TITLE: A Phase II Evaluation of Pembrolizumab in Combination with IV Bevacizumab and Oral Metronomic Cyclophosphamide in the Treatment of Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Roswell Park Cancer Institute

Study Number:  I 270715

Initial Date:  06 November 2015
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Amendment#2:  25 August 2016
Amendment #3:  01 August 2017
Amendment #4:  19 December 2017
Amendment #5:  22 March 2019
Amendment #6:  25 April 2019
Amendment #7:  03 October 2019

IND Holder:  Roswell Park Cancer Institute

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Sponsor:  Roswell Park Cancer Institute

Industry/Other Supporter:  Merck & Co., Inc.
## SYNOPSIS

<table>
<thead>
<tr>
<th>Title / Phase</th>
<th>A Phase II Evaluation of Pembrolizumab in Combination with IV Bevacizumab and Oral Metronomic Cyclophosphamide in the Treatment of Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer.</th>
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<tr>
<td>Roswell Park Cancer Institute Investigator</td>
<td>Emese Zsiros, MD PhD</td>
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<td>Industry/ Other Supporter</td>
<td>Merck &amp; Co., Inc.</td>
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| Study Drug(s) | Pembrolizumab  
Bevacizumab  
Cyclophosphamide |

### Objectives

**Primary:**
- To evaluate improvement in progression-free survival for patients treated with anti-PD1 pembrolizumab in combination with IV bevacizumab and oral metronomic cyclophosphamide as compared to a historical control.

**Secondary:**
- To obtain pilot data on clinical response rates using both RECIST1.1 criteria (Response Evaluation Criteria in Solid Tumors) and immune related response criteria (irRECIST).
- To obtain data on changes in tumor microenvironment prior to and subsequent to therapy and, to screen for potential biomarkers to predict clinical benefit.
- To determine the safety and tolerability of the treatment combination in the study population.
- To evaluate overall survival in patients treated with anti-PD1 pembrolizumab in combination with IV bevacizumab and oral metronomic cyclophosphamide.
- To assess the impact of the combination of anti-PD1 pembrolizumab, IV bevacizumab and oral metronomic cyclophosphamide on anti-tumor immune responses in ovarian cancer.

### Study Design

This is an open label Phase II study (with a safety lead-in cohort of n=5) of anti-PD1 antibody pembrolizumab, in combination with IV bevacizumab and oral metronomic cyclophosphamide in patients with recurrent platinum sensitive, resistant or refractory epithelial ovarian, fallopian tube, or primary peritoneal cancer.

### Target Accrual and Study Duration

The study will enroll approximately 40 evaluable patients in total. Accrual is expected to take 18 months.
### Study Procedures

**Disease Evaluation:** CT at Baseline, after 3rd cycle, after 6th cycle then, after every 6th cycle (or sooner if disease progression)

**Adverse Events:** Day 1 of each cycle, end of treatment, safety follow-up.

**Hematology:** Baseline, Day 1 of each cycle, end of treatment, safety follow-up

**Chemistry:** Baseline, Day 1 of each cycle, end of treatment, safety follow-up

**Performance Status:** Baseline, Day 1 of each cycle, end of treatment, post treatment evaluations

**Full Physical Examination (including basic neurological examination, vital signs, and body weight):** Baseline, Day 1 Cycle 1, Day 1 of every 3rd cycle, end of treatment, post treatment evaluations

**Directed Physical Examination (including basic neurological exam, vital signs, and body weight):** On cycles not requiring a full physical examination (e.g. cycles 2 and 3, cycles 5 and 6)

**Vital Signs:** Baseline, Day 1 of each cycle, end of treatment, post treatment evaluations

**Pregnancy test:** Within 72 hours prior to receiving first dose of study treatment in patients of childbearing potential

**PT/INR and APTT:** Baseline, Cycle 6 Day 1, Cycle 12 Day 1, end of treatment, safety follow-up.

**Urinalysis:** Baseline, Cycle 1 Day 1, every 2nd cycle after Cycle 1, end of treatment.

**UPCR Ratio:** Baseline, Cycle 1 Day 1 and, Day 1 of every 2nd cycle.

**T3, FT4, and TSH:** Baseline, Cycle 3 Day 1 then Day 1 of every 3rd cycle, end of treatment, safety follow-up

**Tissue Biopsy:** Baseline, 2-3 weeks after Cycle 3, end of treatment (optional)

**Blood Collection (correlative studies):** Baseline (within 2 weeks prior to treatment initiation), Cycle 2 – Day 1, Cycle 4- Day 1, Cycle 7- Day 1, Cycle 10 –Day 1, and at the end of study treatment or at time of discontinuation (within two weeks after the last treatment cycle is completed) or, at the time of disease progression or for any other reason that requires study treatment termination, whichever occurs sooner.

On those patients, who have already completed 10 cycles, the one additional correlative blood sample will be collected at the time of their next cycle.

**Study Questionnaires:**
- EORTC QLQ-C30 and EORTC QLQ-OV28: Cycle 1- Day 1, Cycle 4-Day 1, Cycle 7 – Day 1, Cycle 10 –Day 1, End of Treatment (or time of discontinuation)
Sample Size Determination:
The primary objective of the Phase II study is to evaluate the progression-free survival (PFS) for patients treated with pembrolizumab in combination with IV bevacizumab and oral metronomic cyclophosphamide in women with recurrent/persistent platinum-sensitive, -resistant, or -refractory ovarian, primary peritoneal, or fallopian tube cancers. The median PFS of platinum resistant ovarian cancer patients treated with standard chemotherapy is approximately 3.5 months. In a recent study platinum-resistant ovarian cancer patient treated with a combination of IV bevacizumab and oral metronomic cyclophosphamide had a median PFS and overall survival (OS) of 4.5 and 10.7 months, respectively. In another study, patients with recurrent ovarian cancer treated with bevacizumab plus low-dose metronomic oral cyclophosphamide had a median response duration of 3.9 months. Therefore, we would consider a PFS of 7 months or greater to be of interest in this population.

Consider a sample size of n=40 patients, with up to 1 year of follow-up, and a maximum drop-out rate of 10%. If the true 7-month PFS rate is 50% (a median PFS of 7 months) for the proposed treatment combination, then a one-sided Wald-type test has approximately an 86.1% chance of resulting in significance. A nominal significance level of 10% is considered.

Safety Analysis: The frequency of toxicities will be tabulated by grade across all dose levels and cycles. Toxicity rates will be estimated using 90% confidence intervals, which will be obtained using Jeffreys prior method. All participants who receive any study treatment will be considered evaluable for toxicity.

The overall and progression free survival will be summarized using standard Kaplan-Meier methods, with estimates of median survival and given survival rates will be obtained with 90% confidence intervals.

Safety Lead-in Cohort: A safety lead-in cohort of n₁=5 patients will be enrolled, and the safety/tolerability of the combination will be examined after each patient completes at least 3 cycles. If 2 or less patients have experienced a drug related toxicity requiring drug/treatment delay or suspension (as defined in Sections 6.4, 6.5, and 6.7.3), then an additional n₂=35 patients are enrolled to complete the Phase II study. Otherwise, the study will be suspended, and the research team will meet to discuss possible safety concerns and will decide what actions to take with respect to study continuation.

Efficacy Analysis: The overall and progression free survival will be summarized using standard Kaplan-Meier methods, with estimates of median survival and given survival rates will be obtained with 90% confidence intervals.

Objective tumor response will be tabulated for all patients that completed at least three cycles of the proposed treatment.
combination. The response rate will be estimated using 90% confidence intervals, obtained using Jeffrey’s prior method.

**Correlative Data Analysis:** The blood and tumor samples will be collected as biomarkers and will be reported using the appropriate descriptive statistics depending on clinical outcome. Associations between these markers and PFS will be evaluated using Cox regression models; while associations with tumor response will be evaluated using logistic regression models.
INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM

Participant Name: ________________________________________________________________

Medical Record No.: ____________________________________________________________

Title: A Phase II Evaluation of Pembrolizumab in Combination with IV Bevacizumab and Oral Metronomic Cyclophosphamide in the Treatment of Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

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<th>Yes</th>
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<th>All answers must be “Yes” or “N/A” for participant enrollment.</th>
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<td>1. Age ≥ 18 years of age on day of signing informed consent</td>
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<td>2. Have an ECOG Performance Status of 0 or 1 (Refer to Appendix A)</td>
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<td>3. Have measurable disease per RECIST 1.1 or irRECIST criteria present.</td>
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|     |    |     | 4. Participant may have serous, endometrioid, clear cell, mucinous or undifferentiated type of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.  
  o Histologic confirmation of the original primary tumor is required via the pathology report. |      |
|     |    |     | 5. Participant can be either platinum-sensitive (platinum free interval (PFI) ≥ 6 months prior to recent recurrence) or platinum-resistant (PFI < 6 months prior to recent recurrence. If the participant has a platinum sensitive disease, she may only enroll in this clinical trial if there is a contraindication for her to receive further treatment with platinum-based chemotherapy (such as serious persistent toxicity or severe hypersensitivity to platinum agents or she declines standard of care). |      |
|     |    |     | 6. Participant must be willing to undergo core or excisional biopsy of a tumor lesion within 4 weeks (28 days) prior to initiation of treatment on Day 1 and, after 3 cycles of study treatment. Participants for whom newly obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the Principal Investigator. |      |
|     |    |     | 7. Have the following clinical laboratory values:  
  • Absolute neutrophil count (ANC): ≥ 1,500/mcL  
  • Platelets: ≥ 100,000/mcL  
  • Hemoglobin: ≥ 9 g/dL or 5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)  
  • Serum creatinine: ≤1.5 X upper limit of normal (ULN) OR measured or calculated creatinine clearance ≥ 60 mL/min for participant with creatinine levels > 1.5 X institutional ULN (refer to Appendix B). GFR can also be used in place of creatinine or CrCl.  
  • Urine Protein Creatine Ratio (UPCR) < 1 prior to starting cycle 1 (refer to Appendix C). |      |
# INCLUSION CRITERIA

All answers must be “Yes” or “N/A” for participant enrollment.

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

9. Participants of childbearing potential must be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (participants of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year). Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately.

10. Participant has recovered from toxicities of prior chemotherapy or other therapy (to grade 2 or less).

11. Participant may have received prior investigational therapy (including immune therapy).

12. Participant may have received prior hormonal therapy.

13. Participant may have received bevacizumab (or another antiangiogenic agent) and/or cyclophosphamide in the past.

14. Participant has had at least 4 weeks of postoperative recovery from surgery prior to enrollment to ensure complete wound healing. Participants with bowel resections at surgery should begin protocol at least 42 days after surgery.

15. Ability to swallow and retain oral medication.

16. Participant or legal representative must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.

Participant meets all entry criteria:  

☐ Yes  ☐ No

If “NO”, do not enroll participant in study.
INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM

Participant Name: ____________________________________________________________

Medical Record No.: __________________________________________________________

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<td>1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.</td>
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<td>2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment or, is taking any other medication that might affect immune function.</td>
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<td>3. Has a known history of active TB (Bacillus Tuberculosis).</td>
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<td>4. Hypersensitivity to bevacizumab, cyclophosphamide, pembrolizumab or any of its excipients.</td>
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<td>5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.</td>
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<td>6. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent. <strong>Note:</strong> Participants with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study. <strong>Note:</strong> If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy and, has to be at least 28 days after the surgery.</td>
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<td>7. Has a known additional malignancy that is progressing or requires active treatment: exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or cervical cancer in situ that has undergone potentially curative therapy.</td>
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<td>8.</td>
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<td>Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.</td>
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<td>9.</td>
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<td>Has active autoimmune disease that has required systemic treatment in the past 6 months (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.</td>
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<td>10.</td>
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<td>Has known history of, or any evidence of active, non-infectious pneumonitis.</td>
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<td>11.</td>
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<td>Has an active infection requiring systemic therapy.</td>
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<td>12.</td>
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<td>Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the participant’s participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating investigator.</td>
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<td>13.</td>
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<td>Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.</td>
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<td>14.</td>
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<td>Is pregnant or breastfeeding or expecting to conceive within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.</td>
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<td>15.</td>
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<td>Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.</td>
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<td>17.</td>
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<td>Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).</td>
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<td>Has received a live vaccine within 30 days of planned start of study therapy. <strong>Note:</strong> 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.</td>
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<td>19.</td>
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<td>Active or history of inflammatory bowel disease (colitis, Crohn's), diverticulitis, irritable bowel disease, celiac disease, or other serious, chronic, gastrointestinal conditions associated with diarrhea. Active or history of systemic lupus erythematosus or Wegener's granulomatosis.</td>
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<td>20. Participant has clinical symptoms or signs of partial or complete gastrointestinal obstruction or, requires parenteral hydration and/or nutrition.</td>
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<td>21. Participant requires, or is likely to require, more than a two-week course of corticosteroids for intercurrent illness. Participant must complete the course of corticosteroids 2 weeks before screening to meet eligibility.</td>
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<td>22. Participant has a serious, non-healing wound, ulcer, or bone fracture.</td>
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|    |     |     | 23. Participant has a clinically significant cardiovascular disease including:  
  - Uncontrolled hypertension, defined as systolic > 150 mmHg or diastolic > 90 mmHg  
  - Myocardial infarction or unstable angina within 6 months prior to enrollment  
  - New York Heart Association (NYHA) Grade II or greater congestive heart failure (refer to Appendix F)  
  - Participant has a grade II or greater peripheral vascular disease  
  - Participant has a clinically significant peripheral artery disease (e.g. those with claudication, within 6 months) |      |
|    |     |     | 24. Participant has organ allografts. |      |
|    |     |     | 25. Participant is receiving medication(s) that might affect immune function. |      |
|    |     |     | 26. Unwilling or unable to follow protocol requirements. |      |

Investigator Signature: ___________________________ Date: __________

Printed Name of Investigator: ___________________________
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1 BACKGROUND

1.1 Advanced Solid Tumors and Immunotherapy

Despite advances in surgery and chemotherapy over the past two decades, epithelial ovarian cancer (EOC) is still the leading cause of death from gynecologic cancer in the United States. Most ovarian cancer patients present with advance stage disease at the time of the diagnosis, and although most of them respond to first-line chemotherapy, these responses are not durable, and the majority of these women will die of their disease. The clinical course of ovarian cancer patients is marked by periods of remission and relapse of sequentially shortening duration until chemotherapy resistance develops or significant toxicity occurs. Second line chemotherapies achieve very limited clinical benefit; therefore, there is an enormous unmet need for the development of novel therapies.

Recent scientific evidence demonstrated that EOC is an immunogenic tumor that can be recognized by the host immune system, and the increased infiltration of cytotoxic T cells in tumor islets correlates with significantly longer survival (1, 2), while increased numbers of immunosuppressive cells such as CD4\(^+\)CD25\(^+\)FoxP3\(^+\) regulatory T cells (Tregs) or B7-H4 expressing tumor macrophages predict poor survival (2-4). T cell responses to multiple antigens overexpressed by ovarian cancers, such as folate receptor α (FRα), New-York-esophageal-1 (NY-ESO-1), p53, human epidermal growth factor receptor 2 (Her2)/neu, survivin, sperm surface protein Sp17, WT1, MUC1, melanoma associated antigen-3 (MAGE3), human telomerase reverse transcriptase (hTERT) and insulin-like growth factor binding protein-2 have been described in several studies, which further supports the rationale for immunotherapy in ovarian cancer (5-7).

The success of immunotherapy however heavily depends on the homing ability of cytotoxic T lymphocytes (CTLs) into tumors, which is a complex multistep process involving adhesive interactions with vascular cells and migration within the stroma. Much of this process is regulated by tumor endothelial cells (EC) and chemotactic gradients within the tumor microenvironment (8, 9). Even in case of successful CTL infiltration, antitumor immunity is counterbalanced by an immune-suppressive microenvironment, constituted in part by tumor cells, Tregs and tolerance-inducing myeloid cells.

Harnessing the immune system to treat cancer is the major goal of immunotherapy. Although the identification of several tumor-specific antigens in ovarian cancer has provided the foundation for designing successful immunotherapies, immune cells still have to overcome the immune escape of the tumor or cancer immunoediting. The mechanisms for immunomodulation (therapeutic intervention aimed at modifying the body's immune response) in ovarian cancer include activation of professional antigen-presenting cells (APCs) by engaging costimulatory receptors (such as CD40), activation of effector T lymphocytes by immunostimulatory monoclonal antibodies (mAb), improving effector T cell homing by normalizing tumor vasculature and finally depletion of Tregs or immunosuppressive machineries. All of these components are essential to achieve meaningful clinical outcome.

Thus, a renewed emphasis on immunotherapy has emerged over the last several years with the development and testing of a novel class of immunotherapeutic agents called checkpoint inhibitors. The use of immune checkpoint inhibitors, which work by targeting molecules that serve as checks and balances in the regulation of immune responses, might be a promising avenue of immunotherapeutic research in ovarian cancer. Checkpoint inhibitor immunotherapy is still in early-phase testing for ovarian cancer. Understanding the pivotal role of
the tumor microenvironment in suppressing anticancer immunity, the unique adverse effects profiles of these agents, and the exploration of combinatorial treatment regimens will ultimately lead to enhance the efficacy of ovarian cancer immunotherapies and improved patient care (10).

1.2 Antiangiogenic Therapy Improves Immune Therapy

Targeting tumor angiogenesis is an important complementary approach to improve outcomes of patients with solid tumors (11). Tumor neovasculature is characterized by disruption of intercellular adhesion between EC and disorganization of supportive pericytes, which results in increased permeability and effusion formation (ascites in ovarian cancer) as well as in release of tumor cells into lymphatic and vascular spaces (12, 13). Currently the VEGF pathway is the most widely studied angiogenic pathway in carcinogenesis, and is comprised of VEGF-A (also known as VEGF) and the two receptor tyrosine kinases, VEGFR1 and VEGFR2 (14). VEGF was first recognized as an adverse factor in ovarian cancer in the 1990s as patients with increased VEGF expression in early stage ovarian cancer were shown to have significantly worse clinical outcome (15).

Since then we understand that tumor EC often use VEGF to establish a substantial barrier to limit T cell infiltration as VEGF deregulates vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) on EC, thus impedes T cell extravasation (16, 17). Blockade of VEGF has been shown to increase the amount of T cell infiltration in tumors, thus dismantling this tumor endothelial barrier is crucial to improve T cell trafficking to tumor microenvironment (18).

Besides modulating lymphocyte endothelial trafficking VEGF also has profound effects on immune regulatory cell function, specifically inhibiting DC maturation and antigen presentation via VEGFR-1 (19-22) VEGF blockade was shown to restore DC function and enhance immunotherapy (11, 23).

Also in recent studies selective expression of the death mediator Fas ligand (FasL, also called CD95L) was described in the vasculature of human and mouse solid tumors but not in normal vasculature (24, 25). In these tumors, FasL expression was associated with scarce CTL infiltration and a predominance of Tregs (24). Tumor-derived VEGF-A, interleukin 10 (IL-10) and prostaglandin E2 (PGE2) cooperatively induced FasL expression on tumor EC, which was shown to kill effector CTLs but not Tregs because of their higher levels of c-FLIP expression (26). In mice pharmacologic and genetic inhibition of VEGF-A (with bevacizumab) produced a marked increase in the influx of tumor-rejecting CD8+ CTLs over FoxP3+ Tregs that was dependent on attenuation of FasL expression and led to CD8-dependent tumor growth suppression (26).

Current anti-angiogenic therapy using bevacizumab, or other second-generation multitargeted receptor tyrosine kinase inhibitors (RTKIs) such as sunitinib,(27-29) sorafenib (30, 31), or pazopanib (32), improves PFS for a period of time in most types of cancer, but the anti-tumor effects of these drugs are short-lived. Most patients who initially respond will eventually develop drug resistance, tumor recurrence, or metastases indicating that anti-angiogenic therapy alone are not sufficient to prevent tumor progression and cancer metastasis in a long run (33-37). Their modest efficacy is most likely a result of redundant and complementary angiogenic pathways, such as platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), and other pathway that compensate for VEGF blockade and allow angiogenesis to occur despite anti-VEGF treatment (37). Hypoxia induced by anti-angiogenesis therapy also modifies some of the signaling pathways in tumor and stromal cells, which could further contribute to
resistance to therapy (38). In the clinical setting improvements achieved in PFS do not translate to OS benefits for the majority of cancer patients, thus combination of antiangiogenic drugs are necessary to enhance their efficacy.

1.3 PD-1 and PD-L1 Background

1.3.1 PD-1 and PD-L1 Pharmaceutical and Therapeutic Background

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors: Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.
1.3.2 PD-1 and PD-L1 Blockade in Ovarian Cancer

Programmed cell death 1 and its ligand (PD-1-PD-L1) is expressed in many ovarian cancer patients and showed the closest relation to unfavorable prognosis among other immunosuppressive molecules that have been tested in ovarian cancer (39). Checkpoint blocking antibodies, such as those directed against cytotoxic T-lymphocyte antigen 4 (CTLA-4) and PD-1, have demonstrated significant recent promise in the treatment of an expanding list of malignancies, and each plays a non-redundant role in modulating immune responses (40). CTLA-4 attenuates the early activation of naïve and memory T cells, while PD-1 is primarily involved in modulating T cell activity in peripheral tissues via interaction with its ligands, PD-L1 and PD-L2 (40, 41). The blockade of PD-1 or PD-L1 was shown to enhance T-cell function and tumor cell lysis in the tumor microenvironment (42), however has limited effect as a monotherapy as peripheral tolerance is also highly depended on the on tumor endothelial death barrier and CTL infiltration to tumor microenvironment. Thus, efforts to further enhance the efficacy of immune checkpoint blockade through rational treatment combinations are needed.

1.4 Pembrolizumab

Pembrolizumab (formerly MK-3475) 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.

Upon administration, pembrolizumab binds to PD-1, an inhibitory signaling receptor expressed on the surface of activated T cells and blocks the binding to and activation of PD-1 by its ligands, which results in the activation of T-cell-mediated immune responses against tumor cells. The ligands for PD-1 include PD-L1, which is expressed on antigen presenting cells (APCs) and overexpressed on certain cancer cells, and PD-L2, which is primarily expressed on APCs. Activated PD-1 negatively regulates T-cell activation through the suppression of the PI3K/Akt pathway.

Pembrolizumab (Keytruda™) has recently been approved in the United States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

1.4.1 Preclinical and Clinical Studies with Pembrolizumab

A detailed discussion of the preclinical and clinical pharmacology, pharmacokinetics, and toxicology of pembrolizumab can be found in the Investigator’s Brochure.

1.5 Bevacizumab

Bevacizumab (Avastin®) is a recombinant humanized monoclonal antibody that neutralizes VEGF and blocks its signal transduction through both VEGFR-1 and VEGFR-2 as demonstrated by the inhibition of VEGF-induced cell proliferation, survival permeability, nitric oxide production, migration and tissue factor production (43).

The FDA approved bevacizumab as a first-line treatment for patients with unresectable metastatic colorectal cancer in 2004, after a randomized double-blind phase III clinical trial demonstrated significant survival benefit in those patients treated with the addition of bevacizumab to irinotecan, 5-fluorouracil, and leucovorin (44).
1.5.1 Bevacizumab and Ovarian Cancer

In early phase II trials in ovarian cancer patients bevacizumab yielded single-agent activity beyond that was seen in colorectal or lung cancer (45). The median PFS was 4.7 months, which was statistically superior (p< .0001) to median PFS of 1.8 months for a historical cohort of more than 300 similar patients entered onto previous GOG phase II trials of inactive cytotoxic agents. Clinical response rate was 18% (5% complete response) with median response duration of 10.5 months. An additional 55% had stable disease. Single-agent bevacizumab was well tolerated with no hematologic events of grade 3 or higher (45).

To date, four phase III randomized clinical trials testing bevacizumab in ovarian cancer have been published.

In later clinical trials the use of bevacizumab added significant clinical benefit when combined with standard chemotherapy in four randomized, double-blind, phase III trials, both as front-line treatment (GOG-0218 and ICON7) and in patients with recurrent disease (OCEANS and AURELIA) (46, 47).

In two pivotal, well designed, phase III, clinical trials (GOG-0218 and ICON7) in women with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer, first-line treatment with bevacizumab in combination with standard chemotherapy (carboplatin plus paclitaxel) followed by maintenance treatment with bevacizumab alone significantly prolonged progression-free survival (by 3.8 months in GOG-0218 in the concurrent and maintenance arm and by 5.4 months in ICON-7 in patient with high risk for recurrence) relative to standard chemotherapy. Overall survival did not differ significantly between patients receiving standard chemotherapy plus placebo maintenance and those receiving concurrent plus maintenance bevacizumab in any of these trials – in GOG-0218 median OS 39.3 vs 39.7 and 38.7 months vs ICON-7 58.6 vs. 58.0 months respectively (47-49).

OCEANS (50) was a randomized phase III trial testing the combination of carboplatin and gemcitabine with or without the addition of bevacizumab given concurrently and then as maintenance until progression in recurrent platinum-sensitive EOC. PFS for the bevacizumab arm was 12.4 months (vs. 8.4 months in the placebo group; p < .001). By the final analysis, however, there was no difference in overall survival (OS; 33.6 vs. 32.9 months). Of note, nearly all of the women in both arms went on to receive additional therapy, including bevacizumab.

In the AURELIA trial (51), bevacizumab was combined with the investigator’s choice of single-agent chemotherapy (pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan), in platinum-resistant EOC. The addition of bevacizumab improved PFS (6.7 vs. 3.4 months) and response rate, but there was no significant difference in OS (16.6 vs. 13.3 months; p < .17). Crossover to single-agent bevacizumab was permitted after progression with chemotherapy alone. AURELIA was the first phase III trial to show a benefit with combination therapy in the platinum-resistant population and is the basis for the drug FDA approval in EOC.

Bevacizumab was recently FDA approved for use in combination with single-agent chemotherapy for platinum-resistant disease; however, its optimal role in this cancer remains unclear. Although bevacizumab has activity in many patients with EOC, trials have identified neither the optimal setting for treatment nor a predictive biomarker. The lack of a proven OS survival benefit does not necessarily speak against the drug’s efficacy and the median survival in EOC is longer than in many other solid tumors; therefore, OS data can be confounded by subsequent lines of therapy.
A detailed discussion of the preclinical pharmacology, pharmacokinetics, and toxicology of bevacizumab can be found in the Package Insert (http://medlibrary.org/lib/rx/meds/avastin-1/).

1.6 Cyclophosphamide

Besides the normalization of tumor vasculature to improve CTL homing, alteration of Tregs is also crucial in regulating anticancer immune responses. The increased presence of Tregs is associated with poor prognosis in ovarian cancer, while the ability to selective eliminate these cells has been repeatedly shown to bolster immune responses in preclinical cancer models. Tregs not only suppress cognate T cell responses but also blunt the innate arm of immunity, inhibiting NK cell proliferation and effector functions through the capacity to down regulate NKG2D level on these cells, thus associated with poor prognosis in cancer patients (52).

Cyclophosphamide is widely available, inexpensive and has multiple immune-modifying properties. Oral metronomic cyclophosphamide and VEGF blockade have independently been reported to selectively reduce the subset of immunosuppressive Tregs in vivo (53, 54). Metronomic chemotherapy refers to the close, regular administration of a chemotherapeutic drug at relatively low (non-toxic) doses, over prolonged periods, with no extended drug-free break periods (53, 55).

Oral administration of metronomic cyclophosphamide in advanced cancer patients induces a profound and selective reduction of circulating Tregs, associated with a suppression of their inhibitory functions on conventional T cells and NK cells leading to a restoration of peripheral T cell proliferation and innate killing activities (56). Cyclophosphamide also interferes with homeostatic proliferation of Tregs, increases their susceptibility to apoptosis, and impairs Treg functionality by decreasing the expression of suppression markers, such as glucocorticoid-induced TNF receptor–related protein (GITR) and FoxP3 (56-58).

Furthermore it was also shown that high-avidity tumor specific CD8+ T cells are not deleted in the periphery with the use of cyclophosphamide, instead, these high-avidity T cells can be recruited and activated to provide a potent antitumor immune response if Tregs are inhibited, which further validates the addition of cyclophosphamide to enhance immunotherapy (59).

Therefore, metronomic regimen of cyclophosphamide does not only affect tumor angiogenesis but also strongly curtails immunosuppressive regulatory T cells; favoring a better control of tumor progression, thus represent a critical immuno-intervention in the oncologist’s armamentarium.

1.6.1 Rational for Combining Bevacizumab with Cyclophosphamide in Ovarian Cancer

As already discussed above, bevacizumab mainly has clinical benefit in patients who have advanced metastatic disease only or primarily when it is combined with conventional chemotherapy. The exact mechanisms for the chemo-enhancing effects of bevacizumab are still unknown, but this has been investigated along with other antiangiogenic drugs that could be combined with traditional chemotherapy or immunomodulating agents to improve clinical response (60).

Treatment combinations of metronomic chemotherapy and an antiangiogenic drug have moved into phase II clinical trial testing with particularly encouraging results thus far reported in metastatic breast and recurrent ovarian cancer. Oral chemotherapy drugs such as cyclophosphamide and methotrexate are the main chemotherapeutics used for such trials.

There are already several studies in ovarian cancer which showed that the combination of IV bevacizumab (15 mg/kg every 3 weeks) and low dose metronomic oral cyclophosphamide (50 mg)
is an effective, well-tolerated chemotherapy regimen in heavily pretreated patients with recurrent ovarian carcinoma and this combination significantly improved PFS and OS in responders (61, 62). Response rates were more favorable to the rates reported for similar patients receiving other commonly used second-line chemotherapeutic agents or just bevacizumab or cyclophosphamide alone, showing an objective response rate between 40.5-53.5% with approximately 10% of patients in each series demonstrating a complete response (61, 63-65). The reported severe adverse events in these studies were around 1-1.5%, the regimen was overall very well tolerated with only about 10% of patients encountering a side effect that required discontinuing treatment (46, 61, 63, 65). Also the median PFS reported in these studies in patients with recurrent ovarian cancer ranged from 3.9 months to 5.0 months (61, 63-65).

Therefore, the combination of bevacizumab and low dose metronomic oral cyclophosphamide is active in recurrent ovarian cancer with improved clinical outcomes; hence the combination of these drugs is warranted.

1.7 Risks and/or Benefits

1.7.1 Pembrolizumab

The most common adverse reactions (reported in ≥ 20% of patients) to pembrolizumab (KEYTRUDA®) include fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia and, diarrhea. Refer to package insert for additional information (http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125514lbl.pdf).

Pembrolizumab is generally well tolerated and demonstrates a favorable safety profile in comparison to chemotherapy. Pembrolizumab is an immunomodulatory agent, and based on this mechanism of action, immune mediated adverse events are of primary concern. Important identified risks for pembrolizumab are of an immune mediated nature, including pneumonitis, colitis, thyroid disorders (hypothyroidism/ hyperthyroidism), hepatitis, hypophysitis, Type I diabetes mellitus, uveitis, and nephritis.

After a recent review of data, events newly characterized as identified risks also include pancreatitis, myositis, and severe skin reaction; these are included in the reference safety information (refer to IB).

The majority of immune-mediated adverse events were mild to moderate in severity, were manageable with appropriate care, and rarely required discontinuation of therapy. Further details around frequency, reporting, and management of immune-related adverse events (irAEs) are described in the Investigator’s Brochure. In addition to the previously noted identified risks, infusion-related reactions are a risk but are not considered immune mediated see Section 10.2).

1.7.2 Bevacizumab

As VEGF plays an important role in normal physiologic processes – such as stabilization of damaged endothelia and wound healing – thus the inhibition of VEGF carries a unique toxicity profile (66). Bevacizumab in general is well tolerated in all patients. The most common toxicities associated with bevacizumab includes mucosal bleeding, hypertension (HTN), proteinuria and wound healing complications, however these adverse events are generally manageable (67). New-onset HTN and exacerbation of existing HTN are the most commonly reported adverse events attributable to bevacizumab. In randomized trials, the incidence of grade 3/4 HTN in bevacizumab-treated patients ranged from 3.0% to 14.8% compared with 0% to 2.0% for controls (68).
Bevacizumab related proteinuria is typically mild in severity and non-dose-limiting, but it can rarely escalate to nephrotic syndrome. The incidence of grade 3/4 proteinuria in bevacizumab-receiving arms in meta-analysis of 1850 patients treated in seven randomized trials reported statistically significant relative risks of proteinuria equal to 1.4 with low-dose bevacizumab and 2.2 at higher doses (68).

The delay of wound healing, wound dehiscence, fistula, and abscess has been reported in patients receiving bevacizumab. Because of the long half-life of bevacizumab (~20 days), the risk of wound-healing complications persist even after its discontinuation (66). A pooled analysis of two randomized metastatic colorectal cancer trials found no difference in the rate of wound-healing complications in bevacizumab-treated patients and controls, when bevacizumab was given at least 28 days following major surgery; however patients who underwent major surgery while receiving bevacizumab had a wound-healing complication rate of 13% compared to 3.4% in controls (69).

GOG-0218 and ICON7 did not show increased wound-healing complications in women with ovarian cancer, although most participants were not surgical candidates (45, 70). GOG-0218 protocol also delayed the administration of bevacizumab or placebo until the second cycle of chemotherapy, regardless of the timing of primary debulking surgery. In the Bevacizumab Regimens’ Investigation of Treatment Effects (BRiTE) registry, 622 patients had surgery after starting bevacizumab therapy; 23 (3.7%) wound-healing complications were reported, occurring more often in patients undergoing major abdominal surgeries < 60 days following the last bevacizumab dose (69, 71). According to the BRiTE registry (71) and another study by Scappaticci (69), the optimal interval between the last bevacizumab dose administered and subsequent major surgery is generally considered to be 60 days.

The previously reported rare life-threatening complication related to bevacizumab treatment in non-gynecologic tumors included hemorrhagic complications such as gastrointestinal (GI) perforations (2.4%) and arterial and venous thromboembolic events (ATE) (3%) (Genentech BioOncology, 2006). Of these, GI perforations have been observed in ovarian cancer in 5.4% of the patients (67). Identification of clinical risk factors for bevacizumab-related GI perforations minimizes the incidence of this adverse event as the majority of events occurred in patients with at least one of the following characteristics: acute diverticulitis, intra-abdominal abscess, GI obstruction, tumor at the GI perforation site, carcinomatosis, or prior radiation therapy (66).

Venous thromboembolism (VTE) has been reported in many bevacizumab trials, VTE incidence rates in bevacizumab-treated patients that were not statistically different from those seen in controls. The incidence of VTE in phase II ovarian studies was relatively low (2% to 3%) (45).

The rates of both arterial thromboembolism and hemorrhage are increased in patients receiving bevacizumab therapy. Under normal conditions, VEGF mediates the repair of endothelial surfaces that have sustained damage secondary to cardiovascular disease and other microangiopathies (72). This results in exposed subendothelial tissues that initiate the clotting cascade and subsequent clot formation. The underlying prothrombotic state characteristic of cancer patients might exacerbate this process. Though somewhat counterintuitive, the mechanism leading to hemorrhage might also result from a lack of endothelial repair in areas where subendothelial tissues are violated by pathophysiologic processes that may or may not be related to the malignancy.
**Hemorrhage**: The incidence of hemorrhage is increased with bevacizumab therapy. Epistaxis is common, occurring in 20-40% of patients, but it is generally mild and rarely requires medical intervention. Life-threatening and fatal hemorrhagic events have been observed in bevacizumab studies and included pulmonary hemorrhage, CNS bleeding and gastrointestinal (GI) bleeding. In a phase 2 study in non-small cell lung cancer, 6 cases of life-threatening hemoptyisis or hematemesis were reported among 66 patients treated with bevacizumab and chemotherapy; 4 of these events were fatal In the pivotal phase 3 trial in advanced colorectal cancer, the rate of GI hemorrhage (all grades) was 24% in the IFL/bevacizumab arm compared to 6% in the IFL arm; grade 3-4 hemorrhage was 3.1% for IFL/bevacizumab and 2.5% for IFL. Serious GI hemorrhage has also been observed in clinical trials with bevacizumab in patients with pancreatic cancer or varices treated with bevacizumab.

The incidence of **arterial thromboembolic (ATE)** events – such as transient ischemic attacks, cerebral infarction, unstable angina, troponin elevation, and acute myocardial infarction – has been reported to be slightly higher in bevacizumab-treated patients compared to controls (4.4% vs 1.9%) (73, 74). Risk factors for ATE identified in this analysis included age ≥ 65 years, male sex, and history of ATE. Ovarian cancer studies reported similarly low incidences of ATE (0% to 3%) (66, 67, 74).

All patients on bevacizumab should be considered at risk for ATEs, and extra caution should be exercised when prescribing bevacizumab to those > 65 years old with a history of ATE or conditions which predispose them to ATE. There is no modification, aside from discontinuation of therapy, known to be more effective than standard medical treatment for bevacizumab associated ATE events. As with all bevacizumab-related adverse events, the continuation of bevacizumab in specific situations in which bevacizumab benefit was either greater than the severity of toxicity or underlying predisposing factors were reversible (e.g., cardiac revascularization) might be considered, though overall prognosis might preclude such risks.

**Reversible posterior leukoencephalopathy syndrome (RPLS)** is a rare neurological disorder that has been reported in association with HTN, eclampsia, and various states of immunosuppression due to organ transplant, chemotherapy – including bevacizumab, or autoimmune disorders. RPLS can present with headache, seizure, lethargy, confusion, blindness, and other visual and neurologic disturbances, which can occur at any interval following bevacizumab administration. The mechanistic link between bevacizumab and RPLS is unknown, but RPLS not associated with bevacizumab involves loss of cerebral vascular autoregulation, disruption of the cerebral tissue/capillary interface, and vasogenic edema. There is no specific treatment for RPLS outside of confirming the diagnosis, providing supportive care, which includes aggressive management of HTN, and discontinuing bevacizumab therapy.

In summary, bevacizumab is the first biologic therapy targeted at tumor pathophysiology to show significant activity in ovarian cancer with acceptable added toxicity. The adverse events associated with bevacizumab, however, are specific to its biologic effects and are potentially serious, even fatal.

### 1.7.3 Cyclophosphamide

Common adverse reactions to cyclophosphamide include neutropenia, febrile neutropenia, fever, alopecia, nausea, vomiting and, diarrhea. Refer to package insert for additional information ([http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/040745Orig1s003lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/040745Orig1s003lbl.pdf)).
2 RATIONALE

2.1 Rationale for Dose Selection/Regimen/Modification for Pembrolizumab

An open-label Phase I trial (KEYNOTE 001) is completed, evaluating the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated, and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date.

Recent data from other clinical studies within the pembrolizumab program has shown that a lower dose of pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

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

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

The above data indicate that the proposed fixed dose regimen for pembrolizumab of 200mg Q3W in the current study is similar to the 10 mg/kg Q2W dose regimen, with regard to efficacy and tolerability (refer to Investigator’s Brochure, section 5.4.1.3: Overall Adverse Events: P102, A Phase Ib Study of Pembrolizumab in Patients with Advanced Solid Tumors).

2.2 Rationale for Endpoints

According to the design schema the estimated sample size is 40 patients overall. Noting that the median PFS of platinum-resistant ovarian cancer patients treated with standard chemotherapy is 3.5 months, we would consider a PFS of 7 months or greater to be of interest in this population. We expect that no more than 30% of patients treated with standard chemotherapy would achieve 7 months of PFS. Therefore, we will test the null hypothesis that the PFS response to: Pembrolizumab 200 mg IV + bevacizumab 15 mg/kg every 3 weeks IV + cyclophosphamide 50 mg po every day combination therapy is equal to 30% versus the one-sided hypothesis that it is greater than 30%. Please see section 8.0 for more detailed information on statistical analysis.
3 **OBJECTIVES**

3.1 **Primary Objectives**
- To evaluate improvement in progression-free survival for patients treated with anti-PD1 pembrolizumab in combination with IV bevacizumab and oral metronomic cyclophosphamide as compared to a historical control.

3.2 **Secondary Objectives**
- To obtain pilot data on clinical response rates using both RECIST1.1 criteria (Response Evaluation Criteria in Solid Tumors) and immune related response criteria (irRECIST).
- To obtain data on changes in tumor microenvironment prior to and subsequent to therapy and, to screen for potential biomarkers to predict clinical benefit.
- To determine the safety and tolerability of the treatment combination in the study population.
- To evaluate overall survival in patients treated with anti-PD1 pembrolizumab in combination with IV bevacizumab and oral metronomic cyclophosphamide.
- To assess the impact of the combination of anti-PD1 pembrolizumab, IV bevacizumab and oral metronomic cyclophosphamide on anti-tumor immune responses in ovarian cancer.

4 **METHODOLOGY**

4.1 **Study Design**
This is an open label Phase II study of anti-PD1 antibody pembrolizumab, in combination with IV bevacizumab and oral metronomic cyclophosphamide in patients with recurrent platinum sensitive, resistant or refractory epithelial ovarian, fallopian tube, or primary peritoneal cancer. The study will include an initial safety lead-in cohort of 5 patients. The estimated total sample size is n=40. The study schema is depicted in Figure 1.

**Figure 1 Trial Diagram**

- **Screening (-28 to -1 day)**
- **12 months (max 17 cycles) Pembrolizumab+Bevacizumab+ Cyclophosphamide every 3 weeks (patient may continue after 12 months if clinical response and wishes to continue with treatment)**
- **Surveillance follow-up up to 3 years from initiation of treatment**
- **Treatment up to 12 months (max 17 cycles) or until confirmed disease progression or severe toxicity**
As shown in Figure 1, each cycle consists of 3 weeks. Pembrolizumab with bevacizumab will be administered every 3 weeks IV, while cyclophosphamide will be given continuously orally every day.

**Dosing regimen:** Pembrolizumab 200 mg IV + bevacizumab 15 mg/kg every 3 weeks IV + cyclophosphamide 50 mg po every day up to 12 months (maximum of 17 cycles) or until disease progression, or until development of unacceptable toxicity, whichever occurs sooner.

**Safety Lead-in Cohort:** There will be an initial safety lead-in cohort of 5 patients. The safety/tolerability of the combination will be examined after each patient completes at least 3 cycles (i.e., the first 9 weeks of therapy). If 2 or less patients have experienced a drug related toxicity requiring drug/treatment delay or suspension (as defined in Sections 6.4, 6.5, and 6.7.3), then an additional 35 patients will be enrolled to complete the Phase II study. Otherwise, the study will be suspended, and the research team will meet to discuss possible safety concerns and will decide what actions to take with respect to study continuation.

**Assessing response to treatment:** Tumor response will be assessed after the 3rd and 6th cycles then after every 6 cycles by investigator-assessed clinical exam and immune-related response criteria (irRECIST) by independent, central, blinded radiographic review. Conventional RECIST 1.1 will also be documented during the trial, however RECIST 1.1 will not be used to determine disease progression, as it has been shown in prior clinical trials using Pembrolizumab in large number of patients, that conventional RECIST might underestimate the benefit of pembrolizumab in approximately 15% of patients; thus using irRECIST could permit treatment beyond initial progression per RECIST v1.1 and prevent premature cessation of treatment (75-77).

If, after 12 months of treatment the patient remains without any evidence of disease progression (has stable disease, partial or complete response), they will be offered to continue with the treatment until disease progression or until treatment is tolerated without severe (grade 3 or 4) toxicity that would require drug discontinuation.

**Note:** If the patient has good clinical response and chooses to remain on the treatment beyond 12 months, we will continue to collect the same clinical data as we were during the first 12 months, as these laboratory tests and imaging studies are standard of care when patients are receiving chemotherapy for ovarian cancer.

### 4.2 Study Endpoints

#### 4.2.1 Primary Endpoints

- The hazard of having a disease progression or dying (PFS endpoint) by treatment.

#### 4.2.2 Secondary Endpoints

- The frequency and duration of objective tumor response within 6 months of study entry as assessed by immune-related response criteria (irRECIST).
- The duration of overall survival (OS).
- The frequency and severity of adverse events, as assessed by CTCAE.
4.2.3 Replacement of Participants
Any participant, who discontinues the study prior to completion of at least 4 cycles of therapy (prior to CT scan after cycle 3 to assess for clinical response) for reasons other than treatment related toxicity, will be excluded from the analyses and replaced.

4.3 Target Accrual and Study Duration
The study will enroll approximately 40 evaluable patients in total (includes a safety lead-in cohort of n=5). Accrual is expected to take 18 months.

Study treatment is for 12 months (or a maximum of 17 cycles), with a follow-up period of up to 3 years from initiation of study treatment; for a total study duration of approximately 5 years.

5 PARTICIPANT SELECTION
All participants will sign an informed consent prior to study related tests. All participants will meet the inclusion and exclusion criteria summarized in Section 5.1 and Section 5.2.

5.1 Inclusion Criteria
To be included in this study, participants must meet the following criteria:

1. Age ≥ 18 years of age on day of signing informed consent.
2. Have an ECOG Performance Status of 0 or 1 (refer to Appendix A).
3. Have measurable disease per RECIST 1.1 or irRECIST criteria present.
4. Participant may have serous, endometrioid, clear cell, mucinous or undifferentiated type of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.
   o Histologic confirmation of the original primary tumor is required via the pathology report.
5. Participant can be either platinum-sensitive (platinum free interval (PFI) ≥ 6 months prior to recent recurrence) or platinum-resistant (PFI < 6 months prior to recent recurrence). If the participant has a platinum sensitive disease, she may only enroll in this clinical trial if there is a contraindication for her to receive further treatment with platinum-based chemotherapy (such as serious persistent toxicity or severe hypersensitivity to platinum agents or she declines standard of care).
6. Participant must be willing to undergo core or excisional biopsy of a tumor lesion within 4 weeks (28 days) prior to initiation of treatment on Day 1 and, after 3 cycles of study treatment. Participants for whom newly obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the Principal Investigator.
7. Have the following clinical laboratory values:
   o Absolute neutrophil count (ANC): ≥ 1,500 /mcL
   o Platelets: ≥ 100,000 / mcL
   o Hemoglobin: ≥ 9 g/dL or 5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Serum creatinine: ≤1.5 X upper limit of normal (ULN) OR measured or calculated creatinine clearance ≥ 60 mL/min for participant with creatinine levels > 1.5 X institutional ULN (refer to Appendix B). GFR can also be used in place of creatinine or CrCl.

Urine Protein Creatine Ratio (UPCR) < 1 prior to enrollment (refer to Appendix C).

Serum total bilirubin: ≤ 1.5 X ULN OR direct bilirubin ≤ ULN for participants with total bilirubin levels > 1.5 ULN

AST (SGOT) and ALT (SGPT): ≤ 2.5 X ULN OR ≤ 5 X ULN for participants with liver metastases

Albumin: > 2.5 mg/dL

International Normalized Ratio (INR) or Prothrombin Time (PT): ≤1.5 unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

Activated Partial Thromboplastin Time (aPTT): ≤1.5 X ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

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

Participants of childbearing potential must be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (participants of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year). Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately.

Participant has recovered from toxicities of prior chemotherapy or other therapy (to grade 2 or less).

Participant may have received prior investigational therapy (including immune therapy).

Participant may have received prior hormonal therapy.

Participant may have received bevacizumab (or another antiangiogenic agent) and/or cyclophosphamide in the past.

Participant has had at least 4 weeks of postoperative recovery from surgery prior to enrollment to ensure complete wound healing. Participants with bowel resections at surgery should begin protocol at least 42 days after surgery.

Ability to swallow and retain oral medication.

Participant or legal representative must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.
5.2 Exclusion Criteria

Participants will be excluded from this study for the following:

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

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment or, is taking any other medication that might affect immune function.

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

4. Hypersensitivity to bevacizumab, cyclophosphamide, pembrolizumab or any of its excipients.

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

6. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.
   - Note: Participants with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study
   - Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy and, has to be at least 28 days after the surgery

7. Has a known additional malignancy that is progressing or requires active treatment: exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or cervical cancer in situ that has undergone potentially curative therapy.

8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

9. Has active autoimmune disease that has required systemic treatment in the past 6 months (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.

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

11. Has an active infection requiring systemic therapy.

12. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the participant’s participation for the
full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating investigator.

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

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

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


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

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

19. Active or history of inflammatory bowel disease (colitis, Crohn's), diverticulitis, irritable bowel disease, celiac disease, or other serious, chronic, gastrointestinal conditions associated with diarrhea. Active or history of systemic lupus erythematosus or Wegener's granulomatosis.

20. Participant has clinical symptoms or signs of partial or complete gastrointestinal obstruction or, requires parenteral hydration and/or nutrition.

21. Participant requires, or is likely to require, more than a two - week course of corticosteroids for intercurrent illness. Participant must complete the course of corticosteroids 2 weeks before screening to meet eligibility.

22. Participant has a serious, non-healing wound, ulcer, or bone fracture.

23. Participant has a clinically significant cardiovascular disease including:
   - Uncontrolled hypertension, defined as systolic > 150 mmHg or diastolic > 90 mmHg
   - Myocardial infarction or unstable angina within 6 months prior to enrollment
   - New York Heart Association (NYHA) Grade II or greater congestive heart failure (refer to Appendix F)
   - Participant has a grade II or greater peripheral vascular disease
   - Participant has a clinically significant peripheral artery disease (e.g. those with claudication, within 6 months)

24. Participant has organ allografts.

25. Participant is receiving medication(s) that might affect immune function.

26. Unwilling or unable to follow protocol requirements.

5.3 Inclusion of Women and Minorities

Women of all races and ethnic groups are eligible for this study.
6 TREATMENT PLAN

6.1 Dosing and Administration

Duration of treatment is 12 months (with a maximum of 17 cycles) or until disease progression or development of unacceptable toxicity, whichever occurs sooner, or any severe toxicity that requires drug discontinuation.

If after 12 months of treatment, a patient remains without any evidence of disease progression (has stable disease, partial or complete response), they will be offered to continue with the treatment until disease progression or until treatment is tolerated without severe (grade 3 or 4) toxicity that requires drug discontinuation.

Each cycle consists of 3 weeks: Pembrolizumab with bevacizumab will be administered every 3 weeks IV, while cyclophosphamide will be given continuously orally every day. Pembrolizumab will be administered first, followed by bevacizumab.

Initially, a safety lead-in cohort of n=5 patients will be enrolled under the proposed study treatment regimen (as outlined in Table 1) and the safety/tolerability of the combination will be examined after each patient completes at least 3 cycles. At that time, the study team will decide what action to take, e.g., continue the study as is, make changes to the study with regard to treatment or dose modifications, or discontinue the study.

If 2 or less patients have experienced a drug related toxicity requiring drug/treatment delay or suspension (as defined in Sections 6.4, 6.5, and 6.7.3), then an additional 35 patients will be enrolled to complete the Phase II study. Otherwise, the study will be suspended, and the research team will meet to discuss possible safety concerns and will decide what actions to take with respect to study continuation.

The rationale for selection of doses to be used in this trial is provided in Section 2.1.

Reported adverse events (AEs) and potential risks are described in Section 1.7. Appropriate dose modifications are described in Section 6.4.

The treatment regimen to be used in this trial is outlined below (Table 1):

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/Potency</th>
<th>Dose Frequency</th>
<th>Route of Administration</th>
<th>Regimen/Treatment Period</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>200 mg</td>
<td>Q3W</td>
<td>IV infusion</td>
<td>Day 1 of each 3-week cycle</td>
<td>Experimental</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>15 mg/kg</td>
<td>Q3W</td>
<td>IV infusion</td>
<td>Day 1 of each 3-week cycle</td>
<td>Standard</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>50 mg</td>
<td>Q.D.</td>
<td>p.o.</td>
<td>Day 1 to day 21 continuously</td>
<td>Standard</td>
</tr>
</tbody>
</table>

In case of significant toxicity, evaluation will be performed to determine which drug could have been responsible for the adverse reaction and also to exclude other possible causes.

If the adverse reaction is attributed to pembrolizumab, drug will be either withheld or permanently discontinued per Section 6.4.
If the adverse reaction is attributed to bevacizumab or cyclophosphamide, drug will be either withheld or permanently discontinued per Section 6.5

**Note:** There are no dose reductions for pembrolizumab, bevacizumab or, cyclophosphamide.

### 6.1.1 Dosing of Pembrolizumab

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

Refer to the *Pharmacy Manual: Pembrolizumab (MK-3475)* for specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

### 6.1.2 Dosing of Bevacizumab

Bevacizumab will be administered at 15 mg/kg IV every 3 weeks (following pembrolizumab infusion), infused over 30 min (first time infusion over 90 min, second time infusion over 60 min, then every subsequent infusion for 30 min). Bevacizumab dosing will be based on the participant’s actual body weight for each treatment cycle.

### 6.1.3 Dosing of Cyclophosphamide

50 mg orally: daily during each 21-day cycle.

Patient will be instructed to swallow cyclophosphamide capsules whole, without cutting, chewing or crushing. Patient should take the capsule in the morning, it can be taken with or without food, and patient is recommended to drink 2-3 quarts of fluid/day.

There will be no dose reductions for cyclophosphamide.

### 6.2 Timing of Dose Administration

Trial treatment will be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed in Table 4 (Schedule of Procedures and Observations). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

### 6.3 Prohibited Concomitant Therapeutic Modalities

Prior to documented disease progression, the following therapeutic modalities are prohibited:

1. Anti-neoplastic therapy not otherwise specified in the current protocol, including cytotoxic, biologic, hormonal, or radiation therapy, regardless of indication (treatment of measurable disease or consolidation therapy).

### 6.4 Dose-Limiting Toxicity and Dose Delays for Pembrolizumab

There will be no dose reductions for pembrolizumab.

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related
toxicities and severe or life-threatening AEs (to include as events only if toxicities are considered related, probably related, or possibly related to the drug) as per Table 2 below. Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0).

A dose limiting toxicity (DLT) will be defined as any ≥ grade 3 clinically significant toxicity, which is deemed to be probably or possibly treatment related and, occurs within the first 9 weeks of therapy (9 weeks = 3 cycles).

See Section 6.7.1 for supportive care guidelines, including use of corticosteroids.

### Table 2 Pembrolizumab: Dose Modification Guidelines for Drug-Related Adverse Events

<table>
<thead>
<tr>
<th>Immune-related AEs</th>
<th>Toxicity grade or conditions (CTCAEv4.0)</th>
<th>Action taken to pembrolizumab</th>
<th>irAE management with corticosteroid and/or other therapies</th>
<th>Monitor and follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis</td>
<td>Grade 2</td>
<td>Withhold</td>
<td>• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper</td>
<td>• Monitor participants for signs and symptoms of pneumonitis</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4, or recurrent Grade 2</td>
<td>Permanently discontinue</td>
<td>• Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Add prophylactic antibiotics for opportunistic infections</td>
<td></td>
</tr>
<tr>
<td>Diarrhea / Colitis</td>
<td>Grade 2 or 3</td>
<td>Withhold</td>
<td>• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper</td>
<td>• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus).</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue</td>
<td>• Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing</td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Grade</td>
<td>Action</td>
<td>Management</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>---------</td>
<td>-------------------------</td>
<td>------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>AST / ALT elevation or Increased bilirubin</td>
<td>Grade 2</td>
<td>Withdraw</td>
<td>• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper</td>
<td></td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td></td>
<td>Permanently discontinue</td>
<td>• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper</td>
<td></td>
</tr>
<tr>
<td>Type 1 diabetes mellitus (T1DM) or Hyperglycemia</td>
<td>Newly on set T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure</td>
<td>Withhold</td>
<td>• Initiate insulin replacement therapy for participants with T1DM</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Administer anti-hyperglycemic in participants with hyperglycemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.</td>
<td></td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>Grade 2</td>
<td>Withhold</td>
<td>• Administer corticosteroids and initiate hormonal replacements as clinically indicated.</td>
<td></td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td></td>
<td>Withhold or permanently discontinue¹</td>
<td>• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)</td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Grade 2</td>
<td>Continue</td>
<td>• Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate</td>
<td></td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td></td>
<td>Withhold or permanently discontinue¹</td>
<td>• Monitor for signs and symptoms of thyroid disorders.</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Grade 2-4</td>
<td>Continue</td>
<td>• Initiate thyroid replacement hormones (e.g., levothyroxine or liothyronine) per standard of care</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Monitor for signs and symptoms of thyroid disorders.</td>
<td></td>
</tr>
<tr>
<td>Nephritis and Renal dysfunction</td>
<td>Grade 2</td>
<td>Withhold</td>
<td>• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.</td>
<td></td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td></td>
<td>Permanently discontinue</td>
<td>• Monitor changes of renal function</td>
<td></td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Grade 1 or 2</td>
<td>Withhold</td>
<td>• Based on severity of AE administer corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td></td>
<td>Permanently discontinue</td>
<td>• Ensure adequate evaluation to confirm etiology and/or exclude other causes</td>
<td></td>
</tr>
</tbody>
</table>

- Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
- Endoscopy to rule out colitis.

¹ If hypophysitis occurs in a patient with type 1 diabetes mellitus (T1DM), this should be managed as hypothyroidism.
### All other immune-related AEs

<table>
<thead>
<tr>
<th>Grade 3</th>
<th>Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 4 or recurrent Grade 3</td>
<td>Permanently discontinue</td>
</tr>
</tbody>
</table>

- Based on type and severity of AE administer corticosteroids
- Ensure adequate evaluation to confirm etiology and/or exclude other causes

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

**NOTE:**
For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

### 6.5 Dose Delays for Bevacizumab

There will be no dose reduction for bevacizumab. Treatment should be interrupted or discontinued for certain adverse events, as described below:

- **Hypertension**

  Patients receiving bevacizumab should be monitored prior to each dose with measurement of blood pressure. Medication classes used for management of patients with Grade 2 or 3 hypertension receiving bevacizumab included angiotensin-converting enzyme inhibitors, beta blockers, diuretics, and calcium channel blockers, but preferably should be a beta blocking agent, if no contraindications. The use of anxiolytics in conjunction with specific antihypertensive agents is not prohibited. The goal for blood pressure control should be consistent with general medical practice guidelines (i.e. <150/90 mmHg in general and <130/80 mmHg for patients with diabetes).

  - For asymptomatic grade 2 or grade 3 hypertension (systolic > 150 mm Hg or diastolic > 90 without any concern for life-threatening consequences) treating physician may administer antihypertensive (and/or anxiolytic) agent in the office and proceed with treatment if blood pressure lowers to <150/90 - per physicians’ discretion. Patient will be asked to monitor BPs regularly at home and follow up with primary care physician within a week.

  - For symptomatic grade 2 or grade 3 hypertension or for grade 4 hypertension (BPs that are concerning for life-threatening consequences), hold bevacizumab treatment (and pembrolizumab, but patient can continue with oral cyclophosphamide) up to 1 week, (see below), administer antihypertensive therapy as clinically needed and arrange appropriate follow up/admission for blood pressure control.

  - During the period of combination chemotherapy with bevacizumab, if hypertension becomes controlled (under 150/90 during the majority of the time) and symptomatic
hypertension has resolved by one week after holding treatment, continue all therapy.

- During the period of combination chemotherapy with bevacizumab, if hypertension remains persistently uncontrolled on one or several antihypertensive agents taken appropriately or remains symptomatic one week after holding treatment, the next treatment cycle should contain pembrolizumab and cyclophosphamide only, if applicable, as otherwise indicated in the protocol, with bevacizumab omitted.

- If uncontrolled or symptomatic hypertension has not resolved by three weeks after holding treatment with bevacizumab (despite patient taking antihypertensive agents appropriately), treatment with bevacizumab should be discontinued for the remainder of the study, but patient may continue with pembrolizumab and oral cyclophosphamide

**Proteinuria**

Patients receiving bevacizumab should be monitored by urine analysis for urine protein: creatinine (UPC) ratio prior to every other dose of bevacizumab. If,

- UPC ratio \( \leq 3.5 \): Continue bevacizumab
- UPC ratio \( > 3.5 \): Hold bevacizumab until UPC ratio recovers to \( < 3.5 \). If therapy is held for \( > 2 \) months due to proteinuria, discontinue bevacizumab
- Grade 4 or nephrotic syndrome: Discontinue bevacizumab

**Hemorrhage**

Bevacizumab will be discontinued in patients with CTCAE Grade 3 hemorrhage and receiving full-dose anticoagulation. For all other patients with CTCAE Grade 3 hemorrhage, bevacizumab should be held until ALL of the following criteria are met:

- bleeding has resolved
- blood hemoglobin level is stable
- there is no bleeding diathesis that would increase the risk of therapy
- there is no anatomical or pathologic condition that can increase the risk of hemorrhage recurrence

Patients who experience delay of resolution according to the above criteria for \( > 3 \) weeks, recurrence of Grade 3 hemorrhage, or any CTCAE Grade 4 hemorrhage will be taken off bevacizumab therapy.

**Thrombosis**

**Arterial Thrombosis:** Bevacizumab will be discontinued for \( \geq \) CTCAE Grade 3 arterial thrombotic events (including cerebrovascular ischemia, transient ischemic attack, cardiac ischemia/infarction, peripheral or visceral arterial ischemia) or CTCAE Grade 2 arterial thrombotic events new or worsened since beginning bevacizumab therapy.

**Venous Thrombosis:** Treatment with bevacizumab will be held for CTCAE Grade 3 or asymptomatic CTCAE Grade 4 (including pulmonary embolism) venous thrombosis. For
patients on therapeutic anticoagulation, PT INR or PTT (whichever appropriate) should be monitored closely during bevacizumab therapy.

- The participant must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin (or other anticoagulant) or on stable dose of heparin prior to restarting treatment.
- The participant must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels).
- The subject must not have had hemorrhagic events while on study.
- The patient is benefiting from treatment (no evidence of disease progression). Patients with symptomatic Grade 4 thromboembolic events after study enrollment but prior to course 2 should be managed according to the above guidelines above.

However, patients with symptomatic CTCAE Grade 4 after receiving any bevacizumab, or recurrent/worsening venous thromboembolic events after resumption of bevacizumab treatment will be taken off bevacizumab therapy.

- **Coagulopathy**

Bevacizumab should be held if the coagulation parameters are higher than the intended therapeutic range or for coagulopathy as follows:

- For CTCAE Grade 3 or 4 coagulopathy: hold treatment, until PT/PTT resolve to Grade 1.
- For patients with PT/INR > therapeutic range while on therapeutic warfarin, treatment with bevacizumab/placebo will be held until PT/INR is within the therapeutic range.

Patients experiencing treatment delay > three weeks because of failure to meet the above criteria will be taken off bevacizumab therapy.

- **Wound Disruption/Bowel Perforation, Fistula, or GI Leak**

Treatment with bevacizumab will be modified in the event of wound disruption requiring medical or surgical intervention, bowel perforation or fistula (including tracheal-esophageal fistula) as follows:

- In the event of superficial wound separations healing by secondary intention with no evidence of fascial dehiscence or infection, therapy with bevacizumab may be initiated with weekly wound examinations until complete closure. After initiation of bevacizumab, bevacizumab will be discontinued for any new event, regardless of Grade.

- **Intestinal Obstruction**

- Bevacizumab will be held for occurrence of CTCAE Grade 3 toxicity, until resolution to ≤CTCAE Grade 1 and will be permanently discontinued for occurrence of CTCAE Grade 4 toxicity.

Since the development of intestinal obstruction could be a result of cancer progression, the investigator should take steps to evaluate such patients for the possibility of disease
progression, using clinical, laboratory and radiographic information as clinically indicated; in the event of disease progression, all protocol-directed therapy would be discontinued.

- **Treatment Guidelines for Reversible Posterior Leukoencephalopathy Syndrome (RPLS)**
  
  o Bevacizumab should be held in patients with symptoms/signs suggestive of RPLS, pending work-up and management, including control of blood pressure. Bevacizumab should be discontinued upon diagnosis of RPLS.

  Note: Resumption of bevacizumab may be considered in patients who have documented benefit from the agent, provided that RPLS was mild and has completely resolved clinically and radiographically within 2-4 weeks; decision to resume bevacizumab in these patients must be discussed with the Principal Investigator and approved by Merck.

6.6 **General Concomitant Medications/Vaccinations**

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

6.6.1 **Acceptable Concomitant Medications**

All treatments that the principal investigator considers necessary for a participant’s welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

All concomitant medications ongoing within 28 days before the first dose of trial treatment as well as any that will be discontinued within 1 week prior to the first dose of study drug will be recorded on the CRF. This is to include all prescription, over the counter (OTC), herbal supplements, and IV medications and fluids. Assessment of concomitant medications occurs at the beginning of every treatment cycle during the trial period. Any changes that occur during the trial period (e.g., drug dosage, frequency, route, date) will be included on the CRF.

Concomitant medications administered after 30 days after the last dose of trial treatment will be recorded for SAEs and ECIs as defined in Section 10.3**Section 10.2**, respectively.

Participants may be pretreated for nausea and vomiting with appropriate anti-emetics.

6.6.2 **Prohibited Concomitant Medications**

Participants are prohibited from receiving the following therapies during the Baseline period and Treatment Phase of the study:

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

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

The Exclusion Criteria (Section 5.2) describes other medications which are prohibited in this trial.

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

6.7 Supportive Care Guidelines

6.7.1 Pembrolizumab Supportive Care Guidelines

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

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

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

• Diarrhea/Colitis
  Participants should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
All participants who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.

For Grade 2 diarrhea/colitis that persists greater than 3 days, administer oral corticosteroids.

For Grade 3 or 4 diarrhea/colitis that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.

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

**Type 1 Diabetes Mellitus or ≥ Grade 3 Hyperglycemia**

For Type 1 diabetes mellitus (TIDM), if new onset, including diabetic ketoacidosis (DKA) or, Grade 3-Grade 4 hyperglycemia if associated with ketosis (ketonuria) or metabolic acidosis (DKA):

- Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria
- Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

**Hypophysitis**

- For Grade 2 events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

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

**Hyperthyroidism or Hypothyroidism**

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

- Grade 2 hyperthyroidism events (and Grade 2-4 hypothyroidism):
  - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.

- Grade 3-4 hyperthyroidism
  - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
• Hematologic  
  o For Grade 2 events, treat with corticosteroids, if indicated.  
  o For Grade 3-4 events, treat with systemic or oral corticosteroids, as appropriate.

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

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

In addition, the event must be reported as a Drug Induced Liver Injury (DILI) ECI, if the patient meets the laboratory criteria for potential DILI defined as:
  o An elevated alanine transaminase (ALT) or aspartate transaminase (AST) lab value that is greater than or equal to three times (3X) the upper limit of normal (ULN) and  
  o An elevated total bilirubin lab value that is greater than or equal to two times (2X) ULN and, at the same time, an alkaline phosphatase (ALP) lab value that is less than 2X ULN,  
  o As a result of within-protocol-specific testing or, unscheduled testing.

• Neurologic  
  o For Grade 2 events, consider treatment with corticosteroids, as appropriate.  
  o For Grade 3-4 events, treat with systemic corticosteroids. If condition worsens, consider IVIG or other immunosuppressive therapies, as per local guidelines.

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

• Ocular  
  o For Grade 2 events, treat with topical steroids, such as 1% prednisolone acetate suspension and iridocyclitics.  
  o For Grade 3-4 events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

• Renal Failure or Nephritis  
  o For Grade 2 events, treat with corticosteroids.  
  o For Grade 3-4 events, treat with systemic corticosteroids.

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

• Skin  
  o For Grade 2 events, symptomatic treatment with topical glucocorticosteroids or urea-containing creams, in combination with oral anti-pruritics.
For **Grade 3-4** events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

**Other Events of Clinical Interest (ECIs)**

The following AEs, regardless of grade, are considered ECIs and should be reported to Merck (see Section 10.3.3):

- Myocarditis
- Pericarditis
- Pancreatitis
- Any additional Grade 3 or higher event which the investigator considers to be immune-related.

- For **Grade 2** events, or **Grade 1** events that do not improve with symptomatic treatment: Systemic corticosteroids may be indicated.

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

**Infusion Reactions**

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. **Table 3** shows treatment guidelines for participants who experience an infusion reaction associated with administration of pembrolizumab.
## Table 3  Infusion Reaction Treatment Guidelines

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

*Note:* Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.
6.7.2 Bevacizumab Supportive Care Guidelines

If an infusion-related adverse reaction occurs, the patient should be premedicated for the next course; however, the infusion time for bevacizumab may not be decreased for the next infusion. If the next infusion is well tolerated with pre-medication, the infusion time for the next dose may then be decreased by 30 ± 10 minutes as long as the patient continues to be pre-medicated. If a patient experiences an infusion-associated adverse event with the 60-minute infusion, all subsequent doses should be given over 90 ± 15 minutes. Similarly, if a patient experiences an infusion-associated adverse event with the 30-minute infusion, all subsequent doses should be given over 60 ± 10 minutes.

6.7.2.1 Suggested Prophylaxis in Event of Prior Bevacizumab Infusion Reaction

In the event of a prior bevacizumab hypersensitivity reaction, subsequent infusions should be delivered over 90 minutes, and the following prophylactic regimen is recommended upon re-exposure:

1. H1 blocker (diphenhydramine 25-50 mg IVP or orally one hour prior to injection; or an equivalent dose of an alternate H1 blocker, such as loratadine 10 mg or fexofenadine 60 mg).

2. H2 blocker (famotidine 20 mg IVP or orally one hour prior to injection; or an equivalent dose of an alternate H2 blocker).

3. Dexamethasone (10 mg administered PO 12 and 6 hours prior to bevacizumab injection). Recommended only for hypersensitivity reaction.

6.7.3 Cyclophosphamide Supportive Care Guidelines

- Oral cyclophosphamide will be held in patients with Grade 3 or higher hematologic, gastrointestinal, hepatic, genitourinary, neurologic, cardiac or pulmonary toxicities until patient recovers to at least grade 1 toxicity level.
- In case of Grade 3 or higher neurologic, cardiac or pulmonary toxicity that is attributed to cyclophosphamide treatment, drug will be discontinued permanently.

6.8 Diet/Activity/Other Considerations

6.8.1 Diet

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

6.8.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the
duration of the study. The two birth control methods can be either: two barrier methods or, a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy. The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

### 6.8.3 Use in Pregnancy

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

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

### 6.8.4 Use in Nursing Women

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

### 6.8.5 Skin Toxicity

Skin reactions are the most common immune-related side effects of checkpoint inhibitor therapy affecting approximately one third of patients on PD-1 inhibitor therapy (78). Currently, no tools are available to identify individuals at highest risk of cutaneous side effects prior to therapy, although changes in the skin microbiome have been shown in several immune mediated skin diseases, such as atopic dermatitis, psoriasis and vitiligo (79, 80).

Prior to starting on study treatment (and after Cycle 3 and at end of treatment or disease progression), participants will be encouraged to have a skin check performed through the Dermatology Department. RPCI Dermatology will schedule appointments at a time that is convenient for the participant (without a wait time) and will monitor their skin for potential cutaneous side effects and will provide preventive/management skin care.

In addition, if any cutaneous symptoms or side effects are noted, participants will be offered immediate follow up with dermatology, particularly if the participant has grade 3-4 skin toxicity.
6.9 Duration of Treatment

Participants may remain on study and continue to receive treatment (12 months with a maximum of 17 cycles) in the absence of disease progression, unacceptable toxicity or withdrawal from study, intercurrent illness that prevents further administration of treatment, participant demonstrates an inability/refusal to comply with oral medication regime or, participant withdraws from study.

If patient has good clinical response after 12 months of treatment without any severe adverse event, she may be offered to continue with the treatment after discussing this with her provider and the Principal Investigator.

Note: If the patient has good clinical response and chooses to remain on the treatment beyond 12 months, we will continue to collect the same clinical data as we were during the first 12 months, as these laboratory tests and imaging studies are standard of care when patients are receiving chemotherapy for ovarian cancer.

6.9.1 Assessing for Secondary Cytoreduction and additional tumor biopsies to evaluate for response to treatment

Patients who have stable disease or showed progression on this clinical trial may be offered to undergo PET CT with biopsy of non-responsive tumor lesions to evaluate for viable tumor tissue and for translational studies or could be considered for secondary cytoreduction, if surgery could provide additional survival benefit. The goal of secondary cytoreduction is to achieve complete resection, which has been shown to increase survival in this patient population. Tumor tissue harvested during secondary cytoreduction will be used for translational studies and also to evaluate for response to treatment by assessing for viable/necrotic tissue. Patients who have found to have mostly necrotic tumor tissue (thus clear clinical benefit from treatment), will be offered to stay on the trial, even if per prior imaging they met criteria for disease progression, as the reliability of CT scans determining disease progression in this patient population has not been reported. Survival data from these patients will be censored based on true progression (new viable tumor tissue growth on CT scan or on biopsy/surgery) and their treatment course will be further described in future publications.

6.10 Treatment Discontinuation

Upon treatment discontinuation all end of treatment evaluations and tests will be conducted. All participants who discontinue due to an AE must be followed until the event resolves or stabilizes. Appropriate medical care should be provided until signs and symptoms have abated, stabilized, or until abnormal laboratory findings have returned to acceptable or pre-study limits. The final status of the AE will be reported in the participant’s medical records and the appropriate eCRF.

Reasons for treatment discontinuation should be classified as follows:

- Death
- Progressive disease
- Toxicity; treatment related or unrelated
- Investigator judgment
  - The Investigator may discontinue a participant if, in his/her judgment, it is in the best interest of the participant to do so.
6.11 Compliance

A medication diary (Appendix E) will be provided to monitor participant compliance for oral cyclophosphamide.

As most studies show that adherence to long-term oral drug therapies are around 40-50%, we will consider a 60% of compliance with oral Cytoxan adequate. We will monitor adherence by patient self-report, pill diaries as well as rates of prescription refills. If patient is below the 60% compliance (which will be assessed each 3 weeks) – she will be asked to increase compliance with the next cycle. If she fails to comply in more than 2 cycles (>6 weeks) without any medical reason, she will be replaced at any point in the study.

7 INVESTIGATIONAL PRODUCTS

7.1 Pembrolizumab

Pembrolizumab (KEYTRUDA®) is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa.

7.1.1 Active Substance and Source

<table>
<thead>
<tr>
<th>Product Name &amp; Potency</th>
<th>Dosage Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab 50 mg</td>
<td>Lyophilized Powder for Injection</td>
</tr>
<tr>
<td>Pembrolizumab 100 mg/ 4mL</td>
<td>Solution for Injection</td>
</tr>
</tbody>
</table>

Pembrolizumab lyophilized powder for injection is a sterile, preservative-free, white- to off-white lyophilized powder in single-use vials. Each vial is reconstituted and diluted for intravenous infusion. Each 2 mL of reconstituted solution contains 50 mg of pembrolizumab and is formulated in L-histidine (3.1 mg), polysorbate 80 (0.4 mg), and sucrose (140 mg); may contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5.

Pembrolizumab solution for injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for intravenous infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.
7.1.2 Drug Shipment

Pembrolizumab will be provided by Merck & Co., Inc. and shipped to the participating site, and will be labeled in accordance with regulatory requirements.

The date of receipt and the amount of drug received will be documented. Drug shipment records will be retained by the investigational pharmacist or designee.

7.1.3 Preparation

Pembrolizumab Powder for Solution for Infusion, 50 mg/vial, is reconstituted with sterile water for injection prior to use.

The lyophilized DP after reconstitution with sterile water for injection and the liquid DP are clear to opalescent solutions, essentially free of visible particles. The reconstituted lyophilized product and the liquid product are intended for intravenous (IV) administration. The reconstituted DP solution or the liquid DP can be further diluted with normal saline or 5% dextrose in the concentration range of 1 to 10 mg/mL in IV containers made of polyvinyl chloride (PVC) or non-PVC material. Reconstituted vials should be used immediately to prepare the infusion solution in the IV bag, and the infusion solution should be administered immediately. Diluted pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion. In addition, IV bags can be stored at 2° to 8°C for up to a cumulative time of 20 hours. This recommendation is based on up to 24 hours of room temperature and up to 24 hours of refrigerated stability data of diluted pembrolizumab solutions in the IV bags.

7.1.4 Storage and Stability

The Investigator or designate will be responsible for ensuring that the investigational product is securely maintained in a locked, limited-access facility, and in accordance with the applicable regulatory requirements.

Pembrolizumab for injection (lyophilized powder): Store vials under refrigeration at 2°C to 8°C (36°F to 46°F).

Pembrolizumab injection (solution): Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.

Drug storage temperature will be maintained and recorded, as applicable.

7.1.5 Handling and Disposal

All products dispensed will be recorded on a product accountability record. Records of product lot numbers and dates received will be entered on a product accountability form. It is the Investigator’s responsibility to ensure that an accurate record of investigational drug issued and returned is maintained.

All unused and/or partially used investigational drug will be destroyed according to standard practices after properly accounting for the dispensing. Partially used vials of study drug will not be re-used for other participants.

Under no circumstances will the Investigator supply investigational drug to a third party or allow the investigational drug to be used in a manner other than as directed by this protocol.
7.1.6 Overdose

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab.

In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

7.2 Bevacizumab

Please refer to package insert. Use of biosimilar per Institute standard is allowed.

7.3 Cyclophosphamide

Please refer to package insert.

8 STUDY PROCEDURES

Eligibility of each participant will be established prior to enrollment.

Informed consent MUST be completed prior to receiving any study related procedures.

The individual trial procedures are described in detail below and summarized in Table 4.

All on-study visit procedures are allowed a window of ± 3 days unless otherwise noted (Note: It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator).

Unless otherwise defined in the written protocol text, all procedures/assessments will be conducted in accordance with RPCI Clinical Research Services Standard Operating Procedures.
# Table 4  Schedule of Procedures and Observations

<table>
<thead>
<tr>
<th>Trial Period:</th>
<th>Screening Phase</th>
<th>Treatment Cycles(^1)</th>
<th>End of Treatment(^2) OR At time of Discontinuation</th>
<th>Post-Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Cycle/Title:</td>
<td>Baseline(^3)</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Administrative Procedures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics and Medical History</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior and Concomitant Medication Review</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial Treatment Administration(^9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-study anticancer therapy status(^10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival Status</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Clinical Procedures/Assessments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Review Adverse Events(^11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full Physical Examination(^12), including vital signs and body weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Directed Physical Examination including vital signs and body weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG Performance Status(^13)</td>
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<tr>
<td>Laboratory Procedures/Assessments: Refer to Appendix D</td>
<td></td>
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<td></td>
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<tr>
<td>Pregnancy Test – Urine or Serum β-HCG</td>
<td></td>
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<tr>
<td>PT/INR and aPTT</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Hematology(^15)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry(^15)</td>
<td></td>
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</tr>
</tbody>
</table>

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\(^3\) Baseline

\(^4\) Safety Follow-up

\(^5\) Follow Up Visits

\(^6\) Survival Follow-Up

\(^7\) X

\(^8\) X

\(^9\) X

\(^10\) X

\(^11\) X

\(^12\) X

\(^13\) X

\(^14\) X

\(^15\) X
<table>
<thead>
<tr>
<th>Trial Period:</th>
<th>Screening Phase</th>
<th>Treatment Cycles&lt;sup&gt;1&lt;/sup&gt;</th>
<th>To be repeated beyond 8 cycles</th>
<th>End of Treatment&lt;sup&gt;2&lt;/sup&gt; OR At time of Discontinuation</th>
<th>Post-Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Cycle/Title:</td>
<td>Baseline&lt;sup&gt;3&lt;/sup&gt;</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Urinalysis&lt;sup&gt;15&lt;/sup&gt; (every other cycle)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urine sample for Urine Protein Creatinine Ratio&lt;sup&gt;16&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>T3, FT4 and TSH&lt;sup&gt;17&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

**Efficacy Measurements**

| Imaging: CT (chest, abdomen, and pelvis)<sup>18</sup> | X | | X | | X | | | | | |

**Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood**

| Newly Obtained (or Archival) Tissue Collection<sup>19</sup> | X | | X | | | | | | | |
| Correlative Studies Blood Collection<sup>20</sup> | X<sup>21</sup> | X | X | X | X | X<sup>24</sup> | X | | | |
| Ascites Collection<sup>22</sup> | | | | | | | | | | |
| Dermatology visit (will be recommended to all patients at RPCI)<sup>23</sup> | X | | X | | | | | | | |
| Quality of Life Questionnaires: EORTC QLQ-C30, QLQ-OV28 | X | X | X | X | X<sup>24</sup> | X | | | | |
1. Each cycle is 3 weeks: pembrolizumab + bevacizumab will be administered on Day 1 of each 3-week cycle and, cyclophosphamide will be taken (po) daily. Treatment will be for 12 months (with a maximum of 17 cycles) or until disease progression or development of unacceptable toxicity (whichever occurs sooner) or, any severe toxicity (e.g. Grade 3 - Grade 4 toxicity requiring drug discontinuation). **Note:** After Cycle I Day 1, all on-study visit procedures are allowed a window of ± 3 days unless otherwise noted.

2. When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation

3. Performed within 28 days prior to first dose of study medication.

4. Safety Follow-Up Visit should be conducted approximately 30 days (± 3 days) after the last dose of trial treatment, or until resolution of any drug-related toxicity or before the initiation of a new anti-cancer treatment, whichever comes first.

5. Participants who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase: assessments every 3 months, for 1 year, following end of treatment then, every 6 months (Section 8.7.2).

6. Once a participant experiences confirmed disease progression or starts a new anti-cancer therapy: Telephone contact every 12 weeks (± 1 week: up to 3 years from initiation of treatment) to assess for survival status until death, withdrawal of consent, or the end of study, whichever occurs first (Section 8.7.3).

7. List any medications that are ongoing, or that will be discontinued, within 1 week prior to first dose of study drug.

8. List any ongoing medications with dose changes, as applicable.

9. Trial treatment is administered on Day 1 of each cycle after all procedures/assessments have been completed. Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle (following Cycle 1) due to administrative reasons.

10. Review all new anti-neoplastic therapy initiated after the last dose of trial treatment (Section 8.1.5)

11. All AEs of unknown etiology associated with pembrolizumab, bevacizumab and cyclophosphamide exposure should be evaluated to determine if it is possibly an ECI of a potentially immunologic etiology (termed immune-related adverse events, or irAEs). Please refer to Section 10.2, as well as the separate Event of Clinical Interest Guidance Document regarding the identification, evaluation and management of potential irAEs.

12. On study treatment days (prior to administration of study treatment), the Full Physical Examination will include basic neurological examination, vital signs and, body weight: height collected at baseline only. For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

13. At baseline, prior to the administration of each dose of trial treatment and discontinuation of trial treatment: (Appendix A)

14. Within 72 hours prior to first study treatment. If the urine test is positive, or cannot be confirmed as negative, a serum pregnancy test will be required.

15. Refer to Appendix D.

16. Baseline, Cycle 1 Day 1 and, Day 1 of every 2nd cycle. **Note:** For the purpose of this study, participant must have a Urine Protein Creatine Ratio (UPCR) < 1 prior to enrollment and < 3.5 for any subsequent cycles. Refer to Appendix C

17. Every 3 cycles
<table>
<thead>
<tr>
<th>Trial Period:</th>
<th>Screening Phase</th>
<th>Treatment Cycles¹</th>
<th>End of Treatment² OR At time of Discontinuation</th>
<th>Post-Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Cycle/Title:</td>
<td>Baseline³</td>
<td>1 2 3 4</td>
<td>To be repeated beyond 8 cycles</td>
<td></td>
</tr>
<tr>
<td>5 6 7 8 10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

18. To be obtained within 30 days of trial start, then after the 3rd and 6th cycles. If patient remains on the regimen longer than that, CT will be performed after every 6th cycle, or sooner if there is clinical suspicion for disease progression. Refer to Section 8.4.1


20. Peripheral blood samples will be collected at baseline (within 2 weeks prior to start of study treatment), Cycle 2 – Day 1, Cycle 4 – Day 1, Cycle 7 – Day 1 and at the end of study treatment or at time of discontinuation (within two weeks after the last cycle is completed or, at the time of progression; or for any other reason that requires study termination, whichever occurs sooner. Note for samples collected while participant is receiving study treatment; Blood is to be collected prior to pembrolizumab administration – it is not required to hold cyclophosphamide dosing until after sample collection.

21. Note: Within 2 weeks prior to start of study treatment

22. If a patient has ascites at any time during the study period and is willing to undergo paracentesis or wishes to undergo paracentesis for symptom relief. This is optional for the patient.

23. Dermatology visit will be recommended to all patients at RPCI prior to starting treatment, after 3 cycles and, at time of progression to monitor cutaneous side effects. In addition to this, if any cutaneous symptoms or side effects are noted, they will be offered immediate follow up with dermatology, particularly if patient has grade 3-4 skin toxicity (see Section 6.8.5).

24. On those patients, who have already completed 10 cycles, the one additional correlative blood and questionnaires will be collected at the time of their next cycle.
8.1 Administrative Procedures

8.1.1 Informed Consent
The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial: Informed consent MUST be completed prior to receiving any study related procedures.

8.1.2 Inclusion/Exclusion Criteria
All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial: The eligibility of each participant will be established prior to study enrollment.

8.1.3 Medical History

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

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

8.1.4 Prior and Concomitant Medications Review

8.1.4.1 Prior Medications
The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the trial.

Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

8.1.4.2 Concomitant Medications
The investigator or qualified designee will record medication, if any, taken by the participant during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 10.1.

8.1.5 Post-Study Anti-Cancer Therapy Status
The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment.

If a participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up visit must occur before the first dose of the new therapy.

Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.
8.1.6 Survival Follow-Up

Once a participant experiences confirmed disease progression or starts a new anti-cancer therapy, the participant moves into the survival follow-up phase and should be contacted by telephone every 12 weeks (up to 3 years from initiation of treatment) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

8.2 Clinical Procedures/Assessments

8.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Schedule of Procedures and Observations and, more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4 (see Section 10.1.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with pembrolizumab, bevacizumab and cyclophosphamide exposure should be evaluated to determine if it is possibly an ECI of a potentially immunologic etiology (termed immune-related adverse events, or irAEs). Please refer to Section 10.2, regarding the identification, evaluation and management of potential irAEs.

8.2.2 Full Physical Examination

The investigator or qualified designee will perform a complete physical exam (including basic neurological, vital signs and body weight) during the baseline screening period (if clinically indicated, a neuro exam will be performed). Height will be collected at baseline only. Clinically significant abnormal findings should be recorded as medical history.

8.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam (to include basic neurological, vital signs and body weight) as clinically indicated prior to trial treatment administration.

8.2.4 Vital Signs

The investigator or qualified designee will take vital signs (temperature, heart rate, respiratory rate, blood pressure) at baseline, prior to the administration of each dose of trial treatment and at treatment discontinuation.

8.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (Appendix A) at baseline screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment.
8.3 Laboratory Procedures/Assessments

Details regarding the timing of specific laboratory procedures/assessments to be performed in this trial are provided in Table 4. The laboratory tests for hematology, chemistry, urinalysis, and others are specified in Appendix D.

8.4 Efficacy Measurements

8.4.1 Tumor Imaging and Assessment of Disease

Radiographic tumor measurements should be obtained via contrast CT of the chest, abdomen and pelvis. Immune related response criteria (irRECIST) (76) will be used to assess disease at baseline and subsequent assessments.

CT needs to be obtained within 30 days of trial start, then after the 3rd and 6th cycles. If patient remains in the regimen longer than that, CT will be performed after every 6th cycle or sooner if there is clinical suspicion for disease progression.

In addition to irRECIST, RECIST 1.1 (81) measurements will also be used for disease assessment.

8.5 Tissue Collection and Correlative Blood Sampling

Mandatory research tumor tissue core biopsies are obtained at two time points: prior to initiating study treatment and after 3 cycles of study treatment. If patient remains on the treatment much longer, at the time of progression she will be offered to undergo another CT guided biopsy for research purposes, however this is not mandatory.

Mandatory research blood samples are obtained at five time points: Baseline (within 2 weeks prior to initiating study treatment), Cycle 2 – Day 1, Cycle 4 – Day 1, Cycle 7 – Day 1, Cycle 10 – Day 1 and at the end of study treatment or at time of discontinuation (within 2 weeks after the last treatment cycle is completed) or, at the time of disease progression or for any other reason that requires study treatment termination, whichever occurs sooner.

On those patients, who have already completed 10 cycles, the one additional correlative blood will be collected at the time of their next cycle.

8.6 End of Treatment/Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation.

Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.2: Assessing and Recording Adverse Events.
8.7  Post-Treatment Visits

8.7.1  Safety Follow-Up Visit
The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first.

All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first.

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

8.7.2  Follow-up Visits
Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 3 months by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 6 months (up to 3 years from initiation of treatment).

Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression or, death.

8.7.3  Survival Follow-Up
Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

8.7.4  Assessing quality of life and emotional well-being and lifestyle using the EORTC QLQ-C30 and QLQ-OV28
EORTC QLQ-C30 (Appendix G) has been developed to assess the quality of life of cancer patients. It is supplemented by disease-specific modules such as breast, lung, head & neck and, ovarian (QLQ-OV28: Appendix H). These questionnaires have been well validated in large number of studies and have been widely used in cancer patients.

EORTC QLQ-C30, EORTC QLQ-OV28 and Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) will be collected on Cycle 7 Day – 1, Cycle 10 Day 1 and at the end of study as well to assess quality of life during the study.

9  EFFICACY EVALUATIONS
Tumor response will be assessed after the 3rd and 6th cycles then after every 6 cycles by immune-related response criteria (irRECIST) (76, 82) by independent, central, blinded radiographic review. Conventional RECIST 1.1 (81) will also be documented during the trial, however RECIST 1.1 will not be used to determine disease progression, as it has been shown in prior clinical trials using
Pembrolizumab in large number of patients, that conventional RECIST might underestimate the benefit of pembrolizumab in approximately 15% of patients; thus using irRECIST could permit treatment beyond initial progression per RECIST v1.1 and prevent premature cessation of treatment (75-77).

The irRECIST will be used for tumor response assessment at time of continuing review and will be used for IRB reporting and formal analysis.

9.1 Baseline

9.1.1 Measurable Lesion Definitions and Target Lesion Selection

- All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, will be identified as target lesions and recorded and measured at baseline

- Measurable lesions must be accurately measured in at least one dimension with a minimum size of:
  - 10 mm in the longest diameter by CT or MRI scan (or no less than double the slice thickness) for non-nodal lesions and ≥ 15 mm in short axis for nodal lesions.
  - 10 mm caliber measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
  - 20 mm by chest X-ray

- A sum of the longest diameter (short axis for lymph nodes) of all target lesions will be calculated and reported as the baseline sum diameters. This will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

9.1.2 Non-measurable Lesion Definitions

- Non-target lesions will include:
  - Measurable lesions not selected as target lesions
  - All sites of non-measurable disease, such as neoplastic masses that are too small to measure because their longest uninterrupted diameter is < 10 mm (or < two times the axial slice thickness), i.e., the longest perpendicular diameter is ≥ 10 and < 15 mm.
  - Other types of lesions that are confidently felt to represent neoplastic tissue, but are difficult to measure in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural or pericardial effusions, ascites, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill-defined abdominal masses, skin lesions, etc.

- All lesions or sites of disease not recorded as target lesions (e.g., small lesions and non-measurable lesions) should be identified as non-target lesions and indicated as present in
the source documents at baseline. There is no limit to the number of non-target lesions that can be recorded at baseline. The general location will also be documented on the images, drawing a regularly-shaped Region of Interest.

- Measurements of the non-target lesions will not be performed, but the presence or absence of each should be noted throughout follow-up and evaluation.

### 9.1.3 Target and Non-Target Lymph Node Lesion Definitions

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

### 9.1.4 Non-Target Lesion Selection

- All lesions or sites of disease not recorded as target lesions should be recorded as non-target lesions at baseline. There is no limit to the number on non-target lesions that can be recorded at baseline.

### 9.1.5 Bone Lesions

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

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

### 9.1.6 Cystic and Necrotic Lesions as Target Lesions

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

- Lesions that are partially cystic or necrotic can be selected as target lesions.

- The longest diameter of such a lesion will be added to the *Total Measured Tumor Burden* (TMTB) of all target lesions at baseline.

If other lesions with a non-liquid/non-necrotic component are present, those should be preferred.

### 9.1.7 Lesions with Prior Local Treatment

- During target lesion selection the radiologist will consider information on the anatomical sites of previous intervention (e.g. previous irradiation, RF-ablation, TACE, surgery, etc.).

- Lesions undergoing prior intervention will not be selected as target lesions unless there has been a demonstration of progress in the lesion.
9.1.8 No Disease at Baseline

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

9.2 Follow-Up

9.2.1 Recording of Target and New Measurable Lesion Measurements

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

9.2.2 Definition of New Measurable Lesions

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

9.2.3 Non-Target Lesion Assessment

- The RECIST 1.1 definitions (81) for the assessment of non-target lesions apply (i.e., measurements of the non-target lesions will not be performed, but the presence or absence of each should be noted throughout follow-up and evaluation).

- The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN).

- Non-target lesions do not affect irPR and irSD assessments.

- Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD.

9.2.4 New Non-Measurable Lesions Definition and Assessment

- All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively.

- Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the time-point.

- Persisting new non-measurable lesions prevent irCR.

9.2.5 irRECIST Overall Tumor Assessments

The irRECIST overall tumor assessment is based on the *TMTB* (total measured tumor burden) of measured target and new lesions, non-target lesion assessment and new non-measurable lesions.
• **irCR:** Complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis.

• **irPR:** Decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions.

• **irSD:** Failure to meet criteria for irCR or irPR in the absence of irPD.

• **irNN:** No target disease was identified at baseline and at follow-up the patient fails to meet criteria for irCR or irPD.

• **irPD:** Minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 6 weeks after the first irPD assessment.

• **irNE:** Used in exceptional cases where insufficient data exists.

• **irND:** In adjuvant setting when no disease is detected.

**New Lesions:** the presence of new lesion(s) does not define progression. The measurements of the new lesion(s) are included in the sum of the measurements (the sum of the measurements = the sum of the longest diameters of all target lesions and new lesions, if any).

### 9.2.6 Confirmation Measurement

A confirmatory assessment is required no less than 6 weeks after an irPR or irCR is deemed by irRECIST (76)

### 9.3 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation. 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. The preferred imaging modality for this clinical trial is conventional CT scan using IV contrast.

• **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:** Chest x-ray is not accurate in assessment of lesion size in the lung and should not be used as a method of measurement. Conventional chest CT is the preferred imaging modality to evaluate response to treatment.
• **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) however, conventional CT scan is the preferred modality to determine response to treatment.

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, which 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 irRECIST or RECIST 1.1 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.

• **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 complete response (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 participant to be considered in complete clinical response.

• **Cytology, Histology:** These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

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 stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
10  SAFETY EVALUATION

10.1  Adverse Events

10.1.1  Definition

An adverse event or adverse experience (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of ‘unrelated’, ‘unlikely’, ‘possible’, ‘probable’, or ‘definite’).

An AE is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan in other study-related documents.

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

10.1.1.1  Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be clinically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

10.1.1.2  Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the CRF.

However, clinically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

10.1.1.3  Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).
If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin $5 \times$ the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the CRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7 mEq/L should be recorded as “hyperkalemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the CRF, unless their severity, seriousness, or etiology changes.

10.1.1.4 Preexisting Medical Conditions (Baseline Conditions)

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

10.1.1.5 Overdose

Refer to Section 7.1.6 for a definition of pembrolizumab overdose.

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

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

10.1.2 Grading and Relationship to Drug

The descriptions and grading scales found in the CTEP Version 4 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. CTEP Version 4 of the CTCAE is identified and located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

AEs not covered by specific terminology listed should be reported with common medical terminology and documented according to the grading scales provided in the CTCAE Version 4.

Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.
The relationship of event to study drug will be documented by the Investigator as follows:

- **Unrelated:** The event is clearly related to other factors such as the participant’s clinical state, other therapeutic interventions or concomitant drugs administered to the participant.

- **Unlikely:** The event is doubtfully related to investigational agent(s). The event was most likely related to other factors such as the participant’s clinical state, other therapeutic interventions, or concomitant drugs.

- **Possible:** The event follows a reasonable temporal sequence from the time of drug administration but could have been produced by other factors such as the participant’s clinical state, other therapeutic interventions or concomitant drugs.

- **Probable:** The event follows a reasonable temporal sequence from the time of drug administration and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the participant’s clinical state, therapeutic interventions or concomitant drugs.

- **Definite:** The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant’s condition, therapeutic interventions or concomitant drugs; AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness. An investigator, who is a qualified physician, will evaluate all adverse events using the following guidelines:
V4.0 CTCAE Grading

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Life threatening consequences; urgent intervention indicated.</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Death related to AE</td>
</tr>
</tbody>
</table>

Seriousness

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

† Results in death or
† Is life threatening; or places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or
† Results in a persistent or significant disability/incapacity (substantial disruption of one’s ability to conduct normal life functions); or
† Results in or prolongs an existing inpatient hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.)); or
† Is a congenital anomaly/birth defect (in offspring of subject taking the product regardless of time to diagnosis); or
† Is a new cancer; (that is not a condition of the study) or
† Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.

Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).

Duration

Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units

Action taken

Did the adverse event cause the Merck product to be discontinued?

Relationship to test drug

Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator’s signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information.

The following components are to be used to assess the relationship between the Merck product and the AE: the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):

**Exposure**

Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

**Time Course**

Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?

**Likely Cause**

Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
### Relationship to Merck product (continued)

<table>
<thead>
<tr>
<th>The following components are to be used to assess the relationship between the test drug and the AE: (continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>De-challenge</strong></td>
</tr>
<tr>
<td>Was the Merck product discontinued or dose/exposure/frequency reduced?</td>
</tr>
<tr>
<td>If yes, did the AE resolve or improve?</td>
</tr>
<tr>
<td>If yes, this is a positive de-challenge. If no, this is a negative de-challenge.</td>
</tr>
<tr>
<td>(Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; or (3) the trial is a single-dose drug trial; or (4) Merck product(s) is/are only used one time.)</td>
</tr>
<tr>
<td><strong>Rechallenge</strong></td>
</tr>
<tr>
<td>Was the subject re-exposed to the Merck product in this study?</td>
</tr>
<tr>
<td>If yes, did the AE recur or worsen?</td>
</tr>
<tr>
<td>If yes, this is a positive rechallenge. If no, this is a negative rechallenge.</td>
</tr>
<tr>
<td>(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial; or (3) Merck product(s) is/are used only one time).</td>
</tr>
<tr>
<td><strong>Consistency with Trial Treatment Profile</strong></td>
</tr>
<tr>
<td>Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Merck product or drug class pharmacology or toxicology?</td>
</tr>
</tbody>
</table>

The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

**Record one of the following**

**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Merck product relationship).**

**Yes, there is a reasonable possibility of Merck product relationship.**

There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.

**No, there is not a reasonable possibility Merck product relationship.**

Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)
10.1.3 Reporting Adverse Events

Table 5 Guidelines for Routine Adverse Event Reporting for Phase 2 Studies (Regardless of Expectedness)

<table>
<thead>
<tr>
<th>Attribution</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Unlikely</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Possible</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Probable</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Definite</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Routine AEs occurring from the time the consent form is signed until 30 days after the last intervention, or until the event has resolved, the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible, will be reported. New information will be reported after it is received.

10.2 Events of Clinical Interest (ECIs)

Participants should be assessed for possible ECIs prior to each dose. Lab results should be evaluated, and participants should be asked for signs and symptoms suggestive of an immune-related event. Participants who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

Any Grade 3 or higher event that the investigator considers to be immune-related should be reported as an ECI regardless of whether the specific event term is in Table 9 and reported to Merck within 24 hours from the time the Investigator/physician is aware of such an occurrence. Adverse events that are both an SAE and an ECI should be reported one time as an SAE only. ECIs will not be indicated in the data base but will be tracked by the clinical research coordinator in an AE log to facilitate reporting to Merck.

Table 6 Events of Clinical Interest

<table>
<thead>
<tr>
<th>Pneumonitis (reported as ECI if ≥ Grade 2)</th>
<th>Interstitial lung disease</th>
<th>Pneumonitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute interstitial pneumonitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Colitis (reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)</th>
<th>Colitis microscopic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal Obstruction</td>
<td></td>
</tr>
<tr>
<td>Enteroctolitis</td>
<td>Gastrointestinal perforation</td>
</tr>
<tr>
<td>Necrotizing colitis</td>
<td>Diarrhea</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)</th>
<th>Adrenal Insufficiency</th>
<th>Hypothyroidism</th>
<th>Hypophysitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal Insufficiency</td>
<td>Hyperthyroidism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>Hypothyroidism</td>
<td>Thyroid disorder</td>
<td></td>
</tr>
</tbody>
</table>
Events of clinical interest for this study include:

- An overdose of pembrolizumab that is not associated with clinical symptoms or abnormal laboratory results.
- An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. Guidance for assessment and follow up of these criteria can be found in the Event of Clinical Interest Guidance Document.

10.3 Serious Adverse Events

10.3.1 Definition

A serious adverse event (SAE) is any adverse event (experience) that in the opinion of either the investigator or sponsor results in ANY of the following:

- Death.
- A life-threatening adverse event (experience). Any AE that places a participant or participants, in the view of the Investigator or sponsor, at immediate risk of death from the reaction as it occurred. It does NOT include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.
- Important Medical Event (IME) that, based upon medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.
- Is associated with an overdose
- Is a new cancer (that is not a condition of the study)

Additionally, any serious adverse event considered by an investigator who is a qualified physician to be related to the investigational drug, 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.

10.3.2 Reporting Serious Adverse Events

All new SAEs occurring from the date the participant signs the study consent until 90 days after the last intervention or a new treatment is started, whichever comes first, will be reported. The RPCI SAE Source Form is to be completed with all available information, including a brief narrative describing the SAE and any other relevant information.

SAEs occurring after the 90-day follow-up period that the investigator determines to be possibly, probably or definitely related to the study intervention should be reported.

SAEs identified as an Unanticipated Problem by the Investigator must be reported. Please refer to Section 10.6 for details on reporting Unanticipated Problems.
10.3.3 Reporting Events of Clinical Interest (ECIs)

ECIs (both non-serious and serious adverse events) from the date of first dose of pembrolizumab through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported within 24 hours to the Principal Investigator and within 2 working days to Merck Global Safety, regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

**Attn:** Worldwide Product Safety  
FAX 215 993-1220

10.3.4 Reporting of Overdose

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

10.3.5 Reporting of Pregnancy and Lactation

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a participant (spontaneously reported to them), including the pregnancy of a male participant's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier. All participants and female partners of male participants who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

10.4 Follow-Up for Serious Adverse Events

All related SAEs should be followed to their resolution, until the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible. New information will be reported when it is received.

10.5 Follow-Up for Events of Clinical Interest

All related ECIs should be followed to resolution. The Adverse Experience eCRF should be updated with information regarding duration and clinical course of the event. Information obtained from the consulting specialist, including diagnosis, should be recorded in the appropriate AE fields. Free-text fields should be used to record narrative information:

- Clinical course of the event
- Course of treatment
• Evidence supporting recovery
• Follow-up to the clinical course

Any treatments administered for the event should also be entered in the Concomitant Medication eCRF.

10.6 Unanticipated Problems

10.6.1 Definition

An Unanticipated Problem (UP) is any incident, experience, or outcome that meets all of the following criteria:

• Unexpected (in terms of nature, severity, or frequency) given:
  a) The research procedures that are described in the study-related documents, including study deviations, as well as issues related to compromise of participant privacy or confidentiality of data.
  b) The characteristics of the participant population being studied.

• Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).

• Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized and if in relation to an AE is also deemed Serious per Section 10.3.

10.6.2 Reporting Unanticipated Problems

Unanticipated problem reporting will begin at the time of participant consent. The Unanticipated Problem Form will be submitted to the CRS Compliance Office within 1 business day of becoming aware of the Unanticipated Problem. After review, CRS Compliance will submit the UP to the IRB.

When becoming aware of new information about an Unanticipated Problem, submit the updated information to CRS Compliance with an updated Unanticipated Problem Form. The site Investigator or designated research personnel will report all unanticipated problems, whether related or unrelated to the investigational agent(s) to the IRB in accordance with their local institutional guidelines.

10.7 FDA Reporting

When RPCI is the IND holder the following describes the FDA reporting requirements by timeline for AEs and new safety findings that meet the criteria outlined below:

Within 7 Calendar Days

Any adverse event that meets ALL the following criteria:

• Related or possibly related to the use of the study drug;
• Unexpected; and
• Fatal or life-threatening.

**Within 15 Calendar Days**

Any adverse event that meets **ALL** the following criteria:

• Related or possibly related to the use of the study drug;
• Unexpected; and
• Serious but not fatal or life-threatening;

Or, meets **ANY** of the following criteria:

• A previous adverse event that is not initially deemed reportable but is later found to fit the criteria for reporting (report within 15 days from when event was deemed reportable).
• Any findings from other studies, including epidemiological studies, pooled analysis of multiple studies, or other clinical studies conducted with the study drug that suggest a significant risk in humans exposed to the drug.
• Any findings from animal or in vitro testing that suggest a significant risk for human participants including reports of mutagenicity, teratogenicity, or carcinogenicity or reports of significant organ toxicity at or near the expected human exposure.
• Any clinically important increase in the rate of occurrence of a serious, related or possibly related adverse event over that listed in the protocol or investigator brochure.

Sponsors are also required to identify in IND safety reports, all previous reports concerning similar adverse events and to analyze the significance of the current event in the light of the previous reports.

**Reporting Process**

The principal investigator or designee will complete and submit a FDA Form 3500A MedWatch for any event that meets the above criteria. Forms will be submitted to the CRS Compliance Office via email to **CRSCompliance@RoswellPark.org**.

**11 DATA AND SAFETY MONITORING**

The RPCI Data and Safety Monitoring Board will assess the progress of the study, the safety data, and critical efficacy endpoints. The DSMB will review the study annually and will make recommendations that include but not limited to: (a) continuation of the study, (b) modifications to the design (c) or termination of the study.

**12 STATISTICAL METHODOLOGY**

The **primary objective** of this study is:

• To evaluate improvement in progression-free survival for patients treated with anti-PD1 pembrolizumab in combination with IV bevacizumab and oral metronomic
cyclophosphamide as compared to a historical control. Data will be collected to be used for final analysis (Clinical Data Appendix).

The **secondary objectives** of this study are:

- To obtain pilot data on clinical response rates using both RECIST1.1 criteria (Response Evaluation Criteria in Solid Tumors) and immune related response criteria (irRECIST).
- To obtain data on changes in tumor microenvironment prior to and subsequent to therapy and, to screen for potential biomarkers to predict clinical benefit.
- To determine the safety and tolerability of the treatment combination in the study population.
- To evaluate overall survival in patients treated with anti-PD1 pembrolizumab in combination with IV bevacizumab and oral metronomic cyclophosphamide.
- To assess the impact of the combination of anti-PD1 pembrolizumab, IV bevacizumab and oral metronomic cyclophosphamide on anti-tumor immune responses in ovarian cancer.

**12.1 Sample Size Determination**

The primary objective of the Phase II study is to evaluate the progression-free survival (PFS) for patients treated with pembrolizumab in combination with IV bevacizumab and oral metronomic cyclophosphamide in women with recurrent/persistent platinum–sensitive, -resistant, or -refractory ovarian, primary peritoneal, or fallopian tube cancers. The median PFS of platinum resistant ovarian cancer patients treated with standard chemotherapy is approximately 3.5 months. In a recent study, platinum-resistant ovarian cancer patients treated with a combination of IV bevacizumab and oral metronomic cyclophosphamide (61) a median PFS and overall survival (OS) of 4.5 and 10.7 months, respectively. In another study, patients with recurrent ovarian treated with bevacizumab plus low-dose metronomic oral cyclophosphamide (62) had a median response duration of 3.9 months. Therefore we would consider a PFS of 7 months or greater to be of interest in this population.

Based on this we expect that no more than 30% of patients treated with standard chemotherapy would achieve 7 months of PFS. Therefore, we will test the null hypothesis that the 7-month PFS rate (π) in patients treated with pembrolizumab 200 mg IV + bevacizumab 15 mg/kg every 3 weeks IV + cyclophosphamide 50 mg po every day combination therapy is less than or equal to 30% versus the one-sided hypothesis that it is greater than 30%. That is:

\[ H_0: \pi \leq 0.30 \]
\[ H_A: \pi > 0.30 \]

Where \( \pi \) is the 7-month PFS rate.

Consider a sample size of n=40 patients (including 5 patients from the safety cohort), with up to 1 year of follow-up, and a maximum drop-out rate of 10%. If the true 7-month PFS rate is 50% (a median PFS of 7 months) for the proposed treatment combination, then a one-sided Wald-type test has approximately an 86.1% chance of resulting in significance. A nominal significance
level of 10% is considered, this would be the probability of erroneously finding a truly ineffective treatment as worthy of further research.

The study will thus enroll 40 evaluable patients in total, with 5 in the safety cohort and an additional 35 to complete the Phase II study. The accrual is expected to take 18 months.

12.2 Demographics and Baseline Characteristics

Descriptive statistics (as appropriate: n, percent, mean, median, min and max) will be used to summarize demographic and baseline characteristics.

12.3 Phase II Analysis

12.3.1 Safety Lead-in Cohort

A safety lead-in cohort of n₁=5 patients will be enrolled and the safety/tolerability of the combination will be examined after each patient completes at least 3 cycles. If 2 or less patients have experienced a drug related toxicity requiring drug/treatment delay or suspension (as defined in Sections 6.4, 6.5, and 6.7.3), then an additional n₂=35 patients are enrolled to complete the Phase II study. Otherwise, the study will be suspended and the research team (to include RPCI Phase I committee, Study PI and study statistician) will meet to discuss possible safety concerns and will decide what actions to take with respect to study continuation.

If the true SAE rate of the proposed treatment combination is 0.30, then there is an 83% chance of continuing study enrollment. Additional scenarios are given below:
12.3.2 Primary Objective

The primary endpoint is progression free survival (PFS). The PFS will be treated as bivariate time-to-event data, where an event indicator variable (0=censored, 1=event) is paired with a continuous time variable. Patients who are progression-free and still on treatment at last follow-up or those who drop-out of the study, for any reason, will be considered censored events; while patients who experience disease progression or death from disease will be considered PFS events. The PFS time will be measured as the time from the start of the study treatment until PFS event, last follow-up or drop-out.

The primary analysis will consider the following hypotheses about the 7 month PFS rate ($\pi$) in women with recurrent/persistent platinum–sensitive, -resistant, or -refractory ovarian, primary peritoneal, or fallopian tube cancers treated with pembrolizumab in combination with IV bevacizumab and oral metronomic cyclophosphamide:

$H_0: \pi \leq 0.30$

$H_A: \pi > 0.30$

These hypotheses will be assessed using the set of patients whom completed at least 1 cycle treatment or those who stopped the first cycle due to disease progression or toxicity. The PFS will be summarized using standard Kaplan-Meier methods, from which an estimate of the 7-month survival rate and corresponding standard error will be obtained using the methods proposed by Breslow and Day (83). A Wald type test, utilizing these estimates, will be used to evaluate the given hypotheses. These methods have been applied to survival outcomes in similar settings (84). All analysis will be conducted in SAS v9.4 (Cary, NC) at a significance level of 0.10.

12.3.3 Secondary Objectives

The frequency of toxicities, AE’s and SAE’s, will be tabulated by grade (as appropriate) across all dose levels and cycles. The toxicity, AE and SAE, rates will be estimated using 90% confidence intervals, which will be obtained using Jeffreys prior method. All participants who receive any study treatment will be considered evaluable for these outcomes.

The overall and progression free survival will be summarized using standard Kaplan-Meier methods, with estimates of median survival and given survival rates will be obtained with 90% confidence intervals.

Objective tumor response will be tabulated for all patients that completed at least three cycles of the proposed treatment combination. The response rate will be estimated using 90% confidence intervals, obtained using Jeffreys prior method.
The plasma and tumor biomarkers will be reported using the appropriate descriptive statistics. Associations between these markers and PFS will be evaluated using Cox regression models; while associations with tumor response will be evaluated using logistic regression models.

12.4 Interim Analysis and Criteria for Early Termination of the Study

No additional explicit interim analyses or early termination criteria are planned for the Phase II study. However, the toxicity and safety outcomes will be reviewed regularly through the DSMB.

13 ETHICAL AND REGULATORY STANDARDS

13.1 Ethical Principles

This study will not be initiated until the protocol and informed consent document(s) have been reviewed and approved by a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Each participant (or legal guardian) shall read, understand, and sign an instrument of informed consent prior to performance of any study-specific procedure. It is the responsibility of the investigator to ensure that the participant is made aware of the investigational nature of the treatment and that informed consent is given.

The Investigator is responsible for the retention of the participant log and participant records; although personal information may be reviewed by authorized persons, that information will be treated as strictly confidential and will not be made publicly available. The investigator is also responsible for obtaining participant authorization to access medical records and other applicable study specific information according to Health Insurance Portability and Accountability Act regulations (where applicable).

This study will be conducted in compliance with all applicable laws and regulations of the state and/or country and institution where the participant is treated. The clinical trial should be conducted in accordance with the ethical principles embodied in the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, consistent with good clinical practice and the applicable regulatory requirements and according to the guidelines in this protocol, including attached appendices.

13.2 Informed Consent

The Investigator (or IRB specified designee) is responsible for obtaining written consent from each participant or the participant's legally authorized representative in accordance with GCP guidelines using the approved informed consent form, before any study specific procedures (including screening procedures) are performed. The informed consent form acknowledges all information that must be given to the participant according to applicable GCP guidelines, including the purpose and nature of the study, the expected efficacy and possible side effects of the treatment(s), and specifying that refusal to participate will not influence further options for therapy. Any additional information that is applicable to the study must also be included. Additional national or institutionally mandated requirements for informed consent must also be adhered to. The participant should also be made aware that by signing the consent form, processing of sensitive clinical trial data and transfer to other countries for further processing is allowed.
The Investigator shall provide a copy of the signed consent form to the participant and the signed original shall be maintained in the Investigator File. A copy of the signed consent form must be filed in the participant file. At any stage, the participant may withdraw from the study and such a decision will not affect any further treatment options.

14 STUDY RESPONSIBILITIES

14.1 Data Collection

Data entry into the database is to be completed in a timely fashion after the participant’s clinic visit. If an AE is considered serious it is captured on both the Adverse Event page and the Serious Adverse Event Source Form, which is handled in an expedited fashion.

Data management activities will be performed using eClinical. eClinical is a suite of software tools that enables the collection, cleaning and viewing of clinical trial data. CRS data management will design the study-specific database and facilitate its development by the eClinical Information Technology team. Once the database design is approved by the Investigator, Statistician, and Clinical Research Coordinator, the database will be put into production and data entry can begin. Data can be entered and changed only by those with the rights to do so into the eCRFs (via the EXPeRT Module). eClinical is compliant with all relevant technical aspects of relevant GCP guidelines.

- The system can generate accurate copies of stored data and audit trail information in human readable form.
- System access is limited to authorized individuals through the controlled assignment of unique ID and password combinations.
- The system is designed to periodically force users to change their passwords and verifies that user ID and password combinations remain unique.
- The system automatically generates a permanent time-stamped audit trail of all user interactions.

When data entry is complete, data management will review the data and will query any missing, incomplete, or invalid data points for resolution by the Clinical Research Coordinator and Investigator. Once all queries have been resolved, the data can be released to the statistician for analysis.

14.2 Maintenance of Study Documents

Essential documents will be retained per RPCI’s policy for 6 years from the study termination date. These documents could be retained for a longer period, however, if required by the applicable local regulatory requirements or by an agreement with RPCI.
15 ADMINISTRATIVE RULES

15.1 Revisions to the Protocol

RPCI may make such changes to the protocol as it deems necessary for safety reasons or as may be required by the U.S. FDA or other regulatory agencies. Revisions will be submitted to the IRB/ERC for written approval before implementation.

15.2 Termination of the Study

It is agreed that, for reasonable cause, either the RPCI Investigators or Merck, may terminate this study, provided a written notice is submitted within the time period provided for in the Clinical Trial Agreement. In addition, RPCI may terminate the study at any time upon immediate notice if it believes termination is necessary for the safety of participants enrolled in the study.

Merck’s Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

- Quality or quantity of data recording is inaccurate or incomplete
- Poor adherence to protocol and regulatory requirements
- Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
- Plans to modify or discontinue the development of the study drug

In the event of Merck’s decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

15.3 Confidentiality

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.
16 APPENDICES
## Appendix A  ECOG Performance Status Scores

<table>
<thead>
<tr>
<th>Description</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully active, able to carry on all pre-disease performance without restriction.</td>
<td>0</td>
</tr>
<tr>
<td>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.</td>
<td>1</td>
</tr>
<tr>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities.</td>
<td>2</td>
</tr>
<tr>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.</td>
<td>3</td>
</tr>
<tr>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.</td>
<td>4</td>
</tr>
<tr>
<td>Dead</td>
<td>5</td>
</tr>
</tbody>
</table>
Appendix B  Calculation for Creatinine Clearance

Cockroft-Gault Equation*

Men: \[ \text{CrCl} = \frac{[(140 - \text{YR}) \times \text{IBW}]}{\text{SCr} \times 72} \]

Women: \[ \text{CrCl} = 0.85 \times \frac{[(140 - \text{YR}) \times \text{IBW}]}{\text{SCr} \times 72} \]

Where:

- \( \text{CrCl} \) is creatine clearance (mL/min)
- \( \text{IBW} \) is ideal body weight (kg)
- \( \text{SCr} \) is serum creatinine (mg/dL)
- \( \text{YR} \) is age (years)

Appendix C  Procedure for Obtaining a Urine Protein Creatinine Ratio (UPCR)

1. Obtain at least 4 ml of a random urine sample in a sterile container (does not have to be a 24-hour urine)
2. Determine protein concentration (mg/dL)
3. Determine creatinine concentration (mg/dL)
4. Divide #2 by #3 above:

\[
UPCR = \frac{\text{protein concentration (mg/dL)}}{\text{creatinine concentration (mg/dL)}}
\]

The UPC directly correlates with the amount of protein excreted in the urine per 24 hr (i.e., a UPC of 1 should be equivalent to 1 g protein in a 24 hr urine collection).

For the purpose of this study, participant must have a Urine Protein Creatine Ratio (UPCR) < 1 prior to enrollment and \(\leq 3.5\) for any subsequent cycles.
## Appendix D  Laboratory Tests

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Chemistry</th>
<th>Urinalysis</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>Albumin</td>
<td>Blood</td>
<td>Serum β-human chorionic gonadotropin (β-hCG)†</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Alkaline phosphatase</td>
<td>Glucose*</td>
<td>PT (INR)</td>
</tr>
<tr>
<td>Platelet count</td>
<td>Alanine aminotransferase (ALT)</td>
<td>Protein</td>
<td>aPTT</td>
</tr>
<tr>
<td>WBC (total and differential)</td>
<td>Aspartate aminotransferase (AST)</td>
<td>Specific gravity</td>
<td>Total triiodothyronine (T3)</td>
</tr>
<tr>
<td>Red Blood Cell Count</td>
<td>Lactate dehydrogenase (LDH)</td>
<td>Microscopic exam (If abnormal)</td>
<td>Free thyroxine (T4)</td>
</tr>
<tr>
<td>Absolute Neutrophil Count</td>
<td>Carbon Dioxide (CO₂ or bicarbonate)‡</td>
<td>results are noted</td>
<td>Thyroid stimulating hormone (TSH)</td>
</tr>
<tr>
<td>Absolute Lymphocyte Count</td>
<td>Uric Acid</td>
<td>Urine pregnancy test †</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcium</td>
<td>UPCR</td>
<td>Blood for correlative studies</td>
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<tr>
<td></td>
<td>Chloride</td>
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<tr>
<td></td>
<td>Glucose*</td>
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<td></td>
<td>Phosphorus</td>
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<td></td>
<td>Potassium</td>
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<td></td>
<td>Sodium</td>
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<td></td>
<td>Magnesium</td>
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<td></td>
<td>Total Bilirubin</td>
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<td></td>
<td>Direct Bilirubin (If total bilirubin is elevated above the upper limit of normal)</td>
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<td></td>
<td>Total protein</td>
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<td></td>
<td>Blood Urea Nitrogen</td>
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<td></td>
<td>Creatinine</td>
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*If patient has a random blood glucose value $\geq 200$ mg/dL: a fasting blood sugar level and Hemoglobin A1C will be obtained within 48 hours and, treatment will be held until the patient is clinically and metabolically stable – this will be determined by the treating physician.

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

‡ If considered standard of care in your region.
### Appendix E  Medication Diary

**Study No.:** ____________  
**Subject’s Name:** ________________________________  
**Drug Name:** ____________  
**Cycle #:** _____  
**Medical Record No.:** __________________________

#### Study Medication Calendar for Cyclophosphamide

You should swallow your medication whole: without cutting, chewing, or crushing. The capsule should be taken in the morning (with or without food) and, it is recommended to drink 2-3 quarts of fluid per day. Wash your hands immediately if you touch a broken tablet.

Please complete this calendar on a **daily basis** immediately after you take your capsule. Fill in the date for each day and write the total number of capsules you take each day. Take 1 capsule each day, in the morning (with or without food).

**Start Date:** ______________

<table>
<thead>
<tr>
<th>Cycle Day</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
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<tr>
<th>Cycle Day</th>
<th>Day 8</th>
<th>Day 9</th>
<th>Day 10</th>
<th>Day 11</th>
<th>Day 12</th>
<th>Day 13</th>
<th>Day 14</th>
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<tbody>
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<td>Date</td>
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<tr>
<td>Number of capsules taken</td>
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<tr>
<th>Cycle Day</th>
<th>Day 15</th>
<th>Day 16</th>
<th>Day 17</th>
<th>Day 18</th>
<th>Day 19</th>
<th>Day 20</th>
<th>Day 21</th>
</tr>
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<td>Date</td>
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<td>Number of capsules taken</td>
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<tr>
<th>Cycle Day</th>
<th>Day 29</th>
<th>Day 30</th>
<th>Day 31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of capsules taken</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please remember to bring this calendar with you to your next clinic appointment.
% Compliance = \left( \frac{\text{Number of Pills Taken}}{\text{Number of Pills Scheduled}} \right) \times 100

% Compliance = \left( \frac{\text{}}{\text{}} \right) \times 100

Subject’s signature: __________________________________________ Date: __________
CRC’s signature: __________________________________________ Date: __________
Investigator’s Signature: ______________________________________ Date: __________
## Appendix F  NYHA Functional Classification System

### New York Heart Association (NYHA) Congestive Heart Failure (CHF) Functional Classification System

<table>
<thead>
<tr>
<th>Class</th>
<th>Functional Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA Class I</td>
<td>Cardiac disease, but no symptoms and no limitation in ordinary physical activity (e.g., shortness of breath when walking, climbing stairs, etc.).</td>
</tr>
<tr>
<td>NYHA Class II</td>
<td>Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.</td>
</tr>
<tr>
<td>NYHA Class III</td>
<td>Marked limitations in activity due to symptoms, even during less-than-ordinary activity [e.g., walking short distance (20-100 m)]. Comfortable only at rest.</td>
</tr>
<tr>
<td>NYHA Class IV</td>
<td>Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.</td>
</tr>
</tbody>
</table>

---

Appendix G  EORTC QLQ-C30

EORTC QLQ-C30 (version 3)
We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:  
Your birthdate (Day, Month, Year):  
Today's date (Day, Month, Year): 31

<table>
<thead>
<tr>
<th></th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Do you have any trouble taking a long walk?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Do you have any trouble taking a short walk outside of the house?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Do you need to stay in bed or a chair during the day?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Do you need help with eating, dressing, washing yourself or using the toilet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

During the past week:

<table>
<thead>
<tr>
<th></th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Were you limited in doing either your work or other daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Were you limited in pursuing your hobbies or other leisure time activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. Were you short of breath?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. Have you had pain?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. Did you need to rest?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11. Have you had trouble sleeping?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12. Have you felt weak?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13. Have you lacked appetite?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14. Have you felt nauseated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15. Have you vomited?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>16. Have you been constipated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Please go on to the next page
During the past week:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>17. Have you had diarrhea?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18. Were you tired?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19. Did pain interfere with your daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20. Have you had difficulty in concentrating on things,</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>like reading a newspaper or watching television?</td>
<td></td>
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</tr>
<tr>
<td>21. Did you feel tense?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>22. Did you worry?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>23. Did you feel irritable?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>24. Did you feel depressed?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>25. Have you had difficulty remembering things?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>26. Has your physical condition or medical treatment</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>interfered with your family life?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27. Has your physical condition or medical treatment</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>interfered with your social activities?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28. Has your physical condition or medical treatment</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>caused you financial difficulties?</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?  
    1   2   3   4   5   6   7
    Very poor   Excellent

30. How would you rate your overall quality of life during the past week?  
    1   2   3   4   5   6   7
    Very poor   Excellent
## Appendix H  EORTC OLQ-OV28

### EORTC QLQ - OV28

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

<table>
<thead>
<tr>
<th>During the past week:</th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>31. Did you have abdominal pain?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>32. Did you have a bloated feeling in your abdomen / stomach?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>33. Did you have problems with your clothes feeling too tight?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>34. Did you experience change in bowel habit as a result of your disease or treatment?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>35. Were you troubled by passing wind / gas / flatulence?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>36. Have you felt full up too quickly after beginning to eat?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>37. Have you had indigestion or heartburn?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>38. Have you lost any hair?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>39. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>40. Did food and drink taste different from usual?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>41. Have you had tingling hands or feet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>42. Have you had numbness in your fingers or toes?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>43. Have you felt weak in your arms or legs?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>44. Did you have aches or pains in your muscles or joints?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>45. Did you have problems with hearing?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>46. Did you urinate frequently?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>47. Have you had skin problems (e.g. itchy, dry)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>48. Did you have hot flushes?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>49. Did you have night sweats?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Please go on to next page
During the past week:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>50. Have you felt physically less attractive as a result of your disease or treatment?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>51. Have you been dissatisfied with your body?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>52. How much has your disease been a burden to you?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>53. How much has your treatment been a burden to you?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>54. Were you worried about your future health?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

During the past 4 weeks:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>55. To what extent were you interested in sex?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>56. To what extent were you sexually active?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Answer the following two questions only if you were sexually active:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>57. To what extent was sex enjoyable for you?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>58. Did you have a dry vagina during sexual activity?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
17 REFERENCES


