each three week cycle following administration of oxaliplatin, as detailed in Table 3 and the Trial Flow Chart (Section 6.0). Please refer to the product label for additional guidance on administration procedures for oxaliplatin, capecitabine, and epirubicin.

5.2.3 Trial Blinding/Masking

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

5.3 Randomization or Treatment Allocation

Subjects participating in this trial will be allocated by non-random assignment.

5.4 Stratification

No stratification based on age, sex, or other characteristics will be used in this trial.

5.5 Concomitant Medications/Vaccinations

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. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor-Investigator and the subject.

5.5.1 Acceptable Concomitant Medications

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

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

5.5.2 Prohibited Concomitant Medications

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

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

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

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

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

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

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

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

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

    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
    - For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
    - For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week**,** treat with intravenous steroids followed by high dose oral steroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
    - For **T1DM** or **Grade 3-4** Hyperglycemia
        - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
        - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- **Hypophysitis**:
    - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

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

- **Hyperthyroidism or Hypothyroidism**:

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

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

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

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

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

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

Table 5 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) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.6.2 Supportive Care Guidelines for Chemotherapy Agents

Pre-infusion supportive care is permitted including administration of corticosteroids per NCCN or institutional guidelines.

Please refer to the product label or local standards of care for additional supportive measures for all chemotherapy agents (oxaliplatin, capecitabine, epirubicin).

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

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

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

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

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

OR

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

OR

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

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

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

OR

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

Acceptable methods of contraception are[‡]:

Single method (one of the following is acceptable):

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

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

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

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

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

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

5.7.3 Use in Pregnancy

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

5.7.4.1 Pembrolizumab

It is unknown whether pembrolizumab is excreted in human milk.

5.7.4.2 Oxaliplatin

It is unknown whether oxaliplatin is excreted in human milk.

5.7.4.3 Capecitabine

Lactating mice given a single oral dose of capecitabine excreted significant amounts of capecitabine metabolites into the milk. It is not known whether capecitabine is excreted in human milk. Subjects receiving capecitabine should not breast-feed.

5.7.4.4 Epirubicin

It is unknown whether epirubicin is excreted in human milk, however other anthracyclines are known to be excreted in breast milk. Subjects receiving epirubicin should not breast-feed.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor-Investigator 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.

Even if a subject discontinues trial treatments, they will be encouraged to continue to participate in collection of data regarding the endpoints, including DFS and OS.

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression or recurrence
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 12 months of uninterrupted treatment with pembrolizumab following surgical resection or 17 administrations of study medication, whichever is later.

  Note: 12 months of study medication is calculated from the date of first dose following surgical resection.

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6.0 (TRIAL 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 or recurrence, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8.1 Discontinuation of Study Therapy after CR

As this is a maintenance trial following complete resection of the primary tumor, it is anticipated that all subjects will continue on therapy for the duration of the post-operative period (52 weeks) even in the absence of disease and even in the event of pathological CR at the time of surgery.

5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced unless the subject discontinued prior to receiving any doses of study medication.

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.

5.11 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	4	+	5	=	9
Not Hispanic or Latino	13	+	16	=	29
Ethnic Category: Total of all subjects	(17)	+	(21)	=	(38)
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	3	+	3	=	6
Black or African American	2	+	4	=	6
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	12	+	14	=	26

Racial Category: Total of all subjects	(17)	+	(21)	=	(38)

6.0 TRIAL FLOW CHART

Table 6 Study Flow Chart

Trial Period:	**Screening Phase**	**Treatment Cycles [a] (3 weeks per cycle)**								**Maintenance Period**	**End of Treatment and Post-Treatment**		
Treatment Cycle/Title:	Main Study Screening Visit 1	1	2	3	4	Surgical Period	5	6	7	8+ (to maximum 17 cycles post-op)	**End of Treatment (last dose) or Dis-continuation**	Safety Follow-up (30 days from last dose)	Survival Follow-Up (phone)
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3		± 3	± 3	± 3	± 3		± 7	Every 12 weeks
Administrative Procedures													
Informed Consent	X												
Informed Consent for FBR [b]	X												
Inclusion/Exclusion Criteria	X												
Demographics and Medical History	X												
Prior and Concomitant Medication Review	X	X	X	X	X		X	X	X	X	X	X	
Clinical Procedures/Assessments													
Review Adverse Events	X	X	X	X	X		X	X	X	X	X	X	
12- Lead ECG	X												
2-D Echo	X												
Full Physical Examination	X						X				X		
Directed Physical Examination		X	X	X	X		X	X	X	X		X	
Ht (V1 only), Wt & Vital Signs (T/P/BP/RR)	X	X	X	X	X		X	X	X	X	X	X	
ECOG Performance Status	X		X	X	X		X	X	X	X	X		
Trial Treatment Administration		X	X	X	X		X	X	X	X			
IV Chemotherapy Administration [c]		X	X	X			X	X	X				
Post-study anticancer therapy status												X	Q12 wks
Survival Status													Q12 wks
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory													

Trial Period:	**Screening Phase**	**Treatment Cycles [a] (3 weeks per cycle)**								**Maintenance Period**	**End of Treatment and Post-Treatment**		
Treatment Cycle/Title:	Main Study Screening Visit 1	1	2	3	4	Surgical Period	5	6	7	8+ (to maximum 17 cycles post-op)	**End of Treatment (last dose) or Dis-continuation**	Safety Follow-up (30 days from last dose)	Survival Follow-Up (phone)
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3		± 3	± 3	± 3	± 3		± 7	Every 12 weeks
Pregnancy Test – Urine or Serum β-HCG [d]	X												
PT/INR and aPTT	X												
CBC with Differential	X	X [e]	X	X	X		X	X	X	X	X	X	
Comprehensive Serum Chemistry Panel	X	X [e]	X	X	X		X	X	X	X	X	X	
Urinalysis	X												
T3, FT4 and TSH	X		X		X		X		X	X[f]	X	X	
Efficacy Measurements													
Tumor Imaging	X				X [g]		X [h]			X [i]			
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood													
Archival or Newly Obtained Tissue Collection	X					X[j]							X [k]
Correlative Studies Blood Collection	X				X						X		

Trial Period:	**Screening Phase**	**Treatment Cycles [a] (3 weeks per cycle)**								**Maintenance Period**	**End of Treatment and Post-Treatment**		
Treatment Cycle/Title:	Main Study Screening Visit 1	1	2	3	4	Surgical Period	5	6	7	8+ (to maximum 17 cycles post-op)	**End of Treatment (last dose) or Dis-continuation**	Safety Follow-up (30 days from last dose)	Survival Follow-Up (phone)
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3		± 3	± 3	± 3	± 3		± 7	Every 12 weeks

a. Unless otherwise specified, assessments/procedures are to be performed prior to dose administration on Day 1 of each cycle.

b. Informed consent for the optional Future Biomedical Research (FBR) samples must be obtained before DNA sample is collected.

c. Refer to Section 5.2.2 regarding window for timing of dose administrations.

d. For women of reproductive potential, a negative pregnancy test should be performed within 72 hours prior to first dose of trial treatment.

e. Laboratory screening tests should be repeated prior to cycle 1 day 1 if the screening labs were performed more than 14 days prior to study treatment.

f. Labs will be collected every other cycle during the maintenance period.

g. First imaging assessment will be performed between at week 11 (+/- 14 days) from study initiation.

h. Second imaging assessment will be performed post-operatively prior to resumption of therapy.

i. Subsequent imaging will be performed every 12 weeks (+/- 7 days) from the timing of the initial post-op imaging test (second imaging assessment).

j. Surgical specimens will be evaluated for pathological response for primary end point analysis.

k. There will be an optional tumor biopsy at the time of disease recurrence.

7.0 TRIAL PROCEDURES

7.1 CUMC Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Subject Eligibility.

Obtain informed consent, by following procedures defined in section 7.2.1.1.1, General Informed Consent, along with applicable institutional policies and federal regulations.

Only Investigators/Research personnel properly trained and delegated to consent subjects for this protocol will participate in the consenting process. Furthermore, properly delegated/trained Physician Investigators (e.g., MD, MD PhD) are required to sign/verify a protocol specific Eligibility Checklist for each subject enrolled on the study, in addition to providing the relevant source documentation confirmation subject eligibility.

All participants must be centrally registered through the Central Registration Office within Herbert Irving Comprehensive Cancer Center at CUMC prior to initiation of study treatment.

Registration hours are available Monday through Friday from 9:00am – 5:00pm EST (excluding holidays and weekends). Same day patient registrations (and after hour registrations) will be accommodated on a case by case basis provided that the study team has expressed all time sensitive registration concerns/cases in a timely manner to the Central Registration Office.

7.1.1 CPDM Central Registration Procedures:

Within 48 hours of obtaining consent (excluding holidays and weekends), a completed/signed IRB approved informed consent HIPAA form, and demographics forms must be submitted to the CPDM Central Registration Office via an email to CPDMRegistration@columbia.edu or fax to 212.305.5292, with the subject line "AAAQ9871 Pending Subject Registration Request (PHI)". Upon receipt, applicable subject information as well as a "pending eligibility" status will be entered into HICCC's institutional database. This status will remain until further source documentation is made available to confirm overall patient eligibility. Required materials for all pending registration submissions are as follows:

- Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (e.g., tissue, DNA, etc.), as applicable.
- The completed/signed IRB approved HIPAA Authorization form
- Completed/signed CPDM ICF checklist
- Completed/signed HICCC personal census form
- Completed/signed CPDM Demographics Note to File

In order to confirm eligibility status, Investigators/designees (e.g., study specific Clinical Research Coordinator/Research Nurse, etc.) must submit the following documentation to the Central Registration Office via email or fax:

- The completed/signed study specific Eligibility Checklist (signed by an Physician level Investigator)

- Copies of source documentation necessary for each item to be verified on the CPDM specific Eligibility Checklist, including but not limited to:

  - Copy of required laboratory test and procedure reports (e.g., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)

  - Copy of pathology and surgical reports

  - Copy of clinic note(s) or other appropriate medical records capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)

  - Protocol deviation/waiver approvals (if applicable)

- **Please note**: subject line of email or fax should include the protocol number followed by: "Complete Subject Registration Request (PHI)".

Upon receipt of the above mentioned documentation, participant eligibility information will be verified by a qualified Central Registration Registrar. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable study team personnel for clarification prior to enrollment. .All applicable finalized registration/eligibility information will then be entered into HICCC's institutional CTMS database by the Central Registration Registrar. Upon completion, an official subject registration notification email will be sent to the PI/research team which will include eligibility/enrollment status, as well as subject ID information. Protocol therapy may not be initiated prior to receipt of this notification from the Central Registration Office.

All screen fail/ineligible subjects, as well as subject's who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

7.2 Trial Procedures

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

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor-Investigator 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.

7.2.1 Administrative Procedures

7.2.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial.

7.2.1.1.1 General Informed Consent

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

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

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

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

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

7.2.1.2 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.

7.2.1.3 Medical History

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

7.2.1.4 Prior and Concomitant Medications Review

7.2.1.4.1 Prior Medications

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

7.2.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.1.4.2.

7.2.1.5 Disease Details and Treatments

7.2.1.5.1 Disease Details

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

7.2.1.5.2 Prior Treatment Details

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

7.2.1.5.3 Subsequent Anti-Cancer Therapy Status

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

7.2.1.6 Assignment of Screening Number

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

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

Interruptions from the protocol specified treatment plan for greater than 12 weeks between pembrolizumab doses in the post-operative setting require consultation between the investigator and the Sponsor-Investigator and written documentation of the collaborative decision on subject management. Any delay in resumption of study related therapy beyond 12 weeks from surgery will also be reviewed in consultation between the investigator and Sponsor-Investigator.

Administration of trial medication will be witnessed by the investigator and/or trial staff while the subject is in the treatment center. Administration of chemotherapy including oral and IV chemotherapy will be administered as per standard practice without additional verification.

7.2.2 Clinical Procedures/Assessments

7.2.2.1 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 13.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 7.3 for detailed information regarding the assessment and recording of AEs.

7.2.2.2 Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed as specified in the Trial Flow Chart. For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to dosing on Day 1 of each treatment cycle.
After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

7.2.2.3 Vital Signs

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

7.2.2.4 12-Lead Electrocardiogram

A standard 12-lead ECG will be performed using local standard procedures once at screening. Clinically significant abnormal findings should be recorded as medical history. Additional time points may be performed as clinically necessary.

Please note that the ECHO is only required for patients receiving Epirubicin.

7.2.2.5 2-D Echocardiogram

A standard 2-dimensional Echocardiogram (TTE) will be performed using local standard procedures once at screening to assess left ventricular ejection fraction (EF) to determine eligibility for Epirubicin chemotherapy. Additional Echocardiograms will be conducted during therapy and as clinically necessary as described in the Trial Flow Chart.

7.2.2.6 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 13.1) at screening, prior to dosing on Day 1 of each treatment cycle (except Cycle 1) and at discontinuation of trial treatment as specified in the Trial Flow Chart.

7.2.2.7 Tumor Imaging and Assessment of Disease

Tumor imaging may be performed by computed tomography (CT) including PET/CT (preferred) or magnetic resonance imaging (MRI), but the same imaging technique, acquisition, and processing parameters should be used in a subject throughout the trial. If PET/CT was used initially it is not required to use PET/CT for each subsequent tumor imaging assessment, CT is sufficient.

Imaging tests will be reviewed locally and tumors will be quantified utilizing RECIST 1.1. All treatment decisions will be made locally by the treating Investigator's radiographic assessment of disease.

7.2.2.7.1 Baseline Tumor Imaging

To meet screening criteria, subjects do not require measurable disease on imaging. However, if subjects have a lesion quantifiable according to RECIST 1.1 criteria, this will be utilized to assess disease response (RR).

Scans performed as part of routine clinical management are acceptable for use as the baseline scan if they are of diagnostic quality and performed within 28 days prior to the first dose of study treatment.

7.2.2.7.2 Tumor Imaging During Trial

The first on-study imaging assessment will be performed 11 weeks after Cycle 1 Day 1 (78 days +/- 14 days) and will be used to assess response to chemotherapy and eligibility for surgery. Imaging may be conducted prior to Cycle 4 dosing (of Pembrolizumab) if clinically indicated as assessed by local routine practice. Subsequent imaging will be performed

following surgical resection and will begin within 7 days of Cycle 5 day 1 (first post-operative cycle) which is expected to not be later than 8 weeks from the time of surgery (65 days +/- 14 days). Beginning from the first post-operative scan, subsequent tumor imaging will be performed every 12 weeks (+/- 7 days).

Imaging should continue to be performed until whichever one of the following occurs first:

- disease progression limiting a subject from surgical resection
- recurrence of disease following surgical resection
- completion of study treatment
- withdrawal of consent
- death
- end of study

Imaging should follow calendar days and not be delayed for any dose interruptions that may occur (except for delays post-operatively).

7.2.2.7.3 Assessment of Disease- RECIST 1.1 and irRECIST

The primary endpoints in this study are recurrence free survival and pathologic surgical response, and not tumor response based on RECIST. In addition due to the neo-adjuvant nature of the study, it is not expected to have confirmatory scans of response prior to surgery. Thus all responses will be unconfirmed and we do not anticipate using irRECIST measurements.

7.2.2.8 Tumor Tissue Collection and Correlative Studies Blood Sampling

Tumor tissue sample may be collected in either formalin solution or FFPE block is acceptable. A fine needle aspirate (FNA) or cytologic specimen will not be acceptable.
Details regarding time points for collection of tumor tissue are outlined in the Study Flow Chart –Section 6.0.

7.2.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below

7.2.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 7.

Table 7 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

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

‡ If considered standard of care in your region.

Laboratory tests for screening should be performed within 14 days of dosing for eligibility. If performed more than 72 hours prior to Cycle 1 Day 1 they should be repeated on Cycle 1 Day 1 prior to the first dose of treatment for treatment decisions but not for eligibility. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results of standard tests must be reviewed by the investigator or qualified designee per local treating guidelines and found to be acceptable prior to each dose of trial treatment.

7.2.4 Other Procedures

7.2.4.1 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 7.3 - Assessing and Recording Adverse Events.

7.2.4.2 Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

7.2.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.2 - Trial Procedures.

7.2.5.1 Screening

Within 28 days prior to expected start of therapy, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Visit requirements are outlines in Section 6.0 – Trial Flow Chart.
Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of trial treatment except for the following:

- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first dose of trial treatment.
- Biopsy collections may be collected up to 42 days prior to the first dose of trial treatment as presented in Section 5.1.1.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met.

7.2.5.2 Treatment Period

As described in Section 6.0- Trial Flow Chart, the study treatment period is divided into the pre-operative period, the post-operative combination period, and the maintenance period.

7.2.5.2.1 Pre-operative Treatment Period

This will begin on Cycle 1 Day 1 and as outlines will include 4 cycles of therapy. The first 3 cycles will consist of combination chemotherapy and Pembrolizumab and the 4th cycle will consist of study treatment alone with Pembrolizumab. Based on previous studies it is anticipated that subjects will proceed to surgery between 4-6 weeks following completion of perioperative chemotherapy (completion of cycle 3). The pre-operative treatment period will complete once a subject proceeds to surgical exploration.

All subjects will remain on study if they have received a single dose of study medication, even if they did not complete the full course of pre-surgical chemotherapy or combination therapy.

7.2.5.2.2 Post-operative Treatment Period

All subjects who have received at least 1 dose of pre-surgery study medication will be included in the post-treatment therapy. Subjects will be re-evaluated by the treating Investigator between 4-8 weeks post-operatively per local practice. It is anticipated that the majority of subjects will be deemed appropriate to begin chemotherapy within 8 weeks of surgery but subjects may be delayed at the discretion of the treating physician. The decision to modify chemotherapy (to omit or dose reduce agents) will also be at the discretion of the treating physician and will be documented in the patient record. If delay in post-operative chemotherapy is anticipated beyond 9 weeks, subjects may begin therapy with Pembrolizumab alone and add chemotherapy with subsequent cycles. No subject will receive more than 3 cycles of chemotherapy following surgery.

Disease assessment with CT (or MRI) will be performed prior to initiation of Cycle 5 Day 1 (within 14 days). The first dose of Pembrolizumab after surgery will be Cycle 5 Day 1 and all subsequent dosing will be based on this date.

7.2.5.2.3 Maintenance Treatment Period

Subjects will continue receiving study drug with Pembrolizumab for up to 17 cycles post-operatively with 21 day cycles. The first 3 cycles will be scheduled to be administered with chemotherapy and 14 subsequent cycles will be given with Pembrolizumab alone. If a subject is not deemed appropriate for chemotherapy (per treating physician) that subject will begin Pembrolizumab alone and may receive chemotherapy subsequently for up to 3 cycles per standard practice. Chemotherapy does not need to be given on the same day as Pembrolizumab (if delayed) but all cycles will follow Pembrolizumab dosing. During this treatment period, subjects will continue receiving disease assessment with imaging at 12 week intervals.

7.2.5.3 Post-Treatment Visits

7.2.5.3.1 Safety Follow-Up Visit

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

7.2.5.3.2 Survival Follow-up

Once a subject experiences confirmed disease progression or completes 17 cycles of post-operative therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.3 Assessing and Recording Adverse Events

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

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

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

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

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 allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

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

7.3.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor-Investigator 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).
- any standard treatment is any dose >/= 20% over the prescribed dose.

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Overdoses of chemotherapy agents (oxaliplatin, capecitabine, epirubicin), will be managed in accordance with the respective product label.

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

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

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

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

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

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

7.3.3.1 Serious Adverse Events

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event

- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
    - Is a new cancer (that is not a condition of the study);
    - Is associated with an overdose.

Refer to Table 8 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation, 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 that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention,

including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

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

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

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

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

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

7.3.3.2 Events of Clinical Interest

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

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

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

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor-Investigator, 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.

7.3.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

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

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

The Sponsor-Investigator will monitor 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 2 working days of determination that the event is not progression of the cancer under study

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

7.3.4 Evaluating Adverse Events

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

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

Table 8 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-Investigator 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-Investigator 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 investigational product; or (3) the trial is a single-dose drug trial); or (4) Investigational 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) Investigational 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-INVESTIGATOR 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.)	

7.3.5 Sponsor-Investigator Responsibility for Reporting Adverse Events

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

7.3.5.1 IRB Notification by Sponsor-Investigator

Reports of all events (including follow-up information) that meet the definition of an unanticipated problem posing risk to subjects or others must be submitted to the IRB within one week (5 business days) following the occurrence of the unanticipated problem or the principal investigator's acquiring knowledge of the unanticipated problem in accordance with IRB policy. Additionally, the sponsor-investigator will submit a summary of all Unanticipated problems that occurred since the beginning of the study at the time of continuing review. Copies of each report and documentation of IRB notification and receipt will be kept in the Regulatory binder.

7.3.5.2 FDA Notification by Sponsor-Investigator

The Columbia University Medical Center Sponsor-Investigator, as holder of the IND, will be responsible for all communication with the FDA. Columbia University Medical Center Principal Investigator will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and there is evidence to suggest a causal relationship between the drug and the adverse event. These must be reported to the FDA and any affiliate sites as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting. The Sponsor-Investigator will also submit an IND annual report to the FDA in accordance with 21.CFR 312.33.

The Columbia University Medical Center Sponsor Investigator must report to the FDA and any affiliate site investigators as follows:

- Any unexpected fatal or life-threatening event must be reported as soon as possible, but no later than 7 calendar days after the sponsor investigator initial receipt of the information
    - Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND, and whether or not conducted by the sponsor-investigator, that suggest a significant risk in humans exposed to the drug must be reported as soon as possible but no later than 15 calendar days after the sponsor-investigator determines that the information qualifies for reporting
    - Any findings from animal or in vitro testing whether or not conducted under an IND, and whether or not conducted by the sponsor-investigator, that suggest a significant risk in humans exposed to the drug must be reported as soon as possible but no later than 15 calendar days after the sponsor-investigator determines that the information qualifies for reporting

- Any clinically important increase in the rate of a serious suspected adverse reactions over that listed in the protocol or Investigator Brochure
- Expected SAEs and AEs will be included in the IND Annual Reports.

Follow-up information to a safety report should be submitted as soon as the relevant information is available. However, if the results of a sponsor's investigation show that an adverse drug experience not initially determined to be reportable are so reportable, the sponsor investigator must report such experience as soon as possible, but no later than 15 calendar days after the determination is made.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

7.3.6 Reporting Process

Adverse events may be submitted on FDA Form 3500A, the HICCC DSMC Serious Adverse Event Reporting Form, or in a narrative format.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

8.1.1 Primary Endpoint

The primary endpoint for this study is pathological complete response (pCR) defined as no invasive disease within an entirely submitted and evaluated gross lesion, and histologically negative nodes (T0N0). The **primary hypothesis** of this study is that combination induction and maintenance therapy including immunotherapy and chemotherapy will result in increased efficacy compared to historical use of chemotherapy alone. This will be achieved by comparing the pathological complete response (pCR) rate at the time of surgery following 3 cycles of pre-operative chemotherapy (with 4 cycles of pembrolizumab) to historical controls. Previous studies have reported low rates of pCR following neoadjuvant therapy with chemotherapy alone for gastric cancer (3% in the FNCLCC and FFCD study[5] and 0% reported in the MAGIC study[2]). Although this is an uncommon finding this novel combination and increase pre-op dosing may increase the pCR rate to 15% or more. Assuming that 28 out of the 38 patients will be evaluable for pCR, we estimate that with 28 patients we will have 80% power to detect an increase in pCR rate from 3% to 15% with a one-sided binomial test with an actual alpha of 0.05. We reject the null that the pCR rate is 3% or less if 3 or more out of the 28 patients respond.

8.1.2 Secondary Endpoint

The secondary endpoints are ORR, DFS and OS. DFS is defined as time from Cycle 1 Day 1 treatment administration to the first documented event of: disease progression, disease recurrence following surgery (preferably biopsy proven), or death- whichever occurs first. Overall Survival (OS): time from Cycle 1 Day 1 treatment administration to death due to any cause.

The secondary hypothesis of this study is that combination therapy with immune checkpoint blockade and chemotherapy used in the perioperative period will eradicate micrometastatic disease and improve disease free survival (DFS).

8.1.3 Exploratory and Ancillary Studies

Gene expression profiles and IHC will be quantified as continuous variables and results will be compared between baseline and surgical specimens (pre therapy and post 12 weeks of combination therapy). We expect that some samples will be inadequate for analysis but anticipate 35 paired specimens. With 35 paired samples of pre and post specimens, we will have 80% power to detect a change of 0.50 standard deviation with a two-sided alpha of 0.05.

We will analyze changes in immune profiles between subjects (prior to and after treatment) using paired t-tests or non-parametric test if the data is not normally distributed. Moreover, we will compare immune profiles (using presence of TILs and PD-L1 expression among other measurements) between those who have a good response (defined as pathCR, or 24 month DFS) to those who do not have a good response. Given that we expect a small number of patients with pathCR, we will compare the data descriptively using summary statistics such as mean, median and ranges.

8.2 Statistical Analysis Plan Details

8.2.1 Efficacy Endpoints

Pathologic complete response (pCR): The number and proportion of subjects with pCR will be reported along with the exact binomial confidence interval. We reject the null that the pCR rate is 3% or less if 3 or more out of the 28 patients achieve pCR.

Disease Free Survival (DFS) and Overall Survival (OS): The Kaplan-Meier method will be used to evaluate all time to event endpoints. Median DFS and OS will be estimated and reported with 95% confidence intervals. Moreover, we will report the estimated DFS at 24 months with 95% confidence intervals.

Overall Response Rate (ORR): The number and proportion of subjects with initial RECIST 1.1 measurable disease who have complete response (CR) or partial response (PR) at any time will be reported along with the exact binomial confidence interval.

8.2.2 Safety Endpoints

The primary safety objective of this trial is to characterize the safety and tolerability of pembrolizumab in combination with chemotherapy in subjects with gastric cancer. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab, including serious adverse events (SAEs) and events of clinical interest (ECIs).

Safety will be assessed by reported adverse experiences using CTCAE, Version 4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific immune-related adverse events (irAEs) will be collected and designated as immune-related events of clinical interest (ECIs) as described in Section 7.3.3.2.

8.2.3 Statistical Methods for Safety Analysis

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, vital signs. Count and percentage of treatment related AEs will be provided. Confidence interval for rate of AE of clinical interest will be estimated using Exact method based on binomial distribution.

8.2.4 Analysis Populations

All subjects who received at least one dose of study treatment will be included in the primary and secondary efficacy and safety analysis.

8.2.5 Measurement of Effect

8.2.5.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with Pembrolizumab.

Evaluable for primary outcome (pCR):

All subjects who receive a single dose of study medication and are eligible will be considered evaluable for the primary outcome of pCR. Patients who discontinue treatment prior to surgery due to reasons other than eligibility (e.g. disease progression, toxicity, or physician discretion) will be considered as not having achieved pCR. For secondary analysis, we will consider not evaluable those who do not have a pathology report for determination of pCR or discontinue treatment prior to surgery due to reasons other than disease progression and toxicity for the estimation of pCR rate.

Evaluable for secondary outcome (RR, DFS, or OS): All subjects who receive a single dose of study medication will be included in the assessment of ORR, DFS, or OS.

Evaluable for objective response: All patients included in the study must be assessed for response to treatment if they have measurable disease at baseline.

8.2.5.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be

recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

8.2.5.3 Response Criteria

8.2.5.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Disease recurrence: is defined as PD (as above) or appearance of a new lesion following surgical resection. Evidence of recurrence will generally require biopsy confirmation and the time of recurrence will be the time that biopsy is positive. In situations in which a biopsy is not feasible or recommend by the treating physician or is declined by the subject, the evidence of recurrence will be confirmed by the review panel (or Principal Investigator).

8.2.5.4 Response Review

All responses will be reviewed by an expert independent of the study at the study's completion. All imaging will be stored at Columbia NYP.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of

investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by Merck as summarized in Table 9.

Table 9 Product Descriptions

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

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

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

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

10.0 ADMINISTRATIVE/ DATA REPORTING AND REGULATORY DETAILS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.3 (Adverse Events: List and Reporting Requirements). The Data Safety Monitoring Plan is described in Section 10.3.

10.1 Data Collection

The Herbert Irving Comprehensive Cancer Center has an electronic clinical trials and data management system (CTMS) that will be used for data collection. CRFs for the study will be built into the CTMS for data entry. The system has full auditing capabilities which is web-based and housed on a server in a fully HIPAA compliant server room with restricted access and video camera monitoring. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials. Users are only able to see study information if they are indicated as study personnel in our electronic IRB system. Users are limited to access based on the role assigned in their corresponding protocol. Subject data is entered directly into the system, which (in the case of Columbia subjects) confirms the correct identity of patients via an interface with the electronic medical patient index. Staff with the appropriate IRB defined roles can run reports within the system for reporting purposes.

10.2 Data Reporting

Case Report Forms will be completed for each subject enrolled into the clinical study through the CTMS. It is the investigator's responsibility for ensuring that all clinical and laboratory data entered on the corresponding CRFs are complete, accurate and authentic.

10.3 Data and Safety Monitoring Committee

The NCI-approved Data Safety and Monitoring Committee (DSMC) of the Herbert Irving Comprehensive Cancer Center (HICCC) will monitor every subject who receives treatment on this protocol for toxicity. This protocol will adhere to the policies of the currently approved HICCC Data and Safety Monitoring Plan (DSMP), which is in accordance with NCI and CUMC-IRB policy and guidelines. The committee is chair is appointed by the HICCC Director. The committee consists of HICCC faculty and staff with expertise in oncology, research pharmacy, research nursing, and data management. The DSMC convenes twice a month to review patient safety and the conduct of the trial. The PI will submit data and safety monitoring reports to the DSMC at a frequency to be determined by the DSMC based on risk to the subjects.

At the time of renewal, the study team will submit the most recent DSMC approval letter for safety review to the CUMC IRB. Any modifications that are required by the DSMC to ensure patient safety will be submitted to the IRB. All protocol deviations, violations, and eligibility waivers will be submitted to and approved by the DSMC prior to being reported to the IRB. All study data reviewed and discussed during these meetings will be kept confidential.

For multicenter research, the principal investigator will assure that there is a mechanism in place to distribute the report to all participating investigators for submission to their local IRB. The report will document that a review of data and outcomes across all centers took place on a given date. It will summarize the DSMC's review of the cumulative toxicities reported from

all participating sites without specific disclosure by treatment arm. It will also inform site investigators of the study the DSMC's conclusion with respect to progress or need for modification of the protocol.

10.4 Quality Control and Quality Assurance

Independent monitoring of the clinical study for protocol and GCP compliance will be conducted periodically by the CPDM Compliance Core on behalf of the HICCC DSMC. Additionally, the Compliance Oversight Committee of the IRB at Columbia University Medical Center may audit the study at any time per institutional policies and procedures. The Sponsor-investigator and Columbia University Medical Center will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

A risk-based approach will be used by the Compliance Core to determine the frequency, number of subject charts, and data elements to be monitored. The Compliance Coordinator will review the study status and summarize enrollment, toxicities, SAEs/UPs, dose escalation, statistical endpoints (e.g., stopping rules), etc. for the full DSMC membership at the regularly scheduled meetings.

Internal On-site Monitoring:

- Initial, recurrent, and close-out on-site monitoring visits will also be conducted at remote clinical sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).
- The study Monitoring Visit Log will be completed and signed by the monitor and the PI/CRNP/CRN and/or CRC and will be filed in the regulatory binder.
- The Compliance Coordinator will communicate with the site coordinator/Site Principle Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.
- The assigned Compliance Coordinator will monitor IIT trials within 1 month after the first subject is enrolled and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible to notify the PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify that the data reported in the CRF's accurately reflect source documents, that all toxicities have been reported to date, and that all SAE's/UPs/deviations/violations have been reported according to local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies as appropriate.

10.5 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (e.g., that the subject is alive) at the end of their scheduled study period.

The subject binders will be maintained with in the CPDM offices, a secured floor within the Herbert Irving Pavilion and only the investigator and study staff will have access to the file.

10.6 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

10.7 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A".

10.8 Records Retention

Records relating to a specific research activity, including research records collected by investigators, must be maintained for at least three years after completion of the research (45 CFR 46.115(b); 21 CFR 56.115(b); 21 CFR 312.62). This minimum retention period applies whether or not any subjects were enrolled in the study.

If the research is FDA regulated, records should be retained for at least two years after approval of the investigational agent by FDA; if it is not approved, records should be retained at least two years after the study is terminated and FDA is notified (note the additional requirement below for clinical research studies);

Clinical records, including consent forms that document clinical intervention or clinical diagnostic procedure research-related procedures, must be retained in medical records by the institution for at least seven years, per CUMC and NYP policy which is based on state law.

10.9 Ethical Considerations

10.9.1 Institutional Review Board or Ethics Committee Approval

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. The study will be conducted in accordance with FDA, applicable national and local health authorities, and IRB requirements.

The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, the IRB must be updated at least once a year. The Principal Investigator must also keep the IRB informed of any significant AEs.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to SAEs that are not already identified in the Investigator's Brochure and that are considered possibly or probably related to the molecule or study drug by the investigator. Some IRBs may have other specific AE requirements to which investigators are expected to adhere. Investigators must immediately forward to their IRB any written safety report or update provided by Genentech (e.g., IND safety report, Investigator's Brochure, safety amendments and updates, etc.).

10.10 Study Finances

10.10.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the Columbia University Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved prior to participation in this study. All CUMC investigators will follow the University conflict of interest policy. Other investigators will be required to follow conflict of interest policies at their respective institutions.

10.10.2 Subject Stipends or Payments

No payments will be made to study subjects.

10.11 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-Investigator 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.

11.0 PROTECTION OF HUMAN SUBJECTS

This study is to be conducted in accordance with applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be obtained before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, as outlined in the IRB approved protocol, and the investigator-designated research professional obtaining the consent.

12.0 PUBLICATION PLAN

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study. The study drug manufacturers reserve the right to review all manuscripts prior to submission for publication.

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)

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

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

* As published in the European Journal of Cancer[27].

13.4 Guidelines for Affiliate Institutions in Multicenter Studies

1. Multi-site Communication:

The CPDM Office at CUMC provides administration, data management, and organizational support for the affiliate sites in the conduct of a multicenter clinical trial. The CPDM Office will coordinate, at minimum, regularly scheduled conference calls with affiliate sites.
The following issues will be discussed, as appropriate:

- Enrollment information

- Cohort updates (e.g., DLTs)
- Adverse events (e.g., new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study

2. New Protocol Distribution, IRB Submission, Modifications, and Annual Renewals

- Protocol specific documents are distributed to affiliate sites once CUMC IRB approval has been obtained.
- The affiliate site must submit a draft of site specific revisions to protocol and/or consent form documents for review and approval by the sponsor-investigator prior to submission to the local IRB. Draft documents should be sent to the study specific email address. The site will be provided confirmation that they are approved to submit to their local IRB.
- Protocol amendments must be approved by the affiliate site's local IRB within 90 days of distribution to the site by the sponsor-investigator.

3. Regulatory Documents:

Prior to Site Initiation:

Sponsor-Investigator will ensure that proper requests are made of sites and that the following documentation is collected, prior to the initiation of an affiliate site.

- CV of PI, Co-I's and other research staff listed on FDA 1572 (signed and dated copy within 2 years)
- Medical Licenses of PI and Co-I's (current copy)
- Human subjects training certificates for PI and Co-I's
- CLIA/Laboratory Certifications for Local Laboratories listed on FDA 1572
- Local Laboratory Director's CV and License
- Local Laboratory Reference Ranges
- IRB roster or statement of compliance
- FDA Form 1572, if applicable (wet ink originals required)
- Financial Disclosure forms for all members listed on FDA 1572 (wet ink originals required)

Ongoing Regulatory Documentation: Sponsor-Investigator will ensure that proper requests are made of sites and that the following documentation is collected throughout the course of the study.

- IRB approval letters for all protocol modifications and all renewals
- IRB-approved consent forms

- Current IRB roster, if statement of compliance is not provided as part of site initiation
- FDA Form 1572, if applicable as updates are required
- Updated investigator and site information where relevant (e.g., CV, medical licensure and Financial Disclosure for new sub-investigator, local laboratory information)

Regulatory documents may be sent to Q9871@columbia.edu or to the following address if wet ink originals are required:

Clinical Protocol & Data Management Office
161 Fort Washington Ave.
Herbert Irving Pavilion
Mezzanine Level, M-203
New York, NY 10032

4. Site activation

Columbia University will schedule a site initiation visit once IRB approval has been submitted from the affiliate site.

5. Central Registration Procedures- Affiliate Institution Research Participant Registration Process:

All Affiliate Institutions **must** register subjects with the coordinating center (CUMC) **prior** to any administration of study drug/intervention/local institution registration. Please see instructions below:

1. Within 48 hours of obtaining consent (excluding holidays and weekends), the Affiliate Institution CRN and/or CRC is required to submit the following documents to the coordinating center's designee (CUMC's study specific Clinical Research Coordinator or Clinical Research Nurse). The coordinating center's designee will review the documents for accurateness, and subsequently submit the documents to the CPDM Central Registration Office via email at Q9871@columbia.edu (or via fax at 212.305.5292), with a request to register the patient "pending eligibility." The title of the email should read, "AAAQ9871 Pending Subject Registration Request (PHI)". The following documents should be submitted with the pending registration request, as applicable:
    a. Redacted Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (e.g., tissue, DNA, etc.), as applicable
    b. Redacted Signed HIPAA (or institutional equivalent)
    c. MCT CPDM Velos Note to File form
2. The Affiliate Institution's investigator/research nurse/data manager/coordinator must contact the coordinating center's designee (CUMC's study specific Clinical Research

Coordinator or Clinical Research Nurse) via telephone or email to communicate the following:

- Notify of pending registration request
- Confirm method of registration request submission (email or fax)
- Communicate expected time-line of registration request submission (e.g., same day, next day, within the hour, etc.)

3. To complete registration, the Affiliate Institution's investigator/research nurse/data manager/coordinator should then submit the following documents to the CUMC study specific designee:
   - A signed Affiliate Site Eligibility Checklist (signed by the investigator)
   - Copies of redacted source documentation necessary for each item to be verified on the CUMC specific Eligibility Checklist, including but not limited to:
     - Copy of required laboratory test and procedure reports (e.g., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)
     - Copy of pathology and surgical reports
     - Copy of clinic note(s) capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms. (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)
     - Protocol deviation/waiver approvals (if applicable)
   - **Please note**: subject line of email or fax should include the following: "AAAQ9871 Complete Subject Registration Request (PHI)".
4. Upon receipt of the above mentioned documents, the designated study specific Clinical Research Coordinator will review all documents and verify patient eligibility. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable affiliate site study team personnel for clarification prior to enrollment. Upon verification, the CUMC study specific designee will then forward all documents to the CPDM Central Registration Office for central registration (as described above). The CPDM Central Registration Registrar will review all applicable documents and communicate to the CUMC study specific designee in order to clarify any items. The CUMC study specific designee will communicate with the applicable site study team personnel for additional clarifications necessary prior to enrollment.
5. Upon receipt of the subject registration notification email, the CUMC study specific designee will forward the notification email (which will include the study specific patient ID) to the affiliate site's Principal Investigator, Consenting Professional, and applicable research personnel. This notification should be filed in the patient research binder accordingly. Protocol therapy **may not** be initiated prior to receipt of this notification from the coordinating center.

6. All screenfail/ineligible subjects, as well as subject's who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration Office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

6. Protocol Deviation/Subject Waiver request for Affiliate Sites:

The Affiliate site MUST submit a prospective deviation request to the CUMC lead PI for review and submission to the HICCC DSMC and CUMC IRB. Approvals must be obtained from all entities prior to implementation at the Affiliate site. If a prospective protocol deviation request is submitted for review (from an Affiliate site), the PI/site memo(s), HICCC DSMC approval(s) and correspondence and CUMC IRB eligibility deviation approval letter(s) should be forwarded to the Affiliate site for documentation. The Affiliate site is also required to obtain prospective local IRB approval as per institutional policies/procedures prior to implementing the proposed deviation and registering/enrolling the subject via CUMC Central Registration. All documents and determinations must be clearly documented in the study subject's medical record, research chart and regulatory binder, as described.

7. Guidelines for Affiliate Site Monitoring

On-Site MCT Monitoring:

1. Initial, recurrent, and close-out on-site monitoring visits will also be conducted at Affiliate sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).
    a. The study Monitoring Visit Log will be completed and signed by the monitor and the PI/CRNP/CRN and/or CRC and will be filed in the regulatory binder.
2. The Compliance Coordinator will communicate with the Affiliate site coordinator/Site Principle Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.
3. The Compliance Coordinator will monitor IIT trials within 1 month after the first subject is enrolled at the Affiliate site and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible to notify the participating site PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify that the data reported in the CRF's accurately reflect source documents, that all toxicities have been reported to date, and that all SAE's/UPs/deviations/violations have been reported according to Coordinating Center, local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies as appropriate.

4. An SIV (or) teleconference will be scheduled and conducted prior to study drug being made available (if applicable) and before any subjects are enrolled on a study at the Affiliate site.

MCT Remote Monitoring:

- When necessary (due to logistical constraints), Affiliate sites will be monitored remotely by a designated Compliance Coordinator. Sites will be informed of this remote monitoring process on a site by site basis.
- Affiliate sites will be monitored by the Compliance Coordinator on both a regulatory level, as well as a clinical data/source documentation review level.
- Redacted source documents (applicable to supporting the protocol specific CRF data requirements) will be sent to the designated Compliance Coordinator via fax or secure email for all subjects enrolled at Affiliate sites. Timelines for submission procedures will be defined on a case by case basis.
- The Compliance Coordinator will review all submitted redacted source documents against the data entered on the protocol specific CRFs. The Compliance Coordinator will issue queries when/if necessary.
- The Affiliate site research staff will respond to queries within 30 days. If queries remain outstanding, the Compliance Coordinator will send a delinquent query reminder for the outstanding items.
- The remote monitoring procedures will include review of applicable redacted source documentation and supporting applicable documents to determine compliance regarding:
    a. Informed consent procedures
    b. Eligibility criteria
    c. Protocol specific treatment compliance
    d. Protocol specific toxicity/outcome documentation/compliance
    e. Protocol specific schedule of events (e.g., baseline visits, pre-treatment, on study, follow-up)
    f. Participating site IRB documents (e.g., IRB amendment approvals, annual renewals, SAE/UP submissions, violation/deviation submissions, INDSR submissions, etc).
    g. Required specimen submissions (e.g., tissue specimens, research blood specimens, etc.)
    h. Pharmacy accountability records
    i. Adherence to the CRF submission timeframes to CUMC (within the protocol specified timeframes)
- Affiliate site remote monitoring reports will be sent to the lead PI, HICCC DSMC, and Affiliate sites after each remote monitoring review. Reports will include information regarding data submission timeliness/accuracy, protocol adherence items, query resolution status, regulatory status, and overall Affiliate site performance. These reports will be generated by the Compliance Coordinator and reviewed with the Compliance Core Manager prior to dissemination.

8. Dose Level Determinations:

The sponsor-investigator will review enrollment for each dose level cohort during the regularly scheduled conference call with the affiliate sites.
The dose level for newly enrolled subjects will be determined by the study statistician upon notification that a subject has signed informed consent to participate in the study. The assigned dose level for any subject to begin study treatment will be communicated to the affiliate site along with the determination by Central Registration that the subject is eligible for enrollment in the study.
If a Dose Limiting Toxicity (DLT) is identified in a subject, the affiliate site must notify the sponsor-investigator via email at the study specific email address within 1 business day of identification. The lead site will communicate that a DLT has been experienced within 1 business day.

9. Adverse event reporting

Sponsor reporting: Notifying participating investigators at affiliate sites of adverse events

It is the responsibility of the study sponsor to notify all affiliate sites, in a written IND safety report, of any adverse event associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects. Additionally, sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Serious Adverse Event Reporting

Each participating investigator is required to abide by the reporting requirements set by Columbia University Medical Center. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Participating investigators must report each serious adverse event to the Columbia University Medical Center Overall Principal Investigator within 24 hours of learning of the occurrence using the SAE Report Form. In the event that the participating investigator does not become aware of the serious adverse event **immediately** (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Gulam Manji, MD., PhD.
161 Fort Washington Ave
New York, NY 10032
Telephone: 212 305 0592
Email address: gam2140@cumc.columbia.edu

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the

event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow- up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject **continued** or withdrew from study participation or if study drug was interrupted or discontinued.

If the SAE is not previously documented in the Investigator's Brochure for the study drug (new occurrence) and is thought to be related to the investigational agent, the sponsor-investigator may urgently require further information from the investigator for reporting to Health Authorities.

Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the Columbia University Medical Center Overall Principal Investigator on the toxicity Case Report Forms.

Reporting to the Institutional Review Board (IRB) and the Data and Safety Monitoring Committee:

All Unanticipated Problems (UPs) will be reported to the CUMC IRB. SAEs not constituting UPs will reported to the HICCC DSMC.

Each affiliate site will be responsible for safety reporting to their local IRB. Investigators are responsible for complying with their local IRB's reporting requirements, though must submit the required reports to their IRB no later than 7 calendar days following the occurrence of the UP or the Principal's Investigator's acquiring knowledge of the UP. Copies of each report and documentation of IRB notification and receipt must be included in the regulatory binder.

Expected AEs must be reported at the time of continuing review of a protocol.

Guidelines for Processing IND Safety Reports

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. The CUMC Principal Investigator will review all applicable IND Safety Reports and has the responsibly for forwarding the IND Safety Reports to the Affiliate Institutions. The Affiliate Institution investigators are to review, send a copy to their IRB according to their local IRB's policies and procedures, and file a copy with their regulatory documents. All Affiliate site INDSR submissions, along with IRB acknowledgment (per local policies and procedures) are to be forwarded to CUMC for placement within the trial master file.

Reporting to Hospital Risk Management

Affiliate Site investigators will report to their local Risk Management Office any subject safety reports or sentinel events that require reporting according to institutional policy.

10. Confidentiality

Each affiliate site will be assigned a site number. Each subject that signs consent should be assigned a unique code number consisting of site number followed by a number with each new subject being assigned the next sequential number (e.g., 04-10). All sites will be required to enter their data in the Velos eResearch, the Clinical Trial Management System used for all Cancer-related clinical research at CUMC. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials.

Subject confidentiality must be maintained according to HIPAA regulations and GCP recommendations.

Except when required by law, study information shared with persons and organizations outside of Columbia University Medical Center must not identify the patient by name, social security number, address, telephone number, or any other direct personal identifier.

If the results of this research project are published or presented at a scientific or medical meeting, the patient not be identified. Otherwise, all results will be kept confidential and will not be divulged (except as required by law) without permission.

11. Data Reporting Plan

Columbia University Medical Center (CUMC) is deeply committed to research integrity and strong credibility when it comes to the discovery of new treatment concepts, implementation of new clinical research techniques, and acceptance of its researcher's findings by the medical establishment. In accord with these ethics, CUMC encourages and supports its investigators in the sharing of final research data and/or details of newly developed clinical treatments.

CUMC's policies that pertain to patient data sharing conform to CUMC IRB rules, local and state laws, and HIPAA privacy regulations. The primary reason for this is to protect the privacy of patients who participate in clinical trials. The data can be made available for continuing review by federal agencies upon request and for ongoing study safety reviews by the Principal Investigator, Statistician, Data Safety and Monitoring Board (DSMC), and, in other instances, the CUMC IRB.

Data collected during the course of this clinical trial will primarily be shared with other investigators and University staff, the IRB, FDA, and other reporting agencies, and/or transferred to other collaborators. Prior to transfer, the data collected must comply with, and must be limited by, the CUMC's guidelines for Protecting the Rights and Privacy of Human Subjects.

12. Data Acquisition and Submission

Informed consent, including HIPPA authorization, must be obtained on all subjects prior to their participation. Always keep the original signed and dated consent form, with the redacted source documents and eligibility checklist. Velos eResearch will be used as the electronic clinical trials and data management system. Affiliate sites will enter data directly into Velos eResearch via customized case report forms for the study. The research staff will generate reports from Velos eResearch to ensure timely submission of data by affiliate sites. This resource allows for the timely analysis of particular data sets for safety analysis.

13. **Record Keeping and Record Retention**

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.
Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, CHR correspondence and approval, signed patient consent forms). Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.
In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

14.0 LIST OF REFERENCES

1. Siegel, R.L., Miller, K.D. & Jemal, A. Cancer statistics, 2015. *CA: a cancer journal for clinicians* **65**, 5-29 (2015).
2. Cunningham, D.*, et al.* Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *The New England journal of medicine* **355**, 11-20 (2006).
3. Davies, A.R.*, et al.* Tumor Stage After Neoadjuvant Chemotherapy Determines Survival After Surgery for Adenocarcinoma of the Esophagus and Esophagogastric Junction. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* (2014).
4. Fields, R.C.*, et al.* Recurrence and survival after pathologic complete response to preoperative therapy followed by surgery for gastric or gastrooesophageal adenocarcinoma. *British journal of cancer* **104**, 1840-1847 (2011).
5. Ychou, M.*, et al.* Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter

phase III trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **29**, 1715-1721 (2011).
6. Callahan, M.K. & Wolchok, J.D. At the bedside: CTLA-4- and PD-1-blocking antibodies in cancer immunotherapy. *Journal of leukocyte biology* **94**, 41-53 (2013).
7. Gros, A.*, et al.* PD-1 identifies the patient-specific CD8(+) tumor-reactive repertoire infiltrating human tumors. *The Journal of clinical investigation* **124**, 2246-2259 (2014).
8. Wu, C.*, et al.* Immunohistochemical localization of programmed death-1 ligand-1 (PD-L1) in gastric carcinoma and its clinical significance. *Acta histochemica* **108**, 19-24 (2006).
9. Robert, C.*, et al.* Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. *Lancet* (2014).
10. Disis, M.L. Immune regulation of cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **28**, 4531-4538 (2010).
11. Dong, H.*, et al.* Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nature medicine* **8**, 793-800 (2002).
12. Sharpe, A.H. & Freeman, G.J. The B7-CD28 superfamily. *Nature reviews. Immunology* **2**, 116-126 (2002).
13. Brown, J.A.*, et al.* Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. *Journal of immunology* **170**, 1257-1266 (2003).
14. Thompson, R.H.*, et al.* PD-1 is expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. *Clinical cancer research : an official journal of the American Association for Cancer Research* **13**, 1757-1761 (2007).
15. Talmadge, J.E., Donkor, M. & Scholar, E. Inflammatory cell infiltration of tumors: Jekyll or Hyde. *Cancer metastasis reviews* **26**, 373-400 (2007).
16. Hodi, F.S. & Dranoff, G. The biologic importance of tumor-infiltrating lymphocytes. *Journal of cutaneous pathology* **37 Suppl 1**, 48-53 (2010).
17. Lee, H.E.*, et al.* Prognostic implications of type and density of tumour-infiltrating lymphocytes in gastric cancer. *British journal of cancer* **99**, 1704-1711 (2008).
18. Leffers, N.*, et al.* Prognostic significance of tumor-infiltrating T-lymphocytes in primary and metastatic lesions of advanced stage ovarian cancer. *Cancer immunology, immunotherapy : CII* **58**, 449-459 (2009).
19. Hiraoka, N. Tumor-infiltrating lymphocytes and hepatocellular carcinoma: molecular biology. *International journal of clinical oncology* **15**, 544-551 (2010).
20. Polcher, M.*, et al.* Foxp3(+) cell infiltration and granzyme B(+)/Foxp3(+) cell ratio are associated with outcome in neoadjuvant chemotherapy-treated ovarian carcinoma. *Cancer immunology, immunotherapy : CII* **59**, 909-919 (2010).
21. Okazaki, T., Maeda, A., Nishimura, H., Kurosaki, T. & Honjo, T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. *Proceedings of the National Academy of Sciences of the United States of America* **98**, 13866-13871 (2001).
22. Muro, K.*, et al.* Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. *The Lancet. Oncology* **17**, 717-726 (2016).

23. Al-Batran, S.E., et al., *Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial.* Lancet Oncol, 2016. **17**(12): p. 1697-1708.
24. Cancer Genome Atlas Research, N. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* **513**, 202-209 (2014).
25. Cunningham, D.*, et al.* Capecitabine and oxaliplatin for advanced esophagogastric cancer. *The New England journal of medicine* **358**, 36-46 (2008).
26. Gou, H.F., Huang, J., Shi, H.S., Chen, X.C. & Wang, Y.S. Chemo-immunotherapy with oxaliplatin and interleukin-7 inhibits colon cancer metastasis in mice. *PloS one* **9**, e85789 (2014).
27. Pfirschke, C.*, et al.* Immunogenic Chemotherapy Sensitizes Tumors to Checkpoint Blockade Therapy. *Immunity* **44**, 343-354 (2016).
28. Eisenhauer, E.A.*, et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *European journal of cancer* **45**, 228-247 (2009).
29. von Minckwitz, G., et al., *Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials.* Breast Cancer Res Treat, 2011. **125**(1): p. 145-56.
30. Houssami, N., et al., *Meta-analysis of the association of breast cancer subtype and pathologic complete response to neoadjuvant chemotherapy.* Eur J Cancer, 2012. **48**(18): p. 3342-54.
31. Maas, M., et al., *Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data.* Lancet Oncol, 2010. **11**(9): p. 835-44.
32. Petrelli, F., et al., *Correlation of pathologic complete response with survival after neoadjuvant chemotherapy in bladder cancer treated with cystectomy: a meta-analysis.* Eur Urol, 2014. **65**(2): p. 350-7.
33. Becker, K., et al., *Histomorphology and grading of regression in gastric carcinoma treated with neoadjuvant chemotherapy.* Cancer, 2003. **98**(7): p. 1521-30.
34. Cho, H., et al., *Long-term survival outcomes of advanced gastric cancer patients who achieved a pathological complete response with neoadjuvant chemotherapy: a systematic review of the literature.* Ann Surg Oncol, 2015. **22**(3): p. 787-92.
35. Li, Z., et al., *Correlation of pathological complete response with survival after neoadjuvant chemotherapy in gastric or gastroesophageal junction cancer treated with radical surgery: A meta-analysis.* PLoS One, 2018. **13**(1): p. e0189294.
36. Wan, T., et al., *The Prognostic Value of a Pathologic Complete Response After Neoadjuvant Therapy for Digestive Cancer: Systematic Review and Meta-Analysis of 21 Studies.* Ann Surg Oncol, 2019. **26**(5): p. 1412-1420.
37. Tomasello, G., et al., *Tumor regression grade and survival after neoadjuvant treatment in gastro-esophageal cancer: A meta-analysis of 17 published studies.* Eur J Surg Oncol, 2017. **43**(9): p. 1607-1616.