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Phase II Single Arm Study of Combination Pembrolizumab, Chemotherapy and Bevacizumab in Patients with Recurrent, Persistent, or Metastatic Cervical Cancer

VERSION #	6.1
VERSION DATE	28/October/2022

PRINCIPAL INVESTIGATOR (PI): Marilyn Huang, MD, MS
Division of Gynecologic Oncology

CONTACT INFORMATION

Principal Investigator	Marilyn Huang, MD, MS University of Miami (UM) / Sylvester Comprehensive Cancer Center (SCCC) Miami, FL 33136 Telephone: 305-243-2233 [redacted]
Statistician	Isildinha M. Reis, PhD
Clinical Trial Management	Gynecologic Oncology Manager, Research Support Clinical Research Services University of Miami (UM) / Sylvester Comprehensive Cancer Center (SCCC) Miami, FL 33136
Regulatory Sponsor	University of Miami (UM) / Sylvester Comprehensive Cancer Center (SCCC) Miami, FL 33136
Funding Source	Merck Sharp & Dohme Corp.
Investigational Agent	Pembrolizumab – supplied by Merck; commercial supply
Other Agents	Paclitaxel – commercial supply Cisplatin – commercial supply Carboplatin – commercial supply Bevacizumab – commercial supply
IND Status	Exempt

INVESTIGATOR AGREEMENT

I confirm that 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 ICH guidelines for good clinical practices, and the applicable federal, state, and local laws, rules, and regulations relating to the conduct of the protocol.

I have read and understand the information in the Investigators' Brochure (and/or other such pertinent safety information) regarding the risks and potential benefits.

I agree to inform all those who assist/collaborate with me in the conduct of this study of their responsibilities and obligations.

Once the protocol has been reviewed and approved by the Institutional Review Board (IRB) I understand that any change(s) made during the course of the study must also (first) be approved by the IRB prior to implementation, except when such modification is made to remove any immediate hazard(s) to the subject(s).

I certify that I, and the study staff responsible, have received the requisite training to conduct this research protocol.

I agree to maintain adequate and accurate records in accordance with the University of Miami policies, federal, state and local laws and regulations.

I agree to maintain the confidentiality of all information received and/or developed in connection with this protocol.

eProst Number: **20170846**	
Protocol Version Number: **6.1**	Protocol Version Date: **28/October/2022**

Signature of Investigator:	Date:
Name of Investigator (printed):	Institution: **University of Miami (UM) / Sylvester Comprehensive Cancer Center (SCCC)**

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ABBREVIATIONS & DEFINITIONS

Term	Abbreviation	Definition
Overall Survival	OS	The length of time from start of treatment until death due to any cause.
Progression-Free Survival	PFS	The length of time from the date of first dose of study treatment until date of disease progression or death due to any cause, whichever comes first.
Progressive Disease	PD	Cancer that is growing, spreading, or getting worse.
Objective Response Rate	ORR	The percentage of patients whose cancer shrinks or disappears after treatment (partial or complete response).
Stable Disease	SD	Cancer that is neither decreasing nor increasing in extent or severity.

Reference: National Cancer Institute (NCI) Dictionary of Cancer Terms
http://www.cancer.gov/dictionary

PROTOCOL SYNOPSIS

Protocol Title	Phase II Single Arm Study of Combination Pembrolizumab, Chemotherapy and Bevacizumab in Patients with Recurrent, Persistent, or Metastatic Cervical Cancer
Targeted Patient Population	Women with recurrent, persistent, or metastatic cervical cancer dispositioned to receive combination chemotherapy.
Study Design	This is a single arm, two-stage, open-label, phase II study to assess objective response to treatment with Pembrolizumab, chemotherapy, and Bevacizumab in patients diagnosed with recurrent, persistent, or metastatic cervical cancer.
Treatment Schema	Eligible patients will require tissue for diagnostic confirmation of metastatic disease, disease recurrence or persistence. Patients will be treated with 3 cycles of combination therapy – 1) Pembrolizumab, 2) Paclitaxel, 3) Cisplatin OR Carboplatin, and 4) Bevacizumab – on Day 1 every 21 days.
Duration of Treatment	Trial therapy may stop early due to withdrawal of consent or disease progression, and/or if other criteria for discontinuation is met (whichever occurs first). Treatment is considered complete if imaging demonstrates complete resolution of disease. See Section 9.4 for treatment discontinuation criteria.
Follow-up Required Post-Treatment	All patients will be followed for a Safety Evaluation at approximately 30-days (+/-7 days) after study discontinuation. Thereafter, patients will be followed for survival only.
Objectives	**Primary Objective** To determine the objective response rate (ORR) (partial or complete response) of patients treated with combination Pembrolizumab, chemotherapy, and Bevacizumab. **Secondary Objectives** • To determine progression-free survival (PFS) • To determine overall survival (OS) • To determine the safety and tolerability of Pembrolizumab in combination with chemotherapy and Bevacizumab **Exploratory Objectives** • To determine if an immunologic profile will be useful as a predictive biomarker of treatment response and PFS • To perform exploratory translational studies on tissue biopsies at the time of recurrence, persistence, or metastatic disease compared to post-treatment samples

<table>
<tr><td>Expected Number of Patients</td><td>40 total evaluable patients: (Refer to Section 13.0 Statistical Considerations.)</td></tr>
<tr><td>Expected Number of Centers</td><td>University of Miami (UM) / Sylvester Comprehensive Cancer Center (SCCC), including its satellite affiliates</td></tr>
<tr><td>Expected Duration of the Protocol</td><td>Estimated time for accrual is approximately 24 months; estimated duration of the total protocol is approximately 48 months.</td></tr>
<tr><td>Inclusion Criteria</td><td>1. Patients must have histologically-confirmed recurrent, persistent or metastatic (primary stage IVB) squamous cell carcinoma, adenosquamous carcinoma or adenocarcinoma of the cervix that is not amenable to curative treatment with surgery and/or radiation therapy.
2. Patients must have measurable disease as defined by Response Evaluation Criteria In Solid Tumors (RECIST) 1.1.
3. Patients must have recovered from effects of recent surgery, radiotherapy or chemoradiotherapy.
4. Patients should be free of active infections requiring antibiotics (with the exception of uncomplicated urinary tract infection).
5. Tissue from an archival sample or newly-obtained core or excisional biopsy of a tumor lesion confirming diagnosis.
6. Age ≥ 18 years.
7. Life expectancy > 3 months.
8. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1. See Appendix B: Performance Status Scales for more information.
9. Patients must have normal organ and marrow function as defined below:
<table>
<tr><th>SYSTEM</th><th>LABORATORY VALUE</th></tr>
<tr><td colspan="2">Hematological</td></tr>
<tr><td>Absolute neutrophil count (ANC)</td><td>≥1,500 cells/mcL</td></tr>
<tr><td>Platelets</td><td>≥100,000 cells/mcL</td></tr>
<tr><td>Hemoglobin</td><td>≥8 g/dL or ≥5.6 mmol/L without transfusion or erythropoietin (EPO) dependency</td></tr>
<tr><td colspan="2">Renal</td></tr>
<tr><td>Serum creatinine <u>OR</u>
Measured or calculated[a] creatinine clearance (glomerular filtration rate [GFR] can also be used in place of creatinine or creatinine clearance [CrCl])</td><td>≤1.5 X upper limit of normal (ULN)
<u>OR</u>
≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN</td></tr>
<tr><td colspan="2">Hepatic</td></tr>
<tr><td>Serum total bilirubin</td><td>≤ 1.5 X ULN
<u>OR</u></td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td></td><td>Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN</td></tr>
<tr><td>Aspartate aminotransferase (AST; serum glutamic-oxaloacetic transaminase [SGOT]) and alanine transaminase (ALT; serum glutamic-pyruvic transaminase [SGPT])</td><td>≤ 2.5 X ULN
<u>OR</u>
≤ 5 X ULN for subjects with liver metastases</td></tr>
<tr><td>Albumin</td><td>≥2.5 mg/dL</td></tr>
<tr><td colspan="2">Coagulation</td></tr>
<tr><td>International Normalized Ratio (INR) or Prothrombin Time (PT)</td><td>≤1.5 X ULN unless subject is receiving anticoagulant therapy
<u>OR</u>
as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants</td></tr>
<tr><td>Activated Partial Thromboplastin Time (aPTT)</td><td>≤1.5 X ULN unless subject is receiving anticoagulant therapy
<u>OR</u>
as long as PT or PTT is within therapeutic range of intended use of anticoagulants</td></tr>
<tr><td colspan="2">[a] Creatinine clearance should be calculated per institutional standard.</td></tr>
</table>
10. Negative urine or serum pregnancy test ≤72 hours (i.e., 3 days) prior to receiving the first dose of study medication if not surgically sterilized. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
11. Female subjects of childbearing potential (i.e., have not been surgically sterilized or have not been without menses for >1 year) should be willing to use 2 methods of birth control at the same time, be surgically sterile, or abstain from heterosexual activity for the course of the study and at least 120 days after the last study dose. See Appendix F: Protocol-Approved Methods of Contraception for further details.
12. Ability to understand and the willingness to sign a written informed consent document.</td></tr>
<tr><td>Exclusion Criteria</td><td>1. Patients with a history of other invasive malignancies, with the exception of non-melanoma skin cancer, are ineligible if there is any evidence of other malignancy being present within the last 5 years.
2. Patients who have had prior chemotherapy except when used concurrently with radiation therapy.
3. Patients who have received prior radiotherapy to any portion of the abdominal cavity or pelvis other than for the treatment of cervical cancer within the last 5 years are excluded. Prior radiation for localized cancer of the breast, head and neck, or skin is permitted provided that it was</td></tr>
</table>

	completed more than 3 years prior to registration, and the patient remains free of recurrent or metastatic disease. 4. Patients with an ECOG performance status of 2, 3 or 4 (Appendix B). 5. Patients who have received prior therapy with an anti- programmed cell death 1 (PD-1), anti-programmed cell death ligand 1 (PD-L1), or anti-PD-L2 agent. 6. Patients with known active central nervous system (CNS) metastases and/or carcinomatous meningitis. 7. Patients with known history of human immunodeficiency virus (HIV) or active bacillus tuberculosis (TB). 8. Known psychiatric or substance abuse disorders that would interfere with cooperation with requirements of the study. 9. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (i.e., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. 10. History of non-infectious pneumonitis that required steroids, evidence of interstitial lung disease or active, non-infectious pneumonitis, or history of pneumonitis requiring treatment. 11. Is pregnant, breastfeeding or expecting to conceive within the projected duration of the study, starting with the pre-screening or screening visit through 120 days after the last dose of study treatment. 12. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. Note: no testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority. 13. Received live vaccine within 30 days prior to the first dose of study treatment. 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. 14. Patient with known hypersensitivity to Pembrolizumab or any of its excipients (active ingredients). 15. Patient receiving concurrent additional biologic therapy. 16. Patients who are adults and unable to consent, who are not yet adults, pregnant and nursing women, and prisoners are ineligible. 17. Has an active infection requiring systemic therapy. 18. Thromboembolism (either arterial or venous) within 6 weeks of initiation of treatment. 19. Has significant cardiovascular disease, such as New York Heart Association (NYHA) cardiac disease classification of Class II or greater (See Appendix C: NYHA Classification of Heart Disease for more information), myocardial infarction, or cerebrovascular accident within 3

	months prior to initiation of study treatment, unstable arrhythmias, or unstable angina. Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction <50% must be on a stable medical regimen that is optimized in the opinion of the treating physician in consultation with a cardiologist if appropriate. 20. Has undergone major surgical procedure within 28 days prior to first Bevacizumab dose or anticipation of the need for a major surgical procedure during the course of the study. 21. Has proteinuria, as demonstrated by urine dipstick or >2.0 g of protein in a urine protein-to-creatinine ratio and/or 24 hr urine collection. All patients with ≥2+ protein on dipstick urinalysis at baseline must undergo a urine-to-protein ratio and/or 24 hr urine collection and demonstrate <2.0 g of protein.

1.0 BACKGROUND AND RATIONALE

1.1 Cervical Cancer

Cervical cancer is the third most common gynecologic malignancy with nearly 12,990 new cases and 4,120 deaths in the United States (US) in 2016[1]. Women with recurrent or persistent cervical cancer after platinum-based chemoradiation as well as women that present with metastatic (stage IVB) cervical cancer have few options with a 5-year overall survival rate of 5-10% [6-7]. This cohort accounts for the large majority of cervical cancer deaths. As a result, there remains an urgent need to identify novel agents and/or combination regimens to improve survival in women with recurrent, persistent or metastatic cervical cancer. In 2014, results from Gynecologic Oncology Group (GOG) 240, a phase III trial evaluating the effectiveness of Bevacizumab with Paclitaxel and either platinum or a non-platinum agent in women with recurrent, persistent or metastatic cervical cancer, were published. The combination therapy yielded a response rate of 48% compared to 36% (relative probability of a response, 1.35; 95% confidence interval (CI), 1.08 to 1.68; p=0.008) and a median progression-free survival (PFS) of 8.2 months compared to 5.9 months in patients treated with chemotherapy alone (p=0.002). The authors found the addition of Bevacizumab to doublet chemotherapy was associated with a 3.7-month improvement in median overall survival (OS). The results from this trial represent the current standard of care for this population[8]. Despite this, the OS in this cohort of women remains dismal at approximately 17 months. The poor survival outcomes of this patient population represent a large unmet need for active treatments for cervical cancer in the US as well as globally, particularly in developing countries.

1.2 Cancer Immune Surveillance

The programmed death-1 (PD-1) receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells, is to down modulate unwanted or excessive immune responses, including autoimmune reactions[12]. PD-1 (encoded by the gene *PDCD1*) is an Ig superfamily member related to CD28 and cytologic T-lymphocyte antigen (CTLA-4), which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD L2)[13]. Cytotoxic T-lymphocyte antigen (CTLA-4) and PD-1 normally function to counteract T-cell activation to self-antigens[12,14].

In normal healthy individuals, PD-L1 expression is low (i.e., little, if any) while in a variety of cancers, it is richly expressed. Tumors can exploit this pathway to escape antitumor immunosurveillance[16-17]. Blocking the PD-1/PD-L1 pathway may reduce the development of cervical tumor immune evasion and is an attractive target for therapeutic intervention especially in combination with standard lines of treatment[18-19].

1.3 Anti-PD-1/PD-L1 Therapies (Pembrolizumab)

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab can be administered intravenously and is approved in the United States for many oncology indications both as monotherapy and in combination therapy. Please refer to the Investigator Brochure for study details and results[20].

1.3.1 Clinical Experience

Early data from a phase IB study of Pembrolizumab in patients with HPV positive and negative head and neck cancers have been presented at the American Society of Clinical Oncology (ASCO) 2014 conference. The authors screened 104 head and neck cancer patients and found that 78% of the 61 patients enrolled had PD-L1 positive tumors. In this cohort, there were 23 HPV-positive and 37 HPV-negative cases. Interestingly, the ORR was similar in HPV-positive and HPV-negative patients, but the PFS and OS were longer in HPV-positive patients. PD-L1 expression was positively correlated with ORR (p=0.018) and PFS (p=0.024)[21]. Further, other pharmaceutical companies are actively investigating immunotherapy options including vaccine development in HPV associated cervical cancers (AstraZeneca and Advaxis).

KEYNOTE-028 is a Phase IB, multi-cohort study of Pembrolizumab in advanced solid tumors. In this study, Pembrolizumab demonstrated antitumor activity and durability in a heavily pretreated cancer cohort with a manageable safety and toxicity profile. The study demonstrated durable tumor regression (ORR) and prolonged stabilization of disease in advanced cancers. Responses lasted for 1 year or more in 8 of 16 patients with at least 1 year of follow-up[22].

In study KN158, which was used to support Pembrolizumab approval for treatment of cervical cancer in the US, 77 participants with cervical cancer that was previously treated with one or more prior lines of chemotherapy with PD-L1 expression CPS ≥1 had an ORR of 14% (CI: 7, 24) on a regimen of Pembrolizumab. Of these patients, 2.6% had a complete response (CR) and 11.7% had a partial response (PR). The response to Pembrolizumab treatment varied based on the findings that a median duration of response was never determined, the longest duration of participant response reported was over 18 months while the shortest duration was 4.1 months, and 80% of the cohort had a response duration beyond 12 months. The median time to response was 2.2 months, the median PFS was 2.1 months, and the 12-month OS was 47%.

1.3.2 Cisplatin/Paclitaxel plus Pembrolizumab

Safety data for the combination of Paclitaxel/Cisplatin and Pembrolizumab is available for multiple indications. Please refer to the Investigator Brochure for study details and results[20]. Furthermore, the safety of this agent in combination with a platinum and taxane doublet has been previously demonstrated[27].

1.4 Rationale for Use of Pembrolizumab

Human papilloma virus (HPV) has long been shown to play an active role in the development of cervical cancer, particularly in individuals with persistent infections. The causative role of HPV infection in cervical cancer is the rationale for immunotherapy[9] since PD-L1 expression is enhanced in cervical neoplasia and cancer[24]. Therefore, it is theorized that blocking the PD-L1 receptor, PD-1, will subsequently restore the anti-tumor immune responses evoked by HPV infection. Encouragingly, this hypothesis has been supported in other tumor types, particularly in melanoma[25]. Tumor cell killing by cytotoxic chemotherapy expose the immune system to high levels of tumor antigens. Invigorating tumor-specific T-cell immunity in this setting by inhibiting PD-L1/PD-1 signaling may result in deeper and more durable responses compared with standard chemotherapy alone.

Combining immunotherapy with cytotoxic chemotherapy historically was not accepted due to a perceived incompatibility with immune-suppressive chemotherapy. Evidence from clinical studies and general practice, however, suggests a synergy between these two modalities.

1.5 Rationale for Pembrolizumab Dose/Regimen Selection

Based on the totality of data generated in the pembrolizumab development program, 200 mg Q3W is the appropriate dose of Pembrolizumab for adults across all indications and regardless of tumor type.[20] As outlined below, this dose is justified by:

• Consistency in pharmacokinetics (PK) across tumor types.
• Clinical data from 8 randomized studies in melanoma and non-small cell lung cancer (NSCLC) indications demonstrating flat dose and exposure (or dose) and efficacy or safety relationships within the dose range of 2 mg/kg Q3W to 10 mg/kg Q2W representing an approximate 5- to 7.5-fold exposure range.
• Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of fixed dose of 200 mg Q3W [refer to the Investigator's Brochure].
• Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg Q3W across multiple indications.
• Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from PBPK analysis) at 200 mg Q3W.

Based on this body of work, we have selected a fixed dose of 200 mg Pembrolizumab to be administered Q3W in combination with standard chemotherapy and Bevacizumab. A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

1.6 Rationale for Correlative Studies

Although the immune system is suspected to play a role in tumor development and recurrence, the specific mediators of immune surveillance and suppression of tumor growth are largely unknown. Additionally, we have learned from analysis of patients treated thus far with PD-1-directed therapy that biomarkers of response to immunotherapy are extremely complex. Although PD-L1 expression in tumor cells and the presence of lymphocyte infiltration with PD-1/PD-L1 expression seem to be the best predictors of response, 10-15% of patients without tumor PD-L1 expression have responded to therapy, suggesting that other immunomodulatory factors must be playing a role. In addition to CTLA4 expression, other negative regulatory receptors have also been implicated, including LAG-3 and TIM-3, with pre-clinical blockade of some of these pathways resulting in improved anti-tumor response.[15,16] Finally, the presence of myeloid-derived suppressor cells (MDSCs) and regulatory T-cells have been shown to negatively impact response to therapy in many cancers, though these are also understudied in sarcomas.[31-35]

A translational component will aim to evaluate the tumor immune microenvironment and to further explore an immunologic profile that may be a predictive biomarker of treatment response and PFS.

We will assess intra-tumoral variations in perforin+, CD+ T lymphocytes, FOXP3 expression, expression of PD-L1 and PD-L2, and a broad immune gene expression analysis (based on an anti-tumor immune effector gene signature). We will aim to perform molecular analysis on tumor specimens pre- and post-treatment based on tissue availability.

2.0 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

To determine the objective response rate (ORR) (partial or complete response) of patients treated with combination Pembrolizumab, chemotherapy and Bevacizumab.

2.2 Secondary Objectives

- To determine PFS.
- To determine OS.
- To determine the safety and tolerability of Pembrolizumab in combination with chemotherapy and Bevacizumab.

2.3 Exploratory Objectives

- To determine if a specific immunologic profile will be a useful biomarker of treatment response and PFS.
- To perform exploratory translational studies on biopsies at the time of recurrence, persistence, or metastatic disease compared to post-treatment samples.

2.4 Primary Endpoint

The primary endpoint is the objective response rate (ORR), defined as the proportion of patients with partial or complete response. Patients will be evaluated for response during treatment and at follow-up assessments post-treatment (Section 10).

2.4.1 Evaluable for ORR

Eligible patients who receive at least one dose of Pembrolizumab in combination with chemotherapy and Bevacizumab.

2.5 Secondary Endpoints

- Progression-free survival (PFS): the time from start of treatment until documented disease progression or death (by any cause in the absence of progression). In alive, progression-free patients, PFS will be censored at the last evaluable tumor assessment.
- Overall survival (OS): the time from start of treatment until death due to any cause.
- Treatment-related adverse events (AEs), including serious adverse events (SAEs) will be evaluated with respect to grade and relationship to treatment. AEs will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03.

2.5.1 Evaluable for PFS, OS, and Adverse Events

Eligible patients who receive at least one dose of Pembrolizumab in combination with chemotherapy and Bevacizumab.

2.6 Exploratory Endpoints

- To determine if a specific immunologic profile will be a useful biomarker in predicting response. For example, PD-L1 immunohistochemistry. These are exploratory analyses and as such cannot be precisely defined.

2.6.1 Evaluable for Exploratory Endpoints

- Eligible patients who receive at least one dose of Pembrolizumab in combination with chemotherapy and Bevacizumab will undergo blood sample collection and have a pre-treatment tumor biopsy and at least one post-treatment tumor biopsy.

3.0 SUBJECT RECRUITMENT & SCREENING

3.1 Patient Selection

3.1.1 Inclusion Criteria

1. Patients must have histologically-confirmed recurrent, persistent or metastatic (primary stage IVB) squamous cell carcinoma, adenosquamous carcinoma or adenocarcinoma of the cervix that is not amenable to curative treatment with surgery and/or radiation therapy.
2. Patients must have measurable disease as defined by Response Evaluation Criteria In Solid Tumors (RECIST) 1.1.
3. Patients must have recovered from effects of recent surgery, radiotherapy or chemoradiotherapy.
4. Patients should be free of active infections requiring antibiotics (with the exception of uncomplicated urinary tract infection).
5. Tissue from an archival sample or newly obtained core or excisional biopsy of a tumor lesion confirming diagnosis.
6. Age ≥ 18 years.
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8. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1. See Appendix B: Performance Status Scales for more information.
9. Patients must have normal organ and marrow function as defined below:

SYSTEM	LABORATORY VALUE
Hematological	
Absolute neutrophil count (ANC)	≥1,500 cells/mcL
Platelets	≥100,000 cells/mcL
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Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (glomerular filtration rate (GFR) can also be used in place of creatinine or creatinine clearance [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
Aspartate aminotransferase (AST; serum glutamic-oxaloacetic transaminase	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases

[SGOT]) and alanine transaminase (ALT; serum glutamic-pyruvic transaminase[SGPT])	
Albumin	≥2.5mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy **OR** as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy **OR** as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

10. Negative urine or serum pregnancy test ≤72 hours (i.e., 3 days) prior to receiving the first dose of study medication if not surgically sterilized. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
11. Female subjects of childbearing potential (i.e., have not been surgically sterilized or have not been without menses for >1 year) should be willing to use 2 methods of birth control at the same time, be surgically sterile, or abstain from heterosexual activity for the course of the study and at least 120 days after the last study dose. See Appendix F: Protocol-Approved Methods of Contraception for further details.
12. Ability to understand and the willingness to sign a written informed consent document.

3.1.2 Exclusion Criteria

1. Patients with a history of other invasive malignancies, with the exception of non-melanoma skin cancer, are ineligible if there is any evidence of other malignancy being present within the last 5 years.
2. Patients who have had prior chemotherapy except when used concurrently with radiation therapy.
3. Patients who have received prior radiotherapy to any portion of the abdominal cavity or pelvis other than for the treatment of cervical cancer within the last 5 years are excluded. Prior radiation for localized cancer of the breast, head and neck, or skin is permitted provided that it was completed more than 3 years prior to registration, and the patient remains free of recurrent or metastatic disease.
4. Patients with an ECOG performance status of 2, 3 or 4 (Appendix B).
5. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
6. Patients with known active central nervous system (CNS) metastases and/or carcinomatous meningitis.
7. Patients with a known history of human immunodeficiency virus (HIV) or active bacillus tuberculosis (TB).

8. Known psychiatric or substance abuse disorders that would interfere with cooperation with requirements of the study
9. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (i.e., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
10. History of non-infectious pneumonitis that required steroids, evidence of interstitial lung disease or active, non-infectious pneumonitis, or history of pneumonitis requiring treatment.
11. Is pregnant, breastfeeding or expecting to conceive within the projected duration of the study, starting with the pre-screening or screening visit through 120 days after the last dose of study treatment.
12. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. Note: no testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.
13. Received live vaccine within 30 days prior to the first dose of study treatment. 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.
14. Patient with known hypersensitivity to Pembrolizumab or any of its excipients (active ingredients).
15. Patient receiving concurrent additional biologic therapy.
16. Patients who are adults and unable to consent, who are not yet adults, pregnant and nursing women, and prisoners are ineligible.
17. Has an active infection requiring systemic therapy.
18. Thromboembolism (either arterial or venous) within 6 weeks of initiation of treatment.
19. Has significant cardiovascular disease, such as New York Heart Association cardiac disease classification of Class II or greater (See Appendix C: NYHA Classification of Heart Disease for more information), myocardial infarction, or cerebrovascular accident within 3 months prior to initiation of study treatment, unstable arrhythmias, or unstable angina. Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction <50% must be on a stable medical regimen that is optimized in the opinion of the treating physician in consultation with a cardiologist if appropriate.
20. Has undergone major surgical procedure within 28 days prior to first Bevacizumab dose or anticipation of the need for a major surgical procedure during the course of the study.
21. Has proteinuria, as demonstrated by urine dipstick or >2.0 g of protein in a urine protein-to-creatinine ratio and/or 24 hr urine collection. All patients with ≥2+ protein on dipstick urinalysis at baseline must undergo a urine-to-protein ratio and/or 24 hr urine collection and demonstrate <2.0 g of protein.

3.2 Strategies for Recruitment and Retention

Women of all races and ethnic groups are eligible for this trial. Prospective subjects will be recruited at Sylvester Comprehensive Cancer Center (SCCC)/University of Miami Health

(UMH) inclusive of constituent satellite sites. Informed consent forms (ICF) will be translated to Spanish and be available.

4.0 STUDY DESIGN

This is a single arm, two-stage, open-label, phase II study to assess objective response to treatment with Pembrolizumab in combination with chemotherapy agents Paclitaxel, Cisplatin (or Carboplatin if previously received Cisplatin as radiosensitizing agent), and Bevacizumab for recurrent, persistent, or metastatic cervical cancer. Objective response rate (ORR), PFS, and OS will be assessed in patients treated with this combination.

Eligible patients will require tissue biopsy for diagnostic confirmation of metastatic disease, disease recurrence or persistence. Patients will be treated with 3 cycles of combination therapy. A cycle will consist of Pembrolizumab at 200 mg (intravenous [IV]), Paclitaxel 175 mg/m^2 or 135 mg/m^2 (IV), Cisplatin 50 mg/m^2 (or Carboplatin area under the concentration curve [AUC] 5) IV and Bevacizumab 15 mg/kg (IV) on Day 1 of a 21-day cycle. This regimen will be followed by imaging to determine response to treatment at which time repeat biopsies will be obtained if measurable disease remains and is accessible (paired tissue samples).

If patients demonstrate at least stable disease, they will then receive additional cycles of chemotherapy and Bevacizumab plus Pembrolizumab given every 3 weeks with imaging obtained every 3 cycles until disease progression or complete resolution of disease. Blood collection will be performed before and after Pembrolizumab treatment and at the end of study.

Forty subjects total, 25 in Stage 1 and an additional 15 in Stage 2, will be accrued and treated at University of Miami (UM)/SCCC, inclusive of its satellite sites, for approximately 24 months. Therapy will be administered until study completion, withdrawal of consent, disease progression and/or unacceptable toxicity, whichever occurs first.

All subjects will be followed for a Safety Evaluation at approximately 30 days (+/-7 days) after study discontinuation. Post-treatment, patients will be followed for survival.

5.0 TREATMENT PLAN

5.1 Chemotherapy Discontinuation at the PI's Discretion

If patient is deriving clinical benefit from treatment, Bevacizumab and pembrolizumab may be continued while chemotherapy is discontinued at the PI's discretion following a discussion with the patient. Election of withholding Bevacizumab may be made at the PI's discretion based on the clinical scenario. The rationale for this update in the treatment plan is supported by data from the Phase 3 Keynote 836 and GOG 240 studies.[8]

5.2 Pembrolizumab

Pembrolizumab 200 mg flat dose shall be administered in the outpatient setting per standard of care. For further information, please refer to the Investigator's Brochure.

5.3 Paclitaxel

Paclitaxel will be administered based on the patient's body surface area (BSA) in m^2 according to the manufacturer guidelines and institutional policy. Paclitaxel dose will be capped at a BSA of $2.0m^2$. Where Paclitaxel is to be administered, it is recommended that a preparative regimen be employed to reduce the risk associated with hypersensitivity reactions. An example of this regimen is dexamethasone (either IV or oral), anti-histamine H1 (such as diphenhydramine) and anti-histamine H2 (such as cimetidine, ranitidine or famotidine).

5.4 Cisplatin (or Carboplatin)

Cisplatin will be administered per standard of care and institutional practices. Carboplatin may be administered if patient has previously received Cisplatin.

Carboplatin dose will be calculated to reach a target area under the curve (AUC) of concentration x time according to the Calvert formula using an estimated Cockroft and Gault-calculated creatinine clearance to present the GFR.

Carboplatin dose (mg) = (Target AUC) x (GFR + 25)

For this protocol, GFR = CrCl (ml/min) = (140-age in years) x (ABW*) x (0.85) [female]/ (72 x serum creatinine mg/dL)

*ABW: actual body weight: In patients with an abnormally low serum creatinine due to reduced protein intake and/or low muscle mass, the creatinine clearance should be estimated using a minimum value of 0.7 mg/dL.

5.5 Bevacizumab

Bevacizumab will be prepared and administered as per institutional practices.

Table 1: Treatment Schema

Agent	Premedication(s)*	Dose	Route	Schedule	Cycle Length
Pembrolizumab	Monitor for infusion reactions with hypersensitivity kit at bedside. Grade 2 infusion reactions will be premedicated with diphenhydramine 50 mg IV and acetaminophen 1,000 mg PO prior to subsequent infusions. Diet: Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.	200 mg	IV (prior to TC)	Day 1 of each cycle	21 days
Paclitaxel**	Dexamethasone, Diphenhydramine and Famotidine 30 minutes prior	175 mg/m^2	IV (before Cisplatin)		
Cisplatin (or Carboplatin)	NK1R antagonist, 5-HT3 receptor antagonist, dexamethasone +/- olanzapine	50 mg/m^2 (AUC 5)	IV (after Paclitaxel)		
Bevacizumab		15 mg/kg	IV (after Cisplatin)		

**Premedications are suggestions only; use institutional and investigator discretion.*
*** At the discretion of the treating physician, Paclitaxel 135 mg/m^2 IV every (q) 21 days may be administered.*

5.6 Concurrent Medications (as Applicable)

Because there is a potential for interaction of Paclitaxel with other concomitantly administered drugs through the cytochrome P450 system (Appendix E: CYP1A2, CYP2C8, CYP2C19, CYP3A4 Substrates, Inhibitors, & Inducers), the case report form (CRF) must capture the concurrent use of all other drugs, over-the-counter (OTC) medications, or alternative therapies. The Principal Investigator (PI) should be alerted if the patient is taking any agent know to affect

or with the potential to affect selected CYP450 isoenzymes.

5.7 Acceptable Medications

All treatments that the Investigator considers necessary for a subject's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the CRF including all prescription, 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 from first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded.

5.8 Prohibited Medications

The Exclusion Criteria describes medications which are prohibited in this trial. See Section 3.1.2.

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

5.9 Duration of Treatment

Trial therapy will last until completion (if complete response), withdrawal of consent, disease progression, unacceptable toxicity, study end and/or other criteria for treatment discontinuation is met, whichever occurs first. See Section 7.3 for treatment discontinuation criteria.

5.10 Duration of Follow-Up

All subjects will be followed after the last dose of trial treatment only for survival data.

6.0 TREATMENT/DOSE MODIFICATIONS

6.1 Assessment for Causality

Causality for all adverse events will be evaluated for degree of attribution to Pembrolizumab. See also Appendix A for Expedited AE Reporting Requirements.

6.2 General Procedure for Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating Investigator. Adverse events (AEs) associated with Pembrolizumab exposure may represent an immunologic etiology. The AEs may occur shortly after the first dose or several months after the last dose of treatment. The treatment guidelines are intended to be applied when the investigator determines the events to be related to Pembrolizumab. Refer to Table 2: Supportive Care Guidelines.

6.3 Dose Interruptions and Supportive Care Guidelines for AEs associated with Pembrolizumab

6.3.1 Dose Modifications

No dose modification is recommended for Pembrolizumab.

6.3.2 Dose Interruptions

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

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 study treatment.

6.3.3 Supportive Care Guidelines for AEs associated with Pembrolizumab

6.3.3.1 Immune-mediated adverse reactions

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

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold Pembrolizumab

and consider administration of corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Restart Pembrolizumab if the adverse reaction remains at Grade 1 or less following corticosteroid taper. If another episode of a severe adverse reaction occurs, permanently discontinue Pembrolizumab.

Immune-mediated pneumonitis
Pneumonitis (including fatal cases) has been reported in patients receiving Pembrolizumab. Monitor patients for signs and symptoms of pneumonitis. If pneumonitis is suspected, evaluate with radiographic imaging and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper), withhold Pembrolizumab for moderate (Grade 2) pneumonitis, and permanently discontinue Pembrolizumab for severe (Grade 3), life-threatening (Grade 4) or recurrent moderate (Grade 2) pneumonitis.

Immune-mediated colitis
Colitis has been reported in patients receiving Pembrolizumab. Monitor patients for signs and symptoms of colitis and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper), withhold Pembrolizumab for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue Pembrolizumab for life-threatening (Grade 4) colitis.

Immune-mediated hepatitis
Hepatitis has been reported in patients receiving Pembrolizumab. Monitor patients for changes in liver function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and symptoms of hepatitis and exclude other causes. Administer corticosteroids (initial dose of 0.5-1 mg/kg/day [for Grade 2 events] and 1-2 mg/kg/day [for Grade 3 or greater events] prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, withhold or discontinue Pembrolizumab.

Immune-mediated nephritis
Nephritis has been reported in patients receiving Pembrolizumab. Monitor patients for changes in renal function and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper), withhold Pembrolizumab for moderate (Grade 2), and permanently discontinue Pembrolizumab for severe (Grade 3) or life-threatening (Grade 4) nephritis.

Immune-mediated endocrinopathies
Adrenal insufficiency (primary and secondary) has been reported in patients receiving Pembrolizumab. Hypophysitis has also been reported in patients receiving Pembrolizumab. Monitor patients for signs and symptoms of adrenal insufficiency and hypophysitis (including hypopituitarism) and exclude other causes. Administer corticosteroids to treat adrenal insufficiency and other hormone replacement as clinically indicated, withhold Pembrolizumab for

moderate (Grade 2), withhold or discontinue Pembrolizumab for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency or hypophysitis.

Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in patients receiving Pembrolizumab. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes, and withhold Pembrolizumab in cases of severe hyperglycemia until metabolic control is achieved.

Thyroid disorders, including hyperthyroidism, hypothyroidism and thyroiditis, have been reported in patients receiving Pembrolizumab and can occur at any time during treatment; therefore, monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders. Hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids. Hyperthyroidism may be managed symptomatically. Withhold or discontinue Pembrolizumab for severe (Grade 3) or life-threatening (Grade 4) hyperthyroidism.

For patients with severe (Grade 3) or life-threatening (Grade 4) endocrinopathy that improves to Grade 2 or lower and is controlled with hormone replacement, continuation of Pembrolizumab may be considered.

Severe skin reactions

Immune-mediated severe skin reactions have been reported in patients treated with Pembrolizumab. Monitor patients for suspected severe skin reactions and exclude other causes. Based on the severity of the adverse reaction, withhold or permanently discontinue Pembrolizumab and administer corticosteroids.

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported in patients treated with Pembrolizumab. For signs or symptoms of SJS or TEN, withhold Pembrolizumab and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue Pembrolizumab.

Other immune-mediated adverse reactions

The following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% of patients treated with Pembrolizumab in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010: uveitis, myositis, Guillain-Barré syndrome, pancreatitis, encephalitis, sarcoidosis, myasthenic syndrome/myasthenia gravis (including exacerbation), myelitis, and vasculitis. The following were reported in other clinical studies with Pembrolizumab or in postmarketing use: myocarditis and sclerosing cholangitis.

Cases of these immune-mediated adverse reactions, some of which were severe, have been reported in clinical trials or in postmarketing use.

Transplant-related adverse reactions

Solid organ transplant rejection has been reported in the postmarketing setting in patients treated with Pembrolizumab. Treatment with Pembrolizumab may increase the risk of rejection in solid

organ transplant recipients. Consider the benefit of treatment with Pembrolizumab versus the risk of possible organ rejection in these patients.

Acute graft-versus-host-disease (GVHD), including fatal GVHD, after treatment with Pembrolizumab has been reported in patients with a history of allogeneic hematopoietic stem cell transplant (HSCT). Patients who experienced GVHD after their transplant procedure may be at increased risk for GVHD after treatment with Pembrolizumab. Consider the benefit of treatment with Pembrolizumab versus the risk of possible GVHD in patients with a history of allogeneic HSCT.

6.3.3.2 Infusion-related reactions

Severe infusion reactions, including hypersensitivity and anaphylaxis, have been reported in 6 (0.2%) of 2799 patients receiving Pembrolizumab in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010. For severe infusion reactions, stop infusion and permanently discontinue Pembrolizumab. Patients with mild or moderate infusion reaction may continue to receive Pembrolizumab with close monitoring; premedication with antipyretic and antihistamine may be considered.

Table 2: Pembrolizumab: Supportive Care Guidelines for Immune-Mediated Drug-Related Adverse Events

General instructions:

1. Based on the severity of the adverse reaction, withhold Pembrolizumab and consider administration of corticosteroids. Administration of other systemic immunosuppressants can be considered for patients whose immune-related adverse events (irAEs) are not controlled with corticosteroid use.
1. 2. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 1 month. Restart Pembrolizumab if the AE remains at Grade 1 or less following corticosteroid taper. If another episode of a severe adverse reaction occurs, permanently discontinue Pembrolizumab.3. 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.

Immune-related AEs	Toxicity grade or conditions (CTCAE v4.03)	Action taken to Pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Severe Skin Reaction	Any	Withhold or permanently discontinue	Refer patient for specialized care for assessment and treatment.	If SJS or TEN confirmed, permanently discontinue Pembrolizumab.
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg/day prednisone or equivalent) followed by taper.	• Monitor participants for signs and symptoms of pneumonitis. • Evaluate participants with suspected pneumonitis with radiographic imaging and exclude other causes. Initiate corticosteroid treatment.
	Grade 3 or 4 or recurrent Grade 2	Permanently discontinue		
Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg/day prednisone or equivalent) followed by taper.	Monitor participants for signs and symptoms of colitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and exclude other causes.

	Grade 4	Permanently discontinue		
Hepatitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5-1mg/kg/day prednisone or equivalent) followed by taper.	• Monitor patients for changes in liver function with liver function tests (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and symptoms of hepatitis. Exclude other causes for hepatitis. • Based on severity of liver enzyme elevations, withhold or discontinue Pembrolizumab.
	Grade 3 or 4	Withhold or permanently discontinue*	Administer corticosteroids (initial dose of 1-2 mg/kg/day prednisone or equivalent) followed by taper.	

Type 1 diabetes mellitus (T1DM) or Hyperglycemia**	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold until metabolic control is achieved.	• 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.
Adrenal insufficiency and hypophysitis (including hypopituitarism)**	Grade 2	Withhold	Administer corticosteroids to treat adrenal insufficiency and other hormone replacement as clinically indicated.	Monitor patients for signs and symptoms of adrenal insufficiency and exclude other causes.
	Grade 3 or 4	Withhold or permanently discontinue		
Thyroid disorders (including hyperthyroidism, hypothyroidism, and thyroiditis)**	Grade 2	Continue	• Hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids. • Hyperthyroidism may be managed symptomatically.	• Monitor for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue		
Renal failure and immune-mediated nephritis	Grade 2	Withhold	Administer corticosteroids (prednisone 1-2mg/kg/day or equivalent) followed by taper.	Monitor changes of renal function and exclude other causes.
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 2	Withhold	• For grade 2 immune-mediated myocarditis, administer prednisone corticosteroid or	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 3 or 4	Permanently discontinue		

			equivalent at an initial dose of 1-2 mg/kg/day followed by taper. • Permanently discontinue Pembrolizumab for grade 3 or 4 myocarditis OR if toxicity does not resolve within 12 weeks of start of grade 2 toxicity or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.	
*For grade 3 liver toxicity with elevated AST and/or ALT. Since HCC patients may have grade 1-2 elevation of AST/ALT at baseline, if these patients have Grade 3 elevation of AST/ALT, hold therapy and resume treatment when AST/ALT return to baseline or Grade ≤1. The AST/ALT should return to baseline or < 5 x ULN within 12 weeks from start of grade 3; otherwise, patient should be discontinued from study. ** For participants with Grade 3 (severe) or 4 (life-threatening) endocrinopathy that improves to Grade 2 or lower and is controlled with hormone replacement or achieved metabolic control (in case of T1DM), continuation of Pembrolizumab may be considered.				

6.4 Paclitaxel (Taxol®), Cisplatin (Carboplatin), and Bevacizumab

6.4.1 Dose Modifications

Treatment modifications regarding Paclitaxel, Cisplatin (Carboplatin may be used if patient has had previous Cisplatin), and Bevacizumab will be employed in a sequential manner using cycle delay and dose reduction.

Table 3: Dose Reduction Sequence for Paclitaxel at 175 mg/m^2 Cisplatin or Carboplatin
**First dose reduction Paclitaxel to 150 mg/m^2 and/or Cisplatin to 40 mg/m^2 and Bevacizumab to be held at the discretion of the treating Investigator.*

Drug	Initial Dose	1st Reduction*	2nd Reduction	Units
Paclitaxel	175	150	135*	mg/m^2
Cisplatin	50	40	40	mg/m^2
Carboplatin	5	4	4	AUC
Bevacizumab	15	15	15	mg/kg

Table 4: Dose Reduction Sequence for Paclitaxel at 135 mg/m^2 Cisplatin and Carboplatin
**First dose reduction of Paclitaxel or Cisplatin/Carboplatin at the discretion of treating Investigator. Bevacizumab to be held at discretion of treating Investigator*

Drug	Initial Dose	1st Reduction*	2nd Reduction	Units
Paclitaxel	135	135	135*	mg/m^2
Cisplatin	50	40	30	mg/m^2
Carboplatin	5	4	4	AUC
Bevacizumab	15	10	10	mg/kg

The following are criteria for Cisplatin (Carboplatin), Paclitaxel and Bevacizumab treatment modifications and management of toxicities (in relation to Pembrolizumab):

Table 5: Treatment Modifications and Management of Toxicities for Paclitaxel and Cisplatin

Worst toxicity (CTCAE Grade)**	Recommended Dose Modifications & Management of Toxicities
None	
No Toxicity	Maintain dose level
Hematological	
Neutropenia (ANC)	
Grade 1 (ANC< LLN-1.5x10^9 cells/L) Grade 2 (ANC<1.5-1.0x10^9 cells/L)	Hold treatment until ANC ≥ 1.5 x 10^9 cells/L. May maintain dose level (i.e., no need to dose reduce or add G-CSF at discretion of Investigator).
Grade 3 (ANC<1-0.5x10^9 cells/L) Grade 4 (ANC<0.5x10^9 cells/L)	First occurrence: Hold all treatment (chemotherapy & Pembrolizumab) until ANC ≥ 1.5 x 10^9 cells/L, give G-CSF. • If resolved in ≤7 days, then maintain dose level.

	• If resolved in >7 days, then ↓1 dose level. Second occurrence: Hold all treatment (give G-CSF) until ANC ≥1.5x10^9 cells/L, then ↓dose level.
Febrile neutropenia (ANC< 1.0x10^9 cells/L, fever ≥38.5 °C) or Grade 3/4 neutropenia with documented infection	First occurrence: Hold all treatment until resolved to ≤Grade 2 (give G-CSF), then: • If resolved in ≤7 days, then maintain dose level. • If resolved in >7 days, then ↓1 dose level. Second occurrence: Hold all treatment until resolved to ≤ Grade 2 (give G-CSF) then ↓ dose level or discontinue patient from study treatment at the Investigator's discretion.
Thrombocytopenia	
Grade 1 (Platelet [PLT]<LLN-75x10^9 cells/L) Grade 2 (PLT <75-50 x10^9 cells/L)	Hold treatment until Platelets >100K. May maintain dose level.
Grade 3 (PLT<50-25 x10^9 cells/L)	First occurrence: Hold all treatment until resolved to ≤Grade 1, then: • If resolved in ≤7 days, then maintain dose level. • If resolved in >7 days, then ↓1 dose level. Second occurrence: Hold all treatment until resolved to ≤ Grade 1, then ↓dose level.
Grade 4 (PLT<25x10^9 cells/L)	First occurrence: Hold all treatment until resolved to ≤Grade 1, then ↓ 1 dose level. Second occurrence: Hold all treatment until resolved to ≤ Grade 1, then ↓ dose level or discontinue patient from study treatment at the Investigator's discretion.
Bilirubin (For patients with Gilbert Syndrome: these dose modifications apply to changes in direct bilirubin only)	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 3.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Hold all treatment and monitor LFTs* weekly until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then maintain dose level. • If resolved in > 7 days, then ↓ 1 dose level.
Grade 3 (> 3.0 - 10.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Hold all treatment and monitor LFTs* weekly until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, ↓ 1 dose level.

	• If resolved in > 7 days, discontinue patient from study treatment**. Continue to monitor LFTs* every other week or more frequently if clinically indicated until the end of treatment with study medication.
Grade 4 (> 10.0 x ULN)	Hold all treatment and discontinue patient from Pembrolizumab therapy**.
AST or ALT**	
Grade 1 (> ULN - 3.0 x ULN) Grade 2 (> 3.0 - 5.0 x ULN) if not increased from baseline and without bilirubin elevation to > 2.0 x ULN	Maintain dose level
Grade 2 (> 3.0 - 5.0 x ULN) if increased from baseline and without bilirubin elevation to > 2.0 x ULN	Hold all treatment and monitor LFTs* weekly until resolved to ≤ grade 1, then: • If resolved in ≤ 7 days, then maintain dose level. • If resolved in > 7 days, then ↓ 1 dose level.
Grade 3 (> 5.0 - 20.0 x ULN) without bilirubin elevation to > 2.0 x ULN	Hold all treatment and monitor LFTs* weekly until resolved to ≤ Grade 1 (or ≤ Grade 2 in case of liver metastasis), then: • If resolved in ≤ 7 days, then maintain dose level. • If resolved in > 7 days, then ↓ 1 dose level. Continue to monitor LFTs* every other week or more frequently if clinically indicated until the end of treatment with study medication.
Grade 4 (> 20.0 x ULN) without bilirubin elevation to > 2.0 x ULN	Hold all treatment until resolved to ≤ grade 1, then ↓ 1 dose level.
Drug-Induced Liver Injury	
Patients with AST/ALT > 3 x ULN and total bilirubin > 2 x ULN with no evidence of obstruction (such as elevated ALP, malignancy, impaired glucuronidation (Gilbert syndrome) or pharmacologic factors) with no other explanation (e.g., viral, alcoholic or autoimmune hepatitis, hepatobiliary disorders, cardiovascular causes, concomitant medications) may have drug-induced liver injury. In such cases, • discontinue** the patient from Pembrolizumab (remove from study but may continue chemotherapy at discretion of PI) and report as SAE. In any case, • monitor patient, including LFTs* weekly or more frequently if clinically indicated until resolved to ≤ grade 1 or stabilization.	
* LFTs include: albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), AP (fractionated if AP is grade 2 or higher) and GGT). For patients with Gilbert Syndrome: total and direct bilirubin must be monitored; intensified monitoring applies to changes in direct	

bilirubin only. ** Patients who discontinue study treatment should be monitored weekly including LFTs or more frequently if clinically indicated until resolved to ≤ grade 1 or stabilization (no CTCAE grade change over 4 weeks).	
Fatigue (Asthenia)	
Grade 1 or 2	Maintain dose level
Grade 3	Hold all treatment until resolved to ≤ Grade 2, then: • If resolved in ≤ 7 days, maintain dose level. • If resolved in > 7 days, ↓ 1 dose level.
Grade 4	Hold all treatment and discontinue patient from Pembrolizumab (may continue chemotherapy at discretion of PI).
Peripheral Neuropathy	
Grade 1 or 2	Maintain dose level.
Grade 3	Hold all treatment until resolved to ≤ Grade 2, then: • If resolved in ≤ 7 days, maintain dose level. • If resolved in > 7 days, ↓ 1 dose level (Paclitaxel only).
Grade 4	Hold all treatment and discontinue patient from Pembrolizumab (may continue chemotherapy at discretion of PI).
**Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.	

22. **6.4.2 Dose Interruptions**

Under certain conditions, a dose interruption of Carboplatin or Paclitaxel may be required. Should the dose interruption last for greater than 21 days, the patient should be discontinued from study treatment. Further, if a patient does not tolerate the lowest possible dose, treatment with Pembrolizumab must be discontinued.

7.0 TREATMENT DISCONTINUATION

Treatment may be discontinued for any of the following reasons:

- The patient demonstrates progression of disease. Exception: Patients may remain on the study if in the opinion of the Investigator, he/she is deriving clinical benefit from study treatment.
- The patient (or legally authorized representative) withdraws consent from the study.
- Study treatment for participant is past due for >28 days due to an AE (or other such toxicity).
- The patient experiences an AE that in the opinion of the Investigator makes continued study treatment an unacceptable risk.
- The patient becomes pregnant.
- The patient requires continuous treatment with a prohibited concomitant drug(s) for which no safe alternatives can be substituted.
- The patient is significantly noncompliant with the requirements of the protocol.

Should discontinuation of study therapy occur, all efforts should be made to execute/report End-of-Treatment and Follow-up Evaluations as completely as possible and to determine/document the reason for discontinuation (unless the patient withdraws consent for follow-up).

Although unexpected termination of study treatment may occur, it is possible the subject may still agree to survival data collection.

If a patient wishes to withdraw consent from the study, the PI must be notified. The information regarding withdrawal (i.e., subject identifiers and date of withdrawal) should be documented in the subject's record and updated within any other research database(s).

8.0 SCHEDULE OF CLINICAL & LABORATORY EVALUATIONS

Prior to performing any study-specific procedures or evaluations, written informed consent and authorization for the use of protected health information (HIPAA) must be obtained in accordance with all applicable policies, regulations and laws. Correlative evaluations must also be performed at specified visits for patients who consent to these activities. Please refer to Section 10.0, Correlative Studies for specific details.

All evaluations should be completed as detailed below prior to the administration of trial treatment on Day 1 of each cycle. All evaluations will be administered on an outpatient basis.

8.1 Pre-Treatment Evaluations (Screening)

The following must be collected/performed within 30 days prior to Cycle 1, Day 1 of treatment unless otherwise specified. Clinical and laboratory evaluations performed as part of routine standard of care do not need to be repeated if performed within the appropriate window.

- Informed Consent
- Complete medical history, disease history and prior medical treatments
- Concomitant Medications
- Demographic data
- Height
- Weight
- Vital signs (V/S)
  - Oral temperature
  - Blood pressure
  - Heart rate
  - Respiratory rate
- Complete physical examination (PE)
- ECOG Performance Status (PS) (See Appendix B)
- 12-Lead Electrocardiogram (ECG)
- Urine or serum pregnancy test for women of child-bearing potential (WoCBP) ≤72 hours (i.e., 3 days) prior to Cycle 1, Day 1
- Laboratory Evaluations: (if within 7 days of treatment initiation, Cycle 1, Day 1, do not need to repeat)
  - Complete Blood Count (CBC) with differential (diff)
  - Coagulation studies:

    - Prothrombin Time (PT)/International Normalized Ratio (INR)
    - Activated partial thrombobplastin time (aPTT)
  - Comprehensive Serum Chemistry Panel
    - Triiodothyronine (T3)
    - Thyroxine (T4)
    - Thyroid-stimulating hormone (TSH)
  - Urinalysis (U/A)
- IR-guided core biopsy, biopsy obtained by surgeon on exam (fresh tissue) or archival tissue (formalin-fixed paraffin-embedded; FFPE)
- Correlative Studies (See Section 10.0: Schedule of Correlative Evaluations): Blood samples
- Imaging Studies: Imaging studies for tumor assessment for all known sites of disease (including computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen or pelvis with contrast or positron-emission tomography (PET)-CT). CT imaging is the preferred method, but where warranted, PET-CT is allowable. Imaging method used at baseline for tumor assessment should be the same throughout the study.

*Unless laboratory tests obtained within 7 days during screening to start of Cycle 1, Day 1.

8.2 Evaluations on Treatment

Collection of Concomitant Medications and AEs should occur throughout the study as described. Any SAE or follow up to a SAE including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following end of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. All subjects with SAEs must be followed up for outcome. (See Section 12.3 and Appendix A for details).

8.3 All Cycles*, Day 1 (±3 days)

- Medical History
- Physical Exam
- Concomitant Medications
- ECOG PS
- V/S (temperature, blood pressure, heart rate, respiratory rate)
- Weight
- CBC with diff
- Comprehensive Serum Chemistry Panel
- Urine protein/creatinine ratio (every other cycle, C1, C3, C5, etc.)
- T3
- T4
- TSH
- Correlative Studies (Optional, See Section 10.0): Blood collected before and after administration of Pembrolizumab; tissue samples collected after 3–4 cycles of treatment.

- Imaging studies for tumor assessment for all known sites of disease (including CT or MRI of abdomen or pelvis with contrast or PET CT). CT imaging is the preferred method, but where warranted, PET-CT is allowable. Imaging method used at baseline for tumor assessment should be the same throughout the study. Imaging will only be obtained every 3-4 cycles to assess for response unless CR is achieved including confirmatory scan; then imaging thereafter may be obtained at Investigator's discretion.
- Administration of Study Agents (See Section 5.0: Treatment Plan).
- AE reporting

8.4 Safety Evaluation Visit

The following safety assessments must be performed at 30 days (+/-7 days) after study discontinuation for all subjects. These patients will then be followed for survival data only.

- Medical History
- Physical Exam
- Concomitant Medications
- V/S
- Weight
- ECOG PS
- CBC with diff
- Coagulation studies (PT/INR, aPTT)
- Comprehensive Serum Chemistry Panel
- T3
- T4
- TSH
- Correlative Studies (Optional, see Section 10.0): Blood
- AE reporting. Any SAE, or follow up to a SAE, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following end of treatment or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. All subjects with SAEs must be followed up for outcome. (See Section 12.3 and Appendix A for details.)

8.5 Follow-up Evaluations

For all patients, follow up will be survival data only. Data will be collected via standard of care visits or telephone call to patient or family member. Imaging during follow-up will be at Investigator's discretion.

8.6 Calendar of Clinical and Laboratory Evaluations

Table 6: Calendar of Clinical and Laboratory Evaluations

	Screening	**Treatment Cycle(s)** (q21 days)	**Safety Evaluation [K]**	**Follow-Up[L]**
	≤30 days prior [A]	Day 1 (±3 days unless specified)	30-days (+/-7 days) after study discontinuation	
Informed Consent	X			
Eligibility	X			
Demographics [B]	X			
History & Physical [C]	X	X	X	
Height	X			
Weight	X	X	X	
Vital Signs [D]	X	X	X	
ECOG PS	X	X	X	
12-Lead ECG	X			
CBC with diff	X*	X	X	
Comp Serum Chemistry Panel	X*	X	X	
T3, T4 and TSH	X*	X	X	
PT/INR, aPTT	X*		X	
Urine or serum pregnancy test [E]	X			
Urinalysis, urine protein/creatinine ratio	X*	X+		
Pembrolizumab IV		X		
Paclitaxel IV[F]		X		
Cisplatin (Carboplatin) IV[F]		X		
Bevacizumab IV		X		
Core biopsy (fresh tissue sample if possible, will accept archival tissue [FFPE])	X			
Correlative Studies: Tissue Sample [G] (fresh tissue sample, paired)		X		

Correlative Studies: Blood [H]	X	X [H]	X [H]	
Imaging [I]	X	X	X	
Adverse Events [J]		X		
Concomitant Medications	X			
Post-Study Status [M]				X

[A] Screening evaluations should be done within 30 days prior unless otherwise specified.
*Screening labs must be done within 30 days of treatment initiation though if within 7 days of treatment initiation, Cycle 1 Day 1, they do not need to be repeated.
+ Urine protein/creatinine ratio should be obtained every other cycle (C1, C3, C5, etc.)
[B] Demographic data includes age, gender and racial/ethnic background.
[C] Complete Medical History includes disease history and prior medical treatments.
[D] Vital signs include oral temperature, blood pressure, respiratory rate and heart rate.

[E] Urine or serum (beta-HCG) pregnancy test is required for women of childbearing potential **within 72 hours (i.e., 3 days) prior to Cycle 1, Day 1** of trial treatment.
[F] If patient is deriving clinical benefit from Bevacizumab and Pembrolizumab, chemotherapy may be discontinued at the PI's discretion following a discussion with the patient.
[G] Tissue sample collection during Treatment (i.e., following 3–4 cycles) is optional for correlative studies (see Section 10.0 for details).
[H] Collection of serum for biomarkers will be obtained before and after Pembrolizumab treatment and at the end of the study.
[I] Imaging for tumor assessment for all known sites of disease (including CT, PET-CT or MRI of abdomen or pelvis with contrast): preferably with CT imaging for RECIST interpretation, but PET-CT is allowable. Imaging method used at baseline for tumor assessment should be the same throughout the study. Imaging will be done at baseline and after every 3-4 cycles. If CR attained with follow up confirmation, further imaging may be obtained at Investigator's discretion. Imaging during follow up will be at Investigator's discretion.
[J] AE/SAE collections should continue for at least **90 days** after the last dose of treatment. All subjects with SAEs must be followed up for outcome. (See Section 12.3 and Appendix A for details.)
[K] Safety Evaluation visit for all patients; these safety assessments must be performed at 30 days (+/-7 days) after study discontinuation.
[L] Follow-up for all patients will be for survival data only, which will be obtained with a phone call or at regularly scheduled visits with their doctor.

9.0 SCHEDULE OF CORRELATIVE EVALUATIONS

For those patients who consent to additional correlative evaluations, the following procedures will be performed:

Collection of blood will be performed on each cycle of treatment before Pembrolizumab infusion and post infusion. In addition to the study laboratory evaluations (i.e., CBC with differential, comprehensive serum chemistry panel) the patient's immune phenotyping (markers including but not limited to CD3, CD4, CD8, PD-1, PD-L1, Foxp3) will be determined. Intracellular cytokine levels in circulating blood monocytes and the patients' blood concentration of Pembrolizumab will be also measured.[31, 34, 35]

Tumor specimens will be obtained at baseline diagnostic surgery or IR-guided for disease confirmation if no archival tissue is available and following 3-4 cycles of treatment if measurable disease remains and is amenable to biopsy. Immunohistochemistry will be performed to determine tumor expression of PD-1, PD-L1, CD8, FOXP3 on FFPE tumor specimens.[35] Immune gene expression profiling will be performed on snap frozen tumor specimens.[36]

9.1 Pre-Treatment Specimen Collection

The following should be collected at baseline/screening (30 days prior to Cycle 1, Day 1):

- Tumor specimens (archival or fresh – tissue or core)
- Blood (20 mL)

9.2 All Cycles, Day 1

Blood (20 mL) (2 tubes of blood collected per procedures outlined in the lab manual)

9.1.2 On Treatment Specimen Collection

Tissue samples may be collected following every 3-4 cycles if patient consents to biopsy.

9.3 Off Treatment Specimen Collection

9.3.1 Early Treatment Discontinuation OR Safety Evaluation

Patients who discontinue study treatment early and those who complete study treatment will be asked to provide an extra blood sample after their last treatment dose; this may be done during the Safety Evaluation Visit (see Section 8.4).

- Blood (20 mL)

10.0 AGENTS (DRUG FORMULATION AND PROCUREMENT)

10.1 Pembrolizumab

Refer to the FDA-approved package insert and current version of the Investigator's Brochure (IB) for more information.[20]

10.1.2 Mechanism of Action

Pembrolizumab (MK-3475, KEYTRUDA®) is a potent and highly selective humanized monoclonal antibody (mAb) designed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab potently blocks binding to both ligands with half maximal inhibitory concentration (IC_{50}) values below 1 nM in humans and cynomolgus monkey.

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.[20]

10.1.2 Composition

The commercial formulation of Pembrolizumab is being used in this study. Pembrolizumab drug product (DP) (solution for infusion, 100 mg/vial) is packaged in vials that contain 4 mL of sterile solution for IV infusion and 25 mg/mL Pembrolizumab.

10.1.3 Storage Recommendations and Dosage Forms

Two Drug Product (DP) dosage forms are available for Pembrolizumab (MK-3475): a subcutaneous injection form and an IV form. For the purposes of this study, only the IV form of Pembrolizumab will be used. For instructions on dose preparation and administration, refer to the KEYTRUDA® package insert.

Reconstituted vials should be used immediately to prepare the infusion solution in the IV bag, and the infusion solution should be administered immediately. If the diluted Pembrolizumab solution is not used immediately, it may be stored at room temperature for no more than 6 hours from the time of dilution. This hold time includes room temperature storage of the diluted solution and the duration of infusion. The product can also be stored under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 96 hours from the time of dilution. If refrigerated, the diluted solution must be allowed to come to room temperature prior to administration. Do not shake. The solution must be discarded after 6 hours at room temperature or 96 hours under refrigeration.

Do not freeze the diluted solution!

10.1.4 Dispensation and Accountability

For this study, Pembrolizumab will be provided by Merck as the commercial formulation of Pembrolizumab at 100 mg/4mL vial (25 mg/mL) as a solution for injection which is labeled as for investigational use. For further details on drug preparation, please refer to the most recent version of the KEYTRUDA® (MK-3475) Pharmacy Manual.

11.0 MEASUREMENT OF EFFECT

11.1 RECIST Guidelines

New measurable lesions: incorporated into tumor burden (i.e., added to the target lesion measurements). A lymph node has to be ≥ 15 mm in short axis to be a measurable new lesion, and its short axis measurement is included in the sum. Up to 2 new lesions per organ and up to 5 new lesions in total can be added to the measurements.

11.2 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response after completion of 3-4 cycles of therapy and again after every 3-4 cycles. In addition to a baseline scan, confirmatory scans should also be obtained no less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST 1.1) guideline (version 1.1).[37, 38] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.2.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with Pembrolizumab, chemotherapy and Bevacizumab.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.2.2 Disease Parameters

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

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

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

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

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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

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

11.2.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each

identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI that greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an Investigator if it is not routinely or serially performed.

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

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

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published[39-41]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria that are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer[42].

Cytology, Histology: These techniques can be used to differentiate between PR and CR.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or SD is mandatory to differentiate between response or SD (an effusion may be a side effect of the treatment) and PD.

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

- Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.2.4 Response Criteria – Evaluation of Target Lesions

Table 7: Response Criteria (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 progression.)
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum diameters while on study.

11.2.5 Response Criteria – Evaluation of Non-Target Lesions

Table 8: Response Criteria (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 patient 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.

11.2.6 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease):

Table 9: Best Overall Response - Measurable Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**

CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.[37, 38]
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

For Patients with Non-Measurable Disease (i.e., Non-Target Disease):

Table 10: Best Overall Response - Non-measurable Disease

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

11.2.7 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that PD is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.2.8 Progression-Free Survival (PFS)

PFS is defined as the elapsed time from start of treatment to first documentation of progression or date of death. In alive progression-free patients, PFS will be censored at the last evaluable tumor assessment.

11.2.9 Overall Survival (OS)

OS is defined as the elapsed time from start of treatment to date of death. Alive patients will be censored at date last known to be alive.

12.0 ADVERSE EVENTS

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting.[43]

12.1 Purpose

AE data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during a trial. Additionally, certain AEs must be reported in an expedited manner for timelier monitoring of patient safety and care. See Appendix A for more information.

12.2 Adverse Event

Adverse Event (AE): Can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, medical treatment, or procedure without judgment about causality. An AE can arise from any use and from any route of administration, formulation, or dose including an overdose. This includes any newly occurring event or a previous condition that has increased in severity or frequency since initiation of a drug, medical treatment, or procedure.

Abnormal Findings

In any clinical assessment, a value outside the normal or reference range (such as a clinical laboratory, vital sign, or ECG) will **not** be reported or assessed as an AE unless that value is considered to be of clinical significance by the Investigator. A value of clinical significance is one that leads to discontinuation or delay in protocol treatment, dose modification, therapeutic intervention*, or is considered to be a clinically significant new finding or change from baseline by the Investigator.

*Transfusion support administered to offset clinical symptoms of anemia or thrombocytopenia will not be considered therapeutic intervention.

Signs and Symptoms

Signs/symptoms resulting from an underlying clinical diagnosis should be documented as one comprehensive AE. If no underlying clinical diagnosis can be identified, each sign/symptom should be reported as a separate independent event. (A new or worsening event resulting from an underlying clinical diagnosis or a reaction to concurrent medications should be documented as a separate independent AE unless it is within the normal range of fluctuation for that patient.)

Grade Changes/Fluctuations

AEs will be reported at the maximum grade/severity experienced for the duration of the event. Should one particular event warrant further investigation, additional details may be collected at the discretion of the PI.

Progression of Disease

Progression of disease, if documented in accordance to standard of care, should not be reported as an AE.

Tests and Procedures

Tests and procedures should not be reported as AEs. The underlying clinical diagnosis (or sign/symptom in the event an underlying clinical diagnosis is not known) requiring testing or a procedure should be reported as an AE if it meets criteria for reporting.

12.3 Serious Adverse Events (see also Appendix A)

Serious AE (SAE) means any untoward medical occurrence that occurs at any dose that:

1. **Results in death.**
2. **Is life-threatening.**
   The term "life-threatening" in the definition of "serious" refers to an event in which the patient 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.
3. **Requires inpatient hospitalization or prolongation of present hospitalization.**
   Elective hospitalization to simplify protocol treatment/evaluations or to treat a baseline condition that did not worsen from baseline will not be considered an SAE.
4. **Results in persistent or significant disability/incapacity.**
   Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
5. **Is a congenital anomaly/birth defect.**
6. **Is a medically important event.**

A medically important event may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Clarification should be made between the terms *serious* and *severe* because they ARE NOT synonymous. The term *severe* is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or functioning. A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

12.4 Adverse Event Collection Period

In this study, AE include only treatment-emergent AE. A treatment-emergent adverse event

(TEAE) is defined as any event that begins or worsens after the start of protocol treatment. All baseline-emergent AE, any event that begins or worsens after completion of the informed consent but prior to the start of protocol treatment, should be reported as a Baseline/Comorbid Condition.

Adverse events collection period will end with end of treatment (EOT).

12.5 Adverse Event Reporting Requirements

The information to be reported in AEs will be assessed by and assigned severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03. The NCI CTCAE provides descriptive terminology and a grading scale for each AE listed. A copy of the NCI CTCAE v4.03 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page (http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

Information to be reported in the description of each AE may be included, but is not limited to:

1. Clinical Diagnosis of the event as determined by NCI CTCAE, Version 4.03 descriptive terminology. If no clinical diagnosis can be identified, each sign/symptom should be reported as a separate independent event.
2. Date of onset of the AE (start date).
3. Date of resolution of the AE (end date) if available by EOT.
4. Severity of the event determined by NCI CTCAE, Version 4.03 grading scale.
5. Relationship of the AE to study therapy. Categorized as follows:

Definite	The adverse event is clearly related to the investigational agent(s)
Probable	The adverse event is likely related to the investigational agent(s)
Possible	The adverse event may be related to the investigational agent(s)
Unlikely	The adverse event is doubtfully related to the investigational agent(s)
Unrelated	The adverse event is clearly not related to the investigational agent(s)

6. Whether or not the AE is Serious or Not: Serious as defined in Section 12.3 Serious Adverse Events.
7. Whether the AE is Suspected and/or Unexpected.

Suspected	Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of expedited safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE.
Unexpected	Any AE for which the nature or severity of the event is not consistent with the applicable product information, e.g., the Investigator's Brochure or Package Insert.

8. Action taken as a result of the AE.
9. Outcome

12.6 Expedited Adverse Event Reporting Requirements

All AEs, regardless if serious or not, will be described in the source documents, reported on the applicable AE page of the CRFs, and entered into *Velos*. However, certain AEs must also be reported in an expedited manner for timelier monitoring of patient safety and care. Appendix A

provides information about these expedited reporting requirements.

12.7 Events of Clinical Interest

Not applicable.

13.0 STATISTICAL CONSIDERATIONS

This is a single arm, two-stage, open-label, phase II study to assess efficacy of Pembrolizumab, Paclitaxel, Cisplatin (Carboplatin) and Bevacizumab for recurrent, persistent, or metastatic cervical cancer. The primary efficacy endpoint is objective response rate (ORR; partial or complete response).

Secondary objectives include to determine (1) PFS, (2) OS, and (3) safety and tolerability of Pembrolizumab in combination with chemotherapy and Bevacizumab. Exploratory analyses will be to determine if an immunologic profile will be a useful biomarker of treatment response and to perform exploratory translational studies on tissue biopsies at the time of recurrence, persistence, or metastatic disease compared to post-treatment samples.

13.1 Planned Statistical Analysis

Statistical analysis will be based on evaluable patients as defined in Section 8.2. Baseline characteristics will be summarized using descriptive statistics: counts and percentages, ranges, median, mean, and standard deviation as appropriate. This will include demographics (age, weight, and race/ethnicity), performance status, time since diagnosis, and prior treatment.

Safety analysis will include detailed tabulation of worst toxicity and toxicity by type, grade, duration, and attribution to treatment (unrelated, unlikely, possible, probable, or definite) using the NCICTCAE, version 4.03.

The primary study endpoint ORR (partial or complete response) will be reported with corresponding 95% CI calculated using the binomial method. The secondary endpoints PFS and OS will be analyzed with the Kaplan-Meier method.[44]

For the exploratory endpoints, we will evaluate the immunologic profile in predicting response to treatment and PFS. Changes in immune endpoints pre- vs. post- treatment will be compared using paired t-test. The effect of the specific pre-treatment immune potential biomarker on treatment response will be assessed using logistic regression and on PFS using Cox regression analysis.

13.2 Sample Size Justification

In this single-arm, two-stage, open-label phase II study, we plan to enroll at most 40 evaluable patients with planed enrollment of 25 patients in the first stage and possibly an additional 15 patients in the second stage. Based on our institution's enrollment capacity, we anticipate successful enrollment of 40 patients within 24 months with an estimated accrual of 2 patients per month. The expected study duration is 4 years including a desirable minimum follow up of 24 months for progression and survival data.

GOG240 demonstrated 48% ORR (CR+PR) with the addition of Bevacizumab to chemotherapy.[8] We hypothesize that our proposed treatment with Pembrolizumab, Paclitaxel, Cisplatin (Carboplatin) and Bevacizumab will result in ORR greater than 55%. Using PASS 15, we calculated sample size for a Simon's two-stage design setting null hypothesis of ORR<38% (that

is, ORR lower by absolute 10% from the observed 48% ORR in GOG240), one-sided 5% significance level and 80% power to detect ORR=58% under the alternative hypothesis that ORR≥38%[8,45,46]. We determined a minimax two-stage design enrolling at most 40 patients with a probability of early termination of 0.66 after evaluating the proposed treatment in 25 patients in the first stage. The trial will be terminated early if 10 or fewer responses out of the 25 evaluable patients (≤40%) are observed in the first stage. If the trial goes on the second stage (that is, 11 or more responses in the first 25 patients), an additional 15 evaluable patients will be assessed for response in the second stage for a total of 40 study patients. If the total number responding is less than or equal to 20 among 40 total patients (ORR≤50%), the null hypothesis is rejected and the proposed treatment considered not effective. Otherwise, if the total number of CR+PR is greater or equal to 21 among 40 total patients (ORR ≥52.5%), the null hypothesis is rejected and the proposed treatment is considered effective. Under this design, the actual significance level is 4.3%; that is, if the treatment is actually not effective, there is a 0.043 probability of concluding that it is effective (type I error). The actual power is 81.2% yielding 18.8% actual type II error; this is, if the treatment is actually effective, there is a 0.18.8 probability of concluding that it is not effective (type II error).

13.3 Stopping Rules

We propose the following guidelines for the Data and Safety Monitoring Committee (DSMC) consideration in its review of accumulating study data. The proposed guidelines were developed using Bayesian methods, which can be applied at any stage of enrollment without advance specification of the number of interim analyses to be performed, or the number of evaluable patients at the time such assessments are made. Under the Bayesian method, we assign a prior probability (level of belief at the start of the trial) to a range of possible values for the true response rate and similarly, a prior distribution for the true toxicity rate[47,48]. As treatment response and toxicity data on study patients become available, each of these prior probability distributions is revised and the resulting posterior probabilities become the basis for recommending either early termination or continuation of the study. The following sections provide specific stopping guidelines and underlying assumptions for the prior distributions.

13.3.1 Early Stopping Due to Toxicity

The clinical Investigators and the SCCC DSMC will monitor the study patients for study-related toxicities. Toxicities encountered in this trial will be reported according to the NCI CTCAE, version 4.03.

For the purposes of safety monitoring, we define unacceptable toxicity to be any treatment-related (possible, probable, or definite) grade 3 or higher toxicity. Unacceptable toxicity is expected to occur in no more than 20% of patients. If there is evidence that the true rate of this toxicity exceeded 30%, then the study will be suspended and possibly terminated early. Specifically, we suggest as a guideline for early termination a posterior probability of 80% or higher that the true rate exceeds 30%. The table below shows specific instances where this guideline is met and suggests early termination due to evidence of excessive unacceptable toxicity.

Table 11. Stopping Boundaries for Toxicity

(Stop if the number of unacceptable toxicity in N evaluable patients is greater than or equal to X.)

X: Number (%) of patients with unacceptable toxicity*	N: Total evaluable patients assessed for toxicity	Observed unacceptable toxicity rate ≥
4	6 to 8	50.0%
5	9 to 11	45.5%
6	12 to 13	46.2%
7	14 to 16	43.8%
8	17 to 19	42.1%
9	20 to 22	40.9%
10	23 to 25	40.0%
11	26 to 28	39.3%
12	29 to 31	38.7%
13	32 to 34	38.2%
14	35 to 37	37.8%
15	38 to 39	39.5%
* Possible, probable, or definite treatment-related grade 3 toxicity		

To illustrate the stopping guidelines, suppose that 11 evaluable patients have been assessed for toxicity and 5 of them have experienced grade 3 treatment-related toxicity (row 2 of the above table). Under this circumstance, the observed rate of grade 3+ of such toxicity is 45.5%, resulting in a posterior probability of >90% that the true underlying rate exceeds 30% thereby suggesting early termination.

Posterior probabilities for the above table are calculated under a weak prior beta distribution with parameters β_1 =0.4 and β_2 =1.6, which corresponds to an expected unacceptable-toxicity rate of 20% based on very limited information roughly equal to having studied 2 patients. This prior distribution implies also a priori chance of 26.2% that true rate of unacceptable toxicity is 30% or greater.

23. **13.3.2 Early Stopping Due to Lack of Efficacy**

As per Section 13.2, this is a two-stage design enrolling at most 40 patients with a probability of early termination of 0.664 after evaluating the treatment in 25 patients in the first stage. The trial will be terminated if it is observed 10 or fewer responses (CR+PR) out of 25 evaluable patients in the first stage.

14.0 DATA REPORTING, MONITORING, AND AUDITING

Data must be submitted according to the protocol requirements for all patients registered. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.1 Data and Safety Monitoring

The SCCC DSMC will monitor this clinical trial according to the Cancer Center's data safety monitoring (DSM) Plan. In its oversight capacity, the DSMC bears responsibility for suspending or terminating this study. DSMC oversight of the conduct of this trial includes ongoing review of accrual and AE data and periodic review of the study therapy. The guidelines appearing in the Section 13.3 are offered for DSMC consideration in assessing AEs and pathologic objective response. In addition, the DSMC will review reports from all audits, site visits, or study reviews pertaining to this clinical trial and take appropriate action. The SCCC DSM Plan to which this study is subject can also be found at www.sylvester.org.

14.2 Study Auditing and Monitoring

This study will be audited and/or monitored (as applicable) according to UM requirements. See also http://uresearch.miami.edu/regulatory-compliance-services/rcqa and http://research.med.miami.edu/clinical-research/crors.

15.0 INVESTIGATOR RESPONSIBILITIES

15.1 Investigator Responsibility/Performance

The Investigator will ensure that this study is conducted in accordance with all regulations governing the protection of human subjects. The Investigator will ensure that all work and services described in or associated with this protocol will be conducted in accordance with the investigational plan, applicable regulations, and the highest standards of medical and clinical research practice.

15.2 Confidentiality

The Investigator must ensure that each subject's anonymity will be maintained and each subject's identity will be protected from unauthorized parties. A number will be assigned to each subject upon study entry and the number and the subject's initials will be used to identify the subject for the duration of the study. The Investigator will maintain all documents related to this study in strict confidence.

15.3 Informed Consent and Permission to Use Protected Health Information

It is the responsibility of the Investigator to obtain written informed consent from each subject participating in this study after adequate explanation, in lay language, of the methods, objectives, anticipated benefits, and potential hazards of the study. The Investigator must also explain that the subject is completely free to refuse to enter the study or to discontinue participation at any time (for any reason) and receive alternative conventional therapy as indicated. Prior to study participation, each subject will sign an IRB approved informed consent form and receive a copy of same (and information leaflet, if appropriate). The Investigator or designee **must** explain to the subject before enrollment into the study that for evaluation of study results, the subject's protected

health information obtained during the study may be shared with the study sponsor, regulatory agencies, and the IRB. It is the Investigator's (or designee's) responsibility to obtain permission to use protected health information per HIPAA from each subject or if appropriate, the subjects' parent or legal guardian.

15.4 Source Documentation and Investigator Files

The Investigator must maintain adequate and accurate records to fully document the conduct of the study and to ensure that study data can be subsequently verified. Subject clinical source documents may include hospital/clinic patient records; physician's and nurse's notes; appointment book; original laboratory, electroencephalogram (ECG), EEG, radiology, pathology, and special assessment reports; pharmacy dispensing records; subject diaries; signed informed consent forms; and consultant letters. When the CRF or any form is used as the source document, this must be clearly stated in the Investigator study file.

15.5 Recording and Processing of Data

If using hard copies of CRFs, study center personnel will complete individual CRFs in ink. All corrections to entered data will be made by drawing a single line through the information to be corrected without obscuring it. All corrections will be initialed, dated and explained, if necessary. The use of "white-out" or obscuring correction tape will be prohibited. A CRF is required for every patient who received any amount of study treatment. The Investigator will ensure that the CRFs are accurate, complete, legible and timely. Separate source records are required to support all CRF entries except those for which use of the CRF as source document is clearly allowed per note in the Investigator study file.

Data must be submitted according to the protocol requirements for ALL patients registered. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

Data must be submitted according to the protocol requirements for ALL patients registered. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

15.6 Non-Protocol Research

No investigative procedures other than those described in this protocol will be undertaken on the enrolled subjects without the agreement of the IRB.

15.7 Ethics

The Investigator agrees to conduct the study in compliance with the protocol, current good clinical practices, and all applicable (local, FDA) regulatory guidelines and standard of ethics.

UM Ethics Programs' Research Ethics Consultation Service (RECS) is a free resource for UM Researchers. See the website for further information: https://bioethics.miami.edu/clinical-and-research-ethics/research-ethics-consultation-service/index.html.

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APPENDIX A: EXPEDITED ADVERSE EVENT (AE) REPORTING REQUIREMENTS

For all AEs that meet criteria for expedited reporting, the Principal Investigator (PI) is obligated to pursue and provide follow-up reporting information until the event has resolved or until an acceptable medical endpoint has been reached (i.e., for the duration specified in the protocol), or the patient is lost to follow-up.

The PI and all applicable research study team members should become familiar with the safety profile of the investigational agent(s) and/or intervention at the start of the study and for the duration of the research, e.g., by reviewing the Investigator's Brochure (IB) and any Safety Reports released by the Sponsor as applicable.

FDA Expedited Reporting

FDA Expedited Reporting Sponsor-Investigators (i.e., IND Holders) have additional reporting requirements to the FDA and other committees and should consult the applicable regulations and agency guidelines for these requirements.

Since this protocol involves the use of FDA IND agent(s), completion of the FDA MedWatch 3500A Reporting Form is required for Sponsor-Investigators. The Form can be obtained electronically at:
http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

All serious, unexpected (unanticipated) and suspected adverse events must be directly reported to the FDA within 15 calendar days of being made known to the PI.

All fatal or life-threatening AEs must be directly reported to the FDA within 7 calendar days of being made known to the PI.

For more information regarding reporting to the FDA, please refer to the FDA website for REPORTING GUIDELINES: http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm

IRB Expedited Reporting

All Investigators should also be aware of local Institutional requirements for AE reporting. For more information regarding the IRB policy, please refer to the UM HSRO's Investigator Manual: http://hsro.med.miami.edu/documents/HRP-103_-_INVESTIGATOR_MANUAL_4.11.2014.docx and the UM HSRO SOP on New Information (HRP-024)
https://eprost.med.miami.edu/eProst/Doc/0/HLJ5OTJVQEH419E0I6QPT3B199/HRP-024%20-%20SOP%20-%20New%20Information.docx

All AEs that are serious, unanticipated and possibly related will be reported to the IRB within ten (10) working days of being made known to the PI.

Events that are more frequent than anticipated or more severe than expected must be reported to the IRB within ten (10) working days of being made known to the PI.

All unanticipated deaths must be reported to the IRB within 24 hours of being made known to the PI.

Merck Expedited Reporting (Events of Clinical Interest or ECIs)

A. In addition to the mandatory MedWatch 3500A Form, the PI is also required to comply with all reporting requirements as supplied by the Investigational Drug Sponsor: Merck.

B. Any serious adverse event (SAE) or follow up to an SAE including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

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

D. Non-serious ECI will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs.

E. Additionally, any SAE considered by an Investigator who is a qualified physician to be related to Merck product that is brought to the attention of the Investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck.

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

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

H. All subjects with SAEs must be followed up for outcome.

APPENDIX B: PERFORMANCE STATUS SCALES

PERFORMANCE STATUS CRITERIA (ECOG)	
Score	**Description**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of walking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of walking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to a bed or chair.
5	Dead.

As published in Am J Clin Oncol: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655. The Eastern Cooperative Oncology Group, Robert Comis, MD, Group Chair.

APPENDIX C: NYHA CLASSIFICATION OF HEART DISEASE

New York Heart Association (NYHA) classification of heart disease:

NYHA Class	Symptoms
I	No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while **at rest**. Mostly bedbound patients.

APPENDIX D: BIOMARKER, CORRELATIVE AND SPECIAL STUDIES

Samples will be processed and stored at the University of Miami (UM) in Dr. Sophia George's laboratory. Biomarker analysis (PDL-1) will be performed by QualTek Molecular Laboratories. Additional biomarker analysis will be performed through the UM.

1. Email Notification

Dr. Marilyn Huang and collaborator Dr. Sophia George should be contacted via email to notify them of all specimen submissions for banking. The Subject line should read:

"Chemo+Pembro_Cervix Cancer_Biospecimen Banking"

Dr. Huang: m.huang@med.miami.edu
Laboratory Collaborator: sophia.george@med.miami.edu; sramakrishnan@miami.edu

2. Blood Samples Collection

Collection of blood will be performed before and after Pembrolizumab treatment and at EOT visit.

Plasma and blood monocytes will be obtained, aliquoted and stored following the Standard Operating Procedures (SOP) for handling the blood samples, which will be supplied in the Study Manual.

3. Tissue Samples Collection

Collection of tissue samples will be performed pre-treatment (needle core biopsy or vaginal biopsy) and possibly following 3-4 cycles.

For each time point, two (2) specimens will be collected. The first one will be fixed in formalin and submitted to the Pathology Department for paraffin embedding and the second one will be immediately frozen for molecular profiling. Details for sample collection and processing will be available on the study SOPs supplied in the Study Manual.

4. Sample Banking

Upon collection of the tissue samples from the patients, a code system will be used to de-identify all samples, assigning a unique code to each specimen. The samples will be tied to patient-identifying information only at the time of sample collection. The patient's name will be written on the specimen collection case. Once the samples are de-identified, which will happen as soon as the specimens arrive in the TBCF, the patient's name will be blacked out on the original sample case and the original casing will be discarded in biohazardous waste, which is subsequently sent for incineration. Samples will be then identified with a code identified (study number). The list where patient's names will be tied to their code will be kept on a password-protected computer in the TBCF. The only information that will be stored with the actual samples in the bank is the code identifier used to identify each sample. No samples will be accepted into the bank unless the subject's signed consent form has first been submitted. The only Investigators who will have access to samples and data being kept in the bank are Dr. Huang and her research collaborator(s) named in this study.

Samples in the bank will be stored indefinitely or until the patient withdraws consent for inclusion in the protocol. At that time, all samples and data will be destroyed.

Researchers wishing to gain access to either the clinical data (de-identified) or samples must first submit the appropriate IRB protocol for use and analysis of the information. Upon approval, the investigator will then be granted appropriate access to the data and/or samples as indicated by his/her respective protocol.

Study-related data will be maintained entirely in an online platform behind the university firewall and requiring *UM CaneID* password identification. Additional IRB approval will be necessary to use and publish any research performed using the study data and the specimens.

Specimen Storage Conditions
Formalin-fixed, paraffin-embedded (FFPE) blocks will be stored at room temperature 15-25°C
Plasma and blood monocytes will be stored in a -80°C freezer
Flash frozen samples will be stored in liquid nitrogen (-150°C)
DNA/RNA will be stored in a -80°C freezer

Contact Info for Dr. George Lab
Sylvester Comprehensive Cancer Center
Papanicolau Building
1550 NW 10th Ave.
Miami, FL 33136-1013
305-243-2036

5. Biomarker Analysis

All biomarker measurements will be performed at the end of study. Five (5) unstained slides cut from an FFPE block will be provided to QualTek as described below.

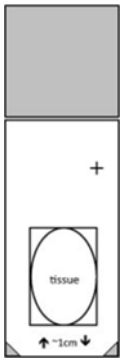
A. Sample Requirements

- For patient samples, the provided positively charged ProbeOn Plus slides (Fisher ProbeOn Plus Catalog Number 22-230-900) must be used for tissue sections. Slide measurements are 75 mm x 25 mm x 1 mm (other slide sizes cannot be accommodated). In the event this requirement cannot be met, please contact QualTek to discuss alternative options.
- Tumor tissue for biomarker analysis must be provided as five (5) unstained slides cut from an FFPE tissue block. Five (5) sectioned slides per patient are required for PD-L1 testing. If additional markers beyond PD-L1 are required to be tested as per the service contract established between QualTek and the Investigator Site, 5 additional sections per marker will be required.
- Samples may be held as blocks indefinitely at the site and then cut in batches. Slides must be shipped to QualTek immediately after sectioning to comply with the protocol's testing requirements. If patient slides are not received by QualTek within seven (7) days of sectioning, new sections may be requested and additional processing charges may be assessed.

- As per Merck protocol requirements, sectioned slides must be shipped cold (2-8°C) and in the dark using the shipping materials provided by QualTek pages 7-8. Be advised that slides received that do not meet these conditions may affect PD-L1 staining.
- Sectioned slides provided should contain tumor specimen sufficient for pathology review and analysis of tumor sample. If available, greater than 50% tumor content is preferred.
- Fine-needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, lavage specimen, frozen sample, plastic embedded sample, or formalin fixed sample that was frozen at any point will not be accepted for IHC analysis. Needle core biopsies that are formalin-fixed and paraffin-embedded are acceptable.

B. Sectioning of Tissue onto ProbeOn Plus Slides from Formalin-Fixed, Paraffin-Embedded (FFPE) Block(s)

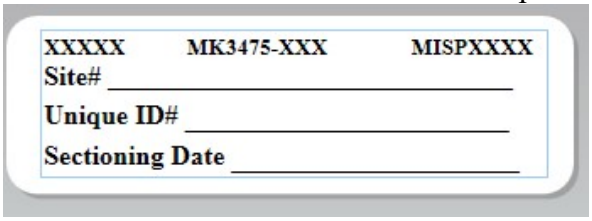
1. Prepare exactly five (5) freshly-cut serial sections at 4 micron thickness onto the provided Fisher ProbeOn Plus Slides, Cat Number 22-230-900. Sections must be placed on the painted/textured side of the slide.
   - Other standard-sized positively-charged slides (75 mm x 25 mm x 1 mm) are acceptable as a last resort, however, QualTek must be notified as there is a risk that outside slides cannot be stained. The slides must be sized as described above or the sample cannot be tested and will be returned.
   - No adhesives should be used in the water bath since the slides are positively-charged.
2. Ensure that the sample has the institutional block ID clearly marked on each slide as well as the slide section levels, if possible.
   - Ensure that the block ID is referenced on the manifest.
   - Note that the sample must be labeled with 2 patient identifiers (Refer to the label provided for the slide holder).
3. When placing the sections onto the slides, ensure that the tissue is towards the bottom third of the slide as pictured at right.
   - Ensure tissue sections are oriented the same direction on all slides.
   - No adhesive labels directly on slides. Slide / patient identifiers must be hand written with indelible / chemical proof ink.
   - Number the slides sequentially (serially), one section per slide.



4. DO NOT OVEN DRY SLIDES. Air dry until completely dry (12-24 hours).
5. Complete an electronic Sample Manifest for each shipment (Excel Spreadsheet provided by QualTek to the Site Contact at study initiation).
   - Email the completed electronic manifest prior to shipment to: MISPsamples@qmlabs.com.
   - Make a copy of the manifest to include with the sample(s).
   - Retain the original at the site for your records.
6. Email or a de-identified (redacted) pathology report(s) if available. Write the block ID on the top of each page of the pathology report.
7. Prepare samples for shipping as detailed on pages 5-6.

C. Packaging Instructions for Formalin-Fixed Paraffin Embedded Slides

1. Affix and complete the label provided for the slide holder with Unique Patient ID number, Site Number/Identifier and Sectioning Date using indelible ink ensuring that the patient identifiers on the slide holder match the patient slides.



Top line of the label are the Study Identifiers and will be pre-printed for the specific study
Left - Investigator Study Number
Center – Merck Protocol Number
Right – QualTek Project Number

2. Place the newly sectioned slides (air dried until completely dry (12-24 hours), exactly five (5) slides, into the labeled slide holder. Ensure only one patient per slide holder.
3. Place the piece of small foam between the top of the slides and the holder's lid to prevent the slides from breaking. Tape the lid closed.
4. Insert the slide holders into the Amber UV bag labeled as "Biohazard" and seal the bag.
5. Place the Amber UV bag into a bubble wrap bag or wrap in a sheet of bubble wrap.
6. More than one shipping box size may have been provided, choose the appropriate size as follows:
   - If shipping 1 patient slide holder:

     Use a 9x12 Insulated Shipping mailer. Place 1 freezer pack in the cooler liner, place the bubble wrap bag containing slides on top of the freezer pack.
   - If shipping between 2 and 10 patient slide holders:

     Use a 10x10x10 Shipping box and cooler box liner. Place 1 freezer pack on the bottom of the cooler liner, place the bubble wrap bag containing slides on top of the freezer pack and include 1 freezer pack on top of the bubble wrap bag.
   - If shipping between 11 and 20 patient slides holders:

     Use a 12x12x12 shipping box and cooler box liner. Place 2 freezer packs on the bottom of the cooler liner, place the bubble wrap bag containing the slides on top of the freezer pack and include 2 freezer packs on top of the bubble wrap bag.
7. Fill remaining space with appropriate cushioning, i.e., additional bubble wrap or other packing material. For extreme temperature conditions additional ice packs may be required. Samples must be shipped cold (2-8°C) and in the dark.
8. Enclose the de-identified (redacted) pathology report and the Sample Manifest, ensure that an electronic copy of the Manifest has been emailed to MISPsamples@qmlabs.com.
9. Seal the mailer/box to ensure it will not open during shipping. Package & ship same day to QualTek.
10. Complete the pre-printed air bill provided by QualTek with sender information.
11. Verify correct shipping address as:

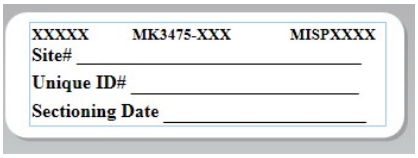
    QualTek Molecular Laboratories
    MISP Receiving
    300 Pheasant Run
    Newtown, PA USA 18940
12. Adhere the pre-printed air bill to the top of the shipping mailer/box.

13. Ship **Standard Overnight** Monday through Thursday; do not ship Friday, Saturday or Sunday.

D. Investigator Studies Supply List for FFPE Sectioned Slides Shipping to QualTek

The following supplies or their equivalent will be provided by QualTek:

1. Positively charged microscope slides used for sectioning of slides (5 per patient) • Fisher ProbeOn Plus 25 mm x 75 mm x 1 mm Capillary Gap Microscope Slides catalog 22-230-900 http://www.fishersci.com	
2. Plastic slide holders (1 per patient, each hold maximum of 5 slides) • Catalog 12-587-17B http://www.fishersci.com	
3. Paraffin embedding cassette sponge to cushion slides in the plastic slide holder during shipping • "square" biopsy foam pad sized 1 7/8" x 1" x 1/16" (catalog 60872-492) http://us.vwr.com	
4. Amber UV bags with biohazard sticker (to keep the slides in dark) • Amber UV bag (6x8 inches) – catalog 89005-326 http://us.vwr.com • Biohazard Sticker – catalog ML1022 http://www.marketlab.com	
5. Shippers • 9x12 (Mailer) *For shipping 1 sample holder* – catalog S18306 http://www.uline.com • 10x10x10 *(Small) For shipping between 2 to 10 patient slide holders* – catalog s4105 http://www.uline.com • 12x12x12 *(Large) For bulk shipments, between 11 to 20 patient slide holders* – catalog s18283 http://www.uline.com • Insulated shippers – catalog s18282 http://www.uline.com	

6. Cold Packs (12 oz. Ice Packs, 1 for the Mailer, 2 for the Small Shipper, 4 for the Large Shipper) • Catalog s7889 http://www.uline.com	
7. Bubble wrap • Catalog s-683 http://www.uline.com	
8. Miscellaneous • Labels for the slide holders • FedEx Pre-Printed Air bills • Site Supply Inventory • Sample Manifest Template (Excel Spreadsheet provided electronically to site contact)	

E. (EXAMPLE) Site Supply Inventory

Date	
QualTek Project #	
Investigator Study #	
Merck Protocol #	
Site Name	
Site Address	
Address Continued	

Quantity	Description	Quantity	Description
	Positively Charged Capillary Gap (ProbeOn Plus) Microscope Slides		Freezer Packs
	Plastic Five (5) Slide Holder (with small Foam Pad)		Fed-Ex Pre-Printed Air Bill(s)
	Labels for Slide Holder		10x10x10 Shipping Box with Cooler Box Liner
	Amber UV Bags (labeled Biohazard)		12x12x12 Shipping Box with Cooler Box Liner
	Bubble Wrap Bags		Other (If Applicable)

F. Unpacking Instructions

1. Confirm material counts and check for breakage.
2. Remove freezer packs and place in freezer as soon as possible.
3. Retain all other materials for return of samples to QualTek Molecular Labs.
4. When ready to section, remove Positively Charged Capillary Gap (ProbeOn Plus) Microscope Slides from slide holder and use only this slide type for sectioning. Retain foam pad for repackaging.

APPENDIX E: CYP1A2, CYP2C8, CYP2C19, CYP3A4 SUBSTRATES, INHIBITORS & INDUCERS *

SUBSTRATE(S)				
1A2	*2C8*	*2C19*	*3A4*	
Amitriptyline caffeine clomipramine clozapine cyclobenzaprine duloxetine estradiol fluvoxamine haloperidol imipramine N-DeMe mexiletine naproxen olanzapine ondansetron phenacetin→ acetaminophen→NAPQI propranolol riluzole ropivacaine tacrine theophylline tizanidine triamterene verapamil (R)warfarin zileuton zolmitriptan	[Paclitaxel] torsemide amodiaquine cerivastatin repaglinide sorafinib	<u>Proton Pump Inhibitors (PPIs)</u>: esomeprazole lansoprazole omeprazole pantoprazole rabeprazole <u>Anti-epileptics</u>: diazepam→Nor phenytoin(O) S-mephenytoin phenobarbitone amitriptyline carisoprodol citalopram chloramphenicol clomipramine chlopidogrel cyclophosphamide hexobarbital imipramine N-DeME indomethacin labetalol R-mephobarbital moclobemide nelfinavir nilutamide primidone progesterone proguanil propranolol teniposide R-warfarin→8-OH voriconazole	<u>Macrolide antibiotics</u>: clarithromycin erythromycin (not 3A5) *NOT azithromycin* telithromycin <u>Anti-arrhythmics</u>: quinidine→3OH (not 3A5) <u>Benzodiazepines</u>: alprazolam diazepam→3OH midazolam triazolam <u>Immune Modulators</u>: cyclosporine tacrolimus (FK506) <u>HIV Antivirals</u>: indinavir nelfinavir ritonavir saquinavir <u>Prokinetic</u>: cisapride <u>Antihistamines</u>: astemizole chlorpheniramine terfenadine <u>Calcium Channel Blockers</u>: amlodipine diltiazem felodipine lercanidipine nifedipine nisoldipine nitrendipine verapamil	<u>Steroid 6beta-OH</u>: estradiol hydrocortisone progesterone testosterone <u>Miscellaneous</u>: alfentanyl aprepitant aripiprazole boceprevir buspirone carbamazepine cafergot caffeine→TMU cilostazol cocaine codeine-N-demethylation dapsone dexamethasone dextromethorphan docetaxel domperidone eplerenone fentanyl finasteride gleevec haloperidol irinotecan LAAM lidocaine methadone nateglinide nevirapine ondansetron pimozide propranolol quetiapine quinine risperidone romidepsin NOT rosuvastatin salmeterol

SUBSTRATE(S)			
1A2	*2C8*	*2C19*	*3A4*
			HMG CoA Reductase Inhibitors: atorvastatin cerivastatin lovastatin NOT pravastatin NOT rosuvastatin simvastatin sildenafil sirolimus sorafenib tamoxifen taxol telaprevir terfenadine torisel trazodone vemurafenib vincristine zaleplon ziprasidone zolpidem

INHIBITOR(S)			
1A2	*2C8*	*2C19*	*3A4*
fluvoxamine ciprofloxacin cimetidine amiodarone efavirenz fluoroquinolones fluvoxamine furafylline interferon methoxsalen mibefradil ticlopidine	gemfibrozil trimethoprim glitazones montelukast quercetin	PPIs: Esomeprazole lansoprazole omeprazole pantoprazole Other: rabeprazole chloramphenicol cimetidine felbamate fluoxetine fluvoxamine indomethacin ketoconazole modafinil oral contraceptives oxcarbazepine probenicid ticlopidine topiramate voriconazole	HIV Antivirals: indinavir nelfinavir ritonavir clarithromycin itraconazole ketoconazole nefazodone saquinavir telithromycin aprepitant erythromycin fluconazole grapefruit juice verapamil diltiazem cimetidine amiodarone NOT azithromycin Chloramphenicol boceprevir ciprofloxacin delaviridine diethyldithiocarbamate fluvoxamine gestodene imatinib mibefradil mifepristone

			norfloxacin norfluoxetine star fruit telaprevir voriconazole
INDUCER(S)			
1A2	*2C8*	*2C19*	*3A4*
broccoli brussel sprouts carbanazepine char-grilled meat insulin methylcholanthrene modafinil nafcillin beta-naphthoflavone omeprazole rifampin tobacco	rifampin	carbamazepine nevirapine phenobarbital rifampin secobarbital St. John's Wort	HIV Antivirals: efavirenz nevirapine barbiturates carbamazepine glucocorticoids modafinil oxcarbazepine phenobarbital phenytoin pioglitazone rifabutin rifampin St. John's wort troglitazone

*Reference: http://medicine.iupui.edu/clinpharm/ddis/main-table/

APPENDIX F: PROTOCOL-APPROVED METHODS OF 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.

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

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

OR

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

OR

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

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

(1) practice abstinence† from heterosexual activity;

OR

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

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

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

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

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

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

Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with Pembrolizumab, the subject will immediately be removed from the study. The site staff will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours to the Sponsor and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor.

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.