TITLE: Phase 2 Study of Paclitaxel, Pembrolizumab and Olaparib in Previously Treated Advanced Gastric Adenocarcinoma

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Merck Supplied Agents: Pembrolizumab (MK-3475; anti-programmed death-1 monoclonal antibody)
Olaparib (poly-(adenosine diphosphate)-ribose) polymerase inhibitor)

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1. OBJECTIVES

1.1. Primary Objective

1.1.1 To estimate overall survival in patients with previously treated advanced gastric cancer (GC) who are treated with paclitaxel plus olaparib and pembrolizumab.

1.2. Secondary Objective

1.2.1. To assess safety and characterize toxicities of paclitaxel plus olaparib and pembrolizumab in patients with previously treated advanced GC.

1.3. Exploratory Objectives

1.3.1. To assess progression free survival (PFS), time to progression (TTP), objective response rate (ORR), disease control rate (DCR), best overall response (BOR), duration of response (DOR), duration of clinical benefit (DCB), and time to objective response (TTOR) in patients with previously treated advanced GC who are treated with paclitaxel, olaparib and pembrolizumab using RECIST 1.1 and by immune-related response criteria (iRECIST).

1.3.2. To collect archival tissue (when available) and pre- and on-treatment biopsies to explore the association of features of the tumor microenvironment with response to therapy, including assessment of T cell subset markers (CD4, CD8, FoxP3, Granzyme A/B, CD69), immune regulation (PD-L1, PD-L2, CTLA4, LAG-3, IDO1, TIM-3), and immune cell population markers (NK, DC, B cell, MDSC).

1.3.3. To evaluate molecular determinants of response using next generation sequencing and other sequencing techniques.

1.3.4. To assess tumor burden dynamics using standard protein biomarkers when available as well as circulating biomarkers (i.e. ctDNA).

1.3.5. To collect peripheral blood mononuclear cells for analysis including but not limited to the association of lymphocyte activation markers with clinical response.

1.3.6. To collect stool and oral wash (and/or buccal mucosal) samples at baseline and throughout treatment to explore the association of changes in the host microbiome and clinical outcome.

- Microbial community analyses to correlate gut microbiome composition with response (OS, PFS and best overall response).

- Whole metagenome functional profiling analysis via shotgun sequencing to correlate microbiome composition and microbial functions and pathways with response (OS, PFS and best overall response).

1.4. Study Design

This is an open-label, phase 2 study to evaluate the safety and clinical activity of paclitaxel, olaparib and pembrolizumab in patients with previously treated advanced GC.

The study will consist of a screening period (within 28 days of the first dose), a treatment period, and a follow-up period. Treatment will consist of one 21-day cycle of pembrolizumab and olaparib (Cycle 1), followed by pembrolizumab, olaparib, and paclitaxel treatment on 21-day cycles (Cycles 2+). Subjects will come to clinic for dosing and/or assessments on Day 1 of Cycle 1, then on Day 1 and 8 for the following cycles, and on Day 15 for Cycle 2 only, as per the study schedule in **Section 9.** Dose reductions of paclitaxel and/or olaparib will be permitted as indicated for toxicities; no dose reductions of pembrolizumab will be allowed. Subjects may be permitted to discontinue paclitaxel for intolerance after Cycle 2 or if they achieve confirmed response or stable disease and received at least 6 months of treatment, and can start maintenance therapy with pembrolizumab and olaparib. Visits for dosing and/or assessments will occur every 21 days while on the maintenance phase. Complete information on study drug administration, schedule, and dosing can be found in **Section 4** and the study calendar (**Section 9**).

Tumor biopsies, whole blood, PBMC, serum and plasma collection, and computed tomography (CT) scans or magnetic resonance imaging (MRI), if CT is contraindicated or MRI is preferred, will be obtained at baseline and during treatment for clinical assessments and correlative analyses. Tumor assessments will be made using RECIST 1.1 and iRECIST.

Subjects who have measurable disease per RECIST 1.1 will be enrolled into Cohort 1, and subjects who have unmeasurable disease by RECIST 1.1 will be enrolled into Cohort 2. Enrollment will continue until 24 subjects have been enrolled into Cohort 1, and 12 subjects have been enrolled into Cohort 2, with a total of 36 subjects receiving at least one dose of the three-drug combination. The primary endpoint is overall survival (OS) from start of treatment. The regimen will be considered to be inactive and of no interest for further evaluation if the median OS is 7 months or less (corresponding to the 12-month survival rate of 30% or less, and is considered active if the median OS is 10.5 months (corresponding to the 12-month survival rate of 45% or greater).

Treatment may continue up to a maximum of 2 years, or until discontinuation due to toxicity, lack of clinical benefit as determined by the investigator, subject withdrawal, or termination of the study by Principal Investigator. Subjects may continue on treatment with radiographic disease progression if subject is clinically stable and investigator believes the treatment is providing benefit. Criteria for removal from treatment are found in **Section 4.8**.

Subjects will return to the study site 30 (+/- 7) days after the final administration of study treatment for an end-of-treatment (EOT) evaluation and AE assessment. Subjects will be considered in the treatment period until 30 days after the last dose of study drug. Subjects will also be contacted 90 days (+14-day reporting window) from the last dose of study drug for safety follow-up. Complete information on safety reporting can be found in **Section 6.3**.

After completion of treatment and EOT assessments, all subjects will continue to be followed per standard of care by telephone, e-mail, or optional clinic visit until death, withdrawal of consent, or closure of study. Information on survival and new cancer therapies will be collected.

All subjects who discontinue study treatment should continue to be monitored for disease status by radiologic imaging every 9 weeks (+/- 4 weeks) until: 1) the start of a new antineoplastic therapy (information of the new cancer therapy will be collected), 2) disease progression, 3) death, 4) withdrawal of consent, or 5) the close of the study, whichever occurs first.

All subjects will be followed after their last dose of study drug for the development of adverse events (AEs) and serious adverse events (SAEs) as described in **Section 6.3.**

The primary analysis will be conducted when the first of the following has occurred: all treated subjects have reached 12 months from Cycle 1, Day 1 or have discontinued the study. Information on survival may continue to be gathered for supplementary analyses after the completion of the primary analysis.

2. BACKGROUND

2.1. Study Disease

Gastric cancer (GC) is common worldwide, representing the 3rd most common cancer in men and 4th most common in women (*1*). While declining in incidence in many countries including the US, likely as a result of changing dietary habits and reduction in H. pylori infections, mortality at advanced stages remains high, with an estimated five year survival rate in the advanced setting of a dismal 5% (*2*). Latency of diagnosis and lack of effective treatment options likely contribute to poor outcomes.

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (*3*). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma (*4, 5*).

The programmed cell death-1 (PD-1) receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (*6, 7*).

The structure of murine PD-1 has been resolved (*8*). PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (*7, 9-11*). The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (*12, 13*). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in GC.

In the last year, the immune checkpoint inhibitors targeting PD-1 have shown promise in the treatment of many cancers including GC and are now entering the standard of care. The PD-1 inhibitor pembrolizumab received FDA approval for PD-L1-overexpressing GC in the third line and beyond, based on the results of Keynote-059. In this study, 259 patients with gastric or GEJ cancer that was PD-L1 positive (≥1% tumor or stromal expression) were treated with pembrolizumab 200 mg every 3 weeks. Objective response was observed in 16%, including 2% complete responses (*14*). Additionally, the PD-1 inhibitor nivolumab has received regulatory approval in Japan based on the results of the phase 3 ATTRACTION-2 trial, in which nivolumab demonstrated superior survival compared to placebo in the third line and beyond for advanced GC/GEJ cancers. While the potential for deep and durable response is encouraging, the overall response rate to these agents even in a biomarker selected population remains disappointingly low. Improved biomarkers for patient selection are needed and rationally designed combination strategies may further enhance the activity of these agents.

Increasingly, a genetic basis of susceptibility to immunotherapy is emerging, and, in particular, PD-1 inhibitors have demonstrated high levels of activity in tumors harboring DNA damage and high numbers of mutations. DNA repair defects, therefore, may be utilized in patient selection for immunotherapy. In particular, exceptionally high response rates have been observed to PD-1 inhibitor monotherapy in cancers deficient in mismatch repair (dMMR), likely as a result of high mutation burden and the production of immunogenic neoantigens (*15, 16*).

An enhanced understanding of the molecular heterogeneity of GC is providing some insights into subgroups with potential to benefit from immunotherapy. Specifically, data from the Cancer Genome Atlas supported classification of gastric adenocarcinoma into four subgroups: Epstein-Barr virus (EBV) positive tumors, microsatellite unstable tumors, genomically stable tumors, and tumors with chromosomal instability. EBV-positive tumors were notably characterized by high PD-L1/2 overexpression and immune cell signaling. As in other tumors, MSI was associated with hypermutation, MLH1 silencing and upregulation of mitotic pathways (*17*).

In GC, dMMR is present in nearly 10% overall, but less than 5% of late stage cases; however, other DNA repair defects are prevalent, particularly in the homology-dependent recombination (HR) pathway, and this represents another potential therapeutic vulnerability. In particular,

alterations in the ataxia telangiectasia mutated (ATM) gene are prevalent in GC, occurring in approximately 7-12% of cases (*18, 19*).

2.2. Rationale

PARP Inhibition in Gastric Cancer

Cancers deficient in ATM and other proteins in the HR pathway may exhibit a "BRCAness" phenotype similar to what is observed with germline BRCA defects, and in particular may exhibit sensitivity to synthetic lethality induced by inhibitors of Poly (ADP-Ribose) Polymerase (PARP). Furthermore, PARP inhibitors may sensitize cancers to chemotherapy by blocking repair of chemotherapy-induced DNA damage (*20*). The combination of the PARP inhibitor olaparib plus paclitaxel demonstrated enhanced survival in the second line for advanced GC in a phase II study, particularly in patients with tumors that poorly expressed ATM (*21*). The larger randomized phase 3 GOLD trial failed to meet its primary endpoint for superiority of paclitaxel plus the PARP inhibitor olaparib over paclitaxel alone in the second line for advanced GC, regardless of ATM expression; however, a modest improvement in overall survival was observed (8.8 vs 6.9 months respectively, p=0.026) suggesting further exploration of the use of these agents is warranted (*22*).

Rationale for Dual Inhibition of PARP and PD-1

In addition to synthetic lethality induced by PARP inhibitors, an immunomodulatory effect has been observed in preclinical models with upregulation of PD-L1 expression (*23*) and CD8 and NK cell infiltration in the tumor microenvironment (*24*). There is therefore strong rationale for combining PARP and PD-1 inhibitors and this is an active area of investigation in several ongoing trials. Preliminary results of a phase 1b trial of the PARP inhibitor pamiparib plus the PD-1 inhibitor tislelizumab in advanced heavily-pretreated cancers of multiple types were recently reported, and demonstrated promising activity with an objective response rate of 20%, including two complete responses (4%). Notably, responses were observed in both BRCA mutant and wild-type cancers (*25*). The ongoing phase II MEDIOLA is evaluating the PD-L1 inhibitor durvalumab with the PARP inhibitor olaparib in *BRCA1/2*-mutated cancers, and recently reported an 80% DCR at 12 weeks in *BRCA1/2*-mutated HER2-negative metastatic breast cancer (*26*). Another phase I trial of the PD-L1 inhibitor durvalumab plus olaparib in women's cancers reported an ORR of 17% (2 responses out of 12) and a DCR of 83%; of note, 11 of the 12 tumors were confirmed negative for *BRCA* mutations and the remaining one tumor was unconfirmed (*27*).

Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to PD-1, thus inhibiting its interaction with PD-L1 and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator Brochure.

Justification for Dose

The FDA approved dose for olaparib is 300 mg twice a day orally (Q12h). In the Gold study, olaparib was decreased (100 mg twice a day) when given in combination with paclitaxel (*22*).

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg (Q2W), representing an approximate 5- to 7.5-fold exposure range
- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

3. PATIENT SELECTION

3.1. Inclusion Criteria

3.1.1. Age ≥18 years.

3.1.2. ECOG performance status of 0-1 (**Appendix A**).

3.1.3. Advanced histologically-confirmed gastric or gastro-esophageal junction adenocarcinoma.

3.1.4. Patients must have received only one prior line of systemic therapy for advanced disease and experienced disease progression on this regimen.
- Prior therapy must include a fluoropyrimidine and platinum-based regimen.
- Adjuvant/neoadjuvant chemotherapy may be considered as a prior regimen per PI discretion.

3.1.5. For Cohort 1 only: Have measurable disease based on RECIST 1.1. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. *Note:* This eligibility criterion is not applicable for those enrolling into Cohort 2.

3.1.6. Patient agreeable to a biopsy of an accessible lesion at baseline and on treatment if the lesion can be biopsied with acceptable clinical risk (as judged by the investigator).

3.1.7. Life expectancy of greater than 3 months.

3.1.8. Patients must have normal organ and marrow function as defined below:

- Leukocytes ≥ 3,000/mm^3
- Absolute neutrophil count ≥ 1,500/mm^3
- Platelets ≥ 100,000/mm^3
- Hemoglobin ≥ 8 g/dL
- Total bilirubin ≤ 1.5 x ULN OR direct bilirubin ≤ULN if total bilirubin >1.5 x ULN
- AST(SGOT) and ALT(SGPT) ≤ 3 x ULN
- Creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 30 mL/min (if using the Cockroft-Gault formula below):

$$\textit{Female}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\textit{Male}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

3.1.9. A female participant is eligible to participate if she is not pregnant, (contraceptive guidance in Section **4.6.2**) not breastfeeding, and at least one of the following conditions applies:

a.) Not a woman of childbearing potential (WOCBP) as defined in **Section 0** OR
b.) A WOCBP who agrees to follow the contraceptive guidance in **Section 4.6.2 0** during the treatment period and for at least 120 days after the last dose of study treatment.

3.1.10. A male participant must agree to use a contraception as detailed in **Section 0** of this protocol during the treatment period and for at least 120 days after the last dose of study treatment and refrain from donating sperm during this period.

3.1.11. Patient understands the study regimen, its requirements, risks and discomforts and is able and willing to sign the informed consent form in accordance with regulatory and institutional guidelines must be obtained before the performance of any protocol related procedures that are not part of normal patient care. Subjects must be competent to report AEs, understand the drug dosing schedule and use of medications to control AEs.

3.2. Exclusion Criteria

3.2.1. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically and clinically 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 without requirement of steroids for at least 14 days prior to first dose of study treatment.

3.2.2. Is expected to require any other form of systemic or localized antineoplastic therapy while on study.

3.2.3. Has received prior therapy with paclitaxel or PARP inhibitor. Previous paclitaxel may be allowed if no progression on or within 6 months of receiving this drug.

3.2.4. History of severe hypersensitivity reaction to paclitaxel, pembrolizumab or related compounds and/or to any of their components.

3.2.5. Allergy to dexamethasone, diphenhydramine and famotidine.

3.2.6. Is taking a moderate or strong CYP3A inhibitor (see **Appendix B**).

3.2.7. Has uncontrolled intercurrent acute or chronic medical illness.

3.2.8. Has a known additional malignancy that is progressing and has required active treatment within the past 1 year. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or other cancers that have undergone potentially curative therapy are not excluded.

3.2.9. a) Has received prior systemic anti-cancer therapy including investigational agents within 2 weeks prior to study treatment.

b) Participants must have recovered from all AEs due to previous therapies to ≤ Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible.

c) If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.

3.2.10. Has received prior radiotherapy within 2 weeks of start of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis.

3.2.11. Has received a live vaccine or live attenuated within 30 days prior to the first dose of study drug. Administration of killed vaccines are allowed. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella,

varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

3.2.12. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment.

Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

3.2.13. Has active autoimmune disease. Subjects with Graves or Hashimoto's disease, vitiligo, type I diabetes mellitus, psoriasis or other conditions not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll. Subjects requiring systemic treatment for autoimmune disease in the past may be approved by the Principal Investigator.

3.2.14. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.

3.2.15. Prior tissue or organ allograft regardless of need for immunosuppression, including corneal allograft. Exceptions can be approved by the Principal Investigator if loss of the graft is not a clinical concern. Patients with history of allogeneic bone marrow transplantation will be excluded.

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

3.2.17. Requirement for daily supplemental oxygen.

3.2.18. Patients with a history of (non-infectious) pneumonitis/ interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.

3.2.19. Has a confirmed history of encephalitis, meningitis, or uncontrolled seizures in the year prior to informed consent.

3.2.20. Has a known history of Human Immunodeficiency Virus (HIV).

3.2.21. Has active Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

Patients who are Hepatitis C antibody positive and viral load negative will be permitted to enroll.

3.2.22. Has uncontrolled infection requiring systemic therapy.

3.2.23. Subjects unable to undergo venipuncture and/or tolerate venous access.

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

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

3.2.26. A WOCBP who has a positive urine pregnancy test within 72 hours prior to study drug initiation. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. In the case of a positive HCG test, a transvaginal ultrasound must be used to confirm lack of pregnancy.

3.3. Inclusion of Women and Minorities

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

4. TREATMENT PLAN

4.1. Agent Administration

Treatment will be administered on an outpatient basis. Appropriate dosing delays are described in **Section 5.** No investigational or commercial agents or therapies other than those described below in **Table 1** may be administered with the intent to treat the patient's malignancy.

Table 1: Trial Treatment

REGIMEN DESCRIPTION					
Agent	***Suggested Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Pembrolizumab	No prophylactic pre-medication will be given unless indicated by previous experience in an individual	200 mg	IV infusion over 30 (-10/+25) min*	Day 1	21 days

	subject per **Section 4.2**				
Olaparib	No premedication; taken approximately Q12h without regard to food	100 or 300 mg	Oral	Days 1-21	
Paclitaxel	Dexamethasone 10 mg IV, diphenhydramine 50 mg IV, famotidine 20 mg IV, all 30 minutes prior to dose. Ondansetron 16 mg IV	80 mg/m2	IV infusion over 60 (+/- 15) min*	Days 1 and 8 starting with Cycle 2[a]	

*Infusion times are approximate and may be adjusted based on subject tolerability.
[a] Paclitaxel dosing initiates after the completion of Cycle 1.

Please see **Section 7** for detailed information on drug preparation and administration. Please see **Sections 5.1-5.4** for guidance regarding dosing criteria/delays. Subjects that are required to stop treatment with olaparib, paclitaxel or pembrolizumab due to toxicity may stay on study and receive the other agents once the drug-related toxicity(s) has resolved to a grade 1. The relationship to the drug causing toxicity should be well documented in the source documents and permission from the Principal Investigator needs to be obtained prior to continuation with drug therapy. Subjects may be permitted to discontinue paclitaxel for intolerance after Cycle 2 or if they achieve confirmed response or stable disease and have received at least 6 months of treatment, and can start maintenance therapy with pembrolizumab and olaparib.

4.1.1. Paclitaxel

Paclitaxel will be administered as a 60 minute IV infusion. On day 1, pembrolizumab will be administered prior to paclitaxel, and subjects should be observed for a minimum of 30 minutes before administration of paclitaxel.

4.1.2. Olaparib

Subjects will self-administer their dose of olaparib in the morning and evening, approximately 12 hours apart, without regard to food. If a dose is missed by more than 4 hours, then that dose should be skipped and the next dose should be taken at the next scheduled time point. If a dose is vomited, it will be skipped.

There is no priority to the order of administration of olaparib with regard to other study drugs; however, the dose of olaparib should be taken as close to the regularly scheduled 12-hour dosing interval as possible.

4.1.2.1. Compliance with Olaparib

Olaparib compliance will be calculated based on the drug accountability documented by the site staff (pill counts). The objective is 100% compliance, and investigators and staff should evaluate compliance at each visit and take appropriate steps to optimize compliance.

4.1.3. Pembrolizumab

Pembrolizumab will be administered as a 30 minute IV infusion. Antiemetic medications should not be routinely administered prior to dosing of pembrolizumab. See **Table 2** for subsequent premedication recommendations following a pembrolizumab-related infusion reaction.

Table 2: Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose.	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

	Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment	
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

4.2. General Concomitant Medication and Supportive Care Guidelines

4.2.1. Paclitaxel

Acute reactions will be managed using standard therapy for acute drug reactions as per institutional guidelines.

4.2.1.1. Infusion Reactions

Paclitaxel and/or the Cremophor vehicle may cause severe or life-threatening allergic reactions. For this reason, all patients must receive premedication with dexamethasone, diphenhydramine and famotidine as per **Table 1**.

Patients should be monitored during paclitaxel administration per institutional policies. Acute reactions will be managed using standard therapy for acute drug reactions as per institutional guidelines. Please see **Section 5.3** for more information.

4.2.1.2. Common Drug-Related Toxicities

Toxicities considered to be associated with the administration of paclitaxel include: Anemia, alopecia, neuropathy, arthralgia, myalgia, nausea, vomiting, hypersensitivity reactions.

4.2.2. Olaparib

Acute reactions will be managed using standard therapy for acute drug reactions as per institutional guidelines.

4.2.2.1. Common Drug-Related Toxicities

Toxicities considered to be associated with the administration of olaparib include hematological effects (anemia, neutropenia, lymphopenia, leukopenia, thrombocytopenia, mean corpuscular volume [MCV] elevation), decreased appetite, nausea and vomiting, diarrhea, dyspepsia, stomatitis, upper abdominal pain, dysgeusia, fatigue (including asthenia), increase in blood creatinine, headache, dizziness, hypersensitivity, rash, dermatitis and cough.

4.2.3. Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin (Ig) G4 antibody. Subjects should be closely monitored for potential AEs during antibody infusion and potential AEs throughout the study.

4.2.3.1. Infusion Reactions

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Patients should be monitored during pembrolizumab administration per institutional policies. Acute reactions will be managed using standard therapy for acute drug reactions as per institutional guidelines. Dose modification and treatment guidelines for pembrolizumab infusion reaction are provided in **Table 2** in **Section 4.1.3**.

4.2.3.2. Immune-Related Adverse Events

Pembrolizumab may lead to a wide range of potential immune-related adverse events, some of which may be life-threatening, and which can occur at any time after initiating treatment. Dose modification and toxicity management guidelines for pembrolizumab-associated immune-related adverse events are provided in **Table 6** in **Section 5.4.1**.

4.3. Prohibited and/or Restricted Treatments

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

- Anti-neoplastic biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab and olaparib
- Radiation therapy
  *Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion as described in **Section 4.4**.
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology or as specified in **Sections 0** and **4.4. Premedication for infusion and/or tumor assessments are allowed.** The use of physiologic doses of corticosteroids may be approved after consultation with the Principal Investigator.
- Strong inhibitors or inducers of CYP3A4 or CYP2C9 (**Appendix B**). At the discretion of the investigator, subjects may be permitted to remain on study after receiving short courses of such medications if needed (i.e. to treat infection). Olaparib should be withheld during the course of treatment with a strong CYP3A4/CYP2C9 inhibitor or inducer.
- It is not recommended to consume grapefruit juice while on olaparib therapy.

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 study. All treatments that the 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.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Principal Investigator and the participant.

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

4.4. Permitted Therapy

All treatments that the 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 medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in **Section 6.3**.

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Immunosuppressive agents and the use of systemic corticosteroids are permitted in the context of treating AEs, prophylaxis prior to a diagnostic procedure (e.g. contrast MRI/CT scans) or as specified in **Section 4.2**. A brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy) is permitted.

Subjects may continue to receive hormone replacement therapy (HRT).

Palliative and supportive care for disease-related symptoms may be offered to all subjects on the trial.

If palliative radiotherapy in short courses and for isolated fields is required to control symptoms, then drug administration should be withheld, if possible, for at least 1 week before radiation and for at least 1 week after its completion. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy. Prior to resuming study drug treatment, radiotherapy-related AEs should resolve to ≤Grade 1 or baseline. The Principal Investigator must be consulted prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks after the last dose.

Details of palliative radiotherapy should be documented in the source records and electronic case report form (eCRF). Details in the source records should include: dates of treatment, anatomical site, dose administered, and AEs. Symptoms requiring palliative radiotherapy should be evaluated for objective evidence of disease progression. Subjects receiving palliative radiation of target lesions will have the evaluation of ORR just prior to radiotherapy but such subjects will no longer be evaluable for determination of response subsequent to the date palliative radiation occurs.

For subjects who need to undergo elective surgery during the study, it is recommended to hold study drug(s) for at least 2 weeks before and 2 weeks after surgery, or until the subject recovers from the procedure, whichever is longer. Prior to resuming study drug treatment, surgically-related AEs should resolve to ≤Grade 1 or baseline. The Prinicipal Investigator must be consulted prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks after the last dose.

4.5. Definition of an Overdose for this Protocol

For purposes of this study, 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.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met (see **Section 6.3** for reporting details).

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Principal Investigator and within 2 working days to Merck Global Safety. Merck contact information can be found in **Section 6.3.1.**

4.6. WOCBP, Contraception, Use in Pregnancy, Use in Nursing

4.6.1. Definition of Women of Childbearing Potential

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:Premenarchal

- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to

continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study Cycle 1, Day 1.

4.6.2. Contraception Requirements

Pembrolizumab may have adverse effects on a fetus in utero. Refer to **Table 3** for approved methods of contraception.

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

Male Participants:
Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in **Section 3.1**:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in **Table 3** when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
    - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:
Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in **Table 3** during the protocol-defined time frame in **Section 3.1**.

Table 3: Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b, c] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b, c] ○ Oral ○ Injectable

Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.) ● It is not necessary to use any other method of contraception when complete abstinence is elected. ● WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in **Section 9**. ● Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence.
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 120 days, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential, after the last dose of study treatment. c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

4.6.3. Use in Pregnancy

The investigational agents used in this protocol may have adverse effects on a fetus; therefore, women with a positive pregnancy test at screening will not be eligible for enrollment. If a participant inadvertently becomes pregnant while on treatment, the participant will be immediately discontinued from study treatment.

Protocol required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck within 2 working days if the outcome is a serious adverse experience (eg, 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. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported (see reporting procedures in **Section 6.3.5**).

4.6.4. 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, participants who are breast-feeding are not eligible for enrollment.

4.7. Duration of Therapy

Subjects who are clinically stable and meet dosing requirements (per **Section 5.1**) may continue to receive treatment for up to a maximum of 2 years.

4.8. Criteria for Removal from Treatment

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Principal Investigator if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at end of treatment are provided in the study calendar (**Section 9)**.

A participant must be discontinued from study treatment for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- Confirmed radiographic disease progression as defined in **Section 4.8.**1, RECIST 1.1 **(Appendix C)** and iRECIST **(Appendix D)**. **NOTE:** Treatment may continue under guidelines discussed in **Section 4.8.1** at the discretion of the Investigator.

- Significant clinical deterioration (clinical progression), defined as new symptoms that are deemed by the Investigator to be clinically significant or significant worsening of existing symptoms.
- Unacceptable adverse experiences are defined as any toxicity that requires permanent discontinuation as described in **Sections 4.8.2, 5.2.2, 5.3.2 and Table 6.**
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator, placed the participant at unnecessary risk from continued administration of study treatment (the Principal Investigator should be involved in this decision).
- The participant has a confirmed positive pregnancy test (urine).
- Major noncompliance with study treatment or procedure requirements
- Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving at least 2 cycles of the combination including 2 doses of pembrolizumab beyond the date when the initial CR was declared. These participants may be eligible to restart treatment where they left off if the cancer progressed; however, the total number of treatments is not to exceed 35 cycles.
- The participant is lost to follow-up
- Completion of 35 cycles of treatment (approximately 2 years)
  *Note: The number of treatments is calculated starting with the first dose.
- Administrative reasons

4.8.1. Disease Progression

Pembrolizumab is expected to trigger immune-mediated responses, which require activation of the immune system prior to the observation of clinical responses. Such immune activation may take weeks to months to be evident. Some subjects may have objective volume increase of tumor lesions or other disease parameters within weeks following the start of immunotherapy. Such subjects may not have had sufficient time to develop the required immune activation or, in some subjects, tumor volume or other disease parameter increases may represent infiltration of lymphocytes into the original tumor. In conventional studies, such tumor volume or relevant laboratory parameter increases during the first 2-4 months of the study would constitute disease progression and lead to discontinuation of imaging to detect response, thus disregarding the potential for subsequent immune-mediated clinical response. This phenomenon was observed in approximately 10% of subjects in the Phase 1 study of nivolumab and has also been reported for ipilimumab monotherapy (*28*).

Subjects will be permitted to continue with treatment beyond RECIST 1.1 defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit, and
- Subject is tolerating study drug.

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. The following criteria need to be taken into consideration:

- No decline in ECOG performance status.
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

All decisions to continue treatment beyond PD must be discussed with the Principal Investigator and documented in the study records.

Tumor assessments will be made using RECIST 1.1 (**Appendix C**) and iRECIST(**Appendix D**).

4.8.2. Pembrolizumab-Related Adverse Events

Permanent discontinuation of study treatment should be considered for any of the following:

1. Severe or life-threatening related AEs, including, but not limited to, any of the following (the Principal Investigator and Merck must be notified in the event of these AEs):

    - Any grade 2 treatment-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to ≤ Grade 1 severity within the re-treatment period OR requires systemic treatment
    - Any grade 3 or 4 myocarditis
    - Any grade 3 non-skin, drug-related AE lasting > 7 days or recurs, with the following exceptions:
        - Grade 3 treatment-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
        - Grade 3 treatment-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
        - Grade 3 treatment-related laboratory abnormalities do not require treatment discontinuation except:
            - Grade 3 treatment-related thrombocytopenia > 7 days OR that is associated with bleeding requires discontinuation
            - Any treatment-related liver function test (LFT) abnormality that meets the following criteria require discontinuation
                - ALT or AST > 8 x ULN, regardless of duration, or
                - ALT or AST > 5 x and ≤ 8 x ULN, that fails to return to ≤ Grade 1 within 2 weeks despite medical intervention, or
                - Total bilirubin > 5 × ULN, or
                - Potential drug-induced liver injury (DILI) event **(Section 6.3.4)**
        - Elevated troponin ≥ Grade 3 requires discontinuation (except Grade 3 elevation without other signs of cardiac toxicity as determined by cardiac evaluation)

- Any grade 4 treatment-related AE or laboratory abnormality, except for the following events which do not require discontinuation:
    - Grade 4 neutropenia ≤ 7 days
    - Grade 4 lymphopenia and leukopenia.
    - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations.
    - Isolated grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
    - Grade 4 treatment-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Principal Investigator.
- Any dosing interruption lasting > 6 weeks with the following exceptions:
    - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Principal Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
    - Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Principal Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Principal Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued pembrolizumab, olaparib or paclitaxel dosing.

Subjects that are required to stop treatment with pembrolizumab due to toxicity may stay on study and receive olaparib and paclitaxel (assessment schedule per **Section 9**) once the pembrolizumab-related toxicity(s) has resolved to a grade 1.

4.9. End of Treatment (EOT) Visit

All subjects will return to the study site 30 days (± 7 days) after the last dose of study drug (or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first) for an EOT evaluation. Procedures and assessments performed at this visit and beyond should follow the respective guidelines described in **Section 4.10** and **Section 9** as appropriate.

If the patient cannot return due to disease progression, inability to travel, or initiation of another anti-cancer treatment, an assessment for AEs should be made by telephone or email on day 30 (-7/+14 days) after last study dose in place of the PE/PS/vitals (clinical laboratory values should still be collected).

4.10. Duration of Follow Up

The Follow-Up Phase of this study begins when the decision to discontinue a subject from study therapy is made (i.e. no further treatment with study therapy).

All subjects who discontinue study drugs should comply with protocol specified follow-up procedures as outlined in the Study Calendar in **Section 9**.

4.10.1. Safety Follow-up

Subjects who discontinue treatment should be contacted by telephone or email at 90 days (+ 14-day reporting window) from their last dose of study drug or within 7 days before initiation of a new antineoplastic treatment (whichever comes first) to assess for treatment related toxicities. In addition, all SAEs occurring during this time should be reported as well.

Subjects who are discontinued from the study treatment due to an unacceptable drug-related AE will be monitored for safety until the resolution of the AE to ≤ grade 1 or stabilization or until initiation of a new therapy for their cancer, whichever occurs first.

4.10.2. Clinical Follow-up

All enrolled subjects who discontinue treatment without disease progression will enter the clinical follow-up portion of the trial. Subjects will begin the clinical follow-up period after they complete the EOT visit. Clinical follow-up visits will occur per standard of care until: 1) start of a new antineoplastic therapy (information of the new cancer therapy will be collected), 2) disease progression, 3) death, 4) withdrawal of consent, or 5) study closure, whichever occurs first. Refer to **Section 9** for the schedule of assessments that should be performed at each visit. After disease progression or start of a new antineoplastic therapy, subjects will enter the survival follow-up portion of the trial (**Section 4.10.3**).

4.10.3. Survival Follow-up

Subjects who discontinue treatment due to disease progression will enter the survival follow-up portion of the trial. Subjects should be contacted (by phone, telemedicine, email, medical record search, or in person visit) per standard of care to monitor overall survival. Information of other cancer therapies after discontinuation from the study treatment will be collected as well.

5. DOSING DELAYS/DOSE MODIFICATIONS

Subjects will be monitored continuously for AEs while on study drug. Subjects will be instructed to notify their physician immediately for any and all AEs. Dose reductions of paclitaxel and olaparib for related toxicities are permitted as per **Table 4**. Dose reductions of pembrolizumab will not be allowed. If the causality of the AE requiring a dose delay is confirmed to be due to one of the study drugs of the combination therapy, the non-offending drugs may be continued per protocol taking into account the safety and clinical benefit to the participant.

Table 4: Dose Modification Guidance for Paclitaxel/Olaparib

Study drug	Initial Dose Level	First Reduction	Second Reduction
Paclitaxel	80 mg/m2 on days 1 and 8	65 mg/m2 on days 1 and 8	50 mg/m2 on days 1 and 8
Olaparib (with paclitaxel)	100 mg BID on days 1-21	100 mg BID on days 1-14[a]	100 mg BID on days 1-7
Olaparib (without paclitaxel)	300 mg BID on days 1-21	200 mg BID on days 1-21	100 mg BID on days 1-21

5.1. Dosing Criteria

Dosing of study therapy will be delayed for the following laboratory criteria:

- ANC < 1,000/uL
- Platelet < 70,000/μL
- Total bilirubin > 1.5x ULN
- AST or ALT > 3x ULN
- Creatinine > 1.5x ULN

5.2. Dose Delays and Modifications for Olaparib

5.2.1. Hematologic Toxicity

Table 5: Dose Modifications for Hematologic Toxicity

Hematologic Toxicity	Olaparib	Paclitaxel
1st occurrence	Resume at same dose level	Resume at same dose level
2nd occurrence	Resume at 1st dose reduction with next cycle	Resume at same dose level
3rd occurrence	Resume at same dose level	Resume at 1st dose reduction
4th occurrence	Resume at 2nd dose reduction with next cycle	Resume at same dose level
5th occurrence	Discontinue	Resume at 2nd dose reduction or discontinue

Both drugs should be held until dosing criteria are met as per **Section 5.1**. If olaparib is reduced, it should not be restarted until the next cycle. Paclitaxel may be resumed at the next scheduled dose when dosing criteria are met. Refer to **Table 4** for dose reductions.

5.2.2. Non-Hematologic Toxicity

Non-hematological CTCAE grade 3 and 4 toxicities observed during the course of the study and attributable to olaparib will first be managed by interruption of the dose. Repeat dose interruptions are to be allowed as required. The maximum duration of any dose interruption due to related olaparib toxicity is 28 days. If an interruption of longer than 28 days is required, the patient should be discussed with the Principal Investigator and must be approved to continue. When olaparib is interrupted, the patient must either recover completely or the toxicity must revert to NCI CTCAE ≤ grade 1 or to the baseline CTCAE grade before restarting treatment. Patients whose NCI CTCAE grade 3 or 4 event does not resolve to ≤ grade 1 or to the baseline CTCAE grade after a full 28 day dose interruption will discontinue olaparib.

Where toxicity recurs following re-challenge with olaparib, and where further dose interruptions are considered inadequate for management of toxicity, then dose reduction or withdrawal is indicated.

Olaparib dose reductions are found in **Table 4**. If olaparib is reduced, it should not be restarted until the next cycle. If the event recurs with the same severity, treatment should be interrupted again and, on resolution, a further dose reduction made.

5.3. Dose Delays and Modifications for Paclitaxel

5.3.1. Hematologic Toxicity

Guidance for management of paclitaxel and olaparib for hematologic toxicities is outlined in **Section 5.2.1.**

5.3.2. Non-Hematologic Toxicity

Paclitaxel should be permanently discontinued for the following non-hematological related toxicities:

- Severe hypersensitivity reactions.
- CTCAE grade 3 or 4 neuropathy lasting more than 4 weeks.
- CTCAE grade 3 or 4 neuropathy recurring after dose reduction.
- AST and/or ALT CTCAE grade 3 or above (CTCAE grade 4 or above in case of liver metastases) lasting more than 7 days
- Bilirubin CTCAE grade 3 or above.

Dose delays of paclitaxel as a consequence of non-hematological toxicities:

The treatment of a patient can be postponed for up to 3 weeks (one cycle) if the patient has not recovered to CTCAE grade 1 or less non-hematological toxicity at the beginning of cycle (day 1). Longer delays should be approved by the Principal Investigator.

Dose reductions of paclitaxel as a consequence of non-hematological toxicities:

For non-hematological toxicities other than those mentioned above and excluding nausea, vomiting and asthenia:

- If CTCAE grade 3, patients should have a permanent dose reduction to 65 mg/m^2
- Patients who experience CTCAE grade 4 non-hematological toxicity may have their dose held for up to 3 weeks (one cycle) to permit recovery to CTCAE grade 3 or below followed by a permanent dose reduction (**Table 4**).

5.3.3. Infusion-Related Toxicity

Hypersensitivity reactions:

Discontinue paclitaxel infusion for significant hypersensitivity reactions defined as:

- Hypotension requiring pressor therapy
- Angioedema
- Respiratory distress requiring bronchodilator therapy
- Generalized urticaria

For other hypersensitivity reactions, paclitaxel may be discontinued at the discretion of the investigator.

Any significant hypersensitivity reaction and any hypersensitivity reaction requiring treatment discontinuation should be reported as an AE or SAE.

The following management of hypersensitivity reactions is recommended or local standard practice:

- Administer diphenhydramine 50 mg IV, or equivalent.
- Administer adrenaline (or its equivalent) sub-cutaneous every 15-20 minutes until the reaction subsides or a total of 6 doses given.
- If hypotension is present that does not respond to adrenaline, administer IV fluids.
- If wheezing is present that is not responsive to adrenaline, administration of nebulized salbutamol solution (or equivalent) is recommended.

  Although corticosteroids have no effect on the initial reaction, they have been shown to block “late” allergic reactions to a variety of substances. Thus, methylprednisolone 125 mg IV (or its equivalent) may be administered to prevent recurrent or ongoing allergy manifestations.

Patients should not be re-challenged with paclitaxel in case of a severe hypersensitivity reaction. These patients should be discontinued from treatment with paclitaxel.

5.4. Dose Delays and Modifications for Pembrolizumab

5.4.1. Dosing Guidance for Immune-Related Adverse Events Associated With Pembrolizumab

AEs associated with pembrolizumab exposure, including coadministration with additional compounds, may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of Pembrolizumab/combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of Pembrolizumab/combination treatment, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab/combination treatment are provided in **Table 6**.

Table 6 Suggested Dose Modification and Toxicity Management Guidelines for Immune-Related AEs Associated with Pembrolizumab and Combinations

General instructions:

1. Severe and life-threatening irAEs, should be treated with IV corticosteroids followed by oral steroid. Other immunosuppressive treatment should begin if irAEs are not controlled by corticosteroids.
2. Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last study intervention treatment.
3. Corticosteroid taper should begin when the irAE is ≤Grade 1 and continue at least 4 weeks.
4. If study intervention has been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper

Immune-related AEs	Toxicity grade or conditions (CTCAEv5.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST / ALT elevation or	Grade 2[a]	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver

Increased bilirubin	Grade 3[b] or 4[c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	enzyme value returned to baseline or is stable
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[d]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes

	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All other immune-related AEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event[e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

5.4.2. Other Allowed Dose Interruptions for Pembrolizumab:

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Principal Investigator. The reason for interruption should be documented in the patient's study record.

6. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

This study will use the descriptions and grading scales found in the revised CTCAE version 5.0 for AE reporting.

Information about all AEs, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected, recorded, and followed as appropriate.

6.1. Definitions

6.1.1. Adverse Event

An AE is defined as any undesirable sign, symptom or medical condition occurring after starting the study drug (or therapy) even if the event is not considered to be related to the study. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). Medical conditions/diseases present before starting the study treatment are only considered AEs if they worsen after starting the study treatment (any procedures specified in the protocol). New medical conditions / diseases occurring before starting the study treatment but after signing the informed consent form will not be recorded as AEs. Additionally, expected progression of the disease being studied will not be recorded as an adverse event.

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

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

6.1.2. Laboratory Abnormalities:

Laboratory abnormalities present at the screening visit will be recorded as pre-treatment signs and symptoms. After study treatment administration, all grade 3 and 4 clinical laboratory results that represent an increase in severity from baseline will be reported as AEs. A grade 1 or 2 clinical laboratory abnormality should be reported as an AE only if it is considered clinically significant by the investigator (induce clinical signs or symptoms or require corrective therapy), meets the definition of an SAE, or requires the participant to have study drug discontinued or interrupted. It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g. anemia versus low hemoglobin value).

6.1.3. Serious Adverse Event

A SAE is an undesirable sign, symptom or medical condition which:

- Results in death
- Is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions) for >24 hours
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Potential drug induced liver injury (DILI) is also considered an important medical event
- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE
- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose
- Is a pregnancy or pregnancy outcome of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, or stillbirth

Events **not** considered to be SAEs are hospitalizations for:

- Visits to the emergency room or other hospital department for <24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Admissions as per protocol for a planned medical/surgical procedure or to facilitate a procedure

- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative)

6.1.4. Overdose

For purposes of this study, 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.

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

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

6.2. Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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

6.2.1. Relationship

The relationship of an AE to the administration of the study drug is to be assessed by the investigator according to the following definitions:

- No (unrelated, not related, no relation): The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

- Yes (related): The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The following factors should also be considered:

- The temporal sequence from study drug administration - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication - The other medications the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study drug - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

6.2.2. Assessment of Grade:

The investigator will make an assessment of grade for each AE and SAE reported during the study, which will be recorded in the CRF. The assessment will be based on the National Cancer Institute's CTCAE (Version 5.0) and graded as shown below:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Any AE that changes in grade during its course will be recorded in the CRF at the highest level experience by the subject.

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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

6.2.3. Expectedness

Unexpected AE: An AE, which varies in nature, intensity or frequency from information on the investigational drug/agent provided in the product IB, package insert or safety reports. Any AE that is not included in the IB, package insert, safety reports or informed consent is considered "unexpected". An expected AE with a fatal outcome should be considered unexpected unless the IB specifically states that the AE might be associated with a fatal outcome.

Expected (known) AE: An AE, which has been reported in the IB, package insert or safety reports. An AE is considered "expected", only if it is included in the IB document as a risk.

6.3. Adverse Event Reporting

6.3.1. Adverse Events (AEs) and Serious Adverse Events (SAEs)

All AEs (both expected and unexpected) occurring from the first dose of study drug will be captured on the appropriate study-specific case report forms (CRFs). Progression of the cancer under study is not considered an adverse event. Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

A non-serious adverse event is an AE not classified as serious. All non-serious AEs (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 30 days following the last dose of study treatment. Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug or for those present at the end of study treatment as appropriate. Non-serious AEs are to be provided to Merck in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [e.g., IND US trial] as part of an annual reporting requirement.

All SAEs (including deaths) occurring from the first dose of study drug, throughout the study, and 90 days (+ 14-day reporting window) after the last dose of study drug or before initiation of a new antineoplastic treatment (whichever comes first) must be reported. All SAEs that the investigator considers related to the study drug occurring after the follow-up periods must be reported.

SAEs will be reported promptly to the Principal Investigator (Katherine Bever), Regulatory Specialist (Julie Nauroth), and Merck within 24 hours of recognition of the adverse event

using the form found in **Appendix E**. If this falls on a weekend or holiday, an email notification is acceptable but must be followed by an SAE reporting form on the next business day.

SAE reports and any other relevant safety information are to be sent to:

Katherine Bever: [redacted]
Julie Nauroth:
Merck:

6.3.2. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each subject and provide further information to the safety department in regards to the subject's condition.

All AE(s) and SAE(s) will be followed until:

- Resolution
- The condition stabilizes
- The event is otherwise explained
- The subject is lost to follow-up
- Death

As soon as relevant information is available, a follow-up SAE report will be submitted to the Principal Investigator and Merck.

6.3.3. Reconciliation of SAEs

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck, the amount dispensed to and returned by the participants, and the amount remaining at the conclusion of the trial. The Principal Investigator will reconcile the clinical database SAE cases (case level only) transmitted to the Principal Investigator and Merck. Frequency of reconciliation should be approximately every 3 months and prior to the database lock or final data summary. Merck will email, upon request from the Investigator, the reconciliation report. Requests for reconciliation should be sent to [redacted] and Merck email. The data elements listed on the Merck reconciliation report will be used for case identification purposes. If the Principal Investigator determines a case was not transmitted to the Principal Investigator and Merck, the case should be sent immediately to the Principal Investigator and Merck.

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

local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

6.3.4. Events of Clinical Interest

Selected non-serious adverse events are also known as Events of Clinical Interest (ECI).

For the first dose of the investigational agent, throughout the study, and will be followed through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

1. An overdose of Merck product, as defined in **Section 6.1.4**, that is not associated with clinical symptoms or abnormal laboratory results.

2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

6.3.5. Pregnancy Reporting

Although pregnancy and infant exposure during breast feeding 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) that occurs during the study.

Pregnancies and infant exposures during breastfeeding that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the participant to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and infant exposures during breastfeeding that occur from the first dose of investigational drug through 120 days following cessation of Principal Investigator's product, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious

events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Principal Investigator and Merck Global Safety. (Attn: Worldwide Product Safety; [redacted]).

6.3.6. Institutional Review Board (IRB)

SAEs will be reported to the IRB per institutional guidelines. The following SAEs will be reported to the Johns Hopkins Medicine IRB per institutional guidelines:

1. Deaths, regardless of causality

2. Serious adverse events that are both related and unexpected

Follow-up information will be submitted to the IRB as soon as relevant information is available.

6.4. Handling of Expedited Safety Reports

In accordance with local regulations, the Principal Investigator (or designee) and Merck will notify investigators of all SAEs that are unexpected (i.e., not previously described in the IB), and related to pembrolizumab, olaparib and paclitaxel. An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of a SUSAR Report that is to be e-mailed to the investigators and the study coordinators. Upon receiving such notices, the investigator must review and retain the notice with the IB and where required by local regulations, the investigator will submit the SUSAR to the appropriate IRB. The investigator and IRB will determine if the informed consent requires revision. The investigator should also comply with the IRB procedures for reporting any other safety information.

7. PHARMACEUTICAL INFORMATION

7.1. Pembrolizumab

7.1.1. Agent Accountability

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

7.1.2. Mode of Action

Pembrolizumab is a potent humanized immunoglobulin (Ig) G4 monoclonal antibody that with high specificity of binding to the programmed cell death (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed

cell death ligand 2 (PD-L2). Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T cell responses to both foreign antigens as well as self antigens.

7.1.3. Description

Pembrolizumab will be provided by Merck as a 100 mg/4 mL solution for injection.

7.1.4. Packaging and Labeling Information

Clinical supplies will be labeled in accordance with regulatory requirements.

7.1.5. Preparation

Pembrolizumab Solution for Infusion can be further diluted with normal saline or 5% dextrose in the concentration range of 1 to 10 mg/mL in intravenous (IV) containers made of polyvinyl chloride (PVC) or non-PVC material.

7.1.6. Storage

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site. Clinical supplies may not be used for any purpose other than that stated in the protocol.

7.1.7. Stability

Diluted pembrolizumab solutions may be stored at room temperature for up to 6 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 24 hours, which may include up to 6 hours at room temperature.

7.1.8. Route of Administration

Pembrolizumab is to be administered as a 30 (-10/+25) minute IV infusion.

7.1.9. Subject Care Implications

Based on results from nonclinical studies, there are currently no specific safety considerations. Pembrolizumab is a humanized monoclonal Ab. Thus far, serious infusion reactions have been infrequent and manageable. However, subjects should be closely monitored for potential adverse reactions during antibody infusion and potential adverse events throughout the study. In the event that a subject experiences an allergic reaction to pembrolizumab, treatment (i.e., vasopressors, H2-blockers, antihistamines, H1-blockers,

steroids) should be administered, as appropriate, and prophylaxis should be considered. Surveillance for the appearance of HAH is included in all protocols.

Pembrolizumab has the same mechanism of action as other anti-PD-1 monoclonal antibodies. Preclinical studies have suggested similar potency, and PK modeling has suggested similar human PK. Accordingly, the adverse events observed with other anti-PD-1 antibodies may serve as in indicator for the adverse events to expect for Pembrolizumab in cancer patients. Events of Clinical Interest (ECI) are of special interest because of the mechanism of action of anti-PD-1. Important identified risks for pembrolizumab are of an immune mediate nature, including: pneumonitis, colitis, thyroid disorders (hypothryoidism/hyperthyroidism), hepatitis, hypophysitis, Type I diabetes mellitis, uveitis, and nephritis. After a recent review of data, events newly characterized as identified risks also include pancreatitis, myositis, and severe skin reaction.

Pembrolizumab is generally well tolerated and demonstrates a favorable safety profile in comparison to chemotherapy. However, prompt identification of ECI and appropriate treatment (e.g. withdrawal of study medication and treatment with corticosteroids) will be critical to optimizing the therapeutic index.

7.1.10. Returns and Reconciliation

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

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

7.2. Olaparib

7.2.1. Agent Accountability

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

7.2.2. Mode of Action

Olaparib is an inhibitor of the poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1, PARP2, and PARP3, enzymes involved in DNA transcription and DNA repair. Olaparib inhibits growth of tumor cells deficient in BRCA and non-BRCA proteins

involved in the homologous recombination repair of DNA damage, inducing synthetic lethality through the formation of double-stranded DNA breaks which cannot be accurately repaired and cell death.

7.2.3. Description

Olaparib is formulated as an immediate release tablet and will be supplied in 2 strengths (100 mg and 150 mg). The tablets contain the active drug (olaparib) along with inactive ingredients (copovidone, mannitol, colloidal silicon dioxide and sodium stearyl fumarate). The tablet coating consists of hypromellose, polyethylene glycol 400, titanium dioxide, iron oxide yellow and iron oxide black. The yellow tablet film coating only differs from the green film coating with the omission of iron oxide black.

7.2.4. Packaging and Labeling Information

Clinical supplies will be labeled in accordance with regulatory requirements.

7.2.5. Dispensing

An initial bulk supply of olaparib will be provided to sites prior to Cycle 1, Day 1 of the first subject. When dispensing to a subject, the investigator or designee will remove the appropriate quantity of olaparib from their stock, dispense the medication, and enter the amount dispensed into the eCRF and drug accountability log.

7.2.6. Storage

Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F). Store in original bottle to protect from moisture.

7.2.7. Route of Administration

Olaparib will be administered orally BID every 12 hours without regard to food at the dose specified.

7.2.8. Subject Care Implications

Safety information regarding olaparib comes from over 750 patients with ovarian cancer treated on clinical trials, as well as from post-marketing experience. Common adverse events (occurring in >20%) observed include anemia (grade 3-4 in up to 20%), nausea, vomiting, diarrhea, stomatitis, upper respiratory infections, fatigue, anorexia, arthralgias, dysgeusia, and headache. Laboratory abnormalities commonly observed included decrease in hemoglobin, decrease in absolute neutrophil count, decrease in platelets, decrease in lymphocytes, mean corpuscular volume elevation and increase in creatinine. Other less common adverse reactions included rash, cough, dyspepsia, hypomagnesemia, dizziness, and edema. Myelodysplastic syndrome/acute myeloid leukemia occurred in <1.5% of

patients exposed and the majority had a fatal outcome. In addition, pneumonitis occurred in <1% of patients exposed, and some cases were fatal.

7.2.9. Returns or Reconciliation

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

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

7.3. Paclitaxel

For complete details on drug administration, storage, clinical pharmacology, and the human pharmacokinetics of paclitaxel, please see the paclitaxel prescribing information.

7.3.1. Mode of Action

Paclitaxel is an antimicrotubule agent. It promotes microtubule assembly and stabilizes tubulin polymers by preventing their depolarization, resulting in the formation of extremely stable and nonfunctional microtubules, and consequently inhibition of many cell functions.

7.3.2. Description

TAXOL (paclitaxel) Injection is a clear, colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. TAXOL is supplied as 30mg (5ml), 100mg (16.7ml), and 300mg (50ml) multidose vials. Each ml of sterile nonpyrogenic solution contains 6mg paclitaxel, 527mg of purified Cremophor EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

7.3.3. Preparation

Paclitaxel reconstitution, preparation, and administration should be completed according to the manufacturer's recommendation. TAXOL (paclitaxel) Injection must be diluted prior to infusion. TAXOL should be diluted in 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/mL.

Paclitaxel may be administered on an outpatient basis and will be administered on day 1 and 8 of each cycle by intravenous infusion over 60 minutes. Infusion times are approximate and may need to be adjusted based on patient tolerability.

7.3.4. Storage

Store the vials in original cartons between 20°–25° C (68°–77° F). Retain in the original package to protect from light.

7.3.5. Stability

Unopened vials of TAXOL (paclitaxel) Injection are stable until the date indicated on the package when stored between 20°–25° C (68°–77° F), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product. Upon refrigeration, components in the TAXOL vial may precipitate, but will redissolve upon reaching room temperature with little or no agitation. There is no impact on product quality under these circumstances. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded. Solutions for infusion prepared as recommended are stable at ambient temperature (approximately 25° C) and lighting conditions for up to 27 hours.

7.3.6. Route of Administration

Paclitaxel is to be administered as a 60 minute IV infusion, through an in-line filter with a microporous membrane no greater than 0.22 microns.

7.3.7. Subject Care Implications

Please see the paclitaxel prescription information for more details on the known precautions, warnings, and adverse reactions of paclitaxel. The most common (> 10% frequency) adverse events associated with weekly paclitaxel are anemia, nausea, fatigue, and peripheral neuropathy. Please refer to the package insert for common adverse effects.

The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when paclitaxel is concomitantly administered with known substrates (eg, midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (eg, rifampin and carbamazepine) of CYP3A4.

Caution should also be exercised when paclitaxel is concomitantly administered with known substrates (eg, repaglinide and rosiglitazone), inhibitors (eg, gemfibrozil), and inducers (eg, rifampin) of CYP2C8.

Potential interactions between paclitaxel, a substrate of CYP3A4, and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials.

7.3.8. Returns and Reconciliation

N/A

8. CORRELATIVE/SPECIAL STUDIES

Sample collection, processing, storage, and shipment instructions will be provided in the Laboratory Manual.

8.1. Tumor Tissue Studies

Tumor biopsies will be collected (if the subject's tumor is thought reasonably safe and easy to biopsy) at baseline (any time after eligibility is met) and at Cycle 2 Day 1 (- 1 week) (4-6 cores per timepoint). If a biopsy was done within 28 days before first dose, archived tissue from this biopsy may be used as a baseline sample. Fine needle aspiration samples do not contain sufficient tissue contextual information and will not be obtained. Additional biopsies may be obtained later in course of therapy. Additional archival tissue from patients no longer receiving treatment may also be collected. Attempts will be made to obtain archival tumor samples (slides and/or blocks) from all subjects.

To explore the association of the tumor microenvironment and clinical responses, archived tumor tissue and tumor tissue obtained at baseline and during treatment will be compared. PD-L1 expression may predict response to anti-PD-1 therapy (*29*); however, PD-L1 is also upregulated in response to IFN-γ released by infiltrating T cells and could potentially be a predictor of response to any active immunotherapy. Pre- and post-treatment tumor biopsies will also be analyzed with immunohistochemistry and gene expression analysis for expression of T cell subset markers (CD3, CD4, CD8, FoxP3, Granzyme A/B, CD69), immune regulation (PD-L1, PD-L2, CTLA4, LAG-3, IDO1, TIM-3), and immune cell population markers (NK, DC, B cell, MDSC, M1/M2 macrophages).

8.2. Whole Blood

Whole blood will be collected to assess the baseline characteristics of the subjects enrolled and to correlate these molecular and clinicopathologic criteria with treatment response and toxicity. DNA will be extracted from whole blood and used to evaluate for any germline mutations that may correlate with response or toxicity.

Detailed instructions for sample collection, processing, storage, and shipment are provided in the laboratory manual.

8.3. Peripheral Blood Mononuclear Cells (PBMCs)

PBMCs will be collected per the study calendar. Post-treatment changes in PBMCs including effector, helper, and regulatory T cells, NK cells and macrophages through cell phenotyping analysis and gene expression profiling will be measured. Post-treatment expression of PD-1 and other lymphocyte activation markers will be measured and correlated with OS.

T cells will be isolated and co-cultured with synthetic peptide neoantigens and will undergo TCR sequencing to assess for clonal expansion as previously described (*15*). Gene expression will also be conducted on pre- and on-treatment PBMCs.

PBMCs are isolated and stored frozen until use. Detailed instructions for sample collection, processing, storage, and shipment are provided in the Laboratory Manual.

8.4. Serum and Plasma Marker Studies

Sera and plasma will be collected per the study calendar to identify potential therapeutic targets, biomarkers, and predictors of response and autoimmune toxicity through proteomic approaches. DNA will be extracted from plasma samples at predetermined time points and ctDNA levels determined by interrogation using a panel of commonly mutated genes. Detailed instructions for collection, processing, storage and shipping are provided in the Laboratory Manual.

8.5. Diagnostic Tissue Samples

Tissue, fluid, or blood may be collected from standard of care procedures used to treat or diagnose immune related toxicities. Detailed instructions for tissue collection, processing, storage and shipment are provided in the laboratory manual.

8.6. Microbiome Studies

Stool and oral wash (and/or buccal mucosal) samples will be collected for microbiome studies per the study calendar. Additional samples may be obtained if the patient has any drug-related toxicity at any point during the trial.

Patients will be asked to complete a questionnaire when they provide stool samples, which asks about specific medications, dental health, and diet.

Microbial DNA will be isolated from stool and oral wash (and/or buccal mucosal) samples and prepared for 16S rRNA V4 amplicon sequencing to profile microbial species represented in the gut pre- and post-treatment. In addition, microbial DNA will be subjected to whole genome metagenomics profiling of microbial species via shotgun sequencing for detailed functional and pathway analysis to determine the change in the species and functions in response to treatment. Further bioinformatics analyses will be performed with these sequencing data to identify candidate microbial biomarkers, and predictors of response. Detailed instructions for sample collection, processing, storage, and shipment are provided in the laboratory manual.

8.7. Genomic Analysis

To explore genetic determinants of response, exome sequencing will be performed on DNA from tumor samples and the presence of DNA repair gene alterations will be assessed. Tumor mutation burden will also be estimated as a correlate for genomic instability.

Gene expression profiling will also be employed to identify gene signatures within the tumor microenvironment (TME) associated with response and survival.

Genomic sequencing library construction, whole genome/exome sequencing, whole transcriptome sequencing, microbial sequencing, neoepitope prediction, mutation burden, single-cell profiling, epigenetics, and bioinformatic analysis will be performed either at an on-campus laboratory or at an off-campus sequencing service. All the samples will be de-identified before sending to any laboratory for sequencing. The BCL, FASTQ files, BAM files and VCF files will be generated and analyzed.

Genomic sequencing data will be stored and computations conducted using either a JH IT managed subscription of Azure or departmental server such as the Joint High Performance Computing Exchange (JHPCE).

Clinical analysis: Several CLIA-certified laboratories now offer molecular profiling of cancer specimens in commercial and noncommercial settings and provide these results to patients and their physicians (e.g. Foundation Medicine, PGDx, Michigan Center for Translational Pathology, or JHU CLIA Laboratories). It is possible, therefore, that some of our research analyses will be conducted in these CLIA-certified environments. If tissue or cells are evaluated with next generation sequencing strategies to provide a molecular profile of individual cancer specimens in a CLIA-certified facility, these results will be made available to the patient and their physician. Patient confidentiality will be maintained, and the patient's identity will not be publicly linked to any study results. Researchers may use the data set generated in the CLIA assay setting to study genetic alterations across a large number of genes important in cancer. Germline mutations are only identified in punitive cancer genes. Researchers will use the data set for exploratory research to study cancer cell heterogeneity. Some of the sequencing data obtained from the NGS strategies will be uploaded to government sponsored databases, such as GEO and dbGAP. The results of the research studies may be published but subjects will not be identified in any publication.

If a germline alteration of clinical importance (as judged by the Investigator) to the subject and his or her family members is identified by a CLIA-certified test in the course of this analysis, attempts will be made in writing to contact the subject and/or family members for genetic counseling referral.

9. STUDY CALENDAR

Study Procedures	Screen	Cycle 1[20] D1	Cycles 2+[21]			Maintenance Cycle M1+ D1[23]	EOT[24]	Safety FU[25]	Clinical FU[26]	Survival FU[27]
			D1	D8	D15[22]					
Visit Windows (days)[1]	-28 to D1		±3	±3	±3	±7	±7	+14	±14	±14
Pembrolizumab		X	X			X				
Olaparib		←---------- PO BID ----------→								
Paclitaxel			X	X						
Informed consent	X									
Inclusion/exclusion criteria	X									
Demographics	X									
Medical, Cancer, & Con Med History[2]	X									
Con Meds, Adverse Events[3]		X	X	X	X	X	X	X	X	
Physical Exam, ECOG PS[3]	X	X	X	X	X	X	X		X	
Vitals[4]	X	X	X	X	X	X	X		X	
Height[5]	X									
Weight	X	X	X			X	X		X	
Oxygen Saturation	X	X	X	X	X	X	X			
Hematology, Chemistry[6,12]	X	X	X	X	X	X	X		X	
Endocrine[7,12]		X	X			X	X			
Coagulation Panel[8,12]	X									

Study Procedures	Screen	Cycle 1[20] D1	Cycles 2+[21]			Maintenance Cycle M1+ D1[23]	EOT[24]	Safety FU[25]	Clinical FU[26]	Survival FU[27]
			D1	D8	D15[22]					
Urinalysis[9,12]	X									
Virology[10]	X									
Pregnancy Test[11,12]	X	X	X							
Relevant tumor marker[12]	X	X	X			X	X		X	
CT/MRI, RECIST/iRECIST[13]	X		X			X	X		X	
Whole blood (up to 10cc)[14,28]		X								
PBMC[15,16, 28]		X[15,16]								
Plasma (up to 20cc)[15,28]		X[15]								
Serum (up to 5cc)[15,28]		X[15]								
Stool and Oral Wash Samples[17,28]		X[17]								
Microbiome Questionnaire[17,28]		X[17]								
Tumor Biopsies[18,28]		X	X							
Archival Tissue[19,28]	X									
Survival Follow-up										X

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a

telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

1: One cycle = 21 days. If necessary, a scheduled cycle may be delayed for up to 1 week. Longer delays to be approved by the Principal Investigator.
2: Cancer history includes: primary site of cancer, gross location of primary tumor, secondary sites of cancer, histology, histologic grade, date of initial diagnosis, date of metastatic diagnosis, prior cancer therapy regimens, tumor mutation testing.
3: Complete physical examination and assessment of ECOG PS will be completed at baseline; focused physical examinations and assessment of ECOG PS will be conducted thereafter. Exams, concomitant medication, AE assessments, and ECOG PS can be evaluated up to 3 days prior to infusion.
4: Blood pressure, pulse, pulse oximetry and temperature. On D1 and D8, vitals will be collected prior to the start of infusion.
5: Height will be obtained at or prior to baseline only.
6: Clinical hematology: Hgb, HCT, RBC count, WBC with differential, ANC, ALC, AEC, and platelet count; serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, calcium.
7: TSH with odd cycles only (i.e. cycles 1, 3, 5, 7, etc) Total T3 and free T4 if TSH abnormal and clinically indicated.
8: PT/INR and aPTT.
9: Blood, glucose, protein, specific gravity, and microscopic exam (if abnormal results are noted).
10: HIV antibody, hepatitis B surface antigen and hepatitis C antibody; additional virology may also be evaluated. Subjects who are hepatitis C antibody positive and confirmed negative viral load at screening will be allowed to enroll.
11: Pregnancy tests will be administered to WOCBP: urine pregnancy tests are required at screening and within 3 days of day 1 dosing of all cycles.
12: Labs may be collected within a window of up to 3 days prior to Day 1 dosing.
13: Spiral CT of thorax, abdomen and pelvis (and other imaging studies as clinically indicated to evaluate suspected sites of metastatic disease). If a subject cannot have a CT scan (e.g., allergy to contrast dye) or if CT is otherwise deemed not optimal for monitoring of subject's disease, an MRI should be performed. For both Cohorts 1 and 2, on-study radiologic evaluations and tumor measurements (RECIST and iRECIST per **Appendices C and D**) will be at baseline, 9 weeks (+/- 2 week), every 9 weeks (+/- 2 week) through week 52, and then every 12 weeks (+/- 2 week) thereafter including the EOT evaluation (± 4 weeks). The EOT scans do not need to be repeated if one has been done within the past 6 weeks. Weeks are in reference to calendar week and should not be adjusted due to dosing delays.
14: Baseline only (any time prior to first dose after eligibility is met).

15: Whole blood for PBMC, plasma, and serum will be collected at baseline (any time prior to first dose after eligibility is met), 3 weeks after first dose (± 3 days), 6 weeks after first dose (+/- 1 week), every 12 weeks (+/- 2 week) through week 55, and then every 24 weeks (+/- 2 week) thereafter, including EOT. Weeks are in reference to calendar week and should not be adjusted due to dosing delays. All bloods should be collected prior to dose.

16: Up to 100 cc of whole blood for PBMC isolation will be collected at baseline (any time prior to first dose after eligibility is met) and 3 and 6 weeks after first dose. Up to 150 cc will be collected at subsequent timepoints.

17: Stool and oral wash (and/or buccal mucosal) specimens will be obtained when available. All stool specimens should be collected within 72 hours (and ideally within 24 hours) of the patient's appointment. Baseline specimens may be obtained any time prior to the first dose after eligibility is met. On study specimens will be obtained every 12 weeks (+/- 2 week) through week 49, and then every 24 weeks (+/- 2 week) thereafter including the EOT evaluation (± 4 weeks). Additional samples may be obtained if the patient has any drug-related toxicity at any point during the trial. Detailed instructions for stool and oral wash/buccal mucosal collection and shipment are provided in the Laboratory Manual.

18: Tumor biopsies to be taken (if a subject's tumor is thought to be reasonably safe and easy to biopsy) at baseline (any time prior to first dose after eligibility is met) and at Cycle 2 (4-6 cores per timepoint). The Cycle 2 biopsy has a -1 week window. Additional optional biopsies may be obtained later in the course of study treatment. If a biopsy was done within 28 days before first dose, archived tissue from this biopsy may be used as a baseline sample. Fine needle aspiration will not be acceptable. Detailed instructions for tissue collection, processing and shipment are provided in the Laboratory Manual.

19: Attempts to obtain surgical or biopsy archival tumor samples will be made for every subject until the sample is obtained or documentation that the sample cannot be obtained is received. Detailed instructions for tissue collection, processing a shipment are provided in the Laboratory Manual.

20: Cycle 1 Day 1 evaluations do not need to be repeated if they were conducted within 3 days of the pre-study evaluations.

21: Subjects may be permitted to discontinue paclitaxel for intolerance after cycle 2 or if they achieve confirmed response or stable disease and received at least 6 months of treatment, and can start maintenance therapy with pembrolizumab and olaparib.

22: Focused physical examinations and clinical laboratory assessments will be conducted on Day 15 of Cycle 2 at the discretion of the PI. In order to minimize the need for in-person visits, this visit may be done virtually and will include only labs and review of AE.

23: Visits for dosing and/or assessments will occur every 21 days while on the maintenance phase.

24: EOT visit will occur 30 (±7) days after the final dose (or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first). NOTE: CT scan assessment at EOT will occur 30 days (± 4 weeks) after the final dose. If the EOT visit occurs early, an assessment for AEs should be made by telephone or email on day 30 (-7/+14 days) after last study dose. Subjects who discontinue from treatment should be contacted every three months (+/- 2 weeks) to monitor overall survival. Information of other cancer therapies after discontinuation from the study treatment will be collected as well.

25: Subjects who discontinue treatment should be contacted by telephone or email at 90 days (+ 14-day reporting window) from their last dose of study drug or within 7 days before initiation of a new antineoplastic treatment (whichever comes first) to assess for treatment related toxicities. In addition, all SAEs occurring during this time should be reported as well.
26: Subjects who discontinue treatment without disease progression (**Section 4.10.2**) will enter the clinical follow-up portion of the trial. Clinical follow-up visits will occur per standard of care until progression. After disease progression, subjects will enter the survival follow-up portion of the trial.
27: Subjects who discontinue treatment due to disease progression (**Section 4.10.3**) will enter the survival follow-up portion of the trial. Subjects should be contacted (by phone, telemedicine, email, medical record search, or in person visit) per standard of care to monitor overall survival. Information of other cancer therapies after discontinuation from the study treatment will be collected as well.
28. Research samples will be collected at the discretion of the PI based on availability of supplies and safety of patient and staff.

10. STUDY ENDPOINTS

10.1. Primary Endpoint

The primary endpoint of this study is overall survival (OS). OS is defined as the number of months from the date of first dose until death or end of follow-up (OS will be censored on the date the subject was last known to be alive for subjects without documentation of death at the time of analysis).

10.2. Secondary Endpoint

The secondary endpoints are as follows:

- Safety assessed by the following measures:
  - AEs
  - Number of participants experiencing drug-related adverse events (AEs) requiring treatment discontinuation
  - Infusion reactions
  - Immune-related AEs
  - Vital signs: BP, pulse, temperature
  - Physical examination
  - Clinical hematology: complete blood count (CBC) with differential ANC, ALC, AEC, and platelet count
  - Clinical serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN), creatinine, ALT, AST, alkaline phosphatase, bilirubin (total and direct), total protein, albumin, calcium, magnesium and phosphate
  - TSH, T3, Free T4

10.3. Exploratory Endpoints

Exploratory endpoints are as follows:

- Progression free survival (PFS), time to progression (TTP), objective response rate (ORR), disease control rate (DCR), best overall response (BOR), duration of response (DOR), duration of clinical benefit (DCB), and time to objective response (TTOR) measured by RECIST 1.1/iRECIST.
  - Progression-free survival (PFS) is defined as the number of months from the date of first treatment to disease progression (PD or relapse from CR as assessed using RECIST 1.1 criteria), clinical progression including worsening symptoms, or death due to any cause. PFS will be censored at the date of the last scan for subjects without documentation of disease progression at the time of analysis.
  - Time to-progression (TTP) is defined as the number of months from the date of first treatment to the date of documented disease progression (PD or relapse from CR as assessed using RECIST 1.1 criteria or clinical progression including worsening symptoms). It differs from PFS in that it does not include death in the definition of an

event. TTP will be censored at the date of the last scan for subjects without documentation of disease progression at the time of analysis
    - Objective Response Rate (ORR) is defined as the percentage of subjects achieving a PR or CR (Cohort 1).
    - Disease Control Rate (DCR) is defined as the percentage of subjects achieving stable disease or better (SD + PR + CR).
    - Best Overall Response (BOR) is defined in **Appendix C** (Cohort 1)**.**
    - Duration of Response (DOR) is defined as the number of months from the first documentation of a response to date of disease progression (Cohort 1).
    - Duration of Clinical Benefit (DCB) is defined as the number of months from first treatment to date of disease progression in those achieving a PR or CR (Cohort 1).
    - Time to Objective Response (TTOR) is defined as the number of months from the date of first treatment to the date of documented partial or complete response (Cohort 1).

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- Immune subset analysis by IHC and gene expression profiling of the tumor
- Assessment of tumor burden dynamics using standard protein biomarkers when available as well as circulating biomarkers (i.e. ctDNA).
- Immune subset analyses by FACS in PBMCs including effector, helper, and regulatory T cells, NK cells and macrophages
- T cell receptor (TCR) repertoire analysis in PBMCs and tumors
- Gene expression analysis of PBMCs
- Microbial community analysis and whole metagenome functional profiling analysis of stool and oral wash (and/or buccal mucosal) samples.
- Peripheral blood specimens, intratumoral core biopsy specimens, and resection specimens will be studied using a variety of other laboratory techniques including but not limited to: CITE-Seq, RNA-Seq, whole exome sequencing, whole genome sequencing, T cell receptor and B cell receptor sequencing, ChIP-seq, ATAC-seq, and MBD-seq.

11. DATA REPORTING/ REGULATORY REQUIREMENTS

AE guidelines and instructions for AE reporting can be found in **Section 6 (Adverse Events: List and Reporting Requirements)**.

11.1. Data Collection and Processing

All information will be collected on study-specific CRFs by study staff. These data will be reviewed for completeness and accuracy by the Principal Investigator..

CRFs will be used to capture study results and data. The study coordinator or other authorized study personnel will transcribe data from source documents onto paper or eCRFs. Before or between visits, the Principal Investigator, or designee may request copies of the CRFs for preliminary medical review. Once the CRFs are complete and source-verified, the investigator must sign and date all required pages, verifying the accuracy of all data contained within the CRF.

11.2. Safety Meetings

Scheduled meetings will take place weekly and will include the protocol Principal Investigator, study coordinator(s), data manager(s), sub-investigators (as appropriate), collaborators (as appropriate), and biostatisticians (as appropriate) involved with the conduct of the protocol. During these meetings matters related to the following will be discussed: safety of protocol participants, validity and integrity of the data, Cycle 2, Day 1 rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for objectives.

11.3. Monitoring

SKCCC Compliance Group will provide external monitoring for JHU-affiliated sites in accordance with SKCCC DSMP (Version 6.0, 2/21/2019). The SMC Subcommittee will determine the level of patient safety risk and appropriate level of monitoring. Data monitoring of this protocol will occur on a regular basis with the frequency dependent on the rate of subject accrual and the progress of the study. The protocol will be monitored internally by Dr. Katherine Bever and externally by the SKCCC CRO QA Office. Additional data and safety monitoring oversight will also be performed by the SKCCC Safety Monitoring Committee (SMC - as defined in the DSMP).

11.4. Study Documentation

11.4.1 Informed Consent and Authorization for Use and Disclosure of Protected Health Information

Written informed consent and authorization of use and disclosure of protected health information (PHI) must be obtained from each subject (or the subject's legally authorized representative) before performing any study-specific screening/baseline period evaluations. The ICF and authorization for use and disclosure of PHI, which is prepared by the investigator or the site, must be reviewed and approved by the Principal Investigator and the site's IRB before the initiation of the study.

11.4.2. Investigator Study Files

Documentation about the investigator and study staff, the IRB and the institution, is required before study site initiation. A list of required documents will be provided by the Principal Investigator or designee to each participating investigator. Copies of these documents as well as supplemental information, such as the investigator's obligations, IB, clinical study protocol and amendments, safety information, investigational agent information, biological samples and laboratory procedures, SRM, study logs and Principal Investigator correspondence will be kept on-site in study site-specific binders.

The Principal Investigator or designee will be responsible for maintaining original and backup of all CRF data. The investigator is responsible for maintaining backup of all electronic data systems used for primary documentation or source documentation. Backup of electronic data will be performed periodically as described in the site-specific SOPs.

Backup records must be stored at a secure location on site and backup and recovery logs must be maintained to facilitate data recovery. If an electronic medical records system that is not supported by the Principal Investigator or designee (or is discontinued or decommissioned) is used, the investigator must maintain a system to retrieve these records or arrange for the transfer of these records to an alternate electronic format or to paper.

Changes to any electronic records require an audit trail and should include who made the changes and when and why the changes were made. An audit trail is defined as a secure, computer-generated, time-stamped electronic record that will allow reconstruction of the course of events relating to the creation, modification and deletion of an electronic record. Audit trails must be created incrementally, in chronological order and in a manner that does not allow new audit trail information to overwrite existing data. Audit trails should be in a readable format and readily available at the study site and any other location where electronic study records are maintained.

Audit trails are generated automatically for eCRFs. The investigator is responsible for maintaining audit trails of all electronic data systems used for primary documentation or source documentation.

11.4.3. Case Report Forms and Source Documentation

The investigator must make study data accessible to the site monitor, to other authorized representatives of the Principal Investigator (or designee) and to the appropriate regulatory authority inspectors. The original CRF for each subject will be checked against source documents at the study site by the site monitor.

11.4.4. Retention of Study Documents

All CRFs, as well as supporting paper and electronic documentation and administrative records, must be retained for at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications, or at least 2 years have elapsed since the formal discontinuation of clinical development of an individual product. Longer retention periods may apply. The Principal Investigator will notify investigators as to when documents no longer need to be retained. No study documents will be destroyed or moved to a new location without prior written approval from the Principal Investigator. If the investigator relocates, retires or withdraws from the clinical study for any reason, all records required to be maintained for the study should be transferred to an agreed-upon designee, such as another investigator at the institution where the study was conducted.

Audit trails for electronic documents must be retained for a period at least as long as that required for the subject electronic records to which they pertain. The investigator must retain either the original or a certified copy of audit trails.

11.4.5. Data Confidentiality and Subject Anonymity

All information about the nature of the proposed investigation provided by the Principal Investigator or their representative to the investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the subject or the appropriate regulatory authority) must be kept in confidence by the investigator.

The anonymity of participating subjects must be maintained. Subjects will be identified by their initials and an assigned subject number on CRFs and other documents retrieved from the site or sent to the Principal Investigator and Merck, regulatory agencies, or central laboratories/reviewers. Documents that identify the subject (e.g., the signed ICF) must be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, Principal Investigator or their representative.

12. STATISTICAL CONSIDERATIONS

12.1. Study Design/Endpoints

This is an open-label phase 2 study to evaluate the safety and clinical activity of paclitaxel, olaparib and pembrolizumab in patients with previously treated advanced GC.

The primary endpoint is overall survival (OS). OS is defined as the number of months from the date of first dose until death or end of follow-up. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

The secondary endpoint is to assess safety and characterize toxicities of paclitaxel plus olaparib and pembrolizumab in patients with previously treated advanced GC.

Exploratory endpoints include progression free survival, objective response rate, disease control rate, best overall response, duration of response, duration of clinical benefit, and time to objective response using RECIST 1.1 and by iRECIST.

Sample Size

A sample size of 36 patients was chosen for feasibility considerations, with 24 patients in Cohort 1 and 12 patients in Cohort 2. OS will be estimated in each Cohort along with 95% confidence interval.

All subjects who receive at least one dose of the three-drug combination will be included in the primary analysis of OS. Subjects who discontinue treatment prior to Cycle 2 will not be included in the primary analysis.

12.2. Statistical Analyses

The descriptive summary including demographics and baseline variables will include counts and percentages for categorical variables and means, medians, standard deviations and minimum and maximum values for continuous variables.

The primary outcome OS will be characterized using Kaplan-Meier method, and median OS with corresponding 95% confidence interval will be estimated. We will also estimate 12-month survival rate and the corresponding 95% CI. For Cohort 1 we will estimate the rate of objective response (ORR), defined as the proportion of patients who have complete response (CR) or partial response (PR) per RECIST 1.1 criteria, and the corresponding 95% confidence interval. Disease control rate (DCR), defined as the proportion of patients who have CR, PR, or stable disease at 6 months, will be estimated. Time-to-event outcomes such as progression-free survival (PFS), and duration of response (DOR), and time to progression (TTP) will be analyzed using Kaplan-Meier estimates (to obtain medians with 95% CI as well as plotting survival curves). The same analysis will be performed for outcomes based on iRECIST.

For correlative studies, plots will be used to show the changes in immune response over time for each individual. Changes pre- and post-treatment will be compared using paired t-tests (or Wilcoxon signed rank tests if appropriate) for continuous variables and McNemar's tests for dichotomous or categorical variables. Associations between immune parameters will be explored graphically (e.g. scatterplots, boxplots) and numerically (e.g., correlations, Fisher's exact tests). Regression techniques will be used to explore longitudinal patterns with appropriate correction for correlation between repeated measurements (e.g., linear mixed effects models). The association of immune parameters and clinical outcomes will be assessed using logistic regression for binary outcomes and Cox regression for time-to-event outcomes.

Sensitivity analyses will include models adjusting for baseline covariables. These covariates will be selected based upon both clinical significance.

12.3. Analysis Sets

Since the focus of this study is on investigating the efficacy of the treatment combination, all efficacy outcomes will be assessed using the patients who receive at least one dose of the three-drug combination treatment as the primary population for analysis. The analysis with all patients who receive at least one dose of study treatment will be supportive.

The safety population includes all subjects who received at least one dose of study treatment. The safety population will be conducted on the basis of the actual treatment received. All safety outcomes will be assessed using the safety population for analysis.

12.4. Safety Analysis

The safety analysis will be performed in all treated subjects. AE data will be listed individually and incidence of AEs summarized by system organ class and preferred terms within a system organ class for each treatment group. When calculating the incidence of AEs, each AE (based on

preferred terminology defined by CTCAE version 5.0 will be counted only once for a given subject. In analyses of grade and causality, if the same AE occurs on multiple occasions, the highest grade and strongest relationship to study drug will be assumed. If 2 or more AEs are reported as a unit, the individual terms will be reported as separate experiences.

Changes in vital signs, hematology and clinical chemistry parameters from baseline to the end of the study will be examined. Toxicity will be tabulated by type and grade. Toxicities will be characterized according to the CTCAE version 5.0. Treatment-emergent changes from normal to abnormal values in key laboratory parameters will be identified.

Safety stopping rules

The trial will be continuously monitoring for adverse events and toxicity. Any related grade 3 or 4 toxicity events requiring IV steroids, related symptomatic grade 3 or 4 events not resolving to grade $\leq$2 within 7 days, or related hematologic grade 3 or 4 events not resolved to $\leq$grade 2 within 7 days will be considered AEs for the purpose of this stopping rule. If the risk of these adverse events appears to be higher than 33%, we will temporarily halt the study pending safety evaluations. Specifically, we apply a Bayesian monitoring rule that suspends the enrollment if the posterior probability of risk being larger than 0.33 is 70% or higher. The monitoring rule uses beta (1.5, 5.5) as prior distribution. This means that our prior guess of the proportion of toxicity is 21%, and there is 90% probability that this proportion is between 3% and 49%. The decision rule for toxicity stopping is as follows:

Stop the study if number of AEs is $\geq$:	3	4	5	6	7	8	9	10	11	12	13	14	15
In number of patients between:	3	4-6	7-9	10-12	13-14	15-17	18-20	21-23	24-26	27-29	30-31	32-34	35-36

Operating characteristics of the stopping rule are shown below based on 5,000 simulations:

Risk of AE	0.20	0.25	0.30	0.33	0.40	0.45
% of time study stops	5.1%	13.5%	28.4%	40%	67.9%	84.5%
Expected sample size	34.7	32.8	29.6	27.3	20.9	16.4

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14. APPENDICES

APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: MODERATE AND STRONG CYP3A INHIBITORS

Examples[1] of Substrates of CYP2C9 and CYP3A4

Substrates of CYP2C9	Substrates of CYP3A4
Celecoxib	Alprazolam
Phenytoin	Astemizole
Tolbutamide	Buspirone
Warfarin	Calcium Channel Blockers
	Carbamazepine
	Cisapride
	Cyclosporine
	Doxorubicin
	Erythromycin
	Etoposide
	Felodipine
	Fentanyl
	HIV protease inhibitors
	Ifosphamide
	Lovastatin (not prevastatin)
	Midazolam
	Nifedipine
	Pimozide
	Quinidine
	Quinine
	Simvastatin
	Tacrolimus
	Terfenadine
	Triazolam

[1]Note that this is not an exhaustive list. Additional information on drugs and possible interactions can be found at http://www.drugs.com.

Examples[1] of Strong Inhibitors and Inducers of CYP2C9 and CYP3A4

Inhibitors of CYP2C9	Inhibitors of CYP3A4
fluconazole miconazole amentoflavone (constituent of Ginkgo biloba and St. John's Wort) sulfaphenazole valproic acid	boceprevir clarithromycin conivaptan grapefruit juice indinavir itraconazole ketoconazole lopinavir/ritonavir mibefradil nefazodone nelfinavir posaconazole ritonavir saquinavir telaprevir telithromycin voriconazole
Inducers of CYP2C9	**Inducers of CYP3A4**
rifampicin secobarbital	carbamazepine phenytoin oxcarbazepine phenobarbital St. John's wort rifampicin rifabutin efavirenz nevirapine pioglitazone troglitazone glucocorticoids modafinil

[1]Note that this is not an exhaustive list. Additional information on drugs and possible interactions can be found at http://www.drugs.com.

APPENDIX C: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST)

1.1 Criteria for Evaluating Response in Solid Tumors

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

Disease Parameters

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

> Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable unless there is evidence of progression in the irradiated site. Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

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

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

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

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

Evaluation of Target Lesions

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

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

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

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

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

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

For Subjects with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

Reference (*30*)

APPENDIX D: DESCRIPTION OF THE IRECIST PROCESS FOR ASSESSMENT OF DISEASE PROGRESSION

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

In participants who show evidence of radiological PD by RECIST 1.1 the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained using the criteria outlined in **Section 4.8.1**.

If the Investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥ 20% and ≥ 5 mm from nadir
    - Please note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including **iUPD** (unconfirmed progressive disease) and **iCPD** (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of ≥ 5 mm, compared to any prior iUPD time point
  - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
  - For new lesions, worsening is any of these:
    - An increase in the new lesion sum of diameters by ≥ 5 mm from a prior iUPD time point
    - Visible growth of new non-target lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the scan on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation scan proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression,

whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (ie, achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the PD threshold (≥ 20% and ≥ 5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
  - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If non-target lesions had shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, except in one respect. If new lesions occurred at a prior instance of iUPD, and at the confirmatory scan the burden of new lesions has increased from its smallest value (for new target lesions, their sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication(*31*).

Table 7: Comparison between RECIST 1.1 and iRECIST

	RECIST 1.1	iRECIST
Definitions of disease: numbers, sites and target or non	Measurable are diameters greater than 10 mm (15 for nodes maximum of 5 (2 per organ)	No change from RECIST 1.1
CR, PR or SD	Cannot have met criteria for progression	Can have had iUPD (more than once) but not iCPD before iCR, iPR or iSD
Confirmation of CR or PR	Only in non-randomized studies	As per RECIST 1.1
Confirmation of SD	Not required	As per RECIST 1.1
New lesions	Progression: recorded but not measured	iUPD but only becomes iCPD if on the next scan there are new lesions or the size increases by greater than 5 mm
Confirmation of progression	Not required	Required
Consideration of clinical status	Not required	Clinical stability considered at iUPD to decide treatment continuation

Table 8: Trajectory of progression in iRECIST

Target Lesions: iCR, Non-target: iCR, no new lesions	iCR	iCR
Target lesions: iCR, Non-target: non iCR/non iUPD, no new lesions	iPR	iPR
Target Lesions: iPR, Non-target: non iCR/non iUPD, no new lesions	iPR	iPR
Target lesions: iSD, Non-target: non iCR/non iUPD, no new lesions	iSD	iSD
Target lesions: iUPD with no change or with a decrease from the last time point, Non-target: iUPD with no change or decrease from last time point, new lesions	NA	New lesions confirm iCPD if new lesions previously identified and increased in size (≥ 5 mm in sum of measures for new lesions or any increase for new lesion non-target) or increase in number. If no change is seen in new lesions assignment remains iUPD

Target lesions: iSD, iPR, iCR, non-target: iUPD, no new lesions	iUPD	Remains iUPD unless iCPD is confirmed by increase in the size of non-targets (does not need to meet RECIST 1.1 criteria)
Target lesions: iUPD, non-target: non iCR/non iUPD, no new lesions	iUPD	Remains iUPD unless iCPD confirmed on the basis of further increase ≥ 5 mm; otherwise stays as iUPD
Target lesions: iUPD, non-target: iUPD, no new lesions	iUPD	Remains iUPD unless iCPD confirmed on previously identified targets iUPD ≥ 5 mm or non-target iUPD
Target lesions: iUPD, non-targets: iUPD, new lesions	iUPD	Remains iUPD unless iCPD confirmed by increase of ≥ 5 mm previously identified target, or non-target or an increase in size or number of new lesions
Target lesions non iUPD or progression, non-targets: non iUPD or progression, new lesions	iUPD	Remains iUPD unless iCPD confirmed by increase in size or number of new lesions previously identified.

Target lesions, non-target lesions and new lesions are defined according to RECIST 1.1 criteria: if no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD are the same. * Previously identified in the assessment prior to this time point. 'I' indicates immune responses assigned using iRECIST

APPENDIX E: SAE REPORTING FORM

Katherine Bever, M.D.
[redacted]

FAX

TO:	Merck Worldwide Safety	FROM:	
FAX:	+ [redacted]	PAGES :	
PHONE :		DATE:	
RE:		CC:	

Study:

Phase 2 Study of Paclitaxel, Pembrolizumab and Olaparib in Previously Treated Metastatic Gastric Adenocarcinoma (J19135, #57851)

Comments:

Please confirm receipt to:

Serious Adverse Event Reporting Form

Please notify: Dr. Bever within 24 hours (email [redacted]

Protocol Title:	Phase 2 Study of Paclitaxel, Pembrolizumab and Olaparib in Previously Treated Metastatic Gastric Adenocarcinoma		
Protocol Number: J19135/ Merck #57851	**Principal Investigator:** Katherine Bever	**Signature of PI:**	**Date of Report:**
Report Type: ☐ Initial ☐ Follow-up ☐ Final Follow-up ☐ Death ☐ Addendum to:	**Serious Criteria (check all that apply):** ☐ Death ☐ Life-threatening ☐ Hospitalization or Elongation Hospitalization ☐ Other Important Medical Event ☐ Cancer ☐ Overdose ☐ Other:_____	**Hospital Admission Date:**	**SAE ID:**
		Hospital Discharge Date:	**Date Event Discovered:**
Section A: Subject Information			
Subject ID:	**Cohort 1** ☐ **Cohort 2** ☐	**Subject Gender:** ☐ Male ☐ Female	**Subject Age:**
Section B: Event Information			
Event diagnosis or symptoms:	**Event Grade:**	**Cause of death (if applicable):**	**Event Outcome:** ☐ Recovering ☐ Recovered ☐ Recovered with sequelae ☐ Death ☐ Unknown
Event Onset Date (or Date of Death):		**Event End Date:**	
Section C: Study Drug Information:			

Investigational Product: Pembrolizamab (200 mg, IV infusion), Olaparib (100 or 300 mg, Oral) and Paclitaxel (80 mg/m2, IV infusion). 21 day treatment cycles.

Indication: Metastatic Gastric Adenocarcinoma

Number of Total Cycles:				**Action Taken with Study Drug:** ☐ None ☐ Interrupted ☐ Delayed ☐ Discontinued
Date of First Dose:	**Date of Last Dose prior to Event:**			
Relationship to:	**Pembro**	**Olaparib**	**Paclitaxel**	**Underlying Disease**
Unrelated	☐	☐	☐	☐
Related	☐	☐	☐	☐

Section D: Brief Description of the Event:

Section E: Relevant Tests/Laboratory Data:

Section F: Relevant Medical History

Section G: Concomitant Drug (Not related to SAE)

Name of the Drug	Start Date	Stop Date	Route	Dose	Frequency

Section H: Comments

Additional Documents: ☐ Please specify

APPENDIX F: ECI REPORTING FORM

Event of Clinical Interest (ECI) Reporting Form

Please notify within 24 hours: [redacted]

Protocol Title:	Phase 2 Study of Paclitaxel, Pembrolizumab and Olaparib in Previously Treated Metastatic Gastric Adenocarcinoma		
Protocol #: J19135 Merck #57851	**Principal Investigator:** Katherine Bever	**Signature of PI:**	**Date:**
Report Type: ☐ **Initial** ☐ **Follow-up** ☐ **Final Follow-up** ☐ **Addendum to:**			
Section A: Subject Information			
Subject ID:	**Cohort 1** ☐ **Cohort 2** ☐	**Subject Initials:**	**Subject Gender:** ☐ **Male** ☐ **Female**
Section B: Event Information			
Event diagnosis or symptoms:		**Date of first dose of study drugs:** **Date of last dose of study drugs prior to event:** **Number of total doses study drug:**	**Action taken with the study drugs:** ☐ **None** ☐ **Interrupted** ☐ **Discontinued**
Event Onset Date:	**Event End Date:**	**Date Event Discovered:**	

Relationship to:	**Pembro**	**Olaparib**	**Paclitaxel**	**Underlying Disease**
Unrelated	☐	☐	☐	☐
Related	☐	☐	☐	☐

Section C: Brief Description of the Event: (please include relevant procedures and laboratory values)

Section D: Relevant Medical History

Section E: Concomitant Drug (Not related to ECI)

Name of the Drug	Start Date	Stop Date	Route	Dose	Frequency

Section F: Comments

Additional Documents: ☐ Please specify