A Phase II Trial of Chemotherapy plus Pembrolizumab in patients with advanced NSCLC previously treated with PD-1 or PD-L1 Inhibitor: Big Ten Cancer Research Consortium BTCRC-LUN15-029

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I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

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Signature of Site Investigator Date

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Site Investigator Name (printed)

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Site Investigator Title

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Name of Facility

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PLASE E-MAIL COMPLETED FORM TO BIG TEN CRC ADMINISTRATIVE HEADQUARTERS

SYNOPSIS

TITLE	A Phase II Trial of Chemotherapy plus Pembrolizumab in patients with advanced NSCLC previously treated with PD-1 or PD-L1 Inhibitor: Big Ten Cancer Research Consortium BTCRC-LUN15-029
SHORT TITLE	Phase II Trial of Continuation Pembrolizumab in NSCLC: BTCRC-LUN15-029
PHASE	2
OBJECTIVES	Primary Objective: • To assess if continuation therapy with pembrolizumab in combination with next-line chemotherapy will improve PFS in patients who have previously benefitted from a PD-1/PD-L1 inhibitor (CR, PR, or SD ≥ 3months) according to RECIST 1.1 criteria as compared to historical controls Secondary Objectives: • To estimate PFS by immune-related RECIST (irRECIST) • To estimate objective response rate (ORR) by RECIST 1.1 and irRECIST • To estimate clinical benefit rate as defined by RECIST 1.1 and irRECIST • To estimate overall survival (OS) • Toxicity of pembrolizumab in combination with next-line chemotherapy (gemcitabine, docetaxel, or pemetrexed-non-squamous only) Exploratory Objectives: • To assess tumor PD-L1 status at baseline (prior to initial treatment with PD-1 inhibitor), at time of progression on PD-1 or PD-L1 inhibitor (study entry), and at time of progression on combination of pembrolizumab and chemotherapy (safety follow up visit) • To correlate ORR, PFS, and clinical benefit rate with the results of proteomic analysis and lipidomic profiling • To correlate ORR, PFS, and clinical benefit rate with the results of NeoTYPE Lung Tumor Profile Genetic Analysis
STUDY DESIGN	Single Arm Phase II
KEY ELIGIBILITY CRITERIA	• Histological or cytological evidence of stage IV non-small cell lung cancer (any histology) • Subjects must have progressed on or after receiving platinum-based chemotherapy. Chemotherapy may have previously been given with a PD-1 or PD-L1 inhibitor. They must also have progressed on or after any PD-1 or PD-L1 inhibitor (including pembrolizumab) as their most recent therapy and must have had at least a 3-month PFS on this therapy. • Subjects must be enrolled on the trial within 12 weeks of their last infusion of PD-1 or PD-L1 inhibitor therapy. • Demonstrates adequate organ function (as defined in Table 1) and performance status (PS 0 or 1)

	• Must be fit enough to receive next-line chemotherapy (either gemcitabine, docetaxel, or pemetrexed [non-squamous only]) according to the discretion of the treating physician. • Subjects whose tumors harbor a mutation in EGFR exon 19 or 21 or have gene rearrangements in ALK or ROS1 must have already been treated with standard targeted therapies. NOTE: Subjects must also have progressed on or after platinum-containing combination chemotherapy. • No evidence of active autoimmune disease requiring systemic treatment within the past 90 days or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. • No history of interstitial lung disease or pneumonitis related to the use of immunotherapeutic drugs. Subjects with a history of pneumonitis which is unrelated to the used of immunotherapeutic drugs may participate at the discretion of the treating physician • No history of an immune-related toxicity requiring treatment with corticosteroids during prior PD-1/ PD-L1 inhibitor treatment.
STATISTICAL CONSIDERATIONS	When the sample size is 31, a non-parametric test of median survival with a one-sided 0.05 significance level will have 80% power to detect the difference between a median survival of 3 months vs 6 months assuming an accrual period of approximately 6 months (6 per month) and maximum follow-up of 1.5 years. To allow for replacement of patients who are not evaluable for efficacy (estimated to be 10%), up to 35 patients will be enrolled. • The historical control is a median PFS of 3 months (in the $2^{nd}/3^{rd}$ line setting). • Null hypothesis - Pembrolizumab plus chemo will have a median PFS of 3 months. • Alternative hypothesis –Pembrolizumab plus chemo will have a median PFS of 6 months Median PFS will be estimated using Kaplan-Meier methodology and tested using a non-parametric test. ORR and clinical benefit rate will be estimated with two-sided 95% exact binomial confidence intervals. Toxicities will be tabulated. Change in tumor levels of PD-L1 will be descriptively summarized and compared over time using paired t-tests. Proportional hazards regression (for PFS) and logistic regression (for ORR and clinical benefit rate) will be used to correlate proteomic, lipidomic and genomic results with clinical outcomes.
TOTAL NUMBER OF SUBJECTS	N = 35
ESTIMATED ENROLLMENT PERIOD	12 months
ESTIMATED STUDY DURATION	30 months

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SCHEMA

A Phase II Trial of Chemotherapy plus Pembrolizumab in patients with advanced NSCLC previously treated with PD-1 or PD-L1 Inhibitor:
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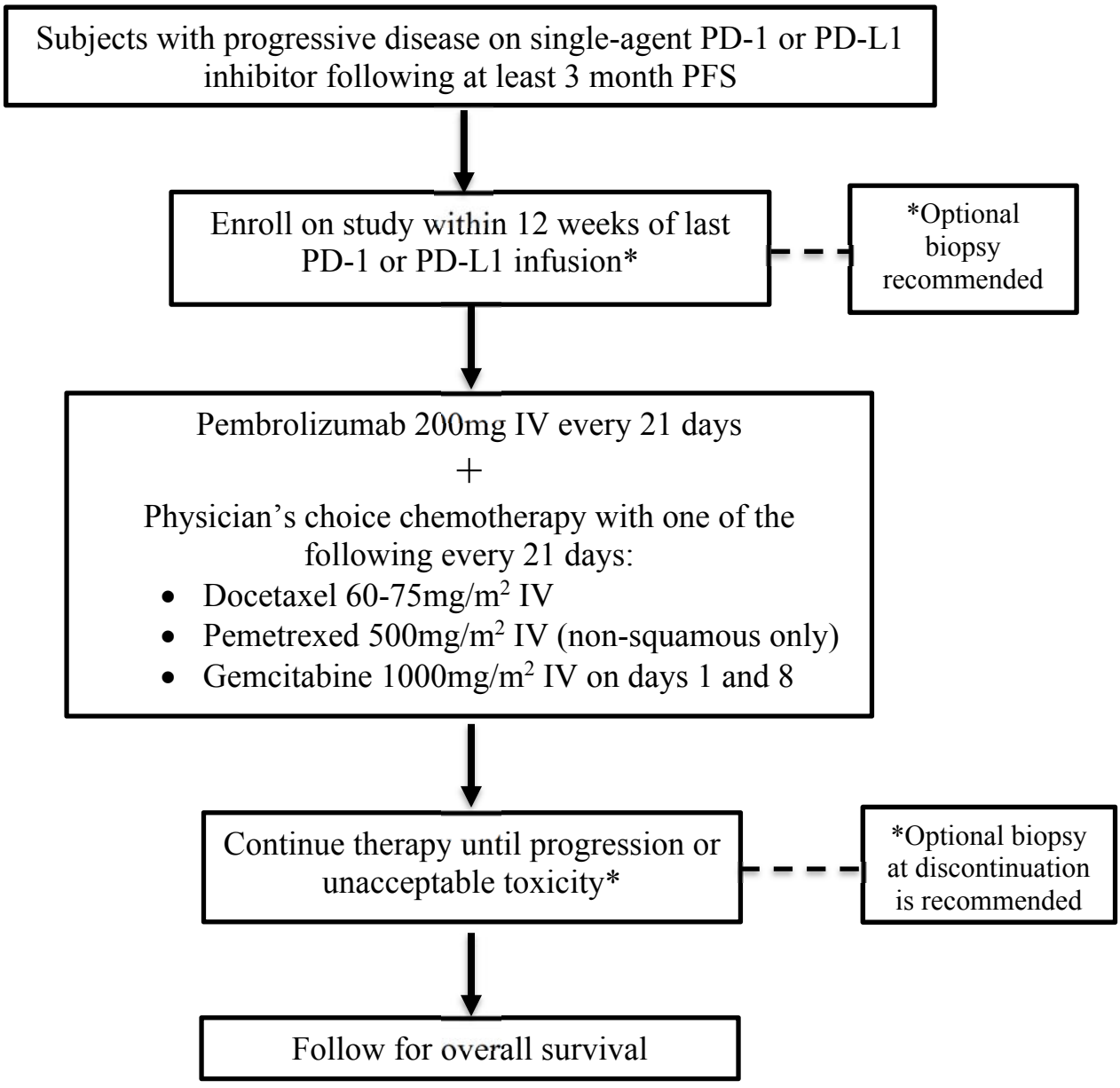

1. BACKGROUND AND RATIONALE

1.1 Lung Cancer Background

Lung cancer remains the leading cause of cancer-related mortality in the United States with an estimated 224,390 new cases and 158,080 deaths in 2016 (1). Non-small cell lung cancer makes up approximately 83% of these cases with several histologic subtypes including adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and a few others which are much less common (2). While a number of new treatments have become available over the last decade, the 5-year overall survival (OS) rate for all lung cancer patients remains poor at 17% and the OS for patients with metastatic disease is only 4% (2). New treatment options and approaches are needed to improve upon these poor outcomes.

1.2 Current Standard of Care for Non-Small Cell Lung Cancer

The current standard of care for non-squamous NSCLC depends in large part on whether targetable mutations exist which can be exploited. Initial biopsy specimens are sent for mutational analysis with particular attention to activating epidermal growth factor receptor (EGFR) mutations in exon 19 and 21or gene rearrangements in either anaplastic lymphoma kinase (ALK) or ROS1. Tumors which harbor sensitizing EGFR mutations are responsive to a number of EGFR tyrosine kinase inhibitors (TKI) including erlotinib, gefitinib, and afatinib, and use of one of these agents is recommended in the 1st line setting. ALK translocations should be treated with crizotinib in the 1st line setting and either ceritinib or alectinib in the 2nd line setting (3). ROS1 mutations can be treated with crizotinib in the 1st line setting, and there is some evidence that cabozantinib may be an active alternative when resistance develops to this therapy (4, 5).

In the majority of patients, there are no mutations for which targeted therapies have been approved. In this setting, the standard of care remains chemotherapy with a platinum doublet for fit patients. These combinations produce response rates of approximately 25-35% and 1-year OS rates of 30-40%. In non-squamous histologies, bevacizumab may also be added to either cisplatin or carboplatin with pemetrexed or to carboplatin and paclitaxel in patients without contraindications. Maintenance therapy with pemetrexed, bevacizumab, or erlotinib can also be considered in eligible patients (3).

In the 2nd line setting, the mainstay of therapy has previously been single-agent chemotherapy with an agent not used as part of initial therapy. The most commonly used medications include docetaxel, pemetrexed (only for non-squamous), and gemcitabine. Erlotinb was also previously approved in this setting though subsequent studies have shown the majority of its activity to be in patients harboring activating mutations in EGFR, and its use for EGFR wild-type patients has declined. Recently, a trial of ramucirumab, a monoclonal antibody against the vascular endothelial growth factor receptor 2 (VEGFR2), in combination with docetaxel showed a modest improvement in PFS and OS compared with docetaxel alone, though there was also a modest increase in toxicity (6). One of the most promising new therapeutic strategies for advanced and metastatic NSCLC is the emergence of immunotherapy, particularly programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1) blockade. In two separate phase III trials, nivolumab, a PD-1 inhibitor, improved OS in both squamous and non-squamous populations when compared to single-agent docetaxel (7, 8). A second PD-1 inhibitor, pembrolizumab, also showed good

activity in advanced and metastatic NSCLC with >50% PD-L1 expression on tumor cells with superior OS when compared with Docetaxel (9). In addition to their efficacy, both nivolumab and pembrolizumab were well tolerated during these trials with side effect profiles that are generally considered more manageable than standard chemotherapy options. Most importantly, there is the potential for durable responses with these agents which gives hope for long-term survival in a patient population for which this has typically been rare (7-10). Given the improvements in OS, potential for durable responses, and favorable toxicity profiles, these drugs were approved by the FDA for the treatment of NSCLC following progression on a platinum doublet, and they are increasingly considered the best option for the 2nd line treatment of advanced and metastatic disease.

Following progression on either nivolumab or pembrolizumab, 3rd line treatment for fit patients typically consists of single-agent chemotherapy. Typical regimens include docetaxel with or without ramucirumab, gemcitabine, or pemetrexed in patients with non-squamous histology. Erlotinib can also be considered as a single agent in this setting. For patients who initially respond or have stable disease on immunotherapies, it is currently unclear whether continuation of these medications at the time of progression has any benefit in the 3rd line setting.

1.3 Background for Pembrolizumab

1.3.1 Pre-clinical Data

The importance of intact functions of immune surveillance in controlling outgrowth of neoplastic transformations has been known for decades (11). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes 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 (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and re-infused, inducing durable objective tumor responses in cancers such as melanoma (12, 13).

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 Tcells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (14, 15). The structure of murine PD-1 has been resolved (16). PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail 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, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch 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 (15, 17-19). The mechanism by which PD-1 down-modulates T-cell responses is similar to, but

distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (20, 21). 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 (22, 23). Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells, as well as subsets of macrophages and dendritic cells (24). The ligands for PD-1(PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types including nonhematopoietic tissues and in various tumors (11, 21, 25-27). Both ligands are type 1 transmembrane receptors containing IgV-like and Ig constant–like (IgC-like) domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-L1 or PD-L2 to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various nonhematopoietic tissues, most notably on vascular endothelium; whereas PD-L2 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 (21). Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including renal cell carcinoma (28), pancreatic carcinoma (29), hepatocellular carcinoma (30), and ovarian carcinoma (31). Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (32).

The observed correlation of clinical prognosis with PD-L1 expression in multiple cancers 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. Therapeutic studies in mouse models show that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other treatment modalities. Anti–mouse PD-1 and anti–mouse PD-L1 have demonstrated antitumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-γ, granzyme B, and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo (29, 33-36). In addition, the combination of gemcitabine and anti–PD-L1 mAb demonstrated synergy in the rejection of pancreatic mouse tumors (29). In-house experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models.

1.3.2 Clinical Data in NSCLC

The 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; previously known as SCH 900475 and ORG 307488- 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 ligands, PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection.

The clinical activity of Pembrolizumab in NSCLC was demonstrated in two clinical trials. In the initial phase I trial (KEYNOTE-001), patients with advanced NSCLC were treated with either 2mg/kg or 10mg/kg every 3 weeks or 10mg/kg every 2 weeks. The treatment was well tolerated with the most frequent side effects including fatigue, pruritus, and decreased appetite. Among all patients, the objective response rate (ORR) was 19.4% and the median duration of response was 12.5months. Median progression free survival (PFS) was 3.7 months and median OS was 12 months. Among patients with >50% PD-L1 expression on tumor cells, the response rate was 45.2% with a PFS of 6.3 months. Median OS in this group was not reached (10).

In a subsequent phase II/III trial (KEYNOTE-010) of single-agent pembrolizumab versus docetaxel for PD-L1 positive (>1% PD-L1 staining on tumor cells) NSCLC, patients were randomized 1:1:1 to receive either pembrolizumab 2mg/kg, pembrolizumab 10mg/kg, or docetaxel 75mg/m^2 intravenously (IV) every 3 weeks. In the total population, median overall survival favored the pembrolizumab arms with 10.4 months in the 2mg/kg arm, 12.7 months in the 10mg/kg arm, and 8.5 months in the docetaxel arm. PFS was not statistically improved in the pembrolizumab arms when considering all patients. In the group of patients with >50% PD-L1 staining, a more substantial benefit was seen for the pembrolizumab arms with a median OS of 14.9 months in the 2mg/kg arm versus 8.2 months in the docetaxel arm (HR 0.54, =0.0002) and 17.3 months in the 10mg/kg arm versus 8.2 months in the docetaxel arm (HR 0.50, p<0.0001). PFS was also statistically significantly longer in the pembrolizumab arms for patients with >50% PD-L1 staining. Pembrolizumab appeared to be much better tolerated than docetaxel with grade 3-5 treatment-related adverse events (TRAEs) of 13% and 16% in the 2mg/kg and 10mg/kg pembrolizumab respectively versus 35% in the docetaxel arm (9). Based on the data from these trials, pembrolizumab was FDA-approved for the 2nd line treatment of PD-L1 positive (>50% staining on tumor cells) NSCLC and is currently under review by the FDA for the tissue polypeptide-specific antigen (TPS) >1% population.

1.3.3 Safety Data in Combination with Chemotherapy

The safety of combining immunotherapy with chemotherapy has been demonstrated in several early phase trials in NSCLC, and larger trials are currently being conducted to assess the efficacy of these combinations. In a phase I trial (KEYNOTE-021), pembrolizumab was added to platinum doublet chemotherapy in patients with treatment-naïve NSCLC. Subjects were randomized to receive either 2mg/kg or 10mg/kg of pembrolizumab in combination with either carboplatin (AUC 6) and paclitaxel (200mg/m^2) or carboplatin (AUC 5) and pemetrexed (500mg/m^2) IV every 3 weeks for 4 cycles followed by either pembrolizumab or pembrolizumab and pemetrexed maintenance. The carboplatin and paclitaxel arm demonstrated 15% grade 3-4 TRAEs including anemia and rash in one patient each. The carboplatin and pemetrexed arm experienced 38% grade 3-4 AEs including reversible transaminase elevations (n=3), anemia (n=2), rash (n=1), and colitis (n=2). No grade3-4 febrile neutropenia was observed, and there were no treatment-related deaths on either arm. ORR were 30% in the carboplatin/paclitaxel arm and 58% in the carboplatin/pemetrexed arm at the time of analysis with the majority of patients remaining on therapy in both arms (37). This study suggests that the combination of pembrolizumab and platinum doublet chemotherapy with a taxane or pemetrexed has a reasonable safety profile, and therefore, it is likely that the combination of pembrolizumab with either single-agent taxane or pemetrexed will be well tolerated as well.

There is no direct safety data with the combination of pembrolizumab and gemcitabine, however, there is a phase I trial of nivolumab (another PD-1 inhibitor) with platinum doublet chemotherapy that includes a gemcitabine arm. In this trial, treatment-naïve patients were randomized to one of 4 treatment regimens. The first three arms combined nivolumab 10mg/kg IV every three weeks with either cisplatin (75mg/m^2) and gemcitabine (1250mg/m^2), cisplatin (75mg/m^2) and pemetrexed (500mg/m^2), or carboplatin (AUC 6) and paclitaxel (200mg/m^2). The last arm combined nivolumab 5mg/m^2 with carboplatin (AUC 6) and paclitaxel (200mg/m^2). All regimens were given for 4 cycles followed by nivolumab maintenance. No dose-limiting toxicities (DLTs) were seen during the first 6 weeks of treatment, and there were no reported treatment-related deaths. Grade 3-4 AEs were seen in 45% of patients (range 25-73% across all arms) and most commonly included pneumonitis (grade 4, n=1; grade 3, n=3), fatigue (grade 3, n=3), and acute renal failure (grade 3, n=3). Grade 3 select AEs occurred in ≤7% of patients, and overall, 20% of patients discontinued any study medication because of treatment-related AEs (38). This study shows that the combination of nivolumab with platinum doublet chemotherapy including gemcitabine, pemetrexed, and paclitaxel has a manageable safety profile and reflects the additive toxicities of immunotherapy and chemotherapy. Based on this, the combination of immunotherapy with single agent gemcitabine, pemetrexed, or a taxane would be expected to have a reasonable safety profile as well.

1.4 Rationale

1.4.1 Study Rationale

While many patients who initially respond to immunotherapy have prolonged durations of response, the majority of patients will still ultimately progress on these therapies. Little is currently known about the resistance mechanisms responsible for this progression, and there is currently no data to suggest whether immunotherapy has any benefit or should be continued following clear progression. Previous studies in both NSCLC and other malignancies have shown differing results in the benefit of continuing targeted agents. A trial of continuation trastuzumab following progression in human epidermal growth factor receptor 2 (HER-2)-positive early and advanced breast cancer shows a significant overall survival benefit for the combination of chemotherapy and trastuzumab compared with chemotherapy alone (39). Furthermore, treatment with bevacizumab, a monoclonal antibody (mAb) targeting vascular endothelial growth factor (VEGF) following progression on first line therapy suggests a significant OS advantage for the patients who were continued on bevacizumab (40). Lastly, androgen deprivation therapy (ADT) is routinely continued beyond progression in the treatment of metastatic prostate cancer (41). Conversely, continued treatment with the TKI erlotinib did not show benefit when continued beyond progression in patients with advanced EGFR-mutated NSCLC (42). Therefore, further study of continuation of immunotherapy at the time of progression is warranted.

1.4.2 Dose Selection Rationale

The dose regimen of 200 mg Q3W of pembrolizumab is planned for all urothelial cancer trials. Available PK results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at a given dose among tumor types. An open-label Phase 1 trial (PN001) in melanoma subjects 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 DLTs 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 maximum tolerated dose (MTD) has been identified.

In KEYNOTE-001, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive pembrolizumab at 2 mg/kg versus 10 mg/kg Q3W. The overall ORR was 26% (21/81) in the 2mg/kg group and 26% (25/79) in the 10 mg/kg group (full analysis set (FAS)). The proportion of subjects with TEAEs, grade 3-5 drug-related AEs, serious drug-related AEs, death or discontinuation due to an AE was comparable between groups or lower in the 10 mg/kg group.

Available pharmacokinetic (PK) results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at a given dose among tumor types. Population PK analysis has been performed and has confirmed the expectation that intrinsic factors do not affect exposure to pembrolizumab to a clinically meaningful extent. Taken together, these data support the use of lower doses (with similar exposure to 2 mg/kg Q3W) in all solid tumor indications.

Selection of 200 mg as the appropriate dose for a switch to fixed dosing is based on simulation results indicating that 200 mg will provide exposures that are reasonably consistent with those obtained with 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed using available data from 476 subjects from PN001. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose, with some tendency for individual values to range slightly higher with the 200 mg fixed dose. The slight increase in PK variability predicted for the fixed dose relative to weight-based dosing is not expected to be clinically important given that the range of individual exposures is well contained within the range of exposures shown in the melanoma studies of 2 and 10 mg/kg to provide similar efficacy and safety. 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 tumor types and indication settings.

1.4.3 Rationale for Historical Control

Previous studies evaluating single-agent chemotherapy following progression on a platinum doublet have shown consistently that the PFS or TTP in these studies is approximately 3 months. In a trial of docetaxel versus best supportive care (BSC), the chemotherapy arm demonstrated a TTP of 10.6 weeks (43), and in a trial of docetaxel versus vinorelbine or ifosfamide, the docetaxel arm showed a TTP of 8.5 weeks (44). A more recent trial comparing single-agent docetaxel versus pemetrexed in the second-line setting demonstrated a PFS of 2.9 months for both arms (45). Given the consistent findings in these studies, a PFS of 3 months appears to be an appropriate historical control arm.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

- To assess whether continuation of pembrolizumab in combination with next-line chemotherapy (either gemcitabine, docetaxel, or pemetrexed [non-squamous only]) will prolong PFS by RECIST 1.1 criteria in patients who previously benefitted from a PD-1/ PD-L1 inhibitor (PFS ≥ 3 months) but now have progressive disease as compared to historical controls

2.1.2 Secondary Objectives

- To estimate PFS by immune-related RECIST (irRECIST)
- To estimate ORR by RECIST 1.1 and irRECIST criteria
- To estimate clinical benefit rate as defined by RECIST 1.1 and irRECIST
- To estimate OS
- Assess the toxicity of pembrolizumab in combination with next-line chemotherapy (gemcitabine, docetaxel, or pemetrexed [non-squamous only])

2.1.3 Correlative/Exploratory Objectives

- To assess tumor PD-L1 status at baseline (prior to initial treatment with PD-1 inhibitor), at time of progression on PD-1 or PD-L1 inhibitor (study entry), and at time of progression on combination of pembrolizumab and chemotherapy (safety follow up visit)
- To correlate ORR, PFS, and clinical benefit rate with the results of proteomic analysis and lipidomic profiling
- To correlate ORR, PFS, and clinical benefit rate with the results of NeoTYPE Lung Tumor Profile Genetic Analysis

2.2 Endpoints

2.2.1 Primary Endpoint

- PFS as measured by RECIST 1.1 criteria

2.2.2 Secondary Endpoints

- PFS as measured by irRECIST criteria
- Objective response rate (CR+PR) assessed via RECIST 1.1 and irRECIST
- Clinical benefit rate - defined as any subject with stable disease (SD) for ≥ 3 months, partial response (PR), or complete response (CR) assessed via RECISIT 1.1 and irRECIST
- OS
- Toxicity will be graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Subjects must meet all of the following applicable inclusion criteria to participate in this study:

1. Written informed consent and HIPAA authorization for release of protected health information
   NOTE: HIPAA authorization may be included in the informed consent or obtained separately.
2. Age ≥ 18 years at the time of consent
3. Histological or cytological evidence of stage IV NSCLC (any histology)
4. Subjects must have progressed on or after previous platinum-based chemotherapy. Chemotherapy may have previously been given with a PD-1 or PD-L1 inhibitor. Subjects must have also progressed on or after receiving any PD-1 or PD-L1 inhibitor (including pembrolizumab) as their most recent therapy and must have had at least a 3-month PFS on this therapy.
5. Subjects must be enrolled on the trial within 12 weeks of their last infusion of PD-1 or PD-L1 inhibitor therapy.
6. Subjects whose tumors harbor a mutation in EGFR exon 19 or 21 or have gene rearrangements in ALK or ROS1 must have already been treated with standard targeted therapies. NOTE: Subjects must also have progressed on or after platinum-containing combination chemotherapy.
7. ECOG Performance Status of 0 or 1 within 28 days prior to registration for protocol therapy.
8. Must be fit enough to receive next-line chemotherapy (either gemcitabine, docetaxel, or pemetrexed [non-squamous only]) according to the discretion of the treating physician.
9. Adequate laboratory values obtained within 28 days prior to registration for protocol therapy (as defined in table 1 below).

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 K/mm^3
Platelets	≥100,000 K/mm^3
Hemoglobin without transfusion or EPO dependency (within 7 days of assessment)	≥9 g/dL or ≥5.6 mmol/L
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN

Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT); Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy. In the case of anticoagulants, PT/INR/PTT must be within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

10. Women of childbearing potential (WOCBP) must have a negative urine or serum pregnancy test within 7 days prior to study registration and/or within 72 hours of first dose of study drugs. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
    Female subjects will be considered of childbearing potential unless they are either:
    (1) postmenopausal--defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. OR
    (2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion at least 6 weeks prior to screening. OR
    (3) have a congenital or acquired condition that prevents childbearing.

11. Women of childbearing potential must be willing to use two methods of contraception (see section 5.5.2) or abstain from heterosexual activity from the point of registration through 120 days after the last dose of study drug.

12. Male subjects capable of fathering a child must agree to use an adequate method of contraception (see section 5.5.2) starting with the first dose of the study drug through 120 days after the last dose of the study drug.
    Male subjects will be considered to be capable of fathering a child unless they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

3.2 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

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

2. Active central nervous system (CNS) metastases.

NOTE: Subjects who are symptomatic and have not undergone prior brain imaging must undergo a head computed tomography (CT) scan or brain MRI within 28 days prior to registration to exclude brain metastases.
NOTE: A subject with prior brain metastasis may be considered if they have completed their treatment for brain metastasis at least 4 weeks prior to study registration, have been off corticosteroids for ≥ 2 weeks, are asymptomatic, and there is no evidence of progression on brain imaging (CT or MRI).

3. Treatment with any investigational agent within 28 days prior to registration for protocol therapy with the exception of PD-1 or PD-L1 inhibitors.

4. No active second cancers with the exception of localized non-melanoma skin cancer, in-situ cervical or in-situ bladder cancer.

5. Evidence of active autoimmune disease requiring systemic treatment within the past 90 days or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents.
NOTES: Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjögren's syndrome will not be excluded.

6. Prior solid organ or stem cell transplant.

7. History of interstitial lung disease or pneumonitis related to the use of immunotherapeutic drugs. Subjects with a history of pneumonitis which is unrelated to the use of immunotherapeutic drugs may participate at the discretion of the treating physician.

8. History of an immune-related toxicity requiring treatment with corticosteroids during prior PD-1/ PD-L1 inhibitor treatment.

9. Diagnosis of immunodeficiency or is receiving chronic systemic corticosteroid therapy or other immunosuppressive therapy (excludes inhaled corticosteroids) within 7 days of study registration

10. History of psychiatric illness or social situations that would limit compliance with study requirements

11. Clinically active infection (≥ Grade 2) as judged by the site investigator.

12. Known history of human immunodeficiency virus (HIV) infection or chronic hepatitis B or C. NOTE: HIV, HBV or HCV testing is not required.

13. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the site investigator.

14. Known history of active TB (Bacillus Tuberculosis).

15. History of hypersensitivity to pembrolizumab, docetaxel, gemcitabine, pemetrexed or any of their excipients.

16. Has received a live vaccine within 30 days prior to planned start of study therapy.
    Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

4. SUBJECT REGISTRATION

All subjects must be registered through Big Ten CRC Administrative Headquarters' (AHQ) electronic data capture (EDC) system OnCore. A subject is considered registered when an 'On Study' date is entered into OnCore.

5. TREATMENT PLAN

This is a single-arm phase II study of continuation immunotherapy with pembrolizumab following initial benefit with a PD-1 or PD-L1 inhibitor. Patients who have been treated with a PD-1 or PD-L1 inhibitor and experienced a PFS of ≥3 months will be enrolled within 12 weeks of last dose of PD-1 or PD-L1 inhibitor. On Day 1 of each 3-week cycle, subjects will first receive pembrolizumab at a dose of 200mg IV every three weeks in combination with chemotherapy. Partner chemotherapy will be either gemcitabine 1000mg/m^2 IV D1 and D8 every three weeks, docetaxel 60-75mg/m^2 IV D1 every three weeks, or pemetrexed 500mg/m^2 IV D1 every 3 weeks (pemetrexed for non-squamous histologies only). Subjects will continue to receive this combination until progression or intolerable toxicity.

5.1 Pre-medication and Hydration

Premedication and hydration will be administered as per institutional standards based on the partner chemotherapy selected (gemcitabine, docetaxel, or pemetrexed). Pembrolizumab does not require any premedication.

5.2 Chemotherapy + Pembrolizumab Administration

Partner chemotherapy will be administered as per institutional standards at the doses outlined below in Table 2.

Table 2 Drug Administration

Drug	Administration Sequence	Dose[1]	Route	Schedule[2]	Cycle Length
Pembrolizumab	1st	200mg	Intravenously	Day 1	21 days
Gemcitabine	2nd	1000mg/m^2	Intravenously	Days 1, 8	21 days
Docetaxel		60-75mg/m^2	Intravenously	Day 1	
Pemetrexed[3]		500mg/m^2	Intravenously	Day 1	
[1] Body surface area (BSA) should be recalculated per institutional standards for weight changes. The starting dose of docetaxel within this range will be at the discretion of the treating physician.					
[2] A window of ±3 days may be applied to all study visits to accommodate observed holidays, inclement weather, scheduling conflicts etc. Date and time of each drug administration should be clearly documented in subject's chart and electronic case report forms (eCRFs).					
[3] Cyanocobalamin (vitamin B_{12}) should be given at a dose of 1000mcg intramuscularly every 3 cycles (9 weeks), and folic acid should be given at a dose of 1mg PO daily while on pemetrexed.					

5.2.1 Pembrolizumab Administration

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

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

5.3 Concomitant Medications

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 site investigator should discuss any questions regarding this with the Big Ten CRC project manager who will communicate with the sponsor-investigator and Merck Clinical team regarding the situation. The final decision on any supportive therapy or vaccination rests with the site investigator and/or the subject's primary physician. There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.3.1 Docetaxel Subjects

Docetaxel is a CYP3A4 substrate. In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4.

In vivo studies showed that the exposure of docetaxel increased 2.2-fold when it was co-administered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of docetaxel and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients receiving

treatment with docetaxel, close monitoring for toxicity and a docetaxel dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided.

5.3.2 Pemetrexed subjects

Although ibuprofen (400 mg four times a day) can decrease the clearance of pemetrexed, it can be administered with pemetrexed in patients with normal renal function (creatinine clearance ≥80 mL/min). No dose adjustment of pemetrexed is needed with concomitant NSAIDs in patients with normal renal function.

Caution should be used when administering NSAIDs concurrently with pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min). NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of 2 days before, the day of, and 2 days following administration of pemetrexed.

In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least 5 days before, the day of, and 2 days following pemetrexed administration. If concomitant administration of NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity.

5.3.3 Allowed Concomitant Medications

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

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered more than 30 days after the last dose of trial treatment should be recorded for serious adverse events (SAE) and events of clinical interest (ECI) as defined in Section 11.2.4.

5.3.4 Prohibited Concomitant Medications

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

- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy- palliative radiation can be permitted per guidelines in section 5.3.5
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an ECI (see section 11.2.4) of suspected immunologic etiology or for use as anti-emetic prophylaxis per standard chemotherapy protocols. The use of physiologic doses of corticosteroids may be approved after consultation with the Big Ten CRC project manager and the sponsor-investigator.

Subjects who, in the assessment by the site investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. The Exclusion Criteria describes other medications which are prohibited in this trial.

5.3.5 Concomitant Palliative Radiotherapy

The potential for overlapping toxicities with radiotherapy and pembrolizumab currently is not known. Therefore, palliative radiotherapy is not recommended while receiving pembrolizumab. If palliative radiotherapy is required, pembrolizumab should be withheld for at least 1 week before, during, and 1 week after radiation. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs should resolve to Grade ≤ 1 prior to resuming pembrolizumab.

- Non-target bone lesions without lung tissue included in the planned radiation field may receive palliative radiotherapy.
- Patients would also be permitted to continue on trial if they undergo palliative radiation to brain metastases if 1) this is their only site of progressive disease (no non-CNS progression) and 2) their treating physician feels restarting trial therapy is safe and in the best interest of the patient.

Details of palliative radiotherapy should be documented in the source records and eCRF. Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and adverse events. If warranted, symptoms requiring palliative radiotherapy should be evaluated for objective evidence of disease progression.

5.4 Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the site investigator. Suggested supportive care measures for the management of AEs 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 (please see section 5.3.2 for guidelines on concomitant administration of NSAIDS and pemetrexed) if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

Management of Pembrolizumab Infusion Related Reactions
Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 3 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 3: Pembrolizumab Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Pembrolizumab Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further pembrolizumab administration (chemotherapy can continue per section 6.2.1)**	Subject may be premedicated 1.5h (± 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.	No subsequent dosing

NCI CTCAE Grade	Pembrolizumab Treatment	Premedication at subsequent dosing
	In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further pembrolizumab (chemotherapy can continue per section 6.2.1).	
Appropriate resuscitation equipment should be available and a physician readily available during the period of drug administration.		

5.4.1 Supportive Care Guidelines for Pneumonitis

Subjects with symptomatic pneumonitis should immediately stop receiving pembrolizumab and have an evaluation. The evaluation may include bronchoscopy and pulmonary function tests to rule out other causes such as infection. If the subject is determined to have study drug associated pneumonitis, the suggested treatment plan is detailed in Table 4.

For Grade 2 pneumonitis that improves to ≤ Grade 1 within 12 weeks, the following rules should apply:

- First episode of pneumonitis
  - May increase dosing interval by one week in subsequent cycles (permanent change)
- Second episode of pneumonitis – permanently discontinue pembrolizumab if upon rechallenge subject develops pneumonitis ≥ Grade 2
  - Partner chemotherapy may continue per physician discretion

5.5 Diet/Activity/Other Considerations

5.5.1 Diet

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

5.5.2 Contraception

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

Non-pregnant, non-breast-feeding women of childbearing potential (see section 3.1.10) may be enrolled if they are willing to use 2 methods of birth control. The two methods of birth control can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from the screening visit, throughout the study period, and up to 120 days after the last dose of study drug.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the

study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 11.2.3. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.5.3 Use in Pregnancy

If a subject becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from all study treatment and followed up per protocol. The site investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Big Ten CRC AHQ who will report to Merck. The site will report the outcome of the pregnancy to Big Ten CRC AHQ within 1 working day of discovery of event. Big Ten CRC will notify the sponsor-investigator and Merck within 1 business day if the outcome is a SAE (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). See also Section 11.2.3.

If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to Big Ten CRC AHQ who will report the event to Merck and followed as described above and in Section 11.2.3.

5.5.4 Use in Nursing Women

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

6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v4 will be used to grade adverse events.

Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations.

Subjects will be evaluated for AEs (all grades), SAEs, and AEs requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

6.1 Dose Delays/Dose Modifications

6.1.1 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be withdrawn from the trial at the discretion of the site investigator should any untoward effect occur. In addition, a subject may be withdrawn by the sponsor-investigator or Big Ten CRC AHQ if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided below.

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

- Confirmed radiographic disease progression by RECIST 1.1 criteria
- Unacceptable AEs as described in Section 6.2.1

- Intercurrent illness that prevents further administration of treatment
- Site investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Subject refuses further treatment

A subject must be discontinued from the trial (no follow up) for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- The subject is lost to follow-up

After the end of treatment, each subject will be followed for 30 days for AE monitoring (SAEs will be collected for 90 days after the end of treatment as described in Sections 11.2.4 and 11.2.5). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. After documented disease progression each subject will be followed for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first. See also Section 7.4.

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any AEs which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 11.2.1.

6.1.2 Treatment Delay

If either Day 1 pembrolizumab or Day 1 of the partner chemotherapy agent is delayed, all study drugs must be delayed until treatment can resume. If the toxicity is clearly attributable to one agent, the other agent can be resumed alone at a normal dose and schedule after one week. If the toxicity resolves, the combination should be resumed at the next scheduled dosing interval (the drugs should not be on differing schedules). If it is unclear which drug is causing the toxicity, all drugs must be delayed until the toxicity resolves to meet treatment parameters.

- Delays of greater than 6 weeks secondary to toxicity from chemotherapy agents should result in permanent discontinuation of chemotherapy
- Delays of greater than 12 weeks secondary to toxicity from pembrolizumab should result in permanent discontinuation of pembrolizumab
- In either case, treatment with the other agent may continue at the discretion of the treating physician as long as the patient meets criteria for continued therapy

If D8 gemcitabine requires a delay, this dose can be omitted or alternatively given on D15 per the treating physician's discretion. Delays for D8 gemcitabine should not prolong a cycle and cycles should continue every 21 days if subjects meet criteria for continued therapy.

6.2 Dose Modifications

6.2.1 Pembrolizumab

The dose of pembrolizumab will not be modified.

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

Table 4: Dose modification and toxicity management guidelines for immune-related adverse events associated with pembrolizumab

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 if irAEs cannot be controlled by corticosteroids.

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 (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.
	Grade 4	Permanently discontinue		
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

	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	until liver enzyme value returned to baseline or is stable
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]		
Hypothyroidism	Grade 2-4	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 is 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).

If toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, pembrolizumab should be discontinued after consultation with the Big Ten CRC project manager and the sponsor-investigator. With site investigator and sponsor-investigator agreement, subjects with a laboratory AE still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. If a subject has more than 3 delays in pembrolizumab dosing due to other toxicities specific to this medication, they will be discontinued from pembrolizumab.

Subjects who experience a recurrence of the same severe or life-threatening event at the same grade or greater with re-challenge of pembrolizumab should be discontinued from pembrolizumab.

Subjects who permanently discontinue pembrolizumab due to toxicity but who have not progressed may remain on single-agent chemotherapy per physician discretion until progression or intolerable toxicity.

6.2.2 Partner Chemotherapy

6.2.2.1 Gemcitabine

- Gemcitabine should be given at an initial dose of 1000mg/m^2 IV day 1 and 8 every 3 weeks.
- Dose delays of >6 weeks will result in permanent discontinuation of gemcitabine.
- Subjects who permanently discontinue gemcitabine due to toxicity but who have not progressed may remain on single-agent pembrolizumab until progression or intolerable toxicity.

Dose Level	Dose Modification
Full dose gemcitabine	1000 mg/m^2
75% of full dose	750 mg/m^2
50% of full dose	500 mg/m^2

If hematologic toxicity develops, dose reductions should be per drug label guidelines **or** as follows at discretion of site investigator:

Hematologic Toxicity	Gemcitabine dose modification
ANC[a] ≥1000/mm^3 and platelet count ≥100,000/mm^3	Administer 100% full dose
ANC[a] 500-999/mm^3 or platelet count 50,000-99,999/mm^3	Administer 75% of full dose
ANC[a] <500/mm^3 or platelet count <50,000/mm^3	Hold dose
[a]=absolute neutrophil count	

Day 1 gemcitabine may resume when ANC is ≥ 1000/mm^3 and platelet count ≥100,000/mm^3. Day 8 gemcitabine may be given when the platelet count is ≥75,000/mm^3. If platelets are <75,000, Day 8 gemcitabine may be given on Day 15 if the platelet count has improved to

≥75,000/mm^3, at the discretion of the treating physician. If the platelet count has not improved, gemcitabine may be completely omitted during that cycle.

For non-hematologic toxicity, dose reductions should be per drug label guidelines or as follows at discretion of site investigator:

Non-Hematologic Toxicity	Gemcitabine dose modification
Severe (grade 3 or 4) non-hematologic toxicity (excludes nausea, vomiting, or alopecia- no dose modifications recommended)	Hold until resolved and then resume at 50% dose
Unexplained dyspnea (or other evidence of pulmonary toxicity), severe hepatotoxicity, hemolytic uremic syndrome (HUS), capillary leak syndrome (CLS), posterior reversible encephalopathy syndrome (PRES)	Permanently discontinue gemcitabine

6.2.2.2 Docetaxel

- Docetaxel should be given at an initial dose of 60-75mg/m^2 IV Day 1 every 3 weeks. If dose reduction is required, recommend restarting at a 20% reduction of full dose every 3 weeks **or** per product labeling at the discretion of the site investigator.
- Dose delays of >6 weeks will result in permanent discontinuation of docetaxel.
- Subjects who permanently discontinue docetaxel due to toxicity but who have not progressed may remain on single-agent pembrolizumab until progression or intolerable toxicity.

Dose Level	Dose Modification
Full Dose Docetaxel	60-75 mg/m^2
Docetaxel Dose Level –1	20% reduction of full dose
Docetaxel Dose Level –2	40% reduction of full dose

Note: A maximum of two dose reductions per subject are allowed. If > 2 dose reductions are required, docetaxel will be permanently discontinued.

Docetaxel dose reductions should be per drug label guidelines **or** as follows, at the discretion of the site investigator:

- Hematologic adjustments:
  Subjects with neutropenic fever or grade 4 neutropenia lasting > 7 days or grade 4 thrombocytopenia or thrombocytopenic bleeding should be retreated after recovery to Grade≤1 or patient baseline with a one level dose reduction.

- Peripheral neuropathy adjustments:
  If subject experiences a grade 2 toxicity, the subsequent retreatment after recovery to ≤ Grade 1 should be with a one level dose reduction.

Subjects who have grade 3 or higher peripheral neuropathy should be permanently discontinued from docetaxel.

- Hypersensitivity reaction adjustments:
  No dose reductions will be made for any hypersensitivity reactions. If the subject experiences a hypersensitivity reaction, treatment should be given as indicated below:
  - Grade 1 symptoms (eg., mild flushing, rash, pruritis)—complete infusion. Supervise at bedside. No treatment required.
  - Grade 2 symptoms (e.g., moderate rash, flushing, mild dyspnea, chest discomfort)—Interrupt infusion. Give intravenous diphenhydramine 25 mg and intravenous dexamethasone 10 mg. Resume infusion after recovery of symptoms at a slower rate, then increase incrementally to the initial planned rate. Depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the next cycle of treatment and the rate of infusion should be decreased initially and then increased back to the planned rate. Report as an AE.
  - Grade 3 symptoms (e.g., hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilation therapy, generalized urticaria)—Stop infusion. Give intravenous diphenhydramine and dexamethasone as above. Add epinephrine or bronchodilators if indicated. If wheezing is present, which is not responsive to administration of 0.35 cc of nebulized salbutamol solution (or equivalent), epinephrine is recommended. The patient will be permanently removed from docetaxel. Report as an AE.
  - Grade 4 symptoms - Anaphylaxis—Permanently remove from docetaxel. Report as an AE.

- Hepatic adjustments:
  Patients who develop abnormal liver function tests for any reason while on the study will have the following docetaxel dose reductions:

Abnormal Liver Function Dose Modifications for Docetaxel

Bilirubin	**Alkaline Phosphatase**	**SGOT (AST)**	**Action**
≥1.5X ULN	**or** > 5 X ULN	**or** > 5 X ULN	Wait up to 6 weeks. If recovered*, reduce docetaxel dose by –1 dose level. If not, permanently d/c docetaxel.
< 1.5X ULN	**and** ≤ 5 X ULN	**and** 2.5-5 X ULN	Reduce docetaxel dose by –1 dose level.
*Bilirubin < 1.5X ULN **and** alkaline phosphatase ≤ 5 X ULN **and** SGOT (AST) ≤ 5 X ULN.			

ULN= upper limit of normal for institution

- Fluid retention adjustments:

If symptomatic, subjects developing fluid retention may be treated with diuretics at the investigator's discretion.
If grade 3, docetaxel should be held until resolution to ≤ grade 1, then reinstituted after recovery, if medically appropriate, with a one level dose reduction.

- Stomatitis adjustments:
  If grade 3 or 4 stomatitis occurs, retreatment after recovery to grade 1 or less with a one level dose reduction.

- Other non-hematologic toxicities:
  If toxicities ≥ 3, docetaxel should be held until resolution to grade 1 or less, then reinstituted, if medically appropriate, after recovery, with a one level dose reduction.

  Patients requiring a > 6 week delay in docetaxel due to non-hematologic toxicity will be removed from docetaxel treatment.

6.2.2.3 Pemetrexed

- Pemetrexed should be given at an initial dose of 500mg/m^2 IV every 3 weeks. Pemetrexed should be discontinued if subjects develop grade 3 or 4 toxicity after two dose reductions or immediately if grade 3 or 4 neurotoxicity develops.
- Dose delays of >6 weeks will result in permanent discontinuation of pemetrexed.
- Subjects who permanently discontinue pemetrexed due to toxicity but who have not progressed may remain on single-agent pembrolizumab until progression or intolerable toxicity.

If a dose reduction for pemetrexed is required for hematologic toxicity, reductions should be per product labeling **or** as follows at the discretion of the investigator:

Hematologic Toxicity	Pemetrexed dose modification
Nadir ANC <500/mm^3 and nadir platelets ≥50,000/mm^3	Reduce dose to 75% of previous dose
Nadir platelets <50,000/mm^3 without bleeding (regardless of nadir ANC)	Reduce dose to 75% of previous dose
Nadir platelets <50,000/mm^3 with bleeding (regardless of ANC)	Reduce dose to 50% of previous dose

If ≥ grade 3 non-hematologic (excluding neurotoxicity) toxicity develops, pemetrexed should be withheld until recovery to baseline. Upon recovery, dose reductions should be per product label or as follows at the discretion of the investigator:

Non-Hematologic Toxicity	Pemetrexed dose modification
Grade 3 or 4 toxicity (excluding mucositis)	Reduce dose to 75% of previous dose
Grade 3 or 4 diarrhea or any diarrhea requiring hospitalization	Reduce dose to 75% of previous dose
Grade 3 or 4 mucositis	Reduce dose to 50% of previous dose

For neurotoxicity: • Grade 0-2 • Grade 3 or 4	 Continue at 100% of previous dose Discontinue treatment

6.3 Protocol Therapy Discontinuation

In addition to discontinuation from therapy related to toxicities as outlined in section 6.1, a subject will also be discontinued from protocol therapy and followed up per protocol under the circumstances outlined below. The reason for discontinuation of protocol therapy will be documented on the eCRF.

- Documented disease progression per RECIST 1.1.
- The treating physician thinks a change of therapy would be in the best interest of the subject
- The subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
    - If a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- A female subject becomes pregnant

6.4 Protocol Discontinuation

If a subject decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete the final study assessments. The site study team should contact the subject by telephone or through a clinic visit to determine the reason for the study withdrawal. If the reason for withdrawal is an AE, it will be recorded on the eCRF.

7. STUDY CALENDAR & EVALUATIONS

Cycle = 21 days	Screening	Cycle 1[1,2]		Cycle 2+[2]		Every other cycle[2,3]	Safety follow up	Long-term Follow up[5]
	-28 days	Day 1	Day 8	Day 1	Day 8	Day 1	30 days[2,4] post last dose	Every 3 months (±14 days)
REQUIRED ASSESSMENTS								
Informed Consent/ HIPAA auth.	X							
Medical history including smoking history[6]	X							
Diagnosis and Staging[6]	X							
Physical exam	X	X		X			X	
Vital signs, ECOG Performance status[7]	X	X		X			X	
AEs, ECIs & concomitant medications	X	X		X			X	X
LABORATORY ASSESSMENTS								
Complete Blood Cell Count with diff (CBC)	X	X[1]	X[11]	X	X[11]		X	
Comprehensive Metabolic Profile (CMP)[8]	X	X[1]		X			X	
Thyroid Function (TSH, T4, free T3)	X					X		
PT, INR, aPTT	X							
Pregnancy test (serum or urine) WOCBP	-7d[9]	-72h[9]						
DISEASE ASSESSMENT[10]								
CT of chest[10]	X					X[10]		X[5]
CT or MRI of abdomen and pelvis, if applicable[10]	X					X[10]		X[5]
MRI Brain[10]	X							
Bone/PET Scan[10]	X					X[10]		
TREATMENT EXPOSURE								
Pembrolizumab		X		X				
Partner chemotherapy drug[11]		X	X[11]	X	X[11]			
CORRELATIVE STUDIES (SPECIMEN COLLECTION)								
Archival tumor tissue[12]		X						
Optional tumor biopsy[13]	X[13]						X[13]	
Whole Blood samples[14]		X						
BANKING SAMPLES (SPECIMEN COLLECTION)								
Whole Blood[15]		X						
Unstained Slides from Tumor Block[16] (if available)		X						
Serum and Plasma[17]		X					X	
FOLLOW-UP								
Survival status, subsequent therapy								X

Key to Footnotes

[1]If screening (baseline) labs were performed within 7 days of D1 of treatment, these do not need to be repeated.

[2]A window of 3 days will be applied to all treatment study visits; for safety follow-up visit and tumor imaging, a 7-day window will apply.

[3]Tumor imaging and thyroid function to continue every other cycle until progression, starting with cycle 3.

[4]A safety follow-up visit will occur 30 days (±7 days) after the last dose of treatment. ECIs and SAEs will be collected for 90 days after the end of treatment. See Sections 11.2.4 and 11.2.5.

[5]Subjects without documented disease progression will be followed for every 3 months for 1 year from end of treatment or until death. Once disease progression is documented, subjects will be followed every 3 months for 1 year from the time of documented progression or death.

[6] Medical History to include demographics, prior treatments, radiation and surgical history, smoking history, and trial awareness question. Diagnosis and staging to include pathology report and Tumor Node Metastasis (TNM) staging.

[7]Vital signs to include blood pressure, weight, and height (screening only) and ECOG performance status

[8]CMP with liver function tests (LFTs) to include sodium, potassium, chloride, creatinine, blood urea nitrogen, AST, ALT, total bilirubin, alkaline phosphatase.

[9]For women of childbearing potential (WOCBP): urine or serum βhCG, within 7 days prior to study registration and within 72 hours prior to receiving the first dose of study medication. If a urine test is done and it is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

[10]Tumor response assessment will be performed every odd numbered cycle starting with cycle 3; tumor imaging to be done at treatment discontinuation at discretion of investigator. Subjects with ongoing response or stable disease after 1 year on study drug may reduce tumor response frequency to every 3 or 4 cycles (9 or 12 wks) at the discretion of the treating physician. **Chest CT** should include the upper abdomen including the adrenals and liver. Baseline (and subsequent) **CT or MRI of abdomen and pelvis** is required only for subjects with known abdominal or pelvic metastasis. **MRI of brain** should be performed at screening as per Section 3.2.2. Baseline **bone scan** will be obtained at discretion of investigator. PET-CT scans may be used for initial staging or follow-up imaging in place of standard CT scans at the discretion of the treating physician.

[11]Partner chemotherapy drug, chosen at discretion of investigator, will be either docetaxel, gemcitabine or pemetrexed [for non-squamous only]. If gemcitabine is chosen, dosing will be on D1 and D8 of each cycle.

[12]Fixed paraffin-embedded blocks/slides will be requested from tissue obtained prior to initial treatment with PD-1 inhibitor.

[13]Optional biopsies will be requested at time of progression on PD-1 or PD-L1 inhibitor (study entry) and at time of progression on combination of pembrolizumab and chemotherapy (safety follow up visit)

[14]Blood samples will be collected to support biomarker research. See Clinical Laboratory Manual (CLM) for additional details.

[15]Submission of whole blood for banking is to be collected at Pre-Treatment Cycle 1 Day 1. See CLM for collection, processing, labeling and shipping instructions.

[16]Submission of unstained slides for banking from an archived FFPE tumor block (if available). See CLM for collection, labeling, and shipping instructions.

[17]Submission of serum and plasma for banking are to be collected at Pre-Treatment Cycle 1 Day 1 and at the 30-Day Safety Follow up visit. See CLM for collection, labeling, processing, and shipping instructions.

A window of ±3 days will be applied to all treatment study visits; a window of ±7 days will be applied to all safety follow-up visits and tumor imaging.

7.1 Screening Evaluations

7.1.1 Within 28 days prior to registration for protocol therapy

- Informed consent, HIPAA authorization
- Medical history to include demographics, prior treatments, radiation and surgical history, and trial awareness question.
- Smoking history to include: amount, frequency, start and stop dates of cigarette, cigar and pipe usage.
- Diagnosis and staging to include pathology report and Tumor Node Metastasis (TNM) staging
- Physical exam
- Vital signs (blood pressure, weight, and height [screening only] and ECOG performance status)
- AEs, ECIs & concomitant medications
- Complete blood cell count with differential
- Comprehensive metabolic profile (sodium, potassium, chloride, creatinine, blood urea nitrogen; liver function tests (LFTs) to include AST, ALT, total bilirubin, alkaline phosphatase)
- Thyroid function (TSH, T4, free T3)
- [-7 days] Pregnancy test (serum or urine) for women of childbearing potential (WOCBP)

Baseline Disease Evaluation

Tumor response assessment will consist of evaluation by CT scans of chest and MR or CT of abdomen and pelvis. Subject imaging modality should remain the same throughout the study. PET-CT scans may be used for initial staging or follow-up imaging in place of standard CT scans at the discretion of the treating physician.

- CT chest: should include the upper abdomen including the adrenals and liver
- CT or MRI of abdomen and pelvis: required only for subjects with known abdominal or pelvic metastasis
- MRI of brain, if indicated. See Section 3.2.2.
- Bone/ PET scan: at discretion of investigator.

Optional Tumor Biopsy (See CLM for additional details)

- Optional biopsy is requested at the time of progression on PD-1 or PD-L1 inhibitor (study entry)

7.2 On Treatment Evaluations

7.2.1 Cycle 1 Day 1

Note: Cycle 1 Day 1 lab testing need not be repeated if completed within 7 days of starting protocol therapy.

- Physical exam
- Vital signs and ECOG performance status
- AEs, ECIs & concomitant medications
- Complete blood cell count with differential
- Comprehensive metabolic profile
- [-72 hours prior to first dose] Pregnancy test (serum or urine) for women of childbearing potential
- Pembrolizumab plus chemo (physician's choice)
- Correlative samples: (See CLM for additional details)
  - Unstained slides from archived tissue
  - Pre-dose blood samples will be collected to support biomarker research
- Banking samples.
  - Whole blood
  - Unstained slides from archived tissue
  - Serum and plasma

7.2.2 Cycle 1 Day 8 (if applicable)

- Complete blood cell count with differential
- Gemcitabine administration

7.2.3 Cycle 2+ Day 1

- Physical exam
- Vital signs and ECOG performance status
- AEs, ECIs & concomitant medications
- Complete blood cell count with differential
- Comprehensive metabolic profile
- Pembrolizumab plus chemo (physician's choice)

7.2.4 Cycle 2+ Day 8 (if applicable)

- Complete blood cell count with differential
- Gemcitabine administration

7.2.5 Day 1 of Every Other Cycle starting with Cycle 3

- Thyroid function (TSH, T4, free T3)
- CT chest
- CT or MRI of abdomen and pelvis
- Bone/ PET scan: at discretion of investigator

7.3 Safety Follow-up Evaluations

A safety follow-up visit should occur when subjects permanently stop study treatment for whatever reason (toxicity, progression, or at discretion of site investigator) and should be performed 30 days (±7 days) after the last dose of treatment. Subjects who have an ongoing ≥ grade 2 or serious AE (SAE) at this visit will continue to be followed until the AE resolves to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever is earlier.

- Physical exam
- Vital signs and ECOG performance status
- AEs, ECIs & concomitant medications
- Complete blood cell count with differential
- Comprehensive metabolic profile

Optional Tumor Biopsy (See CLM for additional details)

- Optional biopsy is requested at the time of progression on combination of pembrolizumab and chemotherapy (safety follow up visit)

7.4 Long Term Follow-up Evaluations

All subjects will be followed until documented disease progression. Subjects who discontinue treatment for any reason without documented disease progression will be followed for disease progression every 3 months for 1 year from end of treatment or until death, whichever occurs first.

- AEs, ECIs & concomitant medications
- CT chest
- CT or MRI of abdomen and pelvis

Once disease progression is documented, subjects will enter a survival follow up period every 3 months for 1 year from the time of documented progression or death, whichever occurs first. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate.

8. BIOSPECIMEN STUDIES AND PROCEDURES

Please refer to the CLM for all sample collection, processing, labeling, and shipping instructions.

8.1 Tissue for assessment of PD-L1 status

8.1.1 Archival

- Prior to initial treatment with PD-1 inhibitor

8.1.2 Optional Biopsies

- At time of progression on PD-1 or PD-L1 inhibitor (study entry)
- At time of progression on combination of pembrolizumab and chemotherapy (safety follow up visit)

8.2 Tissue for genetic analysis

- NeoTYPE Lung Tumor Profile Genetic Analysis will also be performed: Sequencing of select exons of AKT1, BRAF, EGFR, ERBB2, ERBB4, FGFR1, FGFR2, FGFR3, KIT, KRAS, MET, NOTCH1, NRAS, PDGFRA, PIK3CA, PTEN, SMAD4, SMO, SRC, TP53, as well as ALK FISH, HER2 FISH, MET FISH, PTEN FISH, RET FISH, ROS1 FISH.

8.3 Blood for Somatic Baseline DNA

- Peripheral blood will be drawn for somatic baseline DNA by Neogenomics in accordance with the NeoTYPE Lung Tumor Profile (tissue test).

8.4 Blood for proteomic analysis and lipidomic profiling

- Pre-treatment blood samples will be used to explore the association of proteomic and lipidomic tests at baseline with ORR, PFS, and clinical benefit rate. Refer to the CLM for collection, processing, labeling and shipping instructions.

8.5 Confidentiality of Biospecimens

Samples that are collected will be identified by a subject's study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's study number.

8.6 Samples for future studies

Subject consent will be obtained for additional samples collected for future Big Ten CRC studies. HCRN, as Administrative Headquarters for the Big Ten CRC, will manage the banked samples. Samples will be banked indefinitely in the HCRN Biorepository.

This includes:

- Whole blood: Whole blood will be collected prior to treatment on Cycle 1 Day 1.
- Pre- and Post-treatment plasma: Whole blood for plasma will be collected prior to treatment on Cycle 1 Day 1 and at Safety Follow Up visit.
- Pre- and Post-treatment serum: Whole blood for serum will be collected prior to treatment on Cycle 1 Day 1 and at Safety Follow Up visit.
- Unstained slides: Unstained slides will be obtained from the subject's archived formalin fixed paraffin embedded tumor sample.

9. CRITERIA FOR DISEASE EVALUATION

9.1 Measurable Disease

Measurable disease is defined as the presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$20 mm by chest x-ray, as $\geq$10 mm with CT scan, or $\geq$10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

9.1.1 Malignant Lymph Nodes

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

9.2 Non-measurable Lesions

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

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

9.3 Target Lesions

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

9.4 Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

9.5 Evaluation of Target Lesions

NOTE: In addition to the information below, also see section 4.3.2 in the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

9.6 Evaluation of Non-target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
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)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor investigator.

9.7 Evaluation of Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/ or not all evaluated	No	PR

SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Non-evaluable
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

9.8 Definitions for Response Evaluation – RECIST 1.1

9.8.1 First Documentation of Response

The time between initiation of therapy and first documentation of PR or CR.

9.8.2 Confirmation of Response

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

9.8.3 Duration of Response

Duration of overall response—the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since treatment started).

9.8.4 Duration of Overall Complete Response

The period measured from the time that measurement criteria are met for complete response until the first date that recurrent disease is objectively documented.

9.8.5 Objective Response Rate

The objective response rate is the proportion of all subjects with confirmed PR or CR according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

9.8.6 Disease Control Rate:

The disease control rate is the proportion of all subjects with stable disease (SD) for 8 weeks, or partial response (PR), or complete response (CR) according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

9.8.7 Time to Progression:

A measurement from the date of treatment start until the criteria for disease progression is met as defined by RECIST 1.1. Subjects who have not progressed or have died due to any cause will be right-censored at the date of the last disease evaluation or date of death.

9.8.8 Progression Free Survival

A measurement from the date of treatment start until the criteria for disease progression is met as defined by RECIST 1.1 or death occurs. Subjects who have not progressed will be right-censored at the date of the last disease evaluation.

9.8.9 Overall Survival

Overall survival is defined by the date of treatment start to date of death from any cause.

9.9 Immune- Related RECIST Criteria

Please refer to the full publication for complete details on immune-related RECIST criteria: Bohnsack O. et al. Adaptation of the immune-related response criteria: irRECIST. ESMO 2014 Abstract 4958. http://www.irrecist.com/

9.9.1 Measurable lesion definitions and target lesion selection

Follow the definitions from RECIST 1.1.

Measurable lesions must be accurately measured in at least one dimension with a minimum size of:

- 10 mm in the longest diameter by CT or MRI scan (or no less than double the slice thickness) for non-nodal lesions and ≥15 mm in short axis for nodal lesions
- 10 mm caliper measurement by clinical exam
- 20 mm by chest X-ray

9.9.2 Baseline: Non-measurable lesion definitions

Follow the definitions from RECIST 1.1.

Non-target lesions will include:

- Measurable lesions not selected as target lesions
- All sites of non-measurable disease, such as neoplastic masses that are too small to measure because their longest uninterrupted diameter is < 10 mm (or < two times the axial slice thickness), ie. the longest perpendicular diameter is ≥10 and < 15 mm.
- Other types of lesions that are confidently felt to represent neoplastic tissue, but are difficult to measure in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural or pericardial effusions, ascites,

inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill-defined abdominal masses, skin lesions, etc.

9.9.3 Baseline: Target and Non-Target Lymph Node Lesion Definitions

Follow the definitions from RECIST 1.1.

9.9.4 Baseline: Bone Lesions

Follow the definitions from RECIST 1.1.

- Regardless of the imaging modality blastic bone lesions will not be selected as target lesions. Lytic or mixed lytic-blastic lesions with a measurable soft tissue component ≥10 mm can be selected as target lesions.

9.9.5 Baseline: Brain Lesions

- Brain lesions detected on brain scans can be considered as both target or non-target lesions.

9.9.6 Baseline: Cystic and necrotic lesions as target lesions

- Lesions that are partially cystic or necrotic can be selected as target lesions. The longest diameter of such a lesion will be added to the Total Measured Tumor Burden (TMTB) of all target lesions at baseline. If other lesions with a non-liquid/non-necrotic component are present, those should be preferred.

9.9.7 Baseline: Lesions with prior local treatment

- During target lesion selection the radiologist will consider information on the anatomical sites of previous intervention (e.g. previous irradiation, RF-ablation, TACE, surgery, etc.). Lesions undergoing prior intervention will not be selected as target lesions unless there has been a demonstration of progress in the lesion.

9.9.8 Baseline: No Disease at Baseline

- If a patient has no measurable and no non-measurable disease at baseline the radiologist will assign 'No Disease' (irND) as the overall tumor assessment for any available follow-up timepoints unless new measurable lesions are identified and contribute to the TMTB.

9.9.9 Follow-up: Recording of Target and New Measurable Lesion Measurements

- The longest diameters of non-nodal target and new non-nodal measurable lesions, and short axes of nodal target and new nodal measurable lesions will be recorded. Together they determine the Total Measured Tumor Burden (TMTB) at follow-up.

9.9.10 Follow-up: Definition of Measurable New Lesions:

- In order to be selected as new measurable lesions (≤ 2 lesions per organ, ≤ 5 lesions total, per timepoint), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measured lesions.

9.9.11 Follow-up: Non-Target Lesion Assessment

- The RECIST 1.1 definitions for the assessment of non-target lesions apply. The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN). Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD.

9.9.12 Follow-up: New Non-Measurable Lesions Definition and Assessment:

- All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively. Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the timepoint. Persisting new non-measurable lesions prevent irCR.

9.9.13 irRC Overall Tumor Assessments

- Complete response (irCR) is defined by the complete disappearance of all lesions. Lymph nodes must decrease to < 10 mm in short axis. Confirmation of response is not mandatory.
- Partial response (irPR) is defined by the decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions.
- Stable disease (irSD) is when the measurements do not meet criteria for irCR or irPR, in absence of progressive disease (irPD).
- irNN is when no target disease was identified at baseline and at follow-up the patient fails to meet criteria for irCR or irPD.
- irPD is defined by a minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment.

10. DRUG INFORMATION

10.1 Pembrolizumab

Please refer to the current version of the Investigator's Brochure (IB) for additional information regarding this drug

10.1.1 Supplier/How Supplied

Merck will supply pembrolizumab at no charge to subjects participating in this clinical trial.

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

10.1.2 Preparation

Please refer to the Pharmacy Manual for a comprehensive description of pembrolizumab preparation.

Merck will supply pembrolizumab directly to sites at no cost to subjects in this clinical trial.

The product after reconstitution with sterile water for injection and the liquid drug product is a clear to opalescent solution, which may contain extraneous and proteinaceous particulates. The reconstituted product and liquid product is intended for IV administration. The reconstituted drug product solution and liquid drug product can be further diluted with normal saline in IV containers made of polyvinyl chloride (PVC) or non-PVC material. Reconstituted vials should be immediately used to prepare the infusion solution in the IV bag and the infusion solution should be immediately administered. If not used immediately, vials and/or IV bags may be stored at 2-8 °C for up to a cumulative time of 20 hours. If refrigerated, the vials and/or IV bags should be allowed to equilibrate to room temperature prior to subsequent use. 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 and liquid drug product in vials, room temperature storage of infusion solution in the IV bag and the duration of infusion.

10.1.3 Storage and Stability

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

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

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

10.1.4 Dispensing

Pembrolizumab must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Pembrolizumab should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

10.1.5 Adverse Events

Please refer to the current version of the Investigator's Brochure for a complete list of AEs.

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 adverse events are of primary concern. Important identified risks for pembrolizumab monotherapy are primarily of an immune mediate nature, and included the following in the last IB (edition 16): pneumonitis, colitis, hepatitis, nephritis, endocrinopathies that include hypophysitis (including hypopituitarism and secondary adrenal insufficiency), thyroid disorder (hypothyroidism, hyperthyroidism and thyroiditis), Type I diabetes mellitis, uveitis, myositis, Guillain-Barré syndrome, pancreatitis, myocarditis, myasthenic syndrome, encephalitis, sarcoidosis, severe skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome; and "solid organ transplant rejection following pembrolizumab treatment in donor organ recipients" (risk applicable to post-marketing setting only, as such patients are currently excluded from Merck clinical trials with pembrolizumab).

Immune-mediated adverse reactions (ARs), including severe and fatal cases, have occurred in patients receiving pembrolizumab. Immune-mediated ARs can occur after discontinuation of treatment. Immune-mediated ARs affecting more than one body system can occur simultaneously. In clinical studies, most immune-mediated ARs were reversible and managed with interruptions of pembrolizumab, administration of corticosteroids, and/or supportive care.

The safety profile for pembrolizumab also includes 2 important potential risks – i.e. increased risk of severe complications (such as early severe graft versus host disease and veno-occlusive disease) of allogeneic transplant in patients with hematologic malignancies who have previously been treated with PD-1 inhibitors; and GVHD after pembrolizumab administration in patients with a history of allogeneic HSCT.

Since the last IB (Edition 16), 1 new identified risk in the specific population of RCC patients who receive the combination of pembrolizumab plus axitinib, has been added to the safety profile for pembrolizumab. An increase in hepatic events (ie, increased incidences of Grades 3 and 4 elevated ALT and AST) was observed in RCC patients who received the combination of pembrolizumab plus axitinib. Details are provided in section 5.4.2.2 of the IB. The Grade 3 or 4 ALT and AST elevations can be managed with prompt interruption or discontinuation of both study treatments, close liver enzyme and function monitoring, and with or without concomitant steroid treatment.

In addition to 1 new identified risk in the RCC population receiving the combination of pembrolizumab plus axitinib, based upon additional information received from the clinical study and postmarketing environments after release of IB Edition 16, the following changes have been made to the safety information for pembrolizumab:

- Information regarding exacerbation of myasthenia gravis was added to product labeling to further characterize the existing risk of myasthenic syndrome;
- Information regarding primary adrenal insufficiency was added to product labeling to further characterize the existing risk of immune-mediated endocrinopathies;
- A new adverse drug reaction of Vogt-Koyanagi-Harada syndrome was identified based primarily on postmarketing experience. Note: Vogt-Koyanagi-Harada syndrome may include a constellation of signs/symptoms which are already listed in product labeling, namely, the existing AE of special interest/risk of ‘uveitis’. However, considering the clinical significance of timely recognition and treatment of the condition, and that the term was identified primarily based on postmarketing experience, Merck decided to add the distinct preferred term of Vogt-Koyanagi-Harada syndrome to the company core data sheet Postmarketing Experience section.
- A new ADR of hemophagocytic lymphohistiocytosis was identified based primarily on postmarketing experience.

Further details around frequency, reporting, and management of immune-related AEs (irAEs) can be found in the current version of the Investigator’s Brochure. In addition to the previously noted identified risks, infusion-related reactions are a risk but are not considered immune mediated; these are also further described in the current IB.

10.2 Docetaxel

NOTE: Please refer to the current package insert for complete prescribing and toxicity information. Institutional guidelines may be used for preparation and administration of this medication.

10.2.1 Supplier/How Supplied

Docetaxel is commercially available in single-dose vials containing 20 mg (0.5 ml) or 80 mg (2.0 ml) docetaxel (anhydrous).

10.2.2 Preparation

Just prior to use, allow the docetaxel vial to reach room temperature for 5 minutes. Add the entire contents of the ethanol diluent vial and mix by gently rotating the vial for 15 seconds. Allow to stand for 5 minutes at room temperature, and check that the solution is homogeneous and clear (persistent foam is normal). The resulting solution contains 10 mg/mL of docetaxel. Please note that the solution contains 15% overfill. Dosing amounts should be based in the concentration per extractable volume, not the total volume of the vial. The desired dose is diluted in D5W or NS. The volume of the infusion should be adjusted in order to have a final docetaxel concentration of between 0.3 mg/mL and 0.9 mg/mL. Non-PVC-containing intravenous infusion bags and administration sets should be used to avoid patient exposure to the plasticizer DEHP.

10.2.3 Storage and Stability

Docetaxel is stored at 4oC protected from light. The solvent vials may be stored at room temperature or at 4oC. The premix solution is stable for 8 hours at room temperature (15o- 25oC) or refrigerated (at 2o- 8oC). The final dilution is also stable for 8 hours. (Please note that the company is no longer recommending that the final product be placed in PVC bags).

10.2.4 Incompatibilities

Intravenous bags and administration sets containing DEHP (di-[2-ethylexyl] phthalate). No further information is available.

10.2.5 Side Effects

1. Cardiac: arrhythmias, pericardial effusions, palpitations.
2. Hematologic: dose-related neutropenia, leukopenia, thrombocytopenia, anemia, hypoglycemia, hypernatemia.
3. Gastrointestinal: nausea and vomiting, diarrhea, oral mucositis, pancreatitis, esophagitis.
4. Neurologic: reversible dysthesias or paresthesias, peripheral neuropathy, mild or moderate lethargy or somnolence, headache, seizures.
5. Hypersensitivity: hypersensitivity (local or general skin rash, flushing, pruritus, drug-fever, chills and rigors, low back pain), severe anaphylactoid reactions (flushing with hypo- or hypertension, with or without dyspnea).
6. Dermatologic: alopecia, desquamation following localized pruriginous maculopapular eruption, skin erythema with edema, extravasation reaction (erythema, swelling, tenderness, pustules), reversible peripheral phlebitis, nail changes.
7. Hepatic: increased transaminase, alkaline phosphatase, bilirubin; hepatic failure; hepatic drug reaction.
8. Pulmonary: dyspnea with restrictive pulmonary syndrome, pleural effusions.

9. Other: asthenia, dysgeusia, anorexia, conjunctivitis, arthralgia, muscle aches, myopathy, peripheral edema, fluid retention syndrome, ascites, flu-like symptoms, fever.

10.3 Pemetrexed Disodium Heptahydrate (Alimta)

NOTE: Please refer to the current package insert for complete prescribing and toxicity information. Institutional guidelines may be used for preparation and administration of this medication.

10.3.1 Supplier/How Supplied

Pemetrexed is commercially available.

Pemetrexed is supplied as a sterile lyophilized powder for intravenous infusion available in single-dose vials. The product is a white to either light yellow or green-yellow lyophilized solid. Pemetrexed is supplied in 100mg and 500 mg vials. Each 500-mg vial of pemetrexed contains pemetrexed disodium equivalent to 500 mg pemetrexed and 500 mg of mannitol. Each 100-mg vial of pemetrexed disodium contains equivalent to 100mg pemetrexed and 106mg of mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

10.3.2 Preparation

1. Use aseptic technique during the reconstitution and further dilution of pemetrexed for intravenous infusion administration.
2. Calculate the dose and the number of pemetrexed vials needed. Each vial contains 500 mg or 100mg of Pemetrexed. The vial contains an excess of Pemetrexed to facilitate delivery of label amount.
3. Reconstitute 500-mg vials with 20 mL of 0.9% Sodium Chloride Injection (preservative free) to give a solution containing 25 mg/mL Pemetrexed. Gently swirl each vial until the powder is completely dissolved, reconstitute 100mg vials with 4.2 ml of 0.9% Sodium Chloride injection (preservative free) to give a Solution containing 4.3 mg/ml pemetrexed. The resulting solution is clear and ranges in color from colorless to yellow or green-yellow without adversely affecting product quality. The pH of the reconstituted pemetrexed solution is between 6.6 and 7.8. FURTHER DILUTION IS REQUIRED.
4. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter is observed, do not administer.
5. The appropriate volume of reconstituted Pemetrexed solution should be further diluted to 100 mL with 0.9% Sodium Chloride Injection (preservative free) and administered as an intravenous infusion over 10 minutes.
6. Chemical and physical stability of reconstituted and infusion solutions of pemetrexed were demonstrated for up to 24 hours following initial reconstitution, when stored at refrigerated or ambient room temperature [see USP Controlled Room Temperature] and lighting. When prepared as directed, reconstitution and infusion solutions of pemetrexed contain no antimicrobial preservatives. Discard any unused portion. Reconstitution and further dilution prior to intravenous infusion is only recommended with 0.9% Sodium Chloride Injection (preservative free). Pemetrexed is physically incompatible with diluents containing calcium, including Lactated Ringer's Injection, USP and Ringer's Injection, USP and therefore these

should not be used. Co-administration of pemetrexed with other drugs and diluents has not been studied, and therefore is not recommended.

10.3.3 Storage and Stability

Pemetrexed for injection, should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Chemical and physical stability of reconstituted and infusion solutions of pemetrexed were demonstrated for up to 24 hours following initial reconstitution, when stored refrigerated, 2-8°C (36-46°F), or at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). When prepared as directed, reconstituted and infusion solutions of Pemetrexed contain no antimicrobial preservatives. Discard unused portion. Pemetrexed is not light sensitive.

10.3.4 Incompatibilities and Potential Drug Interactions

Ibuprofen — Daily ibuprofen doses of 400 mg QID reduce pemetrexed's clearance by about 20% (and increase AUC by 20%) in patients with normal renal function. The effect of greater doses of ibuprofen on pemetrexed PK is unknown. Pemetrexed is primarily eliminated unchanged renally as a result of glomerular filtration and tubular secretion. Concomitant administration of nephrotoxic drugs could result in delayed clearance of pemetrexed. Concomitant administration of substances that are also tubularly secreted (e.g., probenecid) could potentially result in delayed clearance of pemetrexed. Although ibuprofen (400 mg QID) can be administered with pemetrexed in patients with normal renal function (creatinine clearance (80 mL/min), caution should be used when administering ibuprofen concurrently with pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min). Patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the day of, and 2 days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives, all patients taking these NSAIDs should interrupt dosing for at least 5 days before, the day of, and 2 days following pemetrexed administration. If concomitant administration of an NSAID is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity.

10.3.5 Side Effects

1. Renal: creatinine elevation (10%)
2. Neurologic: neuropathy-sensory (9%), taste disturbance (8%)
3. Hematologic: anemia (33%), neutropenia (29%), leucopenia (18%), thrombocytopenia (10%)
4. Gastrointestinal: nausea (56%), vomiting (40%), anorexia (27%), constipation (21%), stomatitis/pharyngitis (14%), diarrhea (12%), dyspepsia/heartburn (5%)
5. Dermatology/skin: alopecia (12%), rash/desquamation (7%)
6. Other: fatigue, febrile neutropenia, infection, pyrexia, dehydration, increased AST, increased ALT, creatinine clearance decrease, renal failure, conjunctivitis, arrhythmia, chest pain, increased GGT, motor neuropathy

10.4 Gemcitabine

NOTE: Please refer to the current package insert for complete prescribing and toxicity information. Institutional guidelines may be used for preparation and administration of this medication.

10.4.1 Supplier/How Supplied

Gemcitabine is commercially available in 200 mg and 1 gm vials.

10.4.2 Preparation

Reconstitute the 200 mg vial with 5ml and the 1 gm vial with 25 ml preservative free normal saline to make a solution containing 38 mg/ml. Shake to dissolve.

10.4.3 Storage and Stability

Unreconstituted drug vials are stored at controlled room temperature. Reconstituted solution should be stored at controlled room temperature and used within 24 hours. Solutions of gemcitabine should not be refrigerated; crystallization may occur. The unused portion should be discarded.

10.4.4 Side Effects

1. Hematologic: Neutropenia, anemia, thrombocytopenia, and leukopenia are reported.
2. Dermatologic: A rash is seen in about 25% of patients and is associated with pruritus in about 10% of patients. The rash is usually mild, not dose-limiting, and responds to local therapy. Desquamation, vesiculation, and ulceration have been reported rarely. Alopecia is usually minimal. Injection-site reactions.
3. Gastrointestinal: Nausea and vomiting are reported in about two-thirds of patients and requires therapy in about 20% of patients. It is rarely dose-limiting, and is easily manageable with standard antiemetics. Diarrhea, constipation, mucositis.
4. Hepatic: Abnormalities of hepatic transaminase enzymes occur in two-thirds of patients, but they are usually mild, nonprogressive, and rarely necessitate stopping treatment. However, gemcitabine should be used with caution in patients with impaired hepatic function.
5. Pulmonary: In clinical trials, dsypnea, unrelated to underlying disease, has been reported in association with Gemzar therapy. Dyspnea was occasionally accompanied by bronchospasm. Pulmonary toxicity has been reported with the use of Gemzar. [Parenchymal toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS) has been reported rarely following one or more doses of Gemzar administered to patients with various malignancies. Some patients experienced the onset of pulmonary symptoms up to 2 weeks after the last Gemzar dose. Respiratory failure and death occurred very rarely in some patients despite discontinuation of therapy.] The etiology of these effects is unknown. If such effects develop, Gemzar should be discontinued. Early use of supportive care measures may help ameliorate these conditions.
6. Neurologic: Somnolence, insomnia, paresthesia, pain.
7. Cardiovascular: A few cases of hypotension were reported. Some cases of myocardial infarction, congestive heart failure, and arrhythmias have been reported. Peripheral edema is reported in about 30% of patients. Some cases of facial edema have also been reported. Edema is usually mild to moderate, rarely dose-limiting, sometimes painful, and reversible after stopping gemcitabine treatment.
8. Other: Flu-like symptoms are reported for about 20% of patients. This includes fever, headache, back pain, chills, myalgia, asthenia, and anorexia. Malaise and sweating are reported.

11. ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence whether or not considered related to the study drug that appears to change in intensity during the course of the study. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

11.1.2 Serious Adverse Event (SAE)

An SAE is an adverse event that:

- Results in death.
  NOTE: Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization for >24 hours or prolongation of existing hospitalization.
  NOTE: Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

11.1.3 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, package insert, or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.4 Relatedness

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	The Adverse Event is ***not related*** to the drug(s)
Unlikely	The Adverse Event is ***doubtfully related*** to the drug(s)
Possible	The Adverse Event ***may be related*** to the drug(s)
Probable	The Adverse Event is ***likely related*** to the drug(s)
Definite	The Adverse Event is ***clearly related*** to the drug(s)

11.2 Reporting

11.2.1 Adverse Events

- AEs will be recorded from time of registration until 30 days after discontinuation of study drug(s).
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within OnCore.
- All AEs considered related to study drug(s) will be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first.

11.2.2 Definition and Reporting of a Pembrolizumab Overdose:

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by 20% over the prescribed dose. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

- If an AE (s) is associated with ("results from") the overdose of a Merck product, the AE(s) is reported as a SAE, even if no other seriousness criteria are met.
- If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the

overdose is reported as a non-serious ECI, using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an AE must be reported within 1 working day to Big Ten CRC Administrative Headquarters (AHQ). Big Ten CRC AHQ will report the event within 1 working day to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215-993-1220).

11.2.3 Reporting of Pregnancy and Lactation:

Although pregnancy and lactation are not considered AEs, it is the responsibility of investigators or their designees 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 completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. 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 within 1 working day to Big Ten CRC AHQ on the Pregnancy Report Form (See Documents/Info tab of the EDC). Big Ten CRC AHQ will report the event within 1 working day to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215-993-1220).

11.2.4 Definition and Reporting of Events of ECI:

Selected non-serious and SAEs are also known as ECI and must be recorded as such on the Adverse Event case report forms/worksheets and reported to Big Ten CRC AHQ within 1 working day of the event.
ECI for this trial include:

1. An overdose of Merck product, as defined above, that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT lab value that is greater than or equal to 3 × the upper limit of normal, **and** an elevated total bilirubin lab value that is greater than or equal to 2 × the upper limit of normal, **and**, at the same time, an alkaline phosphatase lab value that is less than 2 × the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
   *NOTE: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be

performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

ECIs that occur in any subject from the date of first dose through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates a new anticancer therapy, whichever is earlier, whether or not related to the Merck's product, must be reported within 1 working day to Big Ten CRC AHQ. Big Ten CRC AHQ will report the event within 1 working day to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215-993-1220).

11.2.5 Serious Adverse Events (SAEs)

11.2.5.1 Site Requirements for Reporting SAEs to Big Ten CRC Administrative Headquarters

- SAEs will be reported from time of registration until 90 days after discontinuation of study drug(s).
- SAEs will be reported on the SAE Submission Form and entered in the SAE tab in OnCore **within 1 business day** of discovery of the event.
- SAEs include events related and unrelated to the study drug(s).
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within OnCore.
- All SAEs regardless of relation to study drug will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.

Non-serious ECI will be reported to Big Ten CRC AHQ and will be handled in the same manner as SAEs.

Additionally, any SAE, considered by an investigator to be related to either study drug, which is brought to the attention of the investigator at any time outside of the 90-day time period specified in the previous paragraph, also must be reported immediately to Big Ten CRC AHQ.

The site will submit the completed SAE Submission Form (see Documents/Info tab of the EDC) to Big Ten CRC AHQ within **1 business day** of discovery of the event. The form will be sent electronically to Big Ten CRC AHQ at SAFETY@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies as per local requirements.

The original copy of the SAE Report and the email correspondence or fax confirmation sheet must be kept within the study file at the study site.

Once the SAE has resolved (see resolution guidelines listed in 11.2.2.1), sites must submit a follow up SAE Submission Form within a reasonable timeframe to Big Ten CRC AHQ at SAFETY@hoosiercancer.org.

11.2.5.2 Big Ten CRC AHQ Requirements for Reporting SAEs to Merck

Big Ten CRC AHQ will submit all immediately reportable events (e.g. SAEs, ECIs, overdose, pregnancy, etc.) received from sites to Merck within **1 business day** of receipt of the SAE Reporting Form and to regulatory authorities (FDA) per federal guidelines.

Big Ten CRC AHQ will submit all SAE reports and any other relevant safety information to:

Merck Global Safety (Attn: Worldwide Product Safety) at:
Facsimile number: +1-215-993-1220

Follow-up information will be provided to Merck as reasonably requested.

11.2.5.3 Sponsor-Investigator Responsibilities

Big Ten CRC AHQ will send a SAE summary to the sponsor-investigator **within 1 business day** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

11.2.5.4 Big Ten CRC AHQ Responsibilities for Reporting SAEs to FDA

Big Ten CRC AHQ has been designated to manage the Investigational New Drug Application (IND) associated with this protocol on behalf of the sponsor-investigator. Big Ten CRC AHQ will cross-reference this submission to Merck's parent IND at the time of submission. Additionally, Big Ten CRC AHQ will submit a copy of these documents to Merck at the time of submission to FDA.

Big Ten CRC AHQ will be responsible for all communication with the FDA in accordance with 21CFR312 including but not limited to the 7 and 15 Day Reports, as well as an Annual Progress Report. Additionally, Big Ten CRC AHQ will submit a copy of these reports to Merck at the time of submission to FDA.

11.2.5.5 IND Safety Reports Unrelated to this Trial

Merck will provide Big Ten CRC AHQ with IND safety reports from external studies that involve the study drug(s) per their guidelines. Big Ten CRC AHQ will forward the safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. Big Ten CRC AHQ will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). All IND safety reports will also be made available to sites via OnCore.

Upon receipt from Big Ten CRC AHQ, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

12. STATISTICAL METHODS

Statistical analysis of this study will be the responsibility of Biostatistics and Data Management Core at Indiana University Melvin and Bren Simon Cancer Center (IUSCC). Parameter estimates and relevant summary statistics will be reported where appropriate. For continuous variables, summary statistics will include number of subjects, mean, median, standard deviation, minimum

and maximum. Categorical endpoints will be summarized using number of subjects, frequency, and percentages. Missing data will not be imputed. Data analysis will be performed in SAS.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Changes from this analysis plan will not require an amendment to the protocol unless it changes a significant feature of the protocol.

12.1 Study Design

This is a single-arm phase II study of continuation immunotherapy with pembrolizumab following initial benefit (CR, PR, or SD ≥ 3 months) with a PD-1 or PD-L1 inhibitor.

12.2 Endpoints

12.2.1 Definition of Primary Endpoint

The primary endpoint is PFS assessed by RECIST 1.1 and is defined as the time from date of treatment start until the criteria for disease progression is met as defined by RECIST 1.1 criteria or death as a result of any cause. Those alive and without disease progression at the end of study follow-up will be censored at date of last disease assessment.

12.2.2 Definition of Secondary Endpoints

Secondary endpoints are:

- PFS assessed by irRECIST defined as the time from date of treatment start until the criteria for disease progression is met as defined by irRECIST criteria or death as a result of any cause. Those alive and without disease progression at the end of study follow-up will be censored at date of last disease assessment.
- Objective response rate (CR+PR) assessed via RECISIT 1.1 and irRECIST
- Clinical benefit rate (CR+PR+SD≥3 months) assessed via RECISIT 1.1 and irRECIST
- OS defined as the time from date of treatment start until death
- Toxicity assessed by CTCAE Version 4.

12.3 Sample Size and Accrual

- The historical control is a median PFS of 3 months (in the 2nd/3rd line setting).
- Null hypothesis - Pembrolizumab plus chemo will have a median PFS of 3 months.
- Alternative hypothesis –Pembrolizumab plus chemo will have a median PFS of 6 months

When the sample size is 31, a non-parametric test of median survival with a one-sided 0.05 significance level will have 80% power to detect the difference between a median survival of 3 months vs 6 months assuming an accrual period of approximately 6 months (6 per month) and maximum follow-up of 1.5 years. To allow for replacement of patients who are not evaluable for efficacy (estimated to be 10%), up to 35 patients will be enrolled.

12.4 Analysis Datasets

Population	Definition
Enrolled	This will comprise all subjects who meet the eligibility criteria and are registered onto the study.
Efficacy	This will comprise all subjects who receive at least one dose of trial treatment (both pembrolizumab and partner chemotherapy) and either undergo at least one post-baseline assessment or die before any evaluation.
Safety	This will comprise all subjects that contribute data to the safety analysis including any patient who has received any treatment (including partial treatment or single agent therapy).

12.5 Assessment of Safety

Safety will be assessed by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4. Please refer to the Study Calendar for the schedule of toxicity assessment.

12.6 Assessment of Efficacy

All subjects who have received at least one dose of treatment and have their disease re-evaluated will be evaluable for assessment of PFS and other efficacy outcomes.

12.7 Data Analysis Plans

12.7.1 Analysis Plans for Primary Objective

PFS by RECIST 1.1 will be estimated using Kaplan-Meier methodology in the Efficacy population. Median PFS of H_o: 3 months vs H_a: 6 months by RECIST 1.1 will be tested using a non-parametric test.

12.7.2 Analysis Plans for Secondary Objectives

In the Efficacy population, median PFS by irRECIST will be estimated and tested similarly to the primary endpoint. Objective response rate and clinical benefit rate will be estimated with two-sided 95% exact binomial confidence intervals. OS will be estimated using Kaplan-Meier methodology. Toxicities will be tabulated in the Safety population.

12.7.3 Analysis Plans for Exploratory Objectives

In the Efficacy population, change in tumor levels of PD-L1 will be descriptively summarized and compared over time using paired t-tests. Proportional hazards regression (for PFS) and logistic regression (for ORR and clinical benefit rate) will be used to correlate proteomic, lipidomic and genomic results with clinical outcomes.

12.7.4 Subgroup Analyses

No subgroup analyses are planned.

12.7.5 Other Planned Analyses

For the Enrolled population, descriptive statistics will be used the characterize subject demographic and clinical characteristics, disposition, and significant protocol violations. In the Safety population, concomitant medications and exposure will be described.

12.8 Interim Analysis/Criteria for Stopping Study

No formal interim safety or efficacy analyses are planned.

13. TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP)

The study will be conducted in accordance with Indiana University Melvin and Bren Simon Cancer Center's (IUSCC) DSMP for High Risk Phase II Trials.

Big Ten CRC AHQ facilitated oversight activities for high risk phase II trials include:

- Review and processing of all AEs requiring expedited reporting as defined in the protocol
- Provide trial accrual progress, safety information, and data summary reports to the sponsor-investigator, including a weekly update of aggregate AE data. For any increase in frequency of grade 3 or above adverse events (above the rate reported in the Investigator Brochure or package insert), the sponsor investigator will notify Big Ten CRC AHQ who will notify the DSMC Chair and Compliance Officer immediately. The notification will include the incidence of study adverse events, grades, and attributions, as well as investigator statements regarding comparison with risks per the IB/ package insert.
- Notify participating sites of adverse events potentially requiring expedited reporting and subsequent DSMC recommendations for study modifications.
- Investigators will conduct continuous review of data and patient safety.
- Coordinate monthly (Phase II) meetings which will include representation from each accruing site.
    - These meetings should include review of data, the number of subjects, and significant toxicities as described in the protocol. Big Ten CRC AHQ should maintain meeting minutes and attendance for submission to the DSMC upon request.
- Conduct the trial across all participating sites in accordance with the requirements set forth in the IUSCC DSMP.

13.2 IUSCC Data Safety Monitoring Committee Oversight

The IUSCC Data and Safety Monitoring Committee (DSMC) is responsible for oversight of subject safety, regulatory compliance, and data integrity for this trial. The DSMC will review this study to assess toxicity, compliance, data integrity, and accrual per the Institutional DSMP. Trials managed by Big Ten CRC AHQ are not routinely audited or monitored by IUSCC; however, the IUSCC DSMC retains the right to audit Big Ten CRC AHQ trials on a for cause basis.

The IUSCC DSMC will review study data bi-annually per the IUSCC DSMP.

In preparation for the IUSCC DSMC review, Big Ten CRC AHQ will provide the IUSCC DSMC with the following:

- Monthly summary reports
- Reports of the following, if not already included in the Monthly Summary Report:
  - Adverse event summary report (including serious adverse events)
  - Study accrual patterns
  - Protocol deviations
- Audit and/or monitoring results, if applicable
- Data related to stopping/decision rules described in study design
- Big Ten CRC meeting minutes/ attendance

Documentation of DSMC reviews will be provided to sponsor-investigator and Big Ten CRC AHQ. The IUSCC DSMC will notify the sponsor-investigator and other regulatory bodies, as appropriate, for issues of immediate concern. The sponsor-investigator will work with Big Ten CRC AHQ to address the DSMC's concerns as appropriate.

At any time during the conduct of the trial, if it is the opinion of the sponsor investigator that the risks (or benefits) to the patient warrant early closure of the study, this recommendation should be made in writing to the DSMC Chair and Compliance Officer. Alternatively, the DSMC may initiate suspension or early closure of the study based on its review of the study reports.

13.3 IND Annual Reports

As this trial has an IND held locally by the IU principal investigator, the IND Annual Report will be prepared and submitted to the Compliance Team. This report will be reviewed by the DSMC at the time of FDA submission.

13.4 Data Quality Oversight Activities

Remote validation of OnCore data will be completed on a continual basis throughout the life cycle of the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel.

Monitoring visits to the trial sites will be made periodically during the trial to ensure key aspects of the protocol are followed. Additional for-cause visits may occur as necessary. Source documents will be reviewed for verification of agreement with data entered into OnCore. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by Big Ten CRC AHQ or its designee.

The trial site may also be subject to quality assurance audit by Merck or its designee as well as inspection by appropriate regulatory agencies.

13.5 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the

requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. The sponsor-investigator has delegated responsibility to Big Ten CRC AHQ for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

14. DATA HANDLING AND RECORD KEEPING

14.1 Data Management

Big Ten CRC AHQ will serve as the Clinical Research Organization for this trial. Data will be collected through the web-based clinical research platform, OnCore, a system compliant with Good Clinical Practices and Federal Rules and Regulations. Big Ten CRC AHQ personnel will coordinate and manage data for quality control assurance and integrity. All data will be collected and entered into OnCore by study site personnel from participating institutions.

14.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in OnCore and correlative results will be captured in OnCore or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in OnCore, according to study-specific objectives. Please see the Data and Safety Oversight Process (DSOP) guidelines for further details.

The completed dataset is housed at Big Ten CRC AHQ and is the sole property of the sponsor-investigator's institution. It should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the sponsor-investigator and Big Ten CRC AHQ. After the initial publication, the complete data set will be available to all Big Ten CRC institutions.

14.3 Record Retention

To enable evaluations and/or audits from Health Authorities/Big Ten CRC AHQ, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with local and federal regulations. No records will be destroyed until Big Ten CRC AHQ confirms destruction is permitted.

14.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, Big Ten CRC AHQ, Merck, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subjects's identity will remain confidential.

15. ETHICS

15.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to Big Ten CRC AHQ before he or she can enroll subjects into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB as local regulations require.

Progress reports and notifications of AEs will be provided to the IRB according to local regulations and guidelines.

15.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

15.3 Informed Consent Process

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

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