A Single Arm, Phase II Study of Pembrolizumab, Oxaliplatin, and Capecitabine in the First Line Treatment of Patients with Gastro-esophageal Cancer (KeyLARGO)

Trial: NCT03342937

Protocol

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DUKE CANCER INSTITUTE

A National Cancer Institute-designated Comprehensive Cancer Center

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PROTOCOL SYNPOSIS

Title

A Single Arm, Phase II Study of Pembrolizumab, Oxaliplatin, and Capecitabine in the First Line Treatment of Patients with Gastro-esophageal Cancer (KeyLARGO)

Objectives

Primary Objective

1. To describe the progression free survival (PFS) associated with the combination of pembrolizumab, oxaliplatin and capecitabine (pembro+XELOX) in all patients with previously untreated metastatic esophagogastric adenocarcinoma.

Secondary Objectives

1. To describe the safety and tolerability of the combination of pembro+XELOX in patients with metastatic esophagogastric adenocarcinoma.
2. To describe the response rate (RR) and overall survival (OS) of the combination of pembro+XELOX in patients with previously untreated metastatic esophagogastric adenocarcinoma.

Exploratory Objectives

1. To explore the changes in CD8 and PDL1 expression in tumor tissue related to pembrolizumab treatment.
2. To explore other changes in tissue and blood based biomarkers and their correlation with clinical outcomes.
3. To explore changes in immune cells and biomarkers in those who completed treatment and remain in complete response.

Patient Population

Histologically and/or cytologically documented and radiographically measurable (by RECIST 1.1) adenocarcinoma of the esophagus or stomach (HER2 negative) that is metastatic/recurrent and not amenable to potentially curative treatment (e.g., inoperable metastatic or locally recurrent disease). HER2 positive patients would be considered eligible only if there is a contraindication to Herceptin.

Study Design

The study will be conducted in two stages: 1) safety validation and 2) dose expansion.

1. Safety Validation Cohort: The first portion of the study will preliminarily establish the tolerability of the combination of pembrolizumab, oxaliplatin and capecitabine. Five (5) patients will be enrolled and their safety data after 21 days of treatment will be reviewed before additional patients are enrolled. Subjects on this portion of the study will only be enrolled at the Duke Cancer Institute.

2. Dose Expansion Cohort: The second portion of the study (ie. phase II) will enroll 30 patients. In the dose expansion cohort, the first cycle will be modified to allow one week of pembrolizumab monotherapy before starting capecitabine and oxaliplatin (XELOX) chemotherapy, which will allow analysis of biomarkers related to pembrolizumab. Subjects on this portion of the study will be enrolled at the Duke Cancer Institute and select external collaborating institutions.

Number of Subjects

In the Safety Validation Cohort, 5 evaluable subjects will be enrolled.

In the Dose Expansion Cohort, 30 evaluable subjects will be enrolled.

A total of 35 evaluable subjects will be accrued to this study to assess the efficacy, safety and tolerability of the combination of pembrolizumab, oxaliplatin and capecitabine.

Estimated Length of Study Participation

Estimated duration of subject enrollment is 12 months.

Patients will continue to receive study treatment until they experience unacceptable drug-related toxicity or disease progression. The maximum duration of treatment for pembrolizumab will be up to two years. The duration of treatment for XELOX will be until unacceptable drug-related toxicity or disease progression.

Subjects who discontinue study treatment for any reason (e.g., toxicity) other than disease progression should be followed until documented disease progression or start of a new anti-cancer therapy. All subjects will be followed for survival until death, loss to follow-up, or study completion.

Study completion is 3 years after the last subject starts study drug regimen.

Study Drug Regimen

In the Safety Validation Cohort, the cycle length is 21 days. Patients will receive pembrolizumab and oxaliplatin on day 1 of each cycle. Capecitabine will be taken twice per day on days 1-14 of each cycle. Patients will continue to receive study treatment until they experience unacceptable drug-related toxicity or disease progression.

In the Dose Expansion Cohort (ie. phase II), the first cycle of treatment, referred to as ‘biomarker cycle,’ will be modified to allow assessment of biomarkers related to pembrolizumab; the length will be 28 days. Patients will receive pembrolizumab monotherapy on Cycle 1 Day 1. Treatment with oxaliplatin and capecitabine will begin on Cycle 1 Day 8; capecitabine will be dosed for 14 days (ie. Days 8-21), followed by one week off drug (ie. Days 22-28). Cycle 2 will start on Day 29 of study (ie. 28 days after pembrolizumab monotherapy and 20 days after start of capecitabine and oxaliplatin). For cycles 2 and beyond, the cycle length is 21 days, with a treatment window of +/-3 days allowed for day 1. Patients will receive pembrolizumab and oxaliplatin on day 1 of each cycle. Capecitabine will be taken twice per day on days 1-14 of each cycle. Patients will continue to receive study treatment until they experience unacceptable drug-related toxicity or disease progression.

For both cohorts, patients will continue to receive study treatment until they experience unacceptable drug-related toxicity or disease progression. The maximum duration of treatment for pembrolizumab will be up to two years (35 cycles). The duration of treatment for capecitabine and oxaliplatin will be until unacceptable drug-related toxicity or disease progression. Patients who complete 35 cycles of therapy and have complete response or prolonged stable disease may also elect to end therapy with capecitabine, after a discussion with their treating physician.

Study Assessments

Toxicity will be assessed at every visit using NCI-CTCAE version 4.0. Safety assessments will be performed weekly during the first cycle, then every three weeks thereafter. Safety assessments will include vital signs, ECOG performance status, medical history, physical examination, review of concomitant medications, CBC with differential, and chemistries with liver function tests. Symptom management and supportive care will be provided as clinically indicated to ensure optimal patient care. After discontinuation of study treatment, subjects will have safety assessments 30 days after the last dose of study drug. All subjects will then be followed by telephone or medical record review for survival.

Tumor Assessments

Restaging scans and blood tumor markers will be repeated every three cycles. Tumor response will be assessed using RECIST 1.1 and irRC.

Correlative Studies

The association between biomarker expression and clinical outcomes will be explored with the following blood and tumor tissue specimen collections and specified time points from all subjects:

- *Tumor Tissue*. If available, archived FFPE tumor samples will be obtained from all subjects at baseline and at end of study. In the biomarker cycle (ie. Cycle 1) of the Dose Escalation Cohort, pre-treatment (up to 1 week before starting treatment) and on-treatment (prior to start of oxaliplatin and capecitabine) tumor biopsies will be completed on patients who have lesions amenable to safe biopsy. Subjects in the Dose Escalation Cohort who are not amenable to safe biopsy will only have blood based biomarker collections in the biomarker cycle (ie. Cycle 1).
- *Circulating Immune Cells*. Subjects will have peripheral blood mononuclear cells (PBMC) collected at baseline, at the end of monotherapy lead-in on Day 8 (biomarker cycle of Dose Expansion Cohort only), at end of first cycle of combination therapy on Day 29 (biomarker cycle of Dose Expansion Cohort only), at first restaging, at disease progression or off treatment and complete responders on long term follow-up.
- *Circulating Proteins*. Subjects will have plasma collected at baseline, at the end of monotherapy lead-in on Day 8 (biomarker cycle of Dose Expansion Cohort only), at end of first cycle of combination therapy on Day 29 (biomarker cycle of Dose Expansion Cohort only), at every restaging, at progression or off treatment, at off treatment follow-up, and complete responders on long term follow-up.
- *Pharmacogenomics*. Subjects will have whole blood collected at baseline.

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1.0 INTRODUCTION

1.1 Background

Gastric cancer is the fourth most common cancer worldwide, with over 700,000 confirmed deaths annually[1]. In the United States, approximately 21,000 new cases are registered annually[2]. At presentation, nearly 50% of patients diagnosed with gastric or gastro-esophageal cancer have unresectable disease that is locally advanced or metastatic. Life expectancy in this setting is unfortunately short, usually less than nine months.

Chemotherapy is the main treatment option for patients with advanced disease, and chemotherapy has been shown to prolong survival and improve symptoms compared to best supportive care alone[3]. Traditional first line options include the doublet of capecitabine and cisplatin. This doublet has been used as the consensus international standard for two recently reported phase III studies: (1) capecitabine/cisplatin +/- trastuzumab for HER2 positive gastro-esophageal cancer (ToGA trial)[4], and (2) capecitabine/cisplatin +/- bevacizumab (AVAGAST trial)[5]. Two triplet regimens are also considered standard options. One of these regimens includes docetaxel, cisplatin, and 5-FU (DCF regimen), which was found to have superior outcomes compared to CF alone (TAX 325 trial)[6]. A second triplet regimen includes epirubicin, cisplatin and 5-FU (ECF regimen), a combination that was found to be superior to multiple doublets in a meta-analysis[7]. In the REAL-2 study, a variation of ECF known as EOX was shown to be non-inferior, with a modest trend for superior activity and tolerability[8]. EOX replaces cisplatin with oxaliplatin and 5-FU with capecitabine (Xeloda®). These triplet regimens, however, are often poorly tolerated, which is why the doublet of capecitabine/oxaliplatin is often used as a first line treatment for advanced gastric cancer in the United States. This combination is considered “preferred” by the NCCN Gastric Cancer Guideline committee[17].

Cancers have genetic and epigenetic alterations that may be detectable by the immune system. The endogenous immune response to such alterations provides an attractive anti-tumor strategy by which to target cancers. However, tumors develop multiple resistance mechanisms and can also actively evade immune destruction. One mechanism by which tumors can survive is by escaping endogenous “immune checkpoints” that are involved in terminating immune responses following antigen stimulation. Programmed death ligand 1 and 2 (PD-L1 and PD-L2) are ligands for PD-1, a co-inhibitory receptor on T cells, and the interaction between PD-L1 and PD-1 inhibits T-cell proliferation, cytokine production, and cytolytic activity. PD-1 expression in CD4+ and CD8+ T cells from the peripheral blood of patients with gastric cancer is higher than that from CD4+ and CD8+ T cells from normal controls; this increased expression has been related to disease progression[9]. PD-L1 expression is present in many human tumors (e.g., lung, ovarian, melanoma, and colon carcinoma); elevated PD-L1 expression results in tumor cell evasion of the host’s immune system and a worse prognosis[10-13]. Blockade of this axis has been shown to induce durable tumor regression and prolonged stabilization of disease in patients with advanced cancers, including non-small cell lung cancer (NSCLC), melanoma, and renal cell cancer[10].

Pembrolizumab (MK-3475) is the first humanized monoclonal anti-PD-1-antibody, FDA-approved in September 2014 for the treatment of advanced or unresectable melanoma refractory to other therapies. In the KEYNOTE-001 phase Ib study evaluating pembrolizumab as monotherapy in 411 patients with advanced melanoma, the estimated one-year overall survival was 69% for all patients, 74% for ipilimumab-naïve patients, and 65% for ipilimumab-refractory patients. The median progression-free survival was 5.5 months, and the median overall survival has not yet been reached. Of the patients who

responded to pembrolizumab, 88% had ongoing responses at a median follow-up of 12 months, and some patients receiving pembrolizumab have been on treatment for more than two years. The most common adverse events of any grade were fatigue (36%), pruritis (24%), rash (20%), diarrhea (16%), and arthralgia (16%). The most common grade 3 or 4 treatment-related adverse event reported was fatigue (2%), but no specific adverse event affected more than 1-2% of patients, and only 4% of patients discontinued treatment due to a drug-related side effect. Taken together, pembrolizumab is an anti-PD-1 antibody with a favorable side effect profile that has utility in patients with advanced melanoma, including in ipilimumab-refractory patients. Despite this efficacy, not all melanoma patients respond to pembrolizumab and only a subset of patients with other solid tumors respond to PD-1/PD-L1 axis inhibition. Therefore, molecular biomarkers of response to PD-1/PD-L1 inhibition are still urgently needed.

1.2 Study Drugs

1.2.1 Pembrolizumab

The programmed cell death 1 (PD-1) pathway represents a major immune control switch, which may be engaged by tumor cells to overcome active T-cell immune surveillance. Pembrolizumab (KEYTRUDA®, MK-3475) is a potent and highly selective humanized monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4)/kappa isotype designed to directly block the interaction between PD-1 and its ligants, programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection.

Merck, Sharp & Dohme Corporation, a subsidiary of Merck & Co., Inc. (Merck), is studying pembrolizumab for various oncology indications. Overall, as of 03-Mar-2016, 16,496 patients have been treated in the pembrolizumab development program, of which approximately 9833 patients have been exposed to pembrolizumab in Merck sponsored clinical trials (approximately 6713 subjects received pembrolizumab monotherapy, approximately 876 subjects received pembrolizumab in combination with one or more other chemotherapy or biologic agents, and approximately 2244 subjects received comparator treatment alone). As of the various data cutoff dates for the KEYTRUDA® Investigator Brochure (IB) Version 13 dated17-Feb-2017, pembrolizumab monotherapy and combination therapy have been administered to subjects with hematologic malignancies and solid tumors, in a total of 49 ongoing, Phase 1, 2, and 3 clinical trials sponsored by Merck.

On 04-Sep-2014 the United States (US) Food and Drug Administration (FDA) granted accelerated approval to KEYTRUDA® for treatment of patients with advanced or unresectable melanoma who are no longer responding to other drugs. KEYTRUDA® is the first approved drug that blocks PD-1. KEYTRUDA® is intended for use following treatment with ipilumumab (IPI), a type of immunotherapy. For melanoma patients whose tumors express a gene mutation called BRAF V600, KEYTRUDA® is intended for use after treatment with IPI and a BRAF inhibitor, a therapy that blocks activity of BRAF gene mutations. The recommended dose of KEYTRUDA® is 2 mg/kg administered as an intravenous (IV) infusion over 30 minutes every 3 weeks (Q3W).

On 22-Jul-2015 the European Commission (EC) approved KEYTRUDA® for the treatment of advanced (unresectable or metastatic) melanoma in adults. The EC approval of KEYTRUDA® was based on data from 3 clinical studies (KEYNOTE [KN]001, KN002, and KN006) conducted in more than 1,500 first-line and previously-treated patients with advanced melanoma. KEYTRUDA® received EC regulatory approval based on Phase 3 data that showed it as the first and only anti-PD-1 therapy to provide a statistically superior survival benefit as a monotherapy compared to IPI, the current standard of care for advanced melanoma. This approval allowed marketing of KEYTRUDA® in all 28 EU member states at

the approved dose of 2 mg/kg Q3W. With the EC decision, KEYTRUDA® is now approved in more than 35 countries for the treatment of advanced melanoma.

On 02-Oct-2015 the US FDA granted accelerated approval for KEYTRUDA® to treat patients with advanced (metastatic) non-small cell lung cancer (NSCLC) whose disease has progressed after other treatments and with tumors that express a protein called PD-L1. KEYTRUDA® is approved for use with a companion diagnostic, the PD-L1 IHC 22C3 pharmDx test, the first test designed to detect PD-L1 expression in non-small cell lung tumors. The FDA-approved dose of KEYTRUDA® is 2 mg/kg Q3W.

On 18-Dec-2015, the US FDA expanded the label to include the approval of KEYTRUDA® for the treatment of patients with unresectable or metastatic melanoma. This expansion now includes the initial treatment of patients with unresectable or metastatic melanoma with pembrolizumab. The FDA-approved dose of KEYTRUDA® is 2 mg/kg Q3W.

On 29-Jul-2016 the EC approved KEYTRUDA® for patients with locally advanced or metastatic NSCLC, at a dose of 2 mg/kg Q3W, in patients whose tumors express PD-L1 and who have received at least 1 prior chemotherapy regimen. Patients with EGFR or ALK positive tumor mutations should also have received approved therapy for these mutations prior to receiving KEYTRUDA®. The EC approval allows marketing of KEYTRUDA® in all 28 EU member states. The approval is based on findings from KN010, a pivotal study which showed KEYTRUDA® significantly improved overall survival (OS) compared to standard of care chemotherapy.

On 05-Aug-2016 the US FDA approved KEYTRUDA®, at a fixed dose of 200 mg Q3W, for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy. Under the FDA's accelerated approval regulations, this indication for KEYTRUDA® is approved based on tumor response rate and durability of response. For HNSCC patients, PD-L1 testing is not needed prior to use of KEYTRUDA®. The FDA-approved dose of KEYTRUDA® is 200 mg Q3W.

On 28-Sep-2016, Japan approved KEYTRUDA® for the treatment of radically unresectable melanoma in adults. The approved dose of KEYTRUDA® is 2 mg/kg Q3W.

Merck is advancing a broad and fast-growing clinical development program for KEYTRUDA® both as a monotherapy and in combination with other therapies across more than 30 tumor types and enrolling more than 16,000 patients. Immune-related adverse events (irAEs) are expected based on the nature of the compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action.

1.2.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD L2). The structure of murine PD-1 has been resolved. PD-1 and family

members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD 1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

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

1.2.1.2 Preclinical and Clinical Trial Experience

For complete study information, refer to the current Pembrolizumab Investigator's Brochure (IB).

Non-Clinical Toxicology Summary

In the 1-month and 6-month toxicology study in cynomologus monkeys, pembrolizumab, intravenously administered once a week and once every other week respectively up to a dose of 200mg/kg, resulted in no adverse treatment-related effects. In tissue cross-reactivity studies of pembrolizumab in human and monkey tissues, the expected on-target staining of mononuclear leukocytes membranes was demonstrated in both species. Off-target cross-reactivity staining was also noted in both species but was limited to the cytoplasm of various cell types/tissues and the stroma (extracellular connective tissue matrix), and was considered related to experimental methodological artifacts, i.e. tissue processing for IHC, which are well recognized limitations of tissue cross-reactivity studies and, thus not considered toxicologically relevant.

There was no impact seen on male or female fertility based on evaluation of the Cynomolgus monkeys used in the 1-month and 6-month studies. Reproductive risk assessment was performed using a literature-based approach. In light of the identified potential risk related to inhibition of the PD-1 pathway, no reproductive or developmental toxicity studies were conducted with pembrolizumab. Therefore,

inclusion of women of childbearing potential in clinical trials should be in accordance with the study protocol and applicable regulatory guidance (e.g., ICH M3(R2): Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals).

Clinical Trial Summary

As of the data cutoff dates for Version 13 (17-Feb-2017) of the Pembrolizumab Investigator's Brochure, pembrolizumab monotherapy and combination therapies have been administered to approximately 9833 subjects, with hematologic malignancies and solid tumors, in Merck sponsored trials.

Clinical Pharmacology
The PK profile of pembrolizumab, with low clearance and limited volume of distribution, is typical for therapeutic antibodies. Exposure to pembrolizumab is approximately linear in the dose range of clinical relevance (1 to 10 mg/kg and at 200 mg). Furthermore, pembrolizumab has a low potential fo eliciting the formation of ADAs.

Efficacy
For this Pembrolizumab IB (Version 13, 17-Feb-2017), efficacy data are available for a total fo 1572 melanoma subjects treated with pembrolizumab in KN001, KN002, and KN006; 1529 subjects with NSCLC treated with pembrolizumab in KN001 and KN010; and 174 subjects with HNSCC treated with pembrolizumab in KN012.

KN001 was an open-label, Phase 1, first-in-human study conducted to evaluate clinical activity of pembrolizumab as a single agent in two cancers, melanoma and NSCLC. The ORR demonstrated the antitumor activity of pembrolizumab in subjects with melanoma (ipilumumab-naïve and previously treated with ipilumumab).

KN002 was a randomized Phase 2 study comparing two doses of pembrolizumab to investigator's choice chemotherapy in subjects with unresectable or metastatic (advanced) melanoma, who had progressed after prior treatment with IPI and BRAF (and/or MEK) inhibitor in subjects with BRAF-mutant melanoma. The study demonstrated superior PFS for both pembrolizumab treatment arms compared to the chemotherapy control arm. Treatment with pembrolizumab led to an ORR that was >4-fold higher than the response rate for the chemotherapy control arm. This difference was highly statistically significant.

KN006 was a randomized Phase 3 pivotal study, designed to test whether pembrolizumab was superior to IPI in the co-primary efficacy endpoints of PFS and OS in IPI-naïve subjects with unresectable or metastatic melanoma. This study demonstrated statisticaly significant improvements in OS and PFS for subjects randomized to pembrolizumab compared to subjects randomized to IPI. In the 10 mg/kg treatment groups (Q2W and Q3W), 185 subjects experienced objective responses that ranged from 1.4 months to 8.2 months in duration.

KN010 was a randomized, adaptively designed Phase 2/3 trial of pembrolizumab at 2 dose levels vs docetaxel in subjects with NSCLC with PD-L1 positive tumors, who have experienced disease progression after platinum-containing systemic therapy.

KN012 was a Phase 1b study of pembrolizumab in subjects with advanced solid tumors, including subjects with HPV-negative and HPV-positive head and neck cancer. The primary population for analysis included HNSCC subjects previously exposed to platinum therapy.

The ORRs for pembrolizumab treatment in KN001, KN002, KN006, KN010, and KN012 compared favorably to historical response rates for available treatments for melanoma, NSCLC, and HNSCC, respectively, particularly in subjects who have progressed after multiple prior therapies.

1.2.1.3 Safety Profile

Pembrolizumab is safe and well tolerated, as evidenced by a low rate of toxicity Grade 3 to 5 drug-related AEs (13.8%), discontinuations due to AEs (11.9%), and deaths due to drug-related AEs (3.9%). Furthermore, the frequency of immune-mediated adverse reactions (AEOSIs) is low, and these events are readily managed in the clinical setting.

The safety and efficacy data generated to date provide a favorable benefit-risk assessment for the use of pembrolizumab as a treatment for subjects with advanced/metastatic melanoma, NSCLC, and HNSCC.

There are no specific safety concerns based on the results of nonclinical studies. Pembrolizumab has the same mechanism of action as other anti-PD-1 monoclonal antibodies. Preclinical studies have suggested similar potency, and PK modeling has suggested similar human PK in the class. Accordingly, the AEs observed with other anti-PD-1 antibodies may serve as an indicator for the AEs to expect in cancer subjects.

Pembrolizumab is generally well-tolerated and demonstrates a favorable safety profile in comparison to chemotherapy. Pembrolizumab is an immunomodulatory agent, and based on this mechanism of action, immune-mediated AEs are of primary concern. The important identified risks for pembrolizumab are of an immune-mediated nature, and include the following: pneumonitis; colitis; hepatitis; nephritis; endocrinopathies that include hypophysitis (including hypopituitarism and secondary adrenal insufficiency), thyroid disorder (hypothyroidism, hyperthyroidism) and Type 1 diabetes mellitus; uveitis; myositis; Guillain-Barré syndrome; pancreatitis; and severe skin reactions. Information on the nature and frequency of these identified risks is included in the Reference Safety Information of Version 13 of the Investigator's Brochure. The majority of immune-mediated adverse events were mild to moderate in severity, manageable with appropriate care, and rarely required discontinuation of therapy.

In addition, two important potential risks have been identified, although the data available thus far for these events does not provide sufficient evidence of a causal relationship to pembrolizumab. The two important potential risks are: a) myasthenic syndrome, and b) an increased risk of severe complications (such as early severe graft versus host disease and venoocclusive disease) of allogenic transplant in patients with hematologic malignancies who have previously been treated with PD-1 inhibitors. The Sponsor continues to monitor and collect data on these potential risks in order to further characterize their potential relationship to pembrolizumab.

Further details regarding reporting and management of immune-related AEs (irAEs) in general are described below.

In addition to the immune-related risks noted above, infusion-related reactions are also an important identified risk for pembrolizumab; however, they are not considered immune-mediated. Information regarding the nature and frequency of infusion-related reactions is included in the Reference Safety Information in Version 13 of the Investigator's Brochure (dated 17-Feb-2017).

<u>Immune-Related Adverse Events</u>
Based on the mechanism of action of pembrolizumab and similar immunomodulatory agents, the Sponsor is interested in all potential irAEs, and encourages appropriate investigation of signs and symptoms suggestive of these.

Consultation with the appropriate medical specialist should be considered when investigating a possible irAE. These events can occur after the first dose to several months after the last dose of treatment. Mild irAEs are usually treated symptomatically and infrequently require dosing delays or discontinuation. Higher grade and persistent lower grade irAEs typically necessitate withholding or discontinuing treatment and administration of systemic steroids or other immunosuppressive agents (such as tumor necrosis factor blockers), when systemic steroids are not effective. Early recognition of irAEs and initiation of treatment are critical to reduce the risk of complications, since the majority of irAEs are reversible with the use of steroids and other immune suppressants.

Table 1.2.1.3.1 All AEOSI Adverse Reactions Considered Expected for Pembrolizumab

Adverse Reaction	Frequencies Reference Safety Dataset for MK-3475[a] n	(%)
Rash pruritic	1	(0.0)
Rash pustular	1	(0.0)
Skin lesion	1	(0.0)
Stevens-Johnson Syndrome	1	(0.0)
Hepatitis	**19**	**(0.7)**
Autoimmune hepatitis	12	(0.4)
Hepatitis	6	(0.2)
Drug-induced liver injury	2	(0.1)
Hypophysitis	**17**	**(0.6)**
Hypophysitis	9	(0.3)
Hypopituitarism	8	(0.3)
Uveitis	**14**	**(0.5)**
Uveitis	10	(0.4)
Iridocyclitis	2	(0.1)
Iritis	2	(0.1)
Myositis	**11**	**(0.4)**
Myositis	7	(0.3)
Myopathy	3	(0.1)
Rhabdomyolysis	1	(0.0)
Pancreatitis	**9**	**(0.3)**
Pancreatitis	7	(0.3)
Autoimmune pancreatitis	1	(0.0)
Pancreatitis acute	1	(0.0)
Type 1 diabetes mellitus	**6**	**(0.2)**
Type 1 diabetes mellitus	5	(0.2)
Diabetic ketoacidosis	2	(0.1)
Nephritis	**4**	**(0.1)**
Tubulointerstitial nephritis	4	(0.1)

(Presented by Decreasing Frequency of AEOSI Category)

cont. Table 1.2.1.3.1 All AEOSI Adverse Reactions Considered Expected for Pembrolizumab (Presented by Decreasing Frequency of AEOSI Category)

Adverse Reaction	Frequencies Reference Safety Dataset for MK-3475[a] n	(%)
Guillain-Barre Syndrome	**2**	**(0.1)**
Axonal neuropathy	1	(0.0)
Guillain-Barre syndrome	1	(0.0)
Secondary adrenal insufficiency	**1**	**(0.0)**
Secondary adrenocortical insufficiency	1	(0.0)
Non Immune-Mediated Adverse Reactions		
Infusion related reactions	**70**	**(2.5)**
Infusion related reaction	29	(1.0)
Hypersensitivity	22	(0.8)
Drug hypersensitivity	13	(0.5)
Anaphylactic reaction	3	(0.1)
Cytokine release syndrome	2	(0.1)
Serum sickness	1	(0.0)

KN = KEYNOTE; MedDRA = Medical Dictionary for Regulatory Activities
Every subject is counted a single time for each applicable row and column.
MedDRA version used is 18.1.
[a] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, and KN010 .
(KN001 Database Cutoff Date for Melanoma: 18APR2014).
(KN001 Database Cutoff Date for Lung Cancer: 23JAN2015).
(KN002 Database Cutoff Date: 28FEB2015).
(KN006 Database Cutoff Date: 03MAR2015).
(KN010 Database Cutoff Date: 30SEP2015).

Nephritis: Five additional cases of the AEOSI nephritis were observed in the Reference Safety Dataset; however, they are not contained in the preceeding table because the reported AE coding at the time did not include an AEOSI nephritis term. The coding for each of these 5 cases has since been updated after the data-lock of the Reference Safety Dataset as follows, and each of the terms below is considered an AEOSI adverse reaction expected for pembrolizumab:

- Tubulointerstitial nephritis: n=2 (in addition to 4 cases already included in above table), for an overall frequency of n=6 (0.2%)
- Nephritis: n=2 (0.1%)
- Autoimmune nephritis: n=1 (0%)

Therefore, based on the addition of the above 5 cases, the overall frequency for the AEOSI nephritis in the Reference Safety Dataset should be n=9 (0.3%)

Colitis: One event in the Reference Safety Dataset was initially counted as an AEOSI of colitis. However, it was later determined that the subject did not have colitis, and had been included in the Reference Safety Dataset summary of colitis due to data entry errors. Therefore, the overall frequency of the AEOSI colitis should be n=48 (1.7%), and the frequency for the individual event of colitits should be n=45 (1.6%)

Infusion-Related Reactions: One subject had an event of anaphylactoid reaction that was not counted as an infustion-related reaction since this term was not part of the terms list for the AEOSI infusion-related reactions at the time of reporting. Therefore, the incidence of AEOSI infusion-related reactions in the Referense Safety Dataset should be n=71 (2.5%). The term “anaphylactoid reaction” (n=1 [0%]) is considered an AEOSI expected for pembrolizumab.

Table 1.2.1.3.2 All Additional Adverse Reactions Considered Expected for Pembrolizumab

Preferred Term	Frequencies Reference Safety Dataset for MK-3475[a] n	(%)
Subjects in population	2799	
Diarrhoea	625	(22.3)
Cough	615	(22.0)
Pruritus	562	(20.1)
Arthralgia	504	(18.0)
Rash	499	(17.8)
Pyrexia	357	(12.8)
Back pain	349	(12.5)
Abdominal pain	274	(9.8)
Vitiligo	171	(6.1)
Hyponatraemia	146	(5.2)

KN = KEYNOTE; MedDRA = Medical Dictionary for Regulatory Activities

Every subject is counted a single time for each applicable row and column.

MedDRA version used is 18.1.

Individual PTs were identified from KN002, KN006, and KN010. Each PT occurred at a rate of ≥ 10% in at least one of these studies in patients treated with MK-3475 and at a higher incidence than in the control arm (Between Arm Difference of ≥ 5% [All Grades] or ≥ 2% [Grade 3 or higher])

[a] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, and KN010.

(KN001 Database Cutoff Date for Melanoma: 18APR2014).

(KN001 Database Cutoff Date for Lung Cancer: 23JAN2015).

(KN002 Database Cutoff Date: 28FEB2015).

(KN006 Database Cutoff Date: 03MAR2015).

(KN010 Database Cutoff Date: 30SEP2015).

1.2.1.4 Dose Selection

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

PK data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release

assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

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

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

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

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

1.2.2 Oxaliplatin

Oxaliplatin (Eloxatin®) is a platinum-based anti-cancer agent. It is FDA-approved when used used in combination with infusional 5-fluorouracil /leucovorin for the following indications: 1) for adjuvant treatment of stage III colon cancer in patients who have undergone complete resection of the primary tumor and 2) treatment of advanced colorectal cancer.

Mechanism of Action

Oxaliplatin undergoes nonenzymatic conversion in physiologic solutions to active derivatives via displacement of the labile oxalate ligand. Several transient reactive species are formed, including monoaquo and diaquo DACH platinum, which covalently bind with macromolecules. Both inter-and intrastrand Pt-DNA crosslinks are formed. Crosslinks are formed between the N7 positions of two adjacent guanines (GG), adjacent adenine-guanines (AG), and guanines separated by an intervening nucleotide (GNG). These crosslinks inhibit DNA replication and transcription. Cytotoxicity is cell-cycle nonspecific.

In vivo studies have shown antitumor activity of oxaliplatin against colon carcinoma. In combination with 5-fluorouracil, oxaliplatin exhibits in vitro and in vivo antiproliferative activity greater than either compound alone in several tumor models [HT29 (colon), GR (mammary), and L1210 (leukemia)].

Adverse Events
Most common adverse reactions (incidence ≥ 40%) were peripheral sensory neuropathy, neutropenia, thrombocytopenia, anemia, nausea, increase in transaminases and alkaline phosphatase, diarrhea, emesis, fatigue and stomatitis.

The following are serious adverse reactions as discussed in package insert dated October 2015[14]:

- **Anaphylaxis and Allergic Reactions:** Grade 3/4 hypersensitivity, including anaphylactic/ anaphylactoid reactions, to oxaliplatin has been observed in 2-3% of colon cancer patients. These allergic reactions which can be fatal, can occur within minutes of administration and at any cycle, and were similar in nature and severity to those reported with other platinum-containing compounds, such as rash, urticaria, erythema, pruritus, and, rarely, bronchospasm and hypotension. The symptoms associated with hypersensitivity reactions reported in the previously untreated patients were urticaria, pruritus, flushing of the face, diarrhea associated with oxaliplatin infusion, shortness of breath, bronchospasm, diaphoresis, chest pains, hypotension, disorientation and syncope. These reactions are usually managed with standard epinephrine, corticosteroid, antihistamine therapy, and require discontinuation of therapy. Rechallenge is contraindicated in these patients. Drug-related deaths associated with platinum compounds from anaphylaxis have been reported.

- **Neuropathy:** Oxaliplatin is associated with two types of neuropathy, acute and persistent.

  An acute syndrome of pharyngolaryngeal dysesthesia seen in 1-2% (grade 3/4) of patients previously untreated for advanced colorectal cancer, and the previously treated patients, is characterized by subjective sensations of dysphagia or dyspnea, without any laryngospasm or bronchospasm (no stridor or wheezing). Ice (mucositis prophylaxis) should be avoided during the infusion of oxaliplatin because cold temperature can exacerbate acute neurological symptoms. An acute, reversible, primarily peripheral, sensory neuropathy that is of early onset, occurring within hours or one to two days of dosing, that resolves within 14 days, and that frequently recurs with further dosing. The symptoms may be precipitated or exacerbated by exposure to cold temperature or cold objects and they usually present as transient paresthesia, dysesthesia and hypoesthesia in the hands, feet, perioral area, or throat. Jaw spasm, abnormal tongue sensation, dysarthria, eye pain, and a feeling of chest pressure have also been observed. The acute, reversible pattern of sensory neuropathy was observed in about 56% of study patients who received oxaliplatin with 5-fluorouracil/leucovorin. In any individual cycle acute neurotoxicity was observed in approximately 30% of patients. In adjuvant patients the median cycle of onset for grade 3 peripheral sensory neuropathy was 9 in the previously treated patients the median number of cycles administered on the oxaliplatin with 5-fluorouracil/leucovorin combination arm was 6.

  An acute syndrome of pharyngolaryngeal dysesthesia seen in 1-2% (grade 3/4) of patients previously untreated for advanced colorectal cancer, and the previously treated patients, is characterized by subjective sensations of dysphagia or dyspnea, without any laryngospasm or bronchospasm (no stridor or wheezing). Ice (mucositis prophylaxis) should be avoided during the infusion of oxaliplatin because cold temperature can exacerbate acute neurological symptoms.

  A persistent (>14 days), primarily peripheral, sensory neuropathy that is usually characterized by paresthesias, dysesthesias, hypoesthesias, but may also include deficits in proprioception that can interfere with daily activities (e.g., writing, buttoning, swallowing, and difficulty walking from impaired

proprioception). These forms of neuropathy occurred in 48% of the study patients receiving oxaliplatin with 5-fluorouracil/leucovorin. Persistent neuropathy can occur without any prior acute neuropathy event. The majority of the patients (80%) who developed grade 3 persistent neuropathy progressed from prior Grade 1 or 2 events. These symptoms may improve in some patients upon discontinuation of oxaliplatin.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS, also known as PRES, Posterior Reversible Encephalopathy Syndrome) has been observed in clinical trials (< 0.1%) and postmarketing experience. Signs and symptoms of RPLS could be headache, altered mental functioning, seizures, abnormal vision from blurriness to blindness, associated or not with hypertension. Diagnosis of RPLS is based upon confirmation by brain imaging.

- **Severe Neutropenia:** Grade 3 or 4 neutropenia occurred in 41-44% of patients with colorectal cancer treated with oxaliplatin in combination with 5-flurouracil (5-FU) and leucovorin compared to 5% with 5-FU plus leucovorin alone. Sepsis, neutropenic sepsis and septic shock have been reported in patients treated with oxaliplatin, including fatal outcomes.

- **Pulmonary Toxicity:** Oxaliplatin has been associated with pulmonary fibrosis (<1% of study patients), which may be fatal. The combined incidence of cough and dyspnea was 7.4% (any grade) and <1% (grade 3) with no grade 4 events in the oxaliplatin plus infusional 5-fluorouracil/ leucovorin arm compared to 4.5% (any grade) and no grade 3 and 0.1% grade 4 events in the infusional 5-fluorouracil/leucovorin alone arm in adjuvant colon cancer patients. In this study, one patient died from eosinophilic pneumonia in the oxaliplatin combination arm. The combined incidence of cough, dyspnea and hypoxia was 43% (any grade) and 7% (grade 3 and 4) in the oxaliplatin plus 5-fluorouracil/leucovorin arm compared to 32% (any grade) and 5% (grade 3 and 4) in the irinotecan plus 5-fluorouracil/leucovorin arm of unknown duration for patients with previously untreated colorectal cancer. In case of unexplained respiratory symptoms such as non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates, oxaliplatin should be discontinued until further pulmonary investigation excludes interstitial lung disease or pulmonary fibrosis.

- **Hepatoxicity:** Hepatotoxicity as evidenced in the adjuvant study, by increase in transaminases (57% vs. 34%) and alkaline phosphatase (42% vs. 20%) was observed more commonly in the oxaliplatin combination arm than in the control arm. The incidence of increased bilirubin was similar on both arms. Changes noted on liver biopsies include: peliosis, nodular regenerative hyperplasia or sinusoidal alterations, perisinusoidal fibrosis, and veno-occlusive lesions. Hepatic vascular disorders should be considered, and if appropriate, should be investigated in case of abnormal liver function test results or portal hypertension, which cannot be explained by liver metastases.

- **Cardiovascular Toxicity:** QT prolongation and ventricular arrhythmias including fatal Torsade de Pointes have been reported in postmarketing experiences following oxaliplatin administration. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics, and electrolyte abnormalities. Correct hypokalemia or hypomagnesemia prior to initiating oxaliplatin and monitor these electrolytes periodically during therapy. Avoid oxaliplatin in patients with congenital long QT syndrome.

- **Rhabdomyolysis:** Rhabdomyolysis, including fatal cases, has been reported in patients treated with oxaliplatin. Discontinue oxaliplatin if any signs or symptoms of rhabdomyolysis occur.

Refer to current package insert for full prescription drug information for oxaliplatin.

1.2.3 Capecitabine

Capecitabine (Xeloda®) is a nucleoside metabolic inhibitor with antineoplastic activity. It is FDA-approved for the following indications: 1) adjuvant colon cancer (patients with Dukes' C colon cancer); 2) metastatic colorectal cancer (first-line as monotherapy when treatment with fluoropyrimidine therapy alone is preferred); and 3) metastatic breast cancer (in combination with docetaxel after failure of prior anthracycline-containing therapy or as monotherapy in patients resistant to both paclitaxel and an anthracycline-containing regimen).

Mechanism of Action
Enzymes convert capecitabine to 5-fluorouracil (5-FU) in vivo. Both normal and tumor cells metabolize 5-FU to 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor, N5-10-methylenetetrahydrofolate, bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from 2'-deoxyuridylate. Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA, so that a deficiency of this compound can inhibit cell division. Second, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processing and protein synthesis.

Adverse Events
Most common adverse reactions (≥30%) were diarrhea, hand-and-foot syndrome, nausea, vomiting, abdominal pain, fatigue/weakness, and hyperbilirubinemia.

The following are Warnings and Precautions as discussed in package insert dated December 2016[15]:

- **Coagulopathy:** Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored closely with great frequency and the anticoagulant dose should be adjusted accordingly.

- **Diarrhea:** Capecitabine can induce diarrhea, sometimes severe. Patients with severe diarrhea should be carefully either metastatic breast or colorectal cancer who received capecitabine monotherapy, the median time to first occurrence of grade 2 to 4 diarrhea was 34 days (range from 1 to 369 days). The median duration of grade 3 to 4 diarrhea was 5 days. National Cancer Institute of Canada (NCIC) grade 2 diarrhea is defined as an increase of 4 to 6 stools/day or nocturnal stools, grade 3 diarrhea as an increase of 7 to 9 stools/day or incontinence and malabsorption, and grade 4 diarrhea as an increase of ≥ 10 stools/day or grossly bloody diarrhea or the need for parenteral support.

  Necrotizing enterocolitis (typhlitis) has been reported.

- **Cardiotoxicity:** The cardiotoxicity observed with capecitabine includes myocardial infarction/ ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy. These adverse reactions may be more common in patients with a prior history of coronary artery disease.

- **Dihydropyrimidine Dehydrogenase Deficiency (DPD):** Based on postmarketing reports, patients with certain homozygous or certain compound heterozygous mutations in the DPD gene that result in complete or near complete absence of DPD activity are at increased risk for acute early-onset of toxicity and severe, life-threatening, or fatal adverse reactions caused by capecitabine (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Patients with partial DPD activity may also have increased risk of severe, life-threatening, or fatal adverse reactions caused by capecitabine.

- **Dehydration and Renal Failure:** Dehydration has been observed and may cause acute renal failure which can be fatal. Patients with pre-existing compromised renal function or who are receiving concomitant capecitabine with known nephrotoxic agents are at higher risk. Patients with anorexia, asthenia, nausea, vomiting or diarrhea may rapidly become dehydrated.

- **Embryo-Fetal Toxicity:** Based on findings from animal reproduction studies and its mechanism of action, capecitabine may cause fetal harm when given to a pregnant woman. Limited available data are not sufficient to inform use of capecitabine in pregnant women. In animal reproduction studies, administration of capecitabine to pregnant animals during the period of organogenesis caused embryolethality and teratogenicity in mice and embryolethality in monkeys at 0.2 and 0.6 times the exposure (AUC) in patients receiving the recommended dose respectively. Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of capecitabine.

- **Mucocutaneous and Dermatologic Toxicity:** Severe mucocutaneous reactions, some with fatal outcome, such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis (TEN) can occur in patients treated with capecitabine. Hand-and-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy-induced acral erythema) is a cutaneous toxicity. Median time to onset was 79 days (range from 11 to 360 days) with a severity range of grades 1 to 3 for patients receiving capecitabine monotherapy in the metastatic setting.

- **Hyperbilirubinemia:** In 875 patients with either metastatic breast or colorectal cancer who received at least one dose of capecitabine 1250 mg/m2 twice daily as monotherapy for 2 weeks followed by a 1-week rest period, grade 3 (1.5-3 x ULN) hyperbilirubinemia occurred in 15.2% (n=133) of patients and grade 4 (>3 x ULN) hyperbilirubinemia occurred in 3.9% (n=34) of patients. Of 566 patients who had hepatic metastases at baseline and 309 patients without hepatic metastases at baseline, grade 3 or 4 hyperbilirubinemia occurred in 22.8% and 12.3%, respectively. Of the 167 patients with grade 3 or 4 hyperbilirubinemia, 18.6% (n=31) also had postbaseline elevations (grades 1 to 4, without elevations at baseline) in alkaline phosphatase and 27.5% (n=46) had postbaseline elevations in transaminases at any time (not necessarily concurrent). The majority of these patients, 64.5% (n=20) and 71.7% (n=33), had liver metastases at baseline. In addition, 57.5% (n=96) and 35.3% (n=59) of the 167 patients had elevations (grades 1 to 4) at both prebaseline and postbaseline in alkaline phosphatase or transaminases, respectively. Only 7.8% (n=13) and 3.0% (n=5) had grade 3 or 4 elevations in alkaline phosphatase or transaminases.

  In the 596 patients treated with capecitabine as first-line therapy for metastatic colorectal cancer, the incidence of grade 3 or 4 hyperbilirubinemia was similar to the overall clinical trial safety database of capecitabine monotherapy. The median time to onset for grade 3 or 4 hyperbilirubinemia in the colorectal cancer population was 64 days and median total bilirubin increased from 8 µm/L at baseline to 13 µm/L during treatment with capecitabine. Of the 136 colorectal cancer patients with grade 3 or 4 hyperbilirubinemia, 49 patients had grade 3 or 4 hyperbilirubinemia as their last measured value, of which 46 had liver metastases at baseline.

  In 251 patients with metastatic breast cancer who received a combination of capecitabine and docetaxel, grade 3 (1.5 to 3 x ULN) hyperbilirubinemia occurred in 7% (n=17) and grade 4 (>3 x ULN) hyperbilirubinemia occurred in 2% (n=5).

- **Hematologic:** In 875 patients with either metastatic breast or colorectal cancer who received a dose of 1250 mg/m2 administered twice daily as monotherapy for 2 weeks followed by a 1-week rest period, 3.2%, 1.7%, and 2.4% of patients had grade 3 or 4 neutropenia, thrombocytopenia or

decreases in hemoglobin, respectively. In 251 patients with metastatic breast cancer who received a dose of capecitabine in combination with docetaxel, 68% had grade 3 or 4 neutropenia, 2.8% had grade 3 or 4 thrombocytopenia, and 9.6% had grade 3 or 4 anemia.

- **Geriatric Patients:** Patients ≥80 years old may experience a greater incidence of grade 3 or 4 adverse reactions. In 875 patients with either metastatic breast or colorectal cancer who received capecitabine monotherapy, 62% of the 21 patients ≥80 years of age treated with capecitabine experienced a treatment-related grade 3 or 4 adverse event: diarrhea in 6 (28.6%), nausea in 3 (14.3%), hand-and-foot syndrome in 3 (14.3%), and vomiting in 2 (9.5%) patients. Among the 10 patients 70 years of age and greater (no patients were >80 years of age) treated with capecitabine in combination with docetaxel, 30% (3 out of 10) of patients experienced grade 3 or 4 diarrhea and stomatitis, and 40% (4 out of 10) experienced grade 3 hand-and-foot syndrome.

  Among the 67 patients ≥60 years of age receiving capecitabine in combination with docetaxel, the incidence of grade 3 or 4 treatment-related adverse reactions, treatment-related serious adverse reactions, withdrawals due to adverse reactions, treatment discontinuations due to adverse reactions and treatment discontinuations within the first two treatment cycles was higher than in the <60 years of age patient group.

  In 995 patients receiving capecitabine as adjuvant therapy for Dukes' C colon cancer after resection of the primary tumor, 41% of the 398 patients ≥65 years of age treated with capecitabine experienced a treatment-related grade 3 or 4 adverse event: hand-and-foot syndrome in 75 (18.8%), diarrhea in 52 (13.1%), stomatitis in 12 (3.0%), neutropenia/ granulocytopenia in 11 (2.8%), vomiting in 6 (1.5%), and nausea in 5 (1.3%) patients. In patients ≥65 years of age (all randomized population; capecitabine 188 patients, 5-FU/LV 208 patients) treated for Dukes' C colon cancer after resection of the primary tumor, the hazard ratios for disease-free survival and overall survival for capecitabine compared to 5-FU/LV were 1.01 (95% C.I. 0.80 – 1.27) and 1.04 (95% C.I. 0.79 – 1.37), respectively.

- **Hepatic Insufficiency:** Patients with mild to moderate hepatic dysfunction due to liver metastases should be carefully monitored when capecitabine is administered. The effect of severe hepatic dysfunction on the disposition of capecitabine is not known.

Refer to current package insert for full prescription drug information for capecitabine.

1.3 Study Rationale

This is a single arm, phase II study to assess the safety, tolerability, and efficacy of the RPTD of the combination of pembrolizumab, oxaliplatin and capecitabine in patients with previously untreated metastatic esophagogastric adenocarcinoma. The study will be conducted in two stages: 1) safety validation and 2) dose expansion. In the dose expansion cohort, the first cycle will be modified to allow one week of pembrolizumab monotherapy before starting XELOX chemotherapy, which will allow analysis of biomarkers related to pembrolizumab.

Gastric cancer is likely a PD-1 sensitive tumor type. The KEYNOTE-012 study was a Phase 1b study evaluating the use of pembrolizumab in gastric cancer patients. This study, conducted in the United States, Israel, Japan, South Korea, and Taiwan, screened 162 patients to identify 65 (40%) that were PD-L1 positive. Thirty-nine of these patients (19 from Asia Pacific and 20 from rest of the world) were enrolled and treated with pembrolizumab 10mg/kg every 2 weeks. The therapy was generally well tolerated with the most common adverse events being hypothyroidism and fatigue; few Grade ≥ 3 events were noted. There were 8 (22%, 95% CI 10-39) centrally confirmed partial responses, 13 (33%, 95% CI 19-50) investigator assessed partial responses, and 17 patients (53%) with at least one post-baseline tumor assessment that showed disease response. The median duration of response 40 weeks,

median overall survival was 11.4 months (95% CI 5.7 – not reached), and proportion of patients alive at 6 months was 42% (95% CI 25 – 59)[16]. Pembrolizumab is now in phase III studies as monotherapy in 2nd/3rd line gastric cancer.

The fluoropyrimidine/platinum combination is a common first line therapy for metastatic gastric cancer and it considered "preferred" by the NCCN Gastric Cancer Guideline committee[17]. This combination can either be fluorouracil plus oxaliplatin or capectabine plus oxaliplatin[18-20]. Given the toxicity associated with cisplatin and the non-inferiority data from REAL2[21], many clinicians prefer to use the less toxic and more convenient capecitabine/oxaliplatin combination. There are several studies evaluating the capecitabine/oxaliplatin doublet in the treatment of metastatic gastric cancer as well as others that have evaluated the doublet as a backbone for the addition of newer agents – as in this study[22-26]. In addition, it has recently been appreciated that many chemotherapeutic agents augment anti-tumor responses. Oxaliplatin in particular has been reported by many labs to induce so called 'immunogenic cell death[27-28]. Thus, the combination of pembrolizumab and oxaliplatin can be considered a novel strategy for targeting the immune system for the treatment of advanced gastric cancer. In addition, the effects of pembrolizumab in advanced gastric cancer have not yet been well defined. The overall goals of this study are to both determine the activity of pembrolizumab + XELOX and to explore the immunological mechanisms of sensitivity and resistance to this therapy in patients with advanced gastric cancer with Duke collaborators who have experience in the analysis of immune markers, both in tumor tissue and in peripheral blood.

2.0 OBJECTIVES

2.1 Primary Objective

The primary objective of this trial is:

1. To describe the progression free survival (PFS) associated with the combination of pembrolizumab, oxaliplatin and capecitabine (pembro+XELOX) in all patients with previously untreated metastatic esophagogastric adenocarcinoma.

2.2 Secondary Objectives

The secondary objectives of this trial are:

1. To describe the safety and tolerability of the combination of pembro+XELOX in patients with previously untreated metastatic esophagogastric adenocarcinoma.
2. To describe the response rate (RR) and overall survival (OS) of the combination of pembro+XELOX in patients with previously untreated metastatic esophagogastric adenocarcinoma.

2.3 Exploratory Objectives

The exploratory objectives of this trial are:

1. To explore changes in CD8 and PDL1 expression in tumor tissue related to pembrolizumab treatment.
2. To explore other changes in tissue and blood based biomarkers and their correlation with clinical outcomes.
3. To explore changes in immune cells and biomarkers in those who completed treatment and remain in complete response.

3.0 STUDY DESIGN

3.1 Study Description

This is a single arm, phase II study to assess the safety, tolerability, and efficacy of the recommended phase II dose (RPTD) of the combination of pembrolizumab, oxaliplatin and capecitabine in patients with previously untreated metastatic esophagogastric adenocarcinoma. The study will be conducted in two stages: 1) safety validation and 2) dose expansion. Approximately 50 subjects may be accrued to ensure the trial obtains 5 evaluable subjects in the safety validation cohort and 30 evaluable subjects in the dose expansion cohort. Patients will be enrolled at the Duke Cancer Institute and select external collaborating institutions (dose expansion cohort only).

- Enrolled subjects are defined as subjects who give informed consent.
- Screen failures are defined as subjects who give informed consent and do not meet eligibility criteria.
- Accrued subjects are defined as subjects who give informed consent and meet eligibility criteria.
    - Withdrawal: Subject accrued but later withdrawn from the study, either before or after receiving a study drug.
    - Evaluable: In the Safety Validation Cohort, subjects who are accrued, received study treatment, and completed the first cycle of safety assessments or have dose limiting toxicity (DLT) which is study treatment related that precludes completing the full cycle of assessments will be considered evaluable for DLT. All subjects (in Safety Validation and Dose Expansion) who are accrued and receive any study treatment will be considered evaluable for toxicity. All subjects in Safety Validation and Dose Expansion who are accrued and receive any study treatment will be considered evaluable for efficacy.
    - Non-evaluable: In the Safety Validation Cohort, subjects who accrued but did not complete the first cycle of safety assessments due to reasons other than study treatment-related toxicity (e.g. disease progression or inter-current illness) are considered non-evaluable for DLT.

Table 3.1 Cohorts

Cohort	No. Evaluable Subjects	Oxaliplatin mg/m2 IV, Day 1 every 21 days*	Capecitabine mg/m2 PO, BID Days 1-14 every 21 days*	Pembrolizumab mg IV, Day 1 every 21 days*
Safety Validation	5	130	850 or 1000**	200
Dose Expansion	30	130	850 or 1000**	200

*For dose expansion cohort, Cycle 1, biomarker cycle, is 28 days in length. Cycles 2 and beyond are 21 days.
**The dose of capecitabine is per treating physician discretion. 850mg/m^2 and 1000mg/m^2 are preferred doses for the regimen in US patients based upon safety. While safety and activity in gastric cancer for capecitabine, particularly with oxaliplatin, in US vs non-US patients have not been systematically reviewed, most US doctors and many phase III protocols allow flexibility in dosing of capecitabine for this reason[29-31].

3.2 Safety Validation

The first portion of the study will preliminarily establish the tolerability of the combination of pembrolizumab, oxaliplatin and capecitabine at the RPTD in patients with metastatic esophagogastric adenocarcinoma. Subjects on this portion of the study will only be enrolled at the Duke Cancer Institute.

A total of five (5) evaluable patients will be accrued and their safety data after completion of the first cycle of safety assessments will be reviewed before additional patients are enrolled. Proceeding to dose expansion cohort will be dependent on DLT (refer to Section 3.2.1) within the safety validation cohort.

The following enrollment method will be employed for the safety validation stage of the study:

- If no DLT occurs with the 5 evaluable subjects, enrollment may proceed to the dose expansion cohort.
- If 1 DLT occurs with the 5 evaluable subjects, enrollment may proceed to the dose expansion cohort.
- If ≥ 2 DLTs occurs with the 5 evaluable subjects, enrollment must not proceed to the dose expansion cohort and alternative dose levels for oxaliplatin and capecitabine may be considered.

3.2.1 Dose Limiting Toxicity

Using the NCI-CTCAE version 4.0, the following adverse events will be considered dose limiting toxicity (DLT) if occurring during the first cycle (21 days) of treatment and deemed to be related to study treatment:

- Grade 4 neutropenia, thrombocytopenia or anemia.
- Grade ≥ 3 neutropenia or thrombocytopenia lasting over 7 days.
- Grade 3 thrombocytopenia associated with bleeding.
- Neutropenic fever.
- Grade ≥ 3 nausea/vomiting or diarrhea lasting ≥ 3 days despite adequate supportive measures.
- Grade ≥ 3 ALT, AST, or bilirubin elevation > 7 days.
- Grade ≥ 3 non-hematologic toxicity excluding alopecia, anorexia, fatigue, hypertension, isolated lab abnormalities (not clinically significant) and/or allerigic or idiosyncratic reactions to any of the study drugs. Anorexia, fatigue and hypertension will be considered as DLT only if they reach Grade 4 or are considered unmanageable.
- Treatment delay of ≥ 14 days for Cycle 2 due to unresolved treatment-related toxicity.

Management and dose modifications associated with all adverse events are outlined in Section 7.0.

3.3 Dose Expansion Cohort

Once 5 evaluable subjects have been treated in the safety validation cohort with no more than one occurrence of DLT as defined in Section 3.2.1, the second portion of the study (ie. phase II) will accrue

30 evaluable patients to assess the safety, tolerability, and efficacy of the RPTD of the combination of pembrolizumab, oxaliplatin and capecitabine in patients with previously untreated metastatic esophagogastric adenocarcinoma. Subjects on this portion of the study will be enrolled at the Duke Cancer Institute and select external collaborating institutions.

In the dose expansion cohort, the first cycle will be modified to allow one week of pembrolizumab monotherapy before starting XELOX chemotherapy, which will allow analysis of biomarkers related to pembrolizumab; thus Cycle 1 for the dose expansion cohort will be 4 weeks.

4.0 SUBJECT SELECTION

4.1 Inclusion Criteria

1. Histologically and/or cytologically documented and radiographically measurable (by RECIST 1.1) adenocarcinoma of the esophagus or stomach (HER2 negative only) that is metastatic/recurrent and not amenable to potentially curative treatment (e.g., inoperable metastatic or locally recurrent disease). HER2 positive patients would be considered eligible only if there is a contraindication to Herceptin.
2. No prior chemotherapy for metastatic/recurrent disease. Prior adjuvant or neo-adjuvant treatment with a fluoropyrimidine or fluoropyrimidine based regimen is allowed only if it is completed at least 6 months prior to the start of study drug, whether given alone or with radiation therapy. Patients who have received prior neo-adjuvant therapy (chemotherapy and/or radiation therapy) which did not contain 5-FU or capecitabine and have been diagnosed with metastatic disease (with no previous treatment in the metastatic setting) are eligible. No 6-month window is required for these patients. In the setting of metastatic disease requiring local palliation, only radiosensitizing doses of 5-FU or capecitabine monotherapy are permitted.
3. Prior radiation therapy is permitted, provided it is completed at least 28 days prior to the start of study drug.
4. Age ≥ 18 years with ability to understand and willingness to provide informed consent.
5. ECOG performance status of 0 or 1.
6. Adequate organ and marrow function as defined below by the following:
    a) Absolute neutrophil count (ANC) ≥ 1500 µl
    b) Platelets ≥ 100,000/µl
    c) Hemoglobin (Hgb) ≥ 9 g/dL
    d) Total bilirubin ≤ 1.5 x upper limit of normal (ULN)
    e) AST/ALT ≤ 2 x ULN without liver metastasis; ≤ 5 x ULN with liver metastasis
    f) Creatinine clearance ≥ 50 cc/min

4.2 Exclusion Criteria

1. Prior therapy with an anti-PD-1, anti PD-L1, anti-PD-L2, anti-CD137 antibody, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) agents.
2. Chemotherapy, targeted small molecule therapy, experimental agents, prior therapy with anti-tumor vaccines or other immune-stimulatory antitumor agents, or biological cancer therapy (including monoclonal antibodies) within 14 days prior to the start of study drug, or not recovered (≤ grade 1 or baseline) from adverse events due to a previously administered agent.

3. Known CNS metastases and/or carcinomatous meningitis. Patients with radiated or resected lesions are permitted, provided the lesions are fully treated and inactive, patients are asymptomatic, and no steroids for treatment of CNS lesion have been administered for at least 30 days prior to the start of study drug.
4. Documented history of clinically significant autoimmune disease (other than well-controlled hypothyroidism) or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo, type I diabetes mellitus, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
5. Receiving systemic steroid therapy or any form of immunosuppressive therapy within 1 week prior to the start of study drug. Note: Patients are permitted to receive up to 12 mg dexamethasone prior to administration of oxaliplatin and low dose steroids for up to 48 hours after dosing to prevent nausea and vomiting.
6. Received a live vaccine within 4 weeks prior to the start of study drug.
7. Has known history of, or any evidence of active, non-infectious pneumonitis.
8. Known history of HIV seropositivity, hepatitis C virus, acute or chronic active hepatitis B infection, or other serious chronic infection requiring ongoing treatment. Patients receiving prophylactic antibiotics (e.g., for prevention of urinary tract infection or chronic obstructive pulmonary disease) are eligible.
9. Pregnant or breastfeeding.
10. Not willing to use an effective method of birth control (refer to Section 6.5.1 for acceptable methods of contraception).
11. Concurrent severe and/or uncontrolled medical conditions, which may compromise participation in the study, including impaired heart function or clinically significant heart disease.
12. Current use of medications specified by the protocol as prohibited for administration in combination with study drug. This includes patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days prior to the start of study drug (see section 6.5.2 for exception for prophylactic use with oxaliplatin dosing). Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease. Corticosteroids administered as pre-medication for IV contrast allergy are also allowed.
13. Recent or current active infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment within 2 weeks prior to the start of study drug. Subjects being treated for Helicobacter pylori infection are an exception and are allowed to start protocol based therapy while still on antibiotics.
14. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to the start of study drug (56 days for hepatectomy, open thoracotomy, major neurosurgery) or anticipation of need for major surgical procedure during the course of the study (except for the planned metastatectomy).
15. Serious, non-healing wound, ulcer, or bone fracture.
16. History of myocardial infarction, NYHA class III or IV congestive heart failure, unstable angina, cardiac or other vascular stenting, angioplasty, or surgery within 6 months prior to the start of study drug.

17. History of other carcinomas within the last five years, except cured non-melanoma skin cancer, curatively treated in-situ cervical cancer, or localized prostate cancer with a current PSA of <1.0 mg/dL on 2 successive evaluations, at least 3 months apart, with the most recent evaluation no more than 4 weeks prior to the start of study drug.

4.3 Inclusion of Women and Minorities

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

5.0 STUDY ASSESSMENTS

Note: After Cycle 1, if the subject is unable to have a study assessment taken within the defined time window due to an event outside of his or her control (e.g., clinic closure, personal emergency, inclement weather, vacation), the assessment should be performed as close as possible to the required schedule.

Refer to Appendix D for **Study Calendar**.

5.1 Screening Period

During the Screening Period, subjects are consented and screened for the study. Informed consent must be obtained before initiation of any screening procedure that is performed solely for the purpose of determining eligibility for this study. Evaluations performed as part of routine care before informed consent can be considered as screening evaluations if done within the defined screening period, and if permitted by the local Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) policies. Study eligibility is based on meeting all of the inclusion criteria and none of the exclusion criteria (refer to Section 4.0) before the first dose of study drug on Cycle 1 Day 1.

The following study procedures must be done within 28 days prior to Cycle 1 Day 1:

- Demographics
- Medical and cancer history
- Physical examination
- Height
- Vital signs and weight
- Concomitant medications
- ECOG performance status (perform or repeat within 7 days prior to dosing on Cycle 1 Day 1)
- Thyroid function tests
- Adverse event assessment (review of baseline symptoms)
- Tumor assessment (CT and/or MRI scans)
- Blood tumor marker, if clinically indicated (e.g., CEA or CA19-9)
- Archived tumor tissue (if available)
- PBMC (may be collected pre-dose on Cycle 1 Day 1)
- Plasma (may be collected pre-dose on Cycle 1 Day 1)
- Whole blood (may be collected pre-dose on Cycle 1 Day 1)

The following study procedures must be done within 7 days prior to Cycle 1 Day 1:

- CBC with differential
- Chemistries including liver function tests (LFTs)
- Serum pregnancy test (only for women of childbearing potential)

- Tumor biopsy (only applicable to patients in dose expansion that have lesions amenable to safe biopsy)

Subject eligibility is determined using lab results obtained up to 7 days prior to Cycle 1 Day 1. Any laboratory assessments repeated on Cycle 1 Day 1 must meet eligibility requirements. The Screening Period ends upon receipt of the first dose of study drug or final determination that the subject is ineligible for the study.

5.2 Treatment Period

During the Treatment Period, subjects will receive pembrolizumab and oxaliplatin on Day 1 and capecitabine on Days 1-14 of each 21-day cycle until either: 1) disease progression; 2) the occurrence of unacceptable treatment-related toxicity; or 3) other reason(s) for subject discontinuation as described in Section 5.7. Toxicity-related dose modifications of pembrolizumab, capecitabine and oxaliplatin may occur during the Treatment Period. Dose modification guidelines are described in Section 7.1.

NOTE: For the dose expansion cohort only, the first cycle (i.e. biomarker cycle) will be modified to allow assessment of biomarkers related to pembrolizumab; the length will be 28 days. Patients will receive pembrolizumab monotherapy on Cycle 1 Day 1. Treatment with oxaliplatin and capecitabine will begin on Cycle 1 Day 8; capecitabine will be dosed for 14 days (ie. Days 8-21), followed by one week off drug (ie. Days 22-28). Cycle 2 will start on Day 29 of study (ie. 28 days after pembrolizumab monotherapy and 20 days after start of capecitabine and oxaliplatin). For cycles 2 and beyond, the cycle length is 21 days. A treatment window of +/- 3 days is allowed for day 1 of cycle 2 and all subsequent cycles.

All subjects will have study procedures weekly during the first cycle, then Day 1 of each cycle. After the completion of the first cycle, laboratory assessments may be obtained up to 3 days prior to treatment. If necessary, the treatment visit may be within +/- 3 days of the scheduled day 1 for cycle 2 and all subsequent cycles. If clinically indicated, additional visits and/or safety assessments may be warranted.

The following study procedures must be completed on **Day 1 of each cycle**:

- Physical examination
- Vital signs and weight
- Concomitant medications
- ECOG performance status
- Adverse event assessment
- CBC with differential
- Chemistries including LFTs

The following study procedures must be completed on **weekly in Cycle 1 only**:

- Physical examination
- Vital signs and weight
- Concomitant medications
- ECOG performance status
- Adverse event assessment
- CBC with differential
- Chemistries including LFTs

For **dose expansion cohort only**, the following study procedures must be completed **pre-dose on Cycle 1 Day 8**:

- PBMC
- Plasma
- Tumor biopsy (Can be performed on Day 7 if needed. Only applicable to patients in dose expansion that have lesions amenable to safe biopsy)

For **dose expansion cohort only**, the following study procedures must be completed **pre-dose on Cycle 1 Day 29 (i.e. Cycle 2 Day 1)**:

- PBMC
- Plasma

The following study procedures must be completed **every 3 (± 1) cycles**:

- Thyroid function tests
- Serum pregnancy test (only for women of childbearing potential)
- Tumor assessment (CT and/or MRI scans)
- Blood tumor marker, if clinically indicated (e.g., CEA or CA19-9)
- PBMC - first restaging only
- Plasma

Restaging scans will be performed every 3 cycles (ie. every 9 weeks) and disease reponse will be assessed using guidelines described in Section 5.6.

The Treatment Period ends when a subject receives his or her last dose of study treatment; the subject then enters the Follow-up Period.

5.3 Follow-up Period

Subjects should return 30 (±7) days after their last dose of study drug for an off-treatment visit to complete the following study procedures:

- Physical examination
- Vital signs and weight
- Concomitant medications
- ECOG performance status
- Adverse event assessment
- CBC with differential
- Chemistries including LFTs
- Thyroid function tests
- Serum pregnancy test (only for women of childbearing potential)
- Plasma
- Archived tissue collected at end of study (if available)

Additional follow-up may occur for subjects with adverse events (AEs) related to study drug that are ongoing at the time of this off-treatment visit unless AE is deemed unresolveable or subject has started a new anti-cancer treatment regimen.

For subjects that are discontinued from study treatment for reasons other than disease progression, subjects will have disease status (blood tumor marker(s) and restaging scans per standard of care schedule) followed until disease progression or start of new anti-cancer treatment regimen. Disease status may be collected by personal interviews or review of medical records. Disease progression follow up will continue for as long as patient is in survival follow up, provided they have not progressed or started a new anti-cancer treatment. For subjects that completed therapy and remain in complete response, PBMCs and plasma will be collected approximately every three months with standard of care visits, provided subjects consent to this additional follow-up.

Subjects will be followed for survival up to 3 years after the last subject starts the study drug regimen or until the study is closed (whichever comes first). Survival status may be collected by phone call or review of medical or public records approximately every 12 weeks.

5.4 Laboratory Assessments

Local laboratories will perform all clinical laboratory tests using standard procedures, and results will be provided to the Investigator. Abnormalities in clinical laboratory tests that lead to a change in subject management (e.g., dose modification, requirement for additional medication, treatment or monitoring) are considered clinically significant for the purposes of this study, and will be recorded on the case report form (CRF). If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as a serious adverse event (SAE).

Refer to Appendix E for details of laboratory tests for this study. In addition, blood tumor markers (if clinically indicated) such as CEA and/or CA19-9, will be obtained at baseline and at every restaging.

5.5 Adverse Event Assessment

AE definition is described in Section 10.1. AEs will be documented throughout the study. AE seriousness, grade, and relationship to study drug will be assessed by the Investigator using NCI-CTCAE version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf).

SAE definitions and reporting requirements are described in Section 10.2.

Select non-serious and serious adverse events also known as Events of Clinical Interest (ECI) must be recorded and reported as described in Section 10.3.

5.6 Tumor Assessments

Tumor response will be assessed using RECIST version 1.1 and irRC. Radiographic imaging will be performed with CT scan of chest/abdoment/pelvis with and without contrast and/or MRI scan of abdomen/pelvis every 3 cycles (i.e., every 9 weeks) after the start of study treatment. The same method for tumor assessment should be employed at every assessment.

5.6.1 RECIST version 1.1

RECIST is a set of published rules that define when cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progression") during treatments. The original criteria were published in February 2000 by an international collaboration including the European Organization for Research and Treatment of Cancer (EORTC), National Cancer Institute (NCI) of the United States and the National

Cancer Institute of Canada Clinical Trials Group. RECIST 1.1, published in January 2009, is an update to the original criteria and will be used for this study.

Refer to Appendix A for definition of target lesions, methods of measurement and all other related criteria for RECIST version 1.1. The following summarizes the definitions of the criteria used to determine objective tumor response for 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 diameters of target lesions, taking as reference the baseline sum diameters.

- **Progressive Disease (PD)**: At least a 20% increase in the sum of 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 progression).

- **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.

5.6.2 Immune-Related Response Criteria

The responses that are seen with immunotherapeutic agents may extend beyond those of cytotoxic agents and could include responses after disease progression that is not captured by RECIST. To account for this, for this study, immune-related response criteria (irRC) will be used to allow for more comprehensive evaluation of clinical activity. Conventional response criteria may not adequately assess the activity of immunotherapeutic agents because PD (progressive disease) by initial radiographic evaluation does not necessarily reflect therapeutic failure, thus stopping the study treatment with initial perceived PD may be premature.

Refer to Appendix B for definitions and guidelines of the irRC. The overall response according to the irRC is derived from time-point response assessments (based on tumor burden) as follows:

- **irCR:** complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented

- **irPR:** decrease in tumor burden ≥50%relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation

- **irSD:** not meeting criteria for irCR or irPR, in absence of irPD

- **irPD:** increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden) confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented

5.7 Subject Discontinuation

Subjects will receive study treatment until treatment discontinuation for one of the reasons listed below. However, subjects may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice. All reasons for discontinuation or withdrawal from trial will be recorded.

The maximum duration of treatment for pembrolizumab will be up to 35 cycles. The duration of treatment for XELOX will be until unacceptable drug-related toxicity or disease progression. If capecitabine is not tolerated, monotherapy with pembrolizumab may be continued. Patients who complete 35 cycles of therapy and have complete response or prolonged stable disease may also elect to end therpy with capecitabine after a discussion with their treating physician and with approval of the PI. Re-introduction of oxaliplatin is permitted provided that neuropathy has improved.Reasons for subject discontinuation by the Investigator may include, but are not limited to, the following:

- Death
- Confirmed radiographic disease progression (Note: With approval of the Lead PI, a subject may be granted an exception to continue on study treatment with confirmed radiographic progression if clinically stable or clinically improved.)
- Significant noncompliance by subject or Investigator
- Investigator or Lead PI determination that it is no longer safe and/or no longer in the subject's best interest to continue participation
- Withdrawal of consent
- Lost to follow-up
- Necessity for treatment with other anticancer treatment prohibited by protocol
- Sexually active subjects who refuse to use medically accepted methods of contraception during the course of the study and for 120 days following the last dose of study drug
- Women who become pregnant or are breast feeding
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol
- The following **Treatment-Related Discontinuation Criteria** attributed to pembrolizumab:
  - Any Grade 2 uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 OR requires systemic treatment.
    - Recurrent Grade 2 pneumonitis
    - Any Grade 3 non-skin adverse event lasting > 7 days, with the following exceptions for treatment-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, and infusion reactions:
    - Grade 3 uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of *any duration* requires discontinuation
    - Grade 3 laboratory abnormalities do not require treatment discontinuation except Grade 3 thrombocytopenia > 7 days OR associated with bleeding requires discontinuation
  - Any liver function test (LFT) abnormality that meets the following criteria:

- AST or ALT > 8 x ULN
- Total bilirubin > 5 x ULN
- Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

– Any Grade 4 adverse event or laboratory abnormality, except for the following events:
  - Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations, or radiographic signs of pancreatitis
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 3 days of their onset
  - Grade 4 endocrinopathy adverse events such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidosis, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (steroids, thyroid hormones) or glucose controlling agents, respectively, retreatment can be considered
– Any dosing interruption lasting > 6 weeks with the following exceptions:
  - Dosing interruptions to allow for prolonged steroid tapers to manage treatment-related adverse events are allowed
  - Dosing interruptions > 6 weeks that occur for non-treatment-related reasons may be allowed
– Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued pembrolizumab or lanreotide depot dosing

6.0 STUDY DRUGS

6.1 Treatment Compliance and Study Drug Accountability

The Investigator will maintain accurate records of receipt of all study drugs, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. At completion of the study, to satisfy regulatory requirements regarding drug accountability, all unused study drug will be reconciled and destroyed in accordance with applicable state and federal regulations.

6.2 Pembrolizumab

Pembrolizumab will be provided for this study by Merck & Co., a sterile, non-pyrogenic lyophilized powder for intravenous infusion supplied in single-use Type I glass vial containing 50 mg of pembrolizumab. The product is preservative-free, white to off-white powder and free from visible foreign matter. It is reconstituted with 2.3 mL sterile water for injection (WFI) to yield a 2.4 mL solution containing 25 mg/mL of pembrolizumab. The reconstituted vial contains an excess fill of 10 mg (equivalent to 0.4 mL of reconstituted solution) to ensure the recovery of label claim of 50 mg pembrolizumab per vial (equivalent to 2 mL of reconstituted solution).

6.2.1 Storage and Handling

Pembrolizumab Powder for Solution for Infusion vials should be stored at refrigerated conditions (2-8 °C). Prior to reconstitution, the vial of lyophilized powder can be out of refrigeration (temperatures at or below 25°C (77°F) for up to 24 hours. Following reconstitution with sterile water for injection, Pembrolizumab infusion solutions should be prepared in 0.9% Sodium Chloride Injection, USP (normal saline) or regional equivalent and the final concentration of pembrolizumab in the infusion solutions should be between 1 mg/mL and 10 mg/mL. If normal saline is not available, 5% Dextrose Injection, USP or regional equivalent (5% dextrose) is permissible. The preferred diluent is 0.9% Sodium Chloride and 5% dextrose is only permissible if normal saline is not available.

Pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of reconstituted drug product solution in vials, room temperature storage of admixture solutions in the IV bags and the duration of infusion. In addition, reconstituted vials and/or IV bags may be stored under refrigeration at 2 °C to 8 °C (36 °F to 46 °F) for up to 20 hours. If refrigerated, allow the vials and/or IV bags to come to room temperature prior to use.

Refer to Pembrolizumab Pharmacy Manual for additional drug product stability and handling guidelines.

6.2.2 Administration

Pembrolizumab 200 mg will be administered in an outpatient setting as a 30-minute IV infusion on Days 1 of each cycle. A treatment window of +/- 3 days of day 1 is allowed for cycle 2 and all subsequent cycles. Every effort should be made to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

It is preferred, but not mandatory, that pembrolizumab be administered after oxaliplatin infusion.

Refer to Pembrolizumab Pharmacy Manual specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

6.3 Oxaliplatin

Oxaliplatin will be obtained from commercial sources; the cost of oxaliplatin and its infusion will be billed to the subject and/or subject's insurance.

Oxaliplatin for injection and oxaliplatin injection) is an antineoplastic agent with the molecular formula C8H14N2O4Pt and the chemical name of cis-[(1 R,2 R)-1,2 cyclohexanediamine-N,N'] [oxalato(2-)-O,O'] platinum. Oxaliplatin is an organoplatinum complex in which the platinum atom is complexed with 1,2-diaminocyclohexane(DACH) and with an oxalate ligand as a leaving group. The molecular weight is 397.3. Oxaliplatin is slightly soluble in water at 6 mg/mL, very slightly soluble in methanol, and practically insoluble in ethanol and acetone.

Powder for solution for infusion: Oxaliplatin is supplied in vials containing 50 mg or 100 mg of oxaliplatin as a sterile, preservative-free lyophilized powder for reconstitution. Lactose monohydrate is present as an inactive ingredient at 450 mg and 900 mg in the 50 mg and 100 mg dosage strengths, respectively.

Concentrate for solution for infusion: Oxaliplatin is supplied in vials containing 50 mg, 100 mg or 200 mg of oxaliplatin as a sterile, preservative-free, aqueous solution at a concentration of 5 mg/ml. Water for Injection, USP is present as an inactive ingredient.

6.3.1 Storage and Handling

Powder for Solution for Infusion
Reconstitution or final dilution must never be performed with a sodium chloride solution or other chloride containing solutions. The lyophilized powder is reconstituted by adding 10 mL (for the 50 mg vial) or 20 mL (for the 100 mg vial) of Water for Injection, USP or 5% Dextrose Injection, USP. Do not administer the reconstituted solution without further dilution. The reconstituted solution must be further diluted in an infusion solution of 250-500 mL of 5% Dextrose Injection, USP. After reconstitution in the original vial, the solution may be stored up to 24 hours under refrigeration [2-8°C (36-46°F)]. After final dilution with 250-500 mL of 5% Dextrose Injection, USP, the shelf life is 6 hours at room temperature [20-25°C (68-77°F)] or up to 24 hours under refrigeration [2-8°C (36-46°F)]. Oxalipatin is not light sensitive.

Concentrate for Solution for Infusion
Do not freeze and protect from light the concentrated solution. A final dilution must never be performed with a sodium chloride solution or other chloride-containing solutions. The solution must be further diluted in an infusion solution of 250-500 mL of 5% Dextrose Injection, USP. After dilution with 250-500 mL of 5% Dextrose Injection, USP, the shelf life is 6 hours at room temperature [20-25°C (68-77°F)] or up to 24 hours under refrigeration [2-8°C (36-46°F)]. After final dilution, protection from light is not required.

Incompatibilities
Oxaliplatin is incompatible in solution with alkaline medications or media (such as basic solutions of 5-fluorouracil) and must not be mixed with these or administered simultaneously through the same infusion line. The infusion line should be flushed with 5% Dextrose Injection, USP prior to administration of any concomitant medication.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and discarded if present.

Needles or intravenous administration sets containing aluminum parts that may come in contact with oxaliplatin should not be used for the preparation or mixing of the drug. Aluminum has been reported to cause degradation of platinum compounds.

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions prepared from oxaliplation. The use of gloves is recommended. If a solution of oxaliplatin contacts the skin, wash the skin immediately and thoroughly with soap and water. If oxaliplatin contacts the mucous membranes, flush thoroughly with water.

6.3.2 Administration

The dose of oxaliplatin will be 130 mg/m^2 given on day 1 of a 3-week cycle, except in the “biomarker cycle” (i.e. first cycle for subjects in the dose expansion cohort). During the biomarker cycle, oxaliplatin will be given on Day 8 (to allow for one week of pembrolizumab monotherapy for biomarkers). A treatment window of +/- 3 days of day 1 is allowed for cycle 2 and all subsequent cycles.

It is preferable but not mandatory that oxaliplatin infusion should be administered before pembrolizumab on days when both drugs are given.

Oxaliplatin must be infused either by peripheral vein or central venous line over 2 hours. Infusion lines should be adequately flushed with 5% dextrose solution between the administrations of any other drugs. The administration of oxaliplatin does not require pre-hydration. Oxaliplatin should not be administered with saline or other chloride containing solutions. Oxaliplatin is unstable in the presence of chloride.

6.4 Capecitabine

Capecitabine will be obtained from commercial sources; the cost of capecitabine will be billed to the subject and/or subject's insurance.

Capecitabine is a fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is converted to 5-fluorouracil. The chemical name for capecitabine is 5'-deoxy-5-fluoro-N-[(pentyloxy) carbonyl]-cytidine and has a molecular weight of 359.35. Capecitabine is a white to off-white crystalline powder with an aqueous solubility of 26 mg/mL at 20ºC.

Capecitabine is supplied as biconvex, oblong film-coated tablets for oral administration. Each peach-colored tablet contains 500 mg capecitabine. The inactive ingredients in capecitabine include: anhydrous lactose, croscarmellose sodium, hydroxypropyl methylcellulose, microcrystalline cellulose, magnesium stearate and purified water. The peach or light peach film coating contains hydroxypropyl methylcellulose, talc, titanium dioxide, and synthetic yellow and red iron oxides.

6.4.1 Storage and Handling

Capecitabine tablets should be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). The container should be kept tightly closed.

Care should be exercised in the handling of capecitabine. Capecitabine tablets should not be cut or crushed. Procedures for the proper handling and disposal of anticancer drugs should be considered.

6.4.2 Administration

At the discretion of the treating physician, the patient may receive 850mg/m^2 or 1000mg/m^2 of capecitabine. Capecitabine will be administered at a dose of 850/1000 mg/m^2 twice daily, for a total daily dose of 1700/2000 mg/m^2 beginning the morning of Day 1 of each 3-week cycle and continuing through the evening of Day 14; except in the "biomarker cycle" (i.e. first cycle for subjects in the dose expansion cohort). During the biomarker cycle, capecitabine will begin on Day 8 (to allow for one week of pembrolizumab monotherapy for biomarkers). A treatment window of +/- 3 days of day 1 is allowed for cycle 2 and all subsequent cycles.

See current capecitabine package insert for dosing instructions in patients with moderate renal impairment.

The dose of capecitabine will be calculated on the basis of milligrams of drug per square meter (mg/m^2) of body surface area (BSA). The dose of capecitabine will be rounded to the nearest dose that can be obtained by using the 500 mg tablets. Since capecitabine tablets cannot be split, patients may take different numbers of pills in the morning and evening in order to achieve the appropriate dose. The following is an example of how dose rounding may be performed:

Explanation:	[{BSA} m^2 x {dose level} mg/m^2] x 2 = Daily Dose mg Daily Dose mg ÷ 500 mg tablet = number of tablets per day, rounded to whole tablets Divide number of whole tablets per day into 2 doses for morning (AM) and evening (PM)
Calculation:	[1.68m^2 x 1000mg/m^2] x 2 = 3360mg 3360mg ÷ 500mg tablet = 6.72 tablets per day, rounded to 7 tablets per day Divide 7 tablets into 2 doses = three 500mg tablets in AM and four 500mg tablets in PM

The dose will be recalculated per institutional standard (e.g., based on the new body surface area prior to the start of each cycle only if the weight changes by 10% from baseline).

Capecitabine will be taken orally. The total daily dose should be taken as two divided doses approximately 12 hours apart, within 30 minutes after the ingestion of food, ideally after breakfast and the evening meal. Tablets should be swallowed with approximately 200 ml of water (not fruit juices). Tablets are not scored and should not be split. If needed, capecitabine may be dissolved for administration either orally or via G or J tube but patient must receive safety handling training from pharmacy personnel.

6.5 Concomitant Medications/Vaccinations

Concomittant medications will be documented throughout the study. 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 Lead PI.

6.5.1 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 local standards of medical care. All concomitant medication received from the date of signed informed consent through 30 days after the last dose of study drug should be recorded on the CRF including all prescription, over-the-counter (OTC), herbal supplements, and IV medications.

Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject. Otherwise, subjects must agree to use two birth control methods after informed consent is signed through 120 days after the last dose of study drug. The two methods can either be two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. The following are considered adequate barrier methods of contraception: diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide), cervical cap with spermicide (nulliparous women only), contraceptive sponge (nulliparous women only), and male condom or female condom (cannot be used together). Appropriate hormonal contraceptives will include oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection.

6.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Period of this study:

- 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 to target lesions. If subject needs palliative local radiation (e.g., for relief of dysphagia or of pain from bony metastases), protocol therapy may be delayed with the

approval of the lead PI. Radiation therapy must be completed for at least 14 days prior to resumption of protocol treatment.

- Live vaccines within 30 days prior to the first dose of study drug and while participating in the study. 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. Prophylactic dosing of steroids prior to treatment and administration of low dose steroids for up to 48 hours post treatment is permitted. Corticosteroids administered as pre-medication for IV contrast allergy are also allowed.

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.

There are no prohibited therapies during the Follow-up Period.

7.0 DOSE MODIFICATION AND TOXICITY MANAGEMENT

Subjects will be monitored continuously for AEs throughout the study and for 30 days after the last dose of study drug. Subjects will be instructed to notify their treating physician of any and all AEs. Toxicity will be graded according to NCI-CTCAE version 4.0.

All AEs should also be managed with supportive care at the earliest signs of toxicity considered related to study drug(s).

7.1 Dose Modifications

Subjects experiencing one or more AEs due to the study drug(s) may require dose modification(s) as described in Section 7.1.1 and Section 7.1.2. At the discretion of the Investigator, dose modifications are permitted outside of the those provided in the protocol if the Investigator feels it is in the interest of the subject's safety (e.g., due to multiple toxicities, persistent toxicities, intercurrent illness, or short term compliance or monitoring issues, etc.).

Subjects may need to be followed at least weekly when any study drug is held for toxicity until the toxicity returns to Grade ≤ 1 or is determined to be chronic or irreversible.

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 4 weeks of the scheduled interruption, unless otherwise discussed with the Lead PI. The reason for interruption should be documented in the patient's study record. Dosing may be interrupted if there is a need for local palliative radiation therapy, with the approval of the lead PI. In this case, protocol-based therapy cannot be resumed until patients are at least 14 days out from the end of radiation.

If pembrolizumab is permanently discontinued, the subject will be discontinued from study treatment. Maximum duration of treatment for pembrolizumab will be up to 35 cycles. If patients discontinue oxaliplatin due to intolerance, they can be maintained on capecitabine and pembrolizumab. If capecitabine is not tolerated, pembrolizumab monotherapy may be continued. Re-introduction of oxaliplatin is permitted provided neuropathy has improved.

All dose modifications and reasons for modification must be recorded in the CRF.

7.1.1 Pembrolizumab Dose Modifications

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 treatment-related toxicities as per Table 7.1.1. There are no dose reductions for pembrolizumab.

Note: Subject must be permanently discontinued for any severe or Grade 3 treatment-related toxicity that recurs or any life-threatening event unless otherwise specified in Table 7.1.1.

General Instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Table 7.1.1 Pembrolizumab Dose Modifications

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation
	Grade 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
				(ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Hypothyroidism	Grade 2	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
[1] Withhold or permanently discontinue pembrolizumab at the discretion of the investigator or treating physician. NOTE: For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

7.1.2 XELOX Dose Modifications

Toxicity Grade[a]	Occurrence	Oxaliplatin	Capecitabine
DIARRHEA			
Grade 1	Any	Maintain dose	Maintain dose

Grade 2	Any	If tolerable: Maintain dose If intolerable: Hold until grade ≤1, then resume at 80% of **current** dose	If tolerable: Maintain dose If intolerable: Hold until grade ≤1,then resume at 80% of **current** dose [b]
Grade 3	1st – 3rd	Hold until grade ≤1, then resume at 80% of **current** dose	Hold until grade ≤1, then resume at 80% of **current** dose
	4th and higher	Hold until grade ≤1, –obtain permission of PI to resume at 80% of **current** dose	Hold until grade ≤1, obtain permission of PI to resume at 80% of **current** dose–
Grade 4	1st	Hold until grade ≤1, then resume at 60% of **current** dose	Hold until grade ≤1, then resume at 60% of **current** dose
	2nd and higher	Hold until grade ≤1, obtain permission of PI to resume at 60% of **current** dose [b]	Hold until grade ≤1, obtain permission of PI to resume at 60% of **current** dose [b]

VOMITING			
Grade 1	Any	Maintain dose	Maintain dose
Grade 2	Any	Maintain dose	Maintain dose
Grade 3 [occurring within 3 days of Oxaliplatin dosing despite optimal anti-emetic prophylaxis]	1st	Hold until grade ≤1, then resume at 80% of **current** dose [c]	Maintain dose
	2nd and higher	Hold until grade ≤ 1, then resume at current dose. [c]	Maintain dose
Grade 4 (TPN, intensive care or hemodynamic collapse) [occurring within 3 days of Oxaliplatin dosing despite optimal anti-emetic prophylaxis]	1st	Hold until grade ≤1 [c], then resume at 60% of **current** dose	Hold until grade ≤1, then resume at 60% of **current** dose
	2nd and higher	Discontinue	Hold until grade ≤1, obtain permission of PI to resume at 60% of **current** dose

a. National Cancer Institute Common Terminology Criteria Version 3.
b. Continue treatment if it is considered to be in the best interest of the patient
c. **NOTE:** After Cycle 1, at the discretion of the treating physician, once there is recovery of the toxicity to grade ≤1, the treating physician may choose, to hold oxaliplatin and continue capecitabine and pembrolizumab at current dose as clinically indicated. If the treating physician chooses to restart oxaliplatin later in the patient's treatment course, the dose of oxaliplatin at which the patient restarts should be one dose level lower than last dose level on which patient was treated. The specific treatment approach used and dose modifications that occur are required to be reported in the Case Report Forms.

OTHER CLINICALLY SIGNIFICANT* NON-HEMATOLOGIC ADVERSE EVENTS			
ToxicityGrade[a]	**Occurrence**	**Oxaliplatin**	**Capecitabine**
Grade 1	Any	Maintain dose	Maintain dose
Grade 2	1st	Hold until grade ≤1, then resume at 80% of **current** dose [c]	Hold until grade ≤1, then resume at 80% of **current** dose

OTHER CLINICALLY SIGNIFICANT* NON-HEMATOLOGIC ADVERSE EVENTS			
ToxicityGrade[a]	**Occurrence**	**Oxaliplatin**	**Capecitabine**
	2nd and higher	Hold until grade ≤ 1, then resume at current dose. [b,c]	Hold until grade ≤1, then resume at 80% of **current** dose
Grade 3	1st	Hold until grade ≤1, then resume at 80% of **current** dose [c]	Hold until grade ≤1, then resume at 80% of **current** dose
	2nd and higher	Hold until grade ≤ 1, then resume at current dose. [b,c]	Hold until grade ≤1, then resume at 80% of **current** dose
Grade 4	1st	Hold until grade ≤1, then resume at 60% of **current** dose [c]	Hold until grade ≤1, then resume at 60% of **current** dose
	2nd and higher	Hold until grade ≤1, obtainpermission of PI to resume at 60% of **current** dose [b]	Hold until grade ≤1, obtain permission of PI to resume at 60% of **current** dose [b]

a. National Cancer Institute Common Terminology Criteria Version 3.0
b. Continued treatment if it is considered to be in the best interest of the patient.
c. **NOTE:** After Cycle 1, at the discretion of the treating physician, once there is recovery of the toxicity to grade ≤1, the treating physician may choose, instead of lowering the dose of capecitabine, to hold oxaliplatin and continue capecitabine and pembrolizumab at current dose as clinically indicated. If toxicity recurs, follow original dose modification instructions for capecitabine. If the treating physician chooses to restart oxaliplatin later in the patient's treatment course, the dose of oxaliplatin at which the patient restarts should be one dose level lower than last dose level on which patient was treated. The specific treatment approach used and dose modifications that occur are required to be reported in the Case Report Forms.

* Dose adjustments only for clinically significant toxicities (e.g. asymptomatic lab abnormalities do not necessarily require dose modifications) If non-hematologic toxicities can be attributed solely to either oxaliplatin, capecitabine, or pembrolizumab then no dose adjustments of the other agents are needed.

HEMATOLOGIC ADVERSE EVENTS			
ToxicityGrade[a]	**Occurrence**	**Oxaliplatin**	**Capecitabine**
NEUTROPENIA			
Grade 1	Any	Maintain dose	Maintain dose
Grade 2	Any	Maintain dose	Maintain dose
Grade 3(≥0.5 - <1x10^9/L)	1st	Hold until grade ≤1, then resume at **current** dose	Maintain dose
	2nd and higher	Hold until grade ≤1, then resume at 80% of **current** dose [d]	Maintain dose
Grade 4 (< 0.5 x10^9/L)	1st	Hold until grade ≤ 1, then resume at 80% of **current** dose.[b,c,d]	Hold until grade ≤1, then resume at 80% of the **current** dose [b,c]
	2nd and higher	Hold until grade ≤1, obtain permission of PI to resume at 60% of **current** dose [d]	Hold until grade ≤1, obtain permission of PI to resume at 60% of **current** dose
FEBRILE NEUTROPENIA			
Grade 3 (neutropenia and fever ≥ 38.5C)	1st – 2nd	Hold until resolution of fever and neutropenia to grade ≤ 1, then resume at 60% of **current** dose [d]	Hold until resolution of fever and neutropenia to grade ≤1, then resume at 60% of **current** dose [b,c,d]
	3rd	Discontinue Protocol Therapy	Discontinue Protocol Therapy
Grade 4 (neutropenia and fever ≥ 38.5 C)	Any	Discontinue Protocol Therapy	Discontinue Protocol Therapy
THROMBOCYTOPENIA			
Grade 1 (< LLN - <75.0 x 10^9 /L)	Any	Maintain dose	Maintain dose
Grade 2(≥50.0 - < 75.0 x 10^9 /L)	1st	Hold until grade ≤1, then resume at 80% of **current** dose [d]	Maintain dose
	2nd and higher	If stable grade 2, maintain current dose	Maintain dose
Grade 3(≥25.0 - < 50.0 x 10^9 /L)	1st	Hold until grade ≤1, then resume at 80% current dose [d]	Hold until grade ≤1, then resume at 80% of the **current** dose
	2nd and higher	Hold until grade ≤1, then resume at 80% current dose [d]	Hold until grade ≤1, then resume at 80% of the **current** dose [b]
Grade 4(< 25.0 x 10^9 /L)	1st	Hold until grade ≤1, then resume at 60% of the **current** dose [b,d]	Hold until grade ≤1, then resume at 60% of the **current** dose [b]
	2nd	Discontinue Protocol Therapy	Discontinue Protocol Therapy

HEMOGLOBIN			
Grade 1 < LLN - 10.0 g/dL < LLN - 100 g/L < LLN - 6.2mmol/L	Any	Maintain dose	Maintain dose[b]
Grade 2 8.0 - < 10.0 g/dL 80 - < 100 g/L 4.9 - < 6.2 mmol/L	Any	Maintain dose	Maintain dose
Grade 3 6.5 - < 8.0 g/dL 65 - < 80 g/L 4.0 - < 4.9 mmol/L	Any	Maintain dose	Maintain dose
Grade 4 < 6.5 g/dL < 65 g/L < 4.0 mmol/L	Any	Hold until ≤ grade 2; then resume at current dose, may transfuse [b]	Maintain dose [b]
OTHER HEMATOLOGIC TOXICITY			
Grades 1 - 4	Any	Maintain dose	Maintain dose

a. National Cancer Institute Common Terminology Criteria Version 3.0
b. Continued treatment only if it is considered to be in the best interest of the patient
c. Consider growth factor support if continuing treatment is felt to be in the patient's best interest.
d. **NOTE:** After Cycle 1, at the discretion of the treating physician, once there is recovery of the toxicity to grade ≤1, the treating physician may choose, to hold oxaliplatin and continue capecitabine and pembrolizumab at current dose as clinically indicated. If the treating physician chooses to restart oxaliplatin later in the patient's treatment course, the dose of oxaliplatin at which the patient restarts should be one dose level lower than last dose level on which patient was treated. The specific treatment approach used and dose modifications that occur are required to be reported in the Case Report Forms.

7.1.2.1 Special Guidelines Related to Capecitabine Toxicity

7.1.2.1.1 Diarrhea

Capecitabine can cause diarrhea, and should be ***stopped at diarrhea grade ≥ 2***, and treated symptomatically (recommend IV hydration and use of loperamide for diarrhea, observing loperamide dosage recommendation and treatment start, see below). If control takes longer than 2 days, medical evaluation including relevant diagnostic procedures, alternative treatment and possible investigation of Dihydropyrimidine Dehydrogenase Deficiency (DPD) deficiency should be considered. Capecitabine cannot be re-started until diarrhea has resolved to baseline or grade < 2.

The recommended dosage regimen for loperamide: 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. During the night, the patient may take 4 mg of loperamide every 4 hours. Note: This dosage regimen exceeds the usual dosage recommendations for loperamide. Premedication with loperamide is not recommended.

The use of drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea. Patients should be advised to contact their physician to discuss any laxative use.

Patients with ≥ grade 3 diarrhea should also be evaluated for c-difficile.

Patients with neutropenia and diarrhea should be considered for empiric use of prophylactic antibiotics, such as oral quinolones.

7.1.2.1.2 Hand-Foot Syndrome

Toxicity Grade[a]	Occurrence	Oxaliplatin	Capecitabine
1	Any	Maintain dose	Maintain dose
2	1st – 3rd	Maintain dose	Hold until grade ≤1, then resume 80% of **current** dose
	4th and higher	Discontinue Protocol Therapy	Discontinue Protocol Therapy
3	1st – 2nd	Maintain dose	Hold until grade ≤1, then resume at 80% of **current** dose
	3rd and higher	Discontinue Protocol Therapy	Discontinue Protocol Therapy

a. National Cancer Institute Common Terminology Criteria Version 3.0
b. Continued treatment only if it is considered to be in the best interest of the patient
c. **NOTE:** After Cycle 1, at the discretion of the treating physician, once there is recovery of the toxicity to grade ≤1, the treating physician may choose, to hold oxaliplatin and continue capecitabine and pembrolizumab at current dose as clinically indicated. If the treating physician chooses to restart oxaliplatin later in the patient's treatment course, the dose of oxaliplatin at which the patient restarts should be one dose level lower than last dose level on which patient was treated. The specific treatment approach used and dose modifications that occur are required to be reported in the Case Report Forms.

*Applies only for grading hand–foot syndrome and should not be used to describe any other skin event and/or other cutaneous area.

In the case of a discrepancy between the clinical domain and the functional domain, the assigned grade should correspond to the domain with the higher grade.

Grade 2-3 Hand-Foot Skin Reaction
Treat symptomatically (recommended use of emollients) and according to above table. The use of vitamin B6 (Pyridoxine) has been reported to be of possible benefit for symptomatic or secondary prophylactic treatment, but due to a possible interaction with cisplatin (and thus possibly oxaliplatin) the use of B6 is not permitted in this trial.

7.1.2.1.3 Stomatitis/Oral Mucositis/Mouth Ulcers

Stomatitis/oral mucositis/mouth ulcers due to capecitabine should be treated using local supportive care. Please follow the paradigm below for treatment of stomatitis/oral mucositis/mouth ulcers:

- For mild toxicity (grade 1), use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution.

- For more severe toxicity (grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as, benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®). For patients with grade 2 and above stomatitis, capecitabine may be held or dose reduced according to dose reduction table for non-hematologic toxicities (Section 3.3.4).

- Agents containing hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents. The ingredient list of used toothpastes and mouthwashes should be checked for these agents.

- Antifungal agents must be avoided unless a fungal infection is diagnosed. Topical antifungal agents are preferred if an infection is diagnosed. Similarly, antiviral agents such as acyclovir should be avoided unless a viral infection is diagnosed.

Note: Stomatitis/oral mucositis should be appropriately graded using the functional grading given on the NCI-CTC for Adverse Events, version 3.0.

7.2.1.2 Special Guidelines Related to Oxaliplatin Toxicity

7.2.1.2.1 Dose Modifications for Neurological Toxicity Related to Oxaliplatin

Toxicity Grade	Duration of Toxicity		Persistent Between Cycles[a]
	1-7 Days	> 7 Days	
Grade 1 Paresthesias/dysesthesias[b] that do not interfere with function	Maintain dose	Maintain dose	Maintain dose
Grade 2 *Tolerable* Paresthesias/dysesthesias[b] interfering with function, but not activities of daily living (ADL)	Maintain dose	Maintain dose	Continue to dose but reduce to 80% of current dose [c]
Grade 2 *Intolerable* Paresthesias/dysesthesias[b] interfering with function, but not activities of daily living (ADL)	Hold until grade ≤1; then resume at 80% of **current** dose [d]	Hold until grade ≤1; then resume at 80% of **current** dose [d]	Hold until grade ≤1; then resume at 80% of **current** dose [d]
Grade 3 Paresthesias/dysesthesias[b] with pain or with functional impairment that also interfere with ADL	Hold until grade ≤1; then resume at 80% of **current** dose [d]	Hold until grade ≤1; then resume at 80% of **current** dose [d]	Hold until grade ≤1; then resume at 80% of **current** dose [d]
Grade 4 Persistent paresthesias/dysesthesias[b] that are disabling or life-threatening	Hold until grade ≤1; then resume at 60% of **current** dose [d]	Hold until grade ≤1; then resume at 60% of **current** dose [d]	Hold until grade ≤1; then resume at 60% of **current** dose [d]
ACUTE (during or after the 2 hour infusion) laryngopharyngeal dysesthesias[b]	1st occurrence: Increase duration of next infusion to 4 hours[d] 2nd and higher occurrence: Increase infusion to 6 hours	N/A	N/A

a. Not resolved by the beginning of the next cycle.
b. May be cold-induced.
c. If grade 2 *tolerable* neurologic toxicity persists longer than 6 weeks, despite oxaliplatin dose adjustments, oxaliplatin should be held and therapy with capecitabine and pembrolizumab can be continued. If neurologic toxicity subsequently resolves to ≤ Grade 1, oxaliplatin therapy may resume at 80% of current dose.
d. **NOTE:** After Cycle 1, the treating physician may choose to hold oxaliplatin and continue capecitabine and pembrolizumab at current dose as clinically indicated. If toxicity resolves to grade 1 or less the treating physician may chooses to restart oxaliplatin later in the patient's treatment course, the dose of oxaliplatin at which the patient restarts should be one dose level lower than last dose level on which patient was treated. The specific treatment approach used and dose modifications that occur are required to be reported in the Case Report Forms.

If grade 2 intolerable, grade 3 or grade 4 neurological toxicity (see Table 3E) is evident at the time of the next planned administration of oxaliplatin, then oxaliplatin administration will be held until the next treatment cycle. Capecitabine and pembrolizumab will be administered if otherwise appropriate.

Missed doses will not be made up. If toxicity resolves to grade 1 or less at next treatment cycle, resume oxaliplatin per instructions provided in Table 3E. If neurological toxicity is still present and has not resolved to grade 1 or less at the next treatment cycle, oxaliplatin will continue to be held. Patients may continue to receive capecitabine and pembrolizumab on study if otherwise appropriate.

Oxaliplatin may be repeatedly temporarily discontinued and then re-initiated in this fashion unless the patient has disease progression, whereby the patient will be removed from the study. However, if the patient is not receiving oxaliplatin at the time of progression, if it is appropriate and safe as determined by the treating physician that oxaliplatin can be restarted, oxaliplatin may be restarted and the patient may continue on treatment. If the patient has disease progression on oxaliplatin or it is not safe or appropriate to restart oxaliplatin, the patient will be removed from the study.

Dose escalations of oxaliplatin are not permitted at any time.

Laryngopharyngeal Dysesthesia
An unusual laryngopharyngeal dysesthesia (LPD), a loss of *sensation* of breathing without any *objective* evidence of respiratory distress (laryngospasm, bronchospasm or hypoxia) has also been observed. This neurotoxicity may be induced or exacerbated upon exposure to cold and should be distinguished from a hypersensitivity reaction. If a patient develops LPD, the patient's oxygen saturation should be evaluated via a pulse oximeter and, if normal, reassurance, a benzodiazepine or other anxiolytic agent should be considered and the patient should be observed in the clinic until the episode has resolved. The oxaliplatin infusion may then be continued at a reduced rate, 33% of the original rate. Because this syndrome may be associated with the rapidity of oxaliplatin infusion, subsequent doses of oxaliplatin should be administered as 4-6-hour infusions. To minimize the risk of LPD, patients will be instructed to avoid ice and cold drinks the day of treatment.

Hypersensitivity Reactions
Oxaliplatin, as is the case with all platinum-containing compounds, is associated with a measurable (approximately 11%) incidence of hypersensitivity reactions, usually after multiple doses of treatment. This may present as bronchospasm, hypotension, and even hemolytic anemia. Pre-treatment with glucocorticoids and anti-histamines may be useful for some patients, but may not always prevent the development of anaphylactoid reactions, especially in patients with a prior history of hypersensitivity to this agent. For patients who have experienced a Grade 1 or 2 acute hypersensitivity reaction that is assessed as related to oxaliplatin administration, the following premedication is recommended prior to each subsequent dose of oxaliplatin:

Dexamethasone 20 mg PO or IV, 12 and 6 hours prior to the oxaliplatin dose;
OR

Dexamethasone 20 mg PO or IV, as well as diphenhydramine 50 mg IV, and one of the following: cimetidine 300 mg IV, ranitidine 50 mg IV, or famotidine 20 mg IV 30-60 minutes prior to oxaliplatin administration.

If these prophylactic measures fail to prevent oxaliplatin-related hypersensitivity, therapy with oxaliplatin should be discontinued.

Patients who have grade 3 or 4 acute hypersensitivity reactions should discontinue oxaliplatin therapy.

Pulmonary Fibrosis
In the case of unexplained respiratory symptoms such as nonproductive cough, dyspnea or radiological pulmonary infiltrates, oxaliplatin should be discontinued until further investigation excludes

interstitial pulmonary fibrosis. If interstitial pulmonary fibrosis is confirmed, oxaliplatin therapy should be terminated.

7.2 Toxicity Management

Subjects should receive appropriate supportive care measures as deemed necessary by the Investigator. It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. 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.

7.2.1 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 recurrent **Grade 2 events**, discontinue treatment with pembrolizumab.
- For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
- For first occurrence of **Grade 3-4 events**, discontinue treatment with pembrolizumab.

Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

7.2.2 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.

7.2.3 Diabetes Mellitus

Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or **Grade 3-4 Hyperglycemia**, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)

- 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.

7.2.4 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.

7.2.5 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.

7.2.6 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.

7.2.7 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.

7.2.8 Infusion Reactions

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.

Table 7.2.8 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 7.2.8 Infusion Reaction Treatment Guidelines

NCI-CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None

NCI-CTCAE Grade	Treatment	Premedication at Subsequent Dosing
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 1hr 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 1.5hr (± 30 minutes) prior to infusion of pembrolizumab with: • Diphenhydramine 50 mg po (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
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

8.0 CORRELATIVES

Tissue and blood based biomarker studies will be performed to better understand the role of factors that may be associated with efficacy or toxicity from study treatment and/or cancer biology. Additional markers related to efficacy, toxicity, and/or cancer biology may be analyzed. Anticipated analyses are listed below and focus on factors associated with angiogenesis, inflammation, immunity, and tumor growth. However, final analyte lists and technology platforms will be based upon best science and available funding at the time of analysis. External vendors and collaborators may conduct or participate in these analyses, provided sampels are de-identified. All collaborations will be subject to Duke policies on sample and data sharing.

8.1 Tumor Tissue Biomarkers

Archived formalin fixed paraffin embedded (FFPE) tumor tissue will be collected for all subjects (if available). Refer to *Study Manual* for collection, processing, and submission details.

For patients accrued to the dose expansion cohort, pre-treatment and on-treatment tumor biopsies will be performed only on patients who have a tumor lesion that is amenable to safe biopsy. In the biomarker cycle, patients will undergo tumor biopsy up to 1 week before starting treatment (i.e., pre-treatment) and will undergo a second tumor biopsy on Day 7 or 8 prior to start of oxaliplatin and capecitabine (i.e., on-treatment). The preferred type of biopsy is a core biopsy: five 18-gauge core needle biopsies (diameter about 2 mm) with a throw length of approximately 2 cm will provide adequate tissue for study. Refer to *Study Manual* for collection, processing, and submission details. Note: Those patients accrued to the dose expansion cohort who do not have a tumor lesion that is amenable to safe biopsy will only have blood-based biomarker collections in the biomarker cycle (ie. Cycle 1).

We will interrogate these tissue specimens using whole exomic sequencing studies, spacial transcriptomic analysis, and proximity ligation assays to spatially resolve the impact of pembrolizumab on tumor T cell/PMN-MDSC infiltration and NLRP3 inflammasome activation. These data will be correlated with mutations associated with this resistance pathway as well as with clinical response. This work will leverage a rare tissue bank of pre- and post-pembro tumor specimens to reveal a series of novel pharmacologic targets and potential biomarkers capable of overcoming immunotherapy resistance and improving the management of patients with gastrointestinal maligancies.

Archived FFPE tumor tissue and pre-treatment/on-treatment tumor biopsy samples will be tested by IHC for CD8 and PDL1 staining, the primary biomarker endpoints for this study. Expression of additional proteins that may be associated with sensitivity or resistance to pembrolizumab or XELOX and pembrolizumab, including but, not limited to, TGFβ1, STAT3, and various immune cell populations, including CD3, CD4, CD8, Treg, (FoxP3), Th17 T-cells and monocyte/macrophage and neutrophil populations. RNA Seq or PCR may also be performed for analyses of factors that may be associated with sensitivity or resistance to these agents including but not limited to CD3, CD4, CD8, EOMES, IFNγ, FOXP-3, Granzyme-A, Granzyme-B, Perforin, IL1β, IL6, IL7, IL10, IL11, IL12, IL17A, IL17E, IL22, and IL23. Micro-satellite instability (MSI) by IHC and/or polymerase chain reaction (PCR) may also be assessed.

Genetic alterations, including both gene mutation and copy number alteration, may be characterized using a customized Next Gen Sequencing platform. Samples evaluated will be archived FFPE tumor samples. Further refinement of these approaches can be made depending on interest.

8.2 Circulating Immune Cells (PBMC)

Peripheral blood will be collected for peripheral blood mononuclear cells (PBMCs) from each subject at the following timepoints: baseline, end of monotherapy lead-in on Day 8 (biomarker cycle of dose

expansion cohort only), end of first cycle of combination therapy on Day 29 (biomarker cycle of dose expansion cohort only), first restaging only, disease progression or treatment discontinuation, and for complete responders on long term follow-up. Refer to *Study Manual* for collection and submission details.

PBMCs will be processed and stored by the Duke Immune Profiling Core facility under the direction of Dr. Kent Weinhold. Polychromatic flow cytometry (PFC) panels will be used to compare treatment related changes in both tumor and peripheral immune cell compartments. Up to 50 markers may be analyzed using 3 PFC panels: 1) a 12-color 'Exhaustion Panel', 2) a 12-color 'Tumor Reactive T Cell Panel', and 3) a 14-color regulatory T cell (Treg) and myeloid-derived suppressor cells (MDSC) panel. This analysis will be overseen by Dr. Weinhold.

8.3 Protein Multiplex Arrays (Plasma)

Peripheral blood will be collected for plasma from each subject at the following timepoints: baseline, end of monotherapy lead-in on Day 8 (biomarker cycle of dose expansion cohort only), end of first cycle of combination therapy on Day 29 (biomarker cycle of dose expansion cohort only), every restaging, disease progression or treatment discontinuation, off treatment follow-up, and for complete responders on long term follow-up. Refer to *Study Manual* for collection, processing, and submission details.

Plasma will be stored by the Duke Phase I Biomarker Laboratory under the direction of Dr. Andrew Nixon. Markers of inflammation will be analyzed in the Duke Phase I Biomarker lab. Analyses will be performed on pre-treatment and on-treatment samples. Analyte levels, and changes in analyte levels, will be correlated with clinical outcome (PFS, OS). Plasma and serum samples will be evaluated by ELISA for protein markers that may be associated with sensitivity or resistance to pembrolizumab. These may include CRP and other markers of inflammation, including but not limited to IFNγ, IL1β, IL4, IL6, IL7, IL10, IL12, IL17A, IL17E, and IL23.

8.4 Pharmacogenomics (Whole Blood)

Subjects will have whole blood collected at baseline. Refer to *Study Manual* for collection, processing, and submission details.

Whole blood will be stored for possible future analysis of HLA type and other candidate markers of efficacy and toxicity by the Duke Phase I Biomarker Laboratory under the direction of Dr. Andrew Nixon with the consent of the patient.

8.5 Future Use of Patient Samples

Any remaining biological materials at the end of the study will be deidentified and deidentified samples may be retained for possible use in biomarker research with the consent of the patient.

8.6 Correlative Collaborations

8.6.1. Duke-Personalis Collaboration

In order to identify potential mechanisms of sensitivity and resistance to pembrolizumab in gastric cancer and to better characterize the changes of key tumor and immune factors in response to pembrolizumab therapy, we plan to collaborate with Personalis, Inc. for both tissue- and blood-based biomarker analyses using their comprehensive, state-of-the-art technology platforms (https://www.personalis.com/).

8.6.1.1 The following samples for the specified assays and analytic pipelines will be shared with Personalis.

Sample Type	Sample Format/Quantity	Assay Type
FFPE tumor tissue 50 samples	4 x 5um unstained slides or 2 x 10um curls, 25mm^2 surface area per sample	ImmunoID NeXT
PBMC 36 samples	2-4 million frozen PBMC per sample	ImmunoID NeXT
Plasma 150 samples	Up to 8 ml per sample	NeXT Liquid Biopsy

8.6.1.2 The following clinical data will be shared with Personalis in order to utilize pre-existing biomarker analytic pipelines. Duke statisticians will work with both teams in a collaborative fashion to analyze and interpret the data from each project.

- Deidentified patient metadata.
  - Patient age, gender, race/ethnicity, prior therapies, treatment duration, treatment dosage, smoking status, tumor size, tumor site
- RECIST and iRECIST response data for each patient case per timepoint
- Deidentified patient outcomes data.
  - OS, PFS and response to therapy

No personal health information will be shared with Personalis.

8.6.2 Duke – Olink Collaboration

In order to identify potential mechanisms of sensitivity and resistance to pembrolizumab in gastric cancer and to better characterize the changes of key tumor and immune factors in response to pembrolizumab therapy, we plan to collaborate with Olink for both tissue- and blood-based biomarker analyses using their comprehensive, state-of-the-art technology platforms (https://www.olink.com/)

8.6.2.1 The following samples for the specified assays and analytic pipelines will be shared with Olink.

Sample Type	Sample Format/Quantity	Assay Type
Fresh frozen tumor tissue 25 samples	Tissue lysate, 20 ug per sample	Olink Explore 1536
PBMC 150 samples	Cell lysate, 1000 PBMCs per sample	Olink Explore 1536
Plasma 150 samples	100 µl per sample	Olink Explore 1536

8.6.2.2 The following clinical data will be shared with Olink in order to utilize pre-existing biomarker analytic pipelines. Duke statisticians will work with both teams in a collaborative fashion to analyze and interpret the data from each project.

- Deidentified patient metadata.
  - Patient age, gender, race/ethnicity, prior therapies, treatment duration, treatment dosage, smoking status, tumor size, tumor site
- RECIST and iRECIST response data for each patient case per timepoint
- Deidentified patient outcomes data.
  - OS, PFS and response to therapy

No personal health information will be shared with Olink.

9.0 STATISTICAL ANALYSIS

9.1 General Analysis Considerations

Thirty-five (35) evaluable patients will be enrolled and treated.

9.1.1 Primary Endpoint

The primary endpoint will be progression-free survival (PFS) measured from study entry until documented progression or death from any cause. Patients who have not experienced progression will be censored at the date of the last radiographic assessment. Based on the results of the AVAGAST and ToGA trials a median PFS of approximately 5.5 months is expected for patients treated with oxaliplatin and capecitabine alone. Also, observed PFS hazard ratios of 0.80 and 0.71 were reported for AVAGAST and ToGA, respectively. With 35 patients enrolled, the difference between a historical median PFS of 5.5 months and experimental median of 7.3 months, a hazard ratio of 0.75, can be detected with 80% power (1-sided test of single exponential mean, α=0.2).

PFS and median PFS will be estimated using the Kaplan-Meier method. The 95% confidence interval estimate for median PFS will be computed using the variance estimate proposed by Brookmeyer and Crowley. Under the alternative hypothesis, 32 PFS events are expected at the end of the follow-up period.

The primary analysis of PFS will be intention-to-treat in that all patients who have undergone at least one scheduled restaging on-treatment, or who have had unequivocal progression prior to the first scheduled restaging will be followed for progression. These patients will be followed for PFS, even if they are removed from treatment due to unacceptable toxicity or because they withdrew consent. As a secondary analysis, these patients will be censored at the time they were removed from treatment.

The magnitude of reduction in tumor burden will be summarized descriptively (such as a waterfall plot) based on change in the sum of the longest diameters of target lesions relative to baseline.

9.1.2 Secondary Endpoints

Secondary endpoints include the safety and tolerability of the XELOX/pembro regimen and response rate (RR). Adverse events will be described and presented by Type and Grade according to NCI-CTCAE version 4.03 criteria and descriptively compared with historical controls.

Radiographic imaging will be repeated every three cycles (approximately every 9 weeks) as described in Section 5.0. Tumor response defined as complete response (CR) or partial response (PR) will be assessed using RECIST 1.1 (see Section 5.6).

RR will be estimated by the 90% confidence interval for the binomial proportion. With 35 patients studied (5 in the safety validation and 30 in the expanded cohort), RR can be estimated to within at most +/- 0.14 with 90% confidence.

The magnitude of reduction in tumor burden will be summarized descriptively (such as with a waterfall plot) based on change in the sum of the longest diameters of target lesions relative to baseline.

Overall survival (OS) will be described.

9.1.3 Exploratory Endpoints

CD8 and PDL1 staining measured by IHC are the primary biomarker endpoints for this study. Descriptive statistics will be provided for each of these endpoints at each time point (pre-, P, and on-treatment, OT) and for the change P vs OT.

For continuous CD8 and PDL1 expression measures (e.g., percentages), the paired t-test will be used to compare change in P vs OT. We expect approximately 25 patients to have paired measurements. With 25 patients studied a difference of 0.53 standard deviation (SD) can be detected with 90% power (1-sided α=0.1). With this sample size differences of 13%, 27%, and 40% can be detected with 80% power assuming SDs of 0.25, 0.5, and 0.75, respectively.

For dichotomous paired proportions (e.g., <2+ versus >2+ by IHC) McNemar's test will be used to test the null hypothesis that the difference in P and OT proportions is 0 versus the alternative that it is > 0 or < 0. With 25 paired patient samples studied 79% power is achieved to detect the difference illustrated in Table 1a below and 86% power is achieved to detect the difference illustrated in Table 1b (2-sided α=0.1).

Table 1a: Alternative hypothesis resulting in 79% power using McNemar's test (2-sided α=0.1).

	Post Treatment		Total
Pre Treatment	<2+	>2+	
<2+	0.15	0.45	0.60
>2+	0.10	0.30	0.40
Total	0.25	0.75	1.00

Table 1b. Alternative hypothesis resulting in 86% power using McNemar's test (2-sided α=0.1).

	Post Treatment		Total
Pre Treatment	<2+	>2+	
<2+	0.10	0.50	0.60
>2+	0.10	0.30	0.40
Total	0.20	0.80	1.00

Similar analyses will be conducted for other biomarkers as described in Section 8.0. No adjustments will be made for multiple comparisons. Data transformations or non-parametric methods will be used as appropriate.

Associations between changes in immune infiltrates and outcomes (PFS, RR, OS) will be explored using Cox regression (PFS), 2-sample t-tests or non-parametric Wilcoxon rank-sum tests, or the Chi-square test (6-month PFS, RR) based on the distribution and structure of the data (i.e., either parametric or non-parametric methods will be used as appropriate).

10.0 SAFETY

Refer to *Study Manual* for required reporting forms.

10.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease

temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the supporting company product(s), is also an AE.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered AEs. 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.

Supporting company 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 the supporting company for human use.

AEs may occur during the course of the use of supporting company product(s) in clinical trials or within the follow-up period specified by the protocol, or 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 AE unless it is considered to be drug related by the Investigator.

AEs will be documented from the date of first dose of study drug through 30 days after the last dose of study drug. All Grade 2-5 AEs as well as special reporting circumstances, such as exposure via a parent during pregnancy or breast-feeding, overdose, medication error, misuse, abuse, off-label use or occupational exposure must be recorded on the CRF.

10.2 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

1. Results in death.
2. Is immediately life-threatening (ie, in the opinion of the Investigator, the AE places the subject at immediate risk of death; it does not include a reaction that, had it occurred in a more severe form, might have caused death).
3. Requires inpatient hospitalization or results in prolongation of an existing hospitalization.
4. Results in persistent or significant disability or incapacity. (Note: The term “disability” refers to events that result in a substantial disruption of a subject’s ability to conduct normal life function.)
5. Is a congenital anomaly or birth defect.
6. Is an important medical event (Note: The term “important medical event” refers to an event that, based upon appropriate medical judgment, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the other serious outcomes listed under the definition of SAE. Examples of important medical events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of product dependency or product abuse.)

SAEs and/or follow up to SAEs including death due to any cause other than progression of the cancer under study, that occurs from the date of the first dose of study drug through 30 days following the last

dose of study drug, whether or not related to study drug(s), must be recorded on the CRF and must be reported within 2 business days supporting companies. External sites should report SAEs to the Duke study team within 24 hours. Reporting instructions for external sites can be found in the REDCap study eManual.

All SAEs must be followed until resolution, return to baseline condition, or stabilization. Any SAEs that are ongoing at the time the clinical database is closed will be reported to supporting companies as unresolved.

The initial report for each SAE or death should include at minimum the following information:

- protocol number and title
- patient initials, study identification number, sex, age
- date the event occurred
- description of the event
- seriousness criteria
- event causality or causal relationship
- study drug name(s)
- dose level and cycle number at the time the event occurred
- description of the patient's condition
- study status of patient at time of report
- responsible investigator name and contact details

The Investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The Investigator should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs which occurred as complications. Whenever possible, the Investigator should also provide the batch or lot number of the study drug(s).

SAE Reporting Procedure:

Immediately upon awareness of a SAE, the Investigator (or designee) completes the **DCI SAE Report Form** and will submit the form within 2 business days of knowledge of the event to the funding company. External sites should submit the form within 24 hours to the Duke study team via the REDCap SAE reporting tool. In accordance with applicable regulations, Investigators must report SAEs to their local IRB according to their institutional guidelines.

Note: It is imperative that initial SAE reports are submitted as soon as possible (within 2 business days of knowledge of the event) with available information to the supporting company. Missing and/or clarified event information may be provided in a follow-up report.

Follow-up information including severity, action taken, concomitant medications, and outcome should be communicated to the funding company as soon as possible using the same forms mentioned above.

:

The Lead PI will review the report form with accompanying source document, sign page 5, and then the PI or designee will promptly submit it to the supporting company.

If the event meets the Duke University Health System (DUHS) IRB reporting requirements, the Duke GI Oncology regulatory coordinator will submit information about the SAE including the Lead PI's

assessment as a safety event to the DUHS IRB within 5 business days. Any study-related death must be reported to the IRB within 24 hours of discovery.

Within two business days of receipt, the Duke study team will also submit the SAE report form and other relevant safety information to the following supporting companies:

Merck Global Safety
ATTN: Worldwide Product Safety
Fax: 215-993-1220

Expedited Reporting Procedure for Duke Cancer Institute (Coordinating Center):

Duke Cancer Institute as the coordinating center for this study is responsible for reporting SAEs to the FDA in accordance with 21CFR 312.32. Any SAE that is possibly related and unexpected must be submitted to the FDA attached to the IND. If the SAE meets criteria for reporting to the FDA, the Duke study team will complete the Form FDA 3500A (MedWatch) and send to the Lead PI and the supporting companies that are noted above. This submission of the Form FDA 3500A to the FDA attached to the IND will be completed by the Duke GI Oncology Clinical Trials Regulatory Coordinator.

- All unexpected, drug related SAEs that are fatal or life-threatening will be reported to the FDA by phone or fax within 7 calendar days of initial receipt of the information and will provide a complete report within 8 days of the initial report submission (by calendar day 15).

- All unexpected, treatment-related SAEs that are not fatal or life-threatening will be reported in a written report to the FDA within 15 days of initial receipt of the information.

The Duke study team will forward all expedited reports to all participating investigators in the form of an Investigator Alert. The Investigator Alert template is available on the DCI intranet titled “Safety Reporting for Multi-site IITs Notification Email”.

10.3 Events of Clinical Interest

Select (non-serious and serious) adverse events called Events of Clinical Interest (ECI) that occur from the date of the first dose of study drug through 30 days following the last dose of study drug, must be recorded on the CRF and must be reported within 2 working days to Merck Global Safety.

An ECI for this study is any hepatic toxicity that is ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to the adverse event. Such adverse events include but are not limited to; hepatitis, autoimmune hepatitis, and transaminase elevations (ALT and/or AST).

Any overdose of pembrolizumab (1,000 mg or greater) is also considered an ECI for this study and should be reported as such, regardless of the outcome.

ECI Reporting Procedure:

Immediately upon awareness of an ECI, the Investigator (or designee) completes the **DCI SAE Report Form** and will submit the form within 2 business days of knowledge of the event to the funding company. External sites should submit the form within 24 hours to the Duke study team via the REDCap SAE reporting tool.

Note: It is imperative that initial ECI reports are submitted as soon as possible (within 2 business days of knowledge of the event) with available information to the supporting company. Missing and/or clarified event information may be provided in a follow-up report.

Follow-up information including severity, action taken, concomitant medications, and outcome should be communicated to the funding company as soon as possible using the same form mentioned above.

The Lead PI will review the report form with accompanying source document, sign page 5, and the PI or designee will then promptly submit it to the funding company.

Within two business days of receipt, the study team will also submit the SAE report form and other relevant safety information to the following supporting company:

Merck Global Safety
ATTN: Worldwide Product Safety
Fax: 215-993-1220

10.4 Other Safety Considerations

The Investigator must also report in the same timelines as SAEs any incidence of medication error, occupational exposure, abuse or misuse that is associated with or result in an adverse event. All related fatal outcomes must also be reported in the same timeline as a SAE.

Refer to SAE reporting procedures in Section 10.2.

10.4.1 Pregnancy and Lactation

Although pregnancy and lactation are not considered adverse events, it is the responsibility of Investigator or designee to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of following cessation of treatment. All subjects and female partners of male subjects who become pregnant 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 reported in the same procedure as an SAE. Refer to SAE reporting procedures in Section 10.2.

10.4.2 Medication Overdose and Error

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) and is an event of clinical interest (see Section 10.3 for reporting instructions). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Monitoring should be based upon good medical judgment, taking into account the level of overdose, evolving toxicities, and other relevant medical and social factors specific to the patient. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with (“results from”) the overdose of study drug(s), the adverse event(s) is reported as a SAE, even if no other seriousness criteria are met. Refer to SAE reporting procedures in Section 10.2.

If a dose of pembrolizumab meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as an ECI, using the terminology “accidental or intentional overdose without adverse effect.” Refer to ECI reporting procedures in Section 10.3.

11.0 ADMINISTRATIVE RESPONSIBILITIES

11.1 Institutional Review Board/Independent Ethics Committee

Before study initiation, the Investigator must have written and dated approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects.

The Investigator should provide the IRB/IEC with reports, updates, and other information (e.g., Safety Updates, Amendment IRB/IECs, and Administrative Letters) according to regulatory requirements and institution procedures.

Copies of all IRB/IEC approvals, as well as annual re-approvals and approved/stamped informed consent forms must be submitted to Duke GI Oncology Clinical Trials Office.

11.2 Protocol and Protocol Revisions

All revisions to the protocol will be provided to the supporting companies by the Lead PI or designee(s) at the Duke GI Oncology Clinical Trials Office. The Lead PI must have written and dated approval/favorable opinion from the Duke University Health System (DUHS) IRB of revised protocol prior to distribution to Investigators at external participating sites.

Investigators must obtain written and dated and approval/favorable opinion from the IRB/IEC before conducting any updated protocol version. Study must be conducted as described in the approved protocol. The Investigator must not implement changes of the approved protocol without prior written agreement by the Lead PI and prior review and documented approval/favorable agreement by the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the changes involve only logistical or administrative aspects of the study (e.g., changes in research personnel or change in phone numbers).

Documentation of approval(s) from the IRB/IEC must be sent to Duke GI Oncology Clinical Trials Office.

11.3 Protocol Deviations and Violations

A protocol deviation is non-adherence to protocol specific study procedures or schedules that does not involve inclusion/exclusion criteria, primary objective evaluation criteria, and/or Good Clinical Practice (GCP) guidelines.

A protocol violation is any significant divergence from the protocol such as non-adherence on the part of the subject, the Investigator, or the sponsor to protocol specific inclusion/exclusion criteria, primary objective evaluation criteria, and/or GCP guidelines.

As a matter of policy, the Lead PI (ie. sponsor) will not grant exceptions to protocol specific entry criteria to allow subjects to enter a study. If it is found that a subject who did not meet protocol eligibility criteria was entered in a study (a protocol violation), the Lead PI and/or designee(s) at the Duke GI Oncology Clinical Trials Office must be informed immediately. Such subjects will be discontinued from the study,

except in an exceptional instance following review and written approval by the Lead PI and the responsible IRB/IEC.

Protocol deviations and violations must be documented and reported to the Lead PI and/or designee(s) at the Duke GI Oncology Clinical Trials Office.

In accordance with applicable regulations, Investigators must report protocol deviations and violations to their local IRB/IEC according to their institutional guidelines.

11.4 Informed Consent

The Investigator must ensure that subjects or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and their IRB. A copy of the proposed informed consent document must be submitted to the Lead PI or designee(s) at the Duke GI Oncology Clinical Trials Office for review and comment prior to submission to the local IRB/IEC.

Informed consent must be obtained prior to performing any study-related procedures that are not part of normal subject care, including screening and changes in medications. A copy of the signed informed consent form must be given to the study subject.

11.5 Source and Study Documentation

Source documents include all original recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. Accordingly, source documents include, but are not limited to, laboratory reports (including normal and abnormal results), radiology reports, subject diaries, biopsy reports, ultrasound photographs, subject progress notes, hospital charts or pharmacy records and any other similar reports or records of any procedure performed in accordance with the protocol.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original certified document.

When clinical observations are entered directly into an electronic medical record system (i.e. in lieu of original hardcopy records), the electronic record can serve as the source document if the system has must be validated to meet the FDA requirements for electronic records and signatures (i.e. meets 21 CFR Part 11 compliant).

Regulations require that Investigators maintain information in the study subject's medical records which corroborate data recorded on the CRF. In order to comply with these regulatory requirements, the following information will be maintained and made available as required by the Lead PI or designee(s), monitors, and/or regulatory inspectors:

- Medical history/physical condition of the study subject prior to involvement in the study sufficient to verify protocol entry criteria.
- Dated note that informed consent was obtained for the subject's participation in the study.
- Dated and signed notes for each subject visit including results of examinations.
- Notations on abnormal lab results and their resolution.
- Dated reports of special assessments (e.g., ECG reports).

- Dated and signed notes regarding adverse events (includng event description, severity, onset date, duration, relation to study treatment, outcome and treatment for adverse event).
- Dated notes regarding concomitant medications taken during the study (including start and stop dates).
- Subject condition upon completion of or withdrawal from the study.

Study documentation includes all CRFs, data correction forms, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence and regulatory documents (e.g., protocol and amendments, IRB/IEC correspondence and approvals, approved and signed subject consent forms, Statement of Investigator form, and clinical study supplies receipts and distribution records).

The Investigator will prepare and maintain complete and accurate study documentation in compliance with GCP guidelines and applicable federal, state, and local laws, rules and regulations; and, for each subject participating in the study, promptly complete all CRFs and such other reports as required by this protocol following completion or termination of the clinical study or as otherwise required pursuant to any agreement with the Lead PI and Duke Cancer Institute (DCI).

The Investigator acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, study documentation will be promptly and fully disclosed to Lead PI or designee(s) by the Investigator upon request and also shall be made available at the Investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Lead PI and DCI or responsible government agencies as required by law.

The Investigator agrees to promptly take any reasonable steps that are requested by the Lead PI or designee(s) as a result of an audit to cure deficiencies in the study documentation and case report forms.

11.6 Case Report Forms

Subject data will be entered (ie. CRFs completed) into an electronic data capture (EDC) system called Medidata RAVE. This database is maintained on a secure Duke University server and is accessible via internet with login and password.

CRFs should be completed by trained study personnel according to guidelines provided by the Lead PI or designee(s) at the Duke GI Oncology Clinical Trials Office. The Investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. The Investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the Investigator confirms that all recorded data have been verified as accurate.

In the event of discrepant data, the study monitor or study designee will request data clarification from the Investigator or designee for which may be resolved electronically in the EDC system.

Accurate and reliable data collection will be ensured through verification and crosscheck of the CRFs against the Investigator's study records (source document verification) by the study monitor or study designee.

11.7 Monitoring and Audits/Inspections

The study will be monitored both internally by the Lead PI and externally by the Duke Cancer Institute (DCI) Monitoring Team in accordance with their NCI-approved "Institutional Protocol Monitoring Procedures and Guidelines for NIH-sponsored Research Involving Human Subjects".

In terms of internal review, the Lead PI and/or designee(s) will continuously monitor and tabulate adverse events. Appropriate reporting to the DUHS IRB will be made. If an unexpected frequency of Grade 3 or 4 adverse events occurs, depending on their nature, action appropriate to the nature and frequency of these adverse events will be taken. This may require a protocol amendment, dose de-escalation, or potentially closure of the study. The Lead PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled (if applicable);
- Stopping rules for toxicity and/or response are met;
- Risk/benefit ratio is not altered to the detriment of the subjects;
- Appropriate internal monitoring of adverse events and outcomes is done;
- Over-accrual does not occur;
- Under-accrual is addressed with appropriate amendments or actions;
- Data are being appropriately recorded on the CRF in a reasonably timely manner.

The Duke Cancer Institute (DCI) Monitoring Team will conduct monitoring visits to ensure subject safety and to ensure that the protocol is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, GCP, and applicable regulatory requirements. As specified in the DCI Data and Safety Monitoring Plan, the DCI Monitoring Team will conduct routine monitoring after the third subject is enrolled, followed by annual monitoring of 1-3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk.

An external site monitoring plan addendum describes monitoring at participating sites.

Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns and may be initiated upon request of DUHS and DCI leadership, the DCI Cancer Protocol Committee, the Safety Oversight Committee (SOC), the sponsor, the Principal Investigator, or the IRB. All study documents must be made available upon request to the DCI Monitoring Team and other authorized regulatory authorities, including but not limited to the National Institute of Health, National Cancer Institute, and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring.

The DCI Safety Oversight Committee (SOC) will perform annual reviews on findings from the DCI Monitoring Team visit and additional safety and toxicity data submitted by the Principal Investigator.

DCI Quality Assurance personnel, or designee, may conduct audits at sites. Audits will include, but not be limited to: audit trail of data handling and processes, SOPs, drug supply, presence of required documents, the informed consent process, and comparison of case report forms/database with source documents. The Investigator agrees to accommodate and participate in audits conducted at a reasonable time in a reasonable manner, as needed.

Regulatory authorities may also audit an Investigator during or after the study. The Investigator should contact the Lead PI and designee(s) at the Duke GI Oncology Clinical Trials Office as well as their local IRB, immediately if this occurs, and must fully cooperate with governmental (e.g., FDA) audits conducted at a reasonable time in a reasonable manner.

The Duke University Compliance Program - Human Subject Research Compliance (HSRC) section may conduct confidential audits to evaluate compliance with the protocol and the principles of GCP. The

Lead PI agrees to allow the HSRC auditor(s) direct access to all relevant documents and to allocate his/her time and the time of the study team at the Duke GI Oncology Clinical Trials Office to the CTQA auditor(s) in order to discuss findings and any relevant issues.

11.8 Study Closeout

Upon completion of the study (defined as all subjects have completed all follow-up visits, all CRFs are complete, and all queries have been resolved) the Lead PI or designee(s) at the Duke GI Oncology Clinical Trials Office will notify the Investigator of closeout and a study closeout visit will be performed.

The study monitor or study designee will ensure that the Investigator's regulatory files are up to date and complete, and that any outstanding issues from previous visits have been resolved. Other issues to be reviewed at the closeout visit include: retention of study files, possibility of site audits, publication policy, and study closure with local IRB.

11.9 Records Retention

The Investigator will maintain the records of study drug disposition, worksheets and all other study-specific documentation (e.g., study files, source documentation) until notified by the Lead PI or designee(s) at the Duke GI Oncology Clinical Trials Office that records may be destroyed. If the application is not filed or is withdrawn, the Investigator will maintain the records for at least two (2) years after the formal discontinuation of the clinical development program for this product(s).

To avoid error, the Investigator will contact the Lead PI or designee(s) at the Duke GI Oncology Clinical Trials Office before the destruction of any records pertaining to the study to ensure they no longer need to be retained. In addition, the Lead PI or designee(s) will be contacted if the Investigator plans to leave the institution so that arrangements can be made for the transfer of records.

12.0 REFERENCES

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Appendix A. RECIST 1.1

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.

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

Definitions
Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (version 1.1). Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term “evaluable” in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease
Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10mm)
- 10mm caliper measurement by clinical exam (when superficial)
- 20mm by chest X-ray (if clearly defined and surrounded by aerated lung)

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm 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 to <15 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques are all non-measurable.

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- 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 noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions
All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, 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 organ, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm x 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed.

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 as noted above, 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 pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Guidelines for Evaluation of Measurable Disease

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and >10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors,

where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Response Criteria

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 diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of 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 progression).
- 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.

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Non-target Lesions
While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concept apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New Lesions
The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline

lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow- up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of Best Overall Response
The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response."

The best overall response is determined once all the data for the patient is known. Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Appendix B. Immune-Related Response Criteria

The immune related response criteria* (irRC) has been developed to adequately characterize additional patterns of response and progression specific to patients treated with immunotherapy, that cannot be captured by the conventional criteria such as such as Response Evaluation Criteria in Solid Tumors (RECIST).

*_Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, Maio M, Binder M, Bohnsack O, Nichol G, Humphrey R, Hodi FS. et al_. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009;15(23):7412–7420.

Antitumor response based on total measurable tumor burden.

For the irRC, only index and measurable new lesions are taken into account (in contrast to conventional WHO criteria, which do not require the measurement of new lesions, nor do they include new lesion measurements in the characterization of evolving tumor burden). At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥5 × 5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total tumor burden:

$$\text{Tumor Burden} = SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$$

Time-point response assessment using irRC.

Percentage changes in tumor burden per assessment time point describe the size and growth kinetics of both conventional and new, measurable lesions as they appear. At each tumor assessment, the response in index and new, measurable lesions is defined based on the change in tumor burden (after ruling out irPD). Decreases in tumor burden must be assessed relative to baseline measurements (i.e., the SPD of all index lesions at screening).

Overall response using the irRC.

The overall response according to the irRC is derived from time-point response assessments (based on tumor burden) as follows:

- irCR, complete disappearance of all lesions (whether measurable or not, and no new lesions)
  - confirmation by a repeat, consecutive assessment no less than 4 wk from the date first documented
- irPR, decrease in tumor burden ≥50%relative to baseline
  - confirmed by a consecutive assessment at least 4 wk after first documentation
- irSD, not meeting criteria for irCR or irPR, in absence of irPD
- irPD, increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden)
  - confirmation by a repeat, consecutive assessment no less than 4 wk from the date first documented

Appendix C. ECOG Performance Status

The ECOG Scale of Performance Status, developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair*, describes a patient's level of functioning in terms of their ability to care for themself, daily activity, and physical ability (walking, working, etc.).

**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.

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.

Appendix D. Study Calendar

Study Procedures	Screening Period[1]	Treatment Period[2]			Follow-up Period[3]	
	Days -28 to -1	Day 1[25]	Weekly C1 Only	Every 3 cycles (+/-1 week)[21]	30 (±7) Days[22]	Long Term
Informed Consent	X[4]					
Demographics	X					
Medical and Cancer History	X					
Concomitant Medications	X	X --- (throughout study[5]) --- X				
Physical Examination	X	X	X		X	
Height	X					
Vital Signs and Weight[6]	X	X	X		X	
ECOG Performance Status[7]	X	X	X		X	
CBC with Differential	X[8]	X[10]	X		X	
Chemistries including LFTs	X[8]	X[10]	X		X	
Thyroid Function Tests	X			X	X	
Serum Pregnancy Test[9]	X[8, 9]	X[26]		X[9]	X[9]	
Pembrolizumab		X[11]				
Oxaliplatin		X[12]				
Capecitabine		X[13]				
Adverse Event Assessment	X	X --- (throughout study[5]) --- X				
Tumor Assessment[14]	X			X		X[23]
Blood Tumor Markers[15]	X			X		X[23]
Archived Tumor Tissue[16]	X[16]					X[16]
Tumor Biopsy[17]	X[17]		X[17]			
PBMC[18]	X[18]			X[18]	X[18]	X[27]
Plasma[19]	X[19]			X[19]	X[19]	X[27]
Whole Blood[20]	X[20]					
Survival						X[24]

1. Refer to Section 5.1.
2. Refer to Section 5.2. Cycle length is 21 days. However, for dose expansion cohort, the first cycle (ie. biomarker cycle) is 28 days in length and subsequent cycles are 21 days in length. Visits for each cycle are Day 1 except for Cycle 1 when visits are weekly (ie. C1D8, C1D15 and for dose expansion cohort only, C1D22) and as clinically indicated.
3. Refer to Section 5.3.
4. May be completed more than 28 days prior to Cycle 1 Day 1.
5. Document this data throughout study when changes or events occur.
6. Obtain temperature (^{O}C), blood pressure, heart rate, and weight (kg).
7. At screening, obtain within 7 days to first dose of study treatment. Refer to Appendix C.
8. Must perform within 7 days prior to Cycle 1 Day 1. If completed within 7 days of Cycle 1 Day 1, no need to repeat. If repeated on Cycle 1 Day 1, must wait for results to confirm eligibility prior to starting study drug.
9. Only for women of childbearing potential.
10. After Cycle 1, may perform up to 3 days prior to Day 1.
11. Pembrolizumab (see Section 6.2) is administered on Day 1 of each cycle.
12. Oxaliplatin (see Section 6.3) is administered on Day 1 of each cycle except for first cycle (ie. biomarker) cycle of dose expansion cohort only when administered on Day 8 (ie. pembrolizumab monotherapy lead-in period).
13. Capecitabine (see Section 6.4) is taken on Days 1-14 of each cycle except for first cycle (ie. biomarker) cycle of dose expansion cohort only when taken on Days 8-22 (ie. pembrolizumab monotherapy lead-in period).
14. Radiographic assessments (ie. restaging scans) include CT and/or MRI of chest, abdomen and pelvis after every 3 cycles (9 weeks). Same method for tumor assessment should be employed at every assessment.
15. If clinically indicated (ex. CEA and/or CA19-9).
16. If FFPE tumor tissue is available, refer to Section 8.1 and Study Manual.

17. For patients accrued to the dose expansion cohort with tumor lesion that is amenable to safe biopsy, pre-treatment (up to 1 week prior to pembrolizumab monotherapy lead-in) and on-treatment (C1 D7 or D8, prior to oxaliplatin and capecitabine/end of one week pembrolizumab monotherapy lead-in in Cycle 1) tumor biopsies will be performed in the first cycle (ie. biomarker cycle). Refer to Section 8.1 and Study Manual.
18. Peripheral blood collection for PBMCs (see Section 8.2 and Study Manual) at the following time points: baseline (may be obtained on Cycle 1 Day 1 prior to the first dose of study drug); end of monotherapy lead-in on Day 8 (biomarker cycle of dose expansion cohort only), end of first cycle of combination therapy on Day 29 (biomarker cycle of dose expansion cohort only), first restaging only (ie. after Cycle 3), and disease progression or treatment discontinuation. Note – There is no PBMC collection at 30-day off treatment follow-up.
19. Peripheral blood collection for plasma (see Section 8.3 and Study Manual) at the following time points: baseline (may be obtained on Cycle 1 Day 1 prior to the first dose of study drug); end of monotherapy lead-in on Day 8 (biomarker cycle of dose expansion cohort only), end of first cycle of combination therapy on Day 29 (biomarker cycle of dose expansion cohort only), each restaging, disease progression or treatment discontinuation and 30-day off treatment follow-up.
20. Peripheral blood collection for whole blood (see Section 8.4 and Study Manual at the following time point: baseline (may be obtained on Cycle 1 Day 1 prior to the first dose of study drug).
21. After every 3 cycles.
22. After the last dose of study drug.
23. Subjects discontinued from study treatment with no documented disease progression and no subsequent anti-cancer treatment should have disease status and blood tumor markers (if clinically indicated) followed per standard of care schedule until disease progression or start of new anti-cancer treatment regimen is documented. Disease status may be collected by personal interviews or review of medical records.
24. Subjects are followed for survival up to 3 years after the last subject starts the study drug regimen or until the study is closed (whichever comes first). Survival status may be collected by personal interviews or review of medical or public records.
25. Treatment visits may occur within +/-3 days of D1 for C2 and all subsequent cycles.
26. Cycle 1 day 1 only. After that, will redo at restaging visits.
27. Only for subjects who achieved a complete response and have consented to the additional collection.

Appendix E. Laboratory Tests

CBC with differential		
• hematocrit • hemoglobin • platelet count	• WBC (total and differential) • red blood cell (RBC) count	• absolute neutrophil count • absolute lymphocyte count
Chemistries with liver function tests (LFTs)		
• albumin • alkaline phosphatase (ALP) • ALT • AST • Bicarbonate	• blood urea nitrogen (BUN) • chloride • creatinine • glucose • calcium	• potassium • sodium • total bilirubin • total protein
Thyroid Function Tests		
• thyroid stimulating hormone (TSH)	• total thriiodothyronine (T3)	• free tyroxine (T4)
Pregnancy Test		
• serum β-HCG pregnancy test		