Cover Page for Protocol – J2112

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Principal Investigator: **Dung Le, M.D.**
[redacted]

Co-Investigator: **H. Catherine Wilbur, M.D.**
[redacted]

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Olaparib (poly (adenosine diphosphate-ribose) polymerase) (PARP) inhibitor

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1. OBJECTIVES

1.1. Primary Objective

To determine the 6 month progression-free survival (PFS) rate per RECIST 1.1 of patients treated with maintenance pembrolizumab and olaparib following low dose, multi-agent chemotherapy with gemcitabine, nab-paclitaxel, capecitabine, cisplatin, and irinotecan (GAX-CI) in untreated metastatic pancreatic ductal adenocarcinoma (PDA).

1.2. Secondary Objective

To assess safety and characterize toxicities of maintenance therapy with pembrolizumab and olaparib following GAX-CI in patients with untreated metastatic PDA.

1.3. Exploratory Objectives

1.3.1 To estimate progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and overall survival (OS) of patients treated with pembrolizumab and olaparib maintenance following disease stabilization with GAX-CI (Cohort 1), from cycle 1, day 1 of pembrolizumab and olaparib, per RECIST 1.1 and iRECIST.

1.3.2 To estimate second PFS, objective response rate (ORR), disease control rate (DCR), and overall survival (OS) for retreatment with GAX-CI after progression on maintenance therapy among Cohort 1 patients per RECIST 1.1 and iRECIST.

1.3.3 To estimate progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and overall survival (OS) of patients from cycle 1, day 1 of GAX-CI for Cohort 1 per RECIST 1.1 and iRECIST.

1.3.4 To estimate progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and overall survival (OS) of patients receiving pembrolizumab and olaparib as second-line therapy following disease progression prior to 6 cycles of GAX-CI (Cohort 2), from cycle 1, day 1 of pembrolizumab and olaparib, per RECIST 1.1 and iRECIST.

1.3.5 To estimate progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and overall survival (OS) of all patients (Cohort 1 and Cohort 2) from cycle 1, day 1 of GAX-CI

1.3.6 To assess tumor burden dynamics using standard protein biomarkers such as Cancer Antigen (CA) 19-9, Carcinoembryonic Antigen (CEA) and exploratory biomarkers such as circulating tumor DNA (ctDNA).

1.3.7 To collect tissue biopsies after chemotherapy with GAX-CI and following 2 cycles of maintenance pembrolizumab and olaparib. Tissue biopsies will be utilized to explore association of features of the tumor microenvironment with response to therapy. This will

include but not be limited to the following subsets: T-cells (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).

1.3.8 To evaluate molecular determinants of response using next generation sequencing and other sequencing technologies.

1.3.9 To collect peripheral blood mononuclear cells (PBMC), plasma, and serum to identify potential therapeutic targets, biomarkers and predictors of response (OS, PFS and best overall response) and autoimmune toxicity.

1.4. Study Design

This is an open-label, single-arm phase 2 study to evaluate the safety and clinical activity of maintenance olaparib and pembrolizumab following multi-agent, low dose chemotherapy with gemcitabine, nab-paclitaxel, capecitabine, cisplatin, and irinotecan (GAX-CI) in patients with untreated metastatic PDA. The study will consist of a screening period, a treatment period, and a follow-up period.

The treatment period will consist of a chemotherapy phase with GAX-CI and a maintenance phase with pembrolizumab and olaparib. The chemotherapy phase will consist of 6 cycles of multi-agent chemotherapy with GAX-CI given on a 28 day cycle. After a clinical assessment, subjects will receive gemcitabine, nab-paclitaxel, cisplatin, and irinotecan intravenously on day 1 and day 15 of each cycle. Patients will self-administer capecitabine orally on days 1-7 and days 15-21 of every cycle. Tumor response assessments will be performed utilizing RECIST 1.1 and iRECIST criteria every 8 weeks (±1 week). Both criteria will be assessed because, on occasion, the first post-treatment tumor assessment may show progressive disease despite clinical improvement due to timing of scans and initiation of therapy.

Patients will be evaluated for placement into one of two cohorts based off of response assessment to GAX-CI. Cohort 1 will include patients who have stable disease per RECIST 1.1 or iRECIST after 6 cycles of GAX-CI and meet criteria to proceed to the maintenance phase. If a tumor is felt to be accessible and safe to biopsy, biopsies will be obtained for correlative analyses prior to initiation of the maintenance phase. The maintenance phase will consist of pembrolizumab and olaparib administered on a 21 day cycle. Visits for dosing and clinical assessment will occur on day 1 of every cycle during the maintenance phase. Patients will self-administer olaparib orally on days 1-21. Pembrolizumab will be administered intravenously on day 1 of every other cycle (every 6 weeks). Tumor assessments will be performed utilizing RECIST 1.1 and iRECIST every 9 weeks (± 1 week). A second tumor biopsy for correlative analyses will be obtained after 2 cycles of maintenance therapy (1 dose of pembrolizumab) if the tumor is felt to be accessible and safe to biopsy.

Cohort 2 will be an exploratory cohort and its sample size may vary depending on disease progression prior to 6 cycles of GAX-CI. It will include patients who receive pembrolizumab and olaparib as second-line treatment following disease progression per RECIST 1.1 and iRECIST prior to 6 cycles of GAX-CI and thus do not meet criteria for Cohort 1. Patients will receive

combination pembrolizumab and olaparib on a 21 day cycle as outlined for Cohort 1. Tumor assessments will be performed utilizing RECIST 1.1 and iRECIST every 9 weeks (± 1 week). If the tumor is felt to be accessible and safe to biopsy, tumor biopsies in Cohort 2 will be obtained prior to the first dose of olaparib and pembrolizumab and after 2 cycles of therapy (approximately 6 weeks after first dose of pembrolizumab).

Whole blood, peripheral blood mononuclear cells (PBMCs), serum and plasma collection, and computed tomography (CT) scans or magnetic resonance imaging (MRI) will be obtained at baseline and during treatment for clinical assessments and correlative analyses for both cohorts. Complete information on study drug administration, schedule, and dosing can be found in **Section 4** and in the study calendar **Section 9.**

Enrollment will continue until 18 subjects have received 6 cycles of multi-agent chemotherapy, are deemed stable by RECIST 1.1 or iRECIST, receive one dose of maintenance therapy with pembrolizumab and olaparib, and are evaluable for 6-month PFS in Cohort 1. The primary endpoint is six month progression free survival (PFS) of patients who receive maintenance therapy with olaparib and pembrolizumab among those with stabilized with GAX-CI.

Treatment may continue up to a maximum of 2 years starting from the first dose of pembrolizumab and olaparib in Cohort 1 and Cohort 2, or until discontinuation due to toxicity, lack of clinical benefit as determined by the investigator, progressive disease confirmed by iRECIST, subject withdrawal, or termination of the study by the Principal Investigator (PI). Criteria for removal from treatment are found in **Section 4.11.**

Patients in Cohort 1 who develop clinical or radiographic progressive disease following initiation of maintenance therapy, or those who become intolerant of treatment with either pembrolizumab or olaparib, may be retreated with GAX-CI if the PI deems that the patient will derive meaningful clinical benefit and may continue until confirmed disease progression.

Subjects will have an end-of-treatment (EOT) evaluation and Adverse Event (AE) assessment 30 (+/- 7) days after the final administration of study treatment. Subjects who receive chemotherapy only are considered to be in the treatment period until 30 days after the last dose of chemotherapy. Subjects who receive pembrolizumab are considered to be in the treatment period until 90 days after the last dose of pembrolizumab. Subjects will 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.**

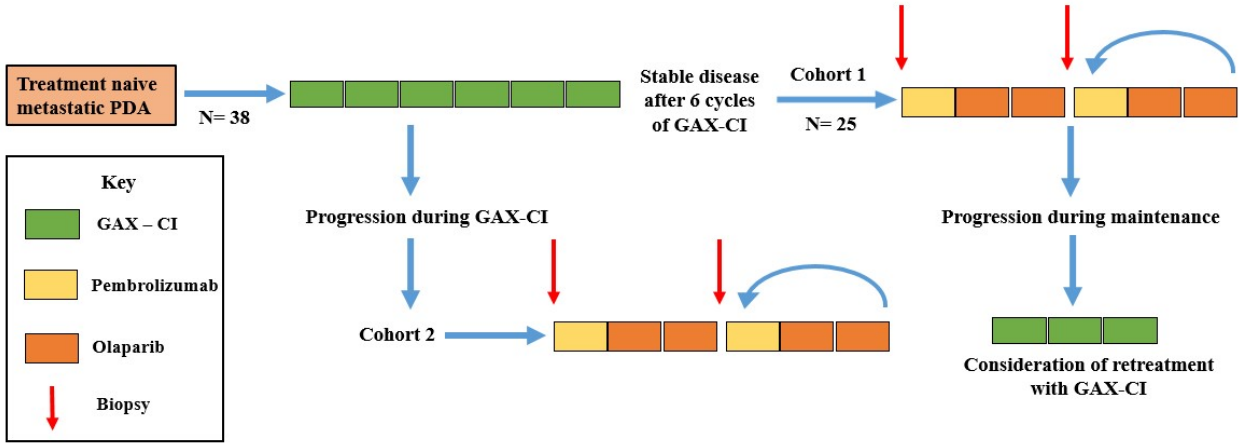
After completion of treatment and EOT assessments, all subjects will continue to be followed every 9-12 weeks by chart review, telephone, e-mail, or optional clinic visit until death, withdrawal of consent, or closure of study. Information on survival and new cancer therapies will be collected.

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, 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 6 months from cycle 1 day 1 of maintenance therapy if disease progression does not occur earlier or have discontinued the study treatment. Information on survival may continue to be gathered for supplementary analyses after the completion of the primary analysis.

Figure 1: Study Schema



1.5. Research Hypothesis

Low dose multi-agent chemotherapy with GAX-CI followed by maintenance treatment with PARP and PD-1 inhibition will be active and well tolerated as first line therapy for metastatic pancreatic cancer. The null hypothesis is that the 6 month PFS rate from cycle 1, day 1 of maintenance therapy of subjects in Cohort 1 will be higher than 10% (half of the 6 months PFS rate of BRCA germline patients on the control arm of the POLO study)[1]. The alternative hypothesis is that the 6 month PFS rate of subjects in Cohort 1 will be at least 30%.

2. BACKGROUND

2.1. Study Disease

Pancreatic cancer is the fourth leading cause of cancer death in the United States with 57,600 new cases estimated in 2020.[2] Less than 20% of patients are eligible for curative intent surgical intervention at the time of diagnosis and those with metastatic disease have a 3% five year overall survival (OS).[2] Thus, chemotherapy is the cornerstone of management in order to improve survival and disease related symptoms. Further investigations to identify novel regimens that will maximize efficacy and minimize toxicity in patients with metastatic PDA are urgently needed.

Historically, single agent gemcitabine was the standard of care for advanced PDA and demonstrated a one year OS of 18% in a landmark study.[3] Since that time, several regimens have been studied in combination with gemcitabine in an effort to improve outcomes.[4-8] Combination nab-paclitaxel and gemcitabine compared to gemcitabine monotherapy resulted in a median

survival 8.5 months compared to 6.7 months, respectively.[9] Of late, combination triplet chemotherapy has shown greater efficacy when compared to monotherapy. Triplet chemotherapy with folinic acid, fluorouracil, irinotecan, oxaliplatin (FOLFIRINOX) was compared to gemcitabine alone and resulted in a superior OS of 11.1 months versus 6.8 months, respectively.[10] Due to increased toxicity, this regimen is typically reserved for patients with a robust performance status and durable responses have been difficult to achieve due to the eventual emergence of resistance mutations.[11, 12] Multi-agent, low dose chemotherapy may be a potentially effective strategy to both overcome mechanisms of resistance and minimize toxicity.

Patients whose disease has stabilized with low dose chemotherapy represent a subset with a favorable tumor biology and may have the opportunity to attain a more durable response with the use of maintenance therapy. While maintenance therapy is a newer concept in pancreatic cancer, recent clinical studies have delivered promising results.[13] Olaparib was found to improve progression free survival in patients with metastatic PDA and a germline *BRCA* mutation stabilized on platinum chemotherapy and was approved for use in this setting in December 2019.[1]

Immunotherapy in metastatic PDA offers both obstacles and opportunities. While immunotherapy has improved survival in several previously recalcitrant malignancies, the immunosuppressive nature of the tumor micro-environment (TME) has rendered immunotherapy largely ineffective to date in pancreas cancer.[14-16] A genetic basis of susceptibility to immunotherapy is emerging, and PD-1 inhibitors have demonstrated high levels of activity in tumors with DNA damage.[17] A subset of PDA is characterized by defective DNA repair via homologous recombination (HR) due to genetic and epigenetic alterations of canonical HR pathway genes.[18] These tumors are sensitive to DNA damaging chemotherapy and the synthetic lethality of PARP inhibition.[1] Additionally, tumors with HR deficiency have increased immune infiltration and higher mutational loads. Preclinical models have shown upregulation of Programmed death-ligand 1 (PD-L1) expression, as well as increased CD8 and Natural Killer (NK) cell infiltration into the TME with use of PARP inhibition.[19, 20] Given these molecular features of PDA and prior preclinical work demonstrating a potential immunomodulatory effect of PARP inhibition on the TME, there is strong rational for further clinical investigation of combination PARP and PD-1 inhibition.[21-23] Investigations across multiple tumor types in both HR proficient and deficient patients have demonstrated favorable outcomes with combination PD-1 and PARP inhibition supporting continued investigation of this combination in an unselected patient population. [21, 23]

2.2. Study Rationale

Optimizing low dose combination chemotherapy to minimize toxicity and maximize response in metastatic PDA.

Over the last several years, combination chemotherapy has led to an improvement in overall survival in patients with metastatic pancreatic cancer.[9, 10] However, durable responses are limited by the emergence of eventual resistance mutations and inability to tolerate aggressive cytotoxic chemotherapy for prolonged periods. Prior work completed at our institution has demonstrated the therapeutic potential of multi-agent low dose chemotherapy to improve outcomes and minimize toxicity by administering 25-50% of standard protocol doses.

[redacted] In a follow up study of GTX-CI (irinotecan), median and 18-month OS is similar to GTX-C. However, 5 of 30 patients underwent resection of their primaries and residual metastatic disease. As of July 2020, 2 of the 5 are without evidence of disease 25+ and 16+ months after the resection. Our currently enrolling study (NCT03535727) aims to optimize these chemotherapy agents and schedule administration. The major change is the exchange of nab-paclitaxel (Abraxane) for docetaxel (**GAX-CI**) given recent work demonstrating the survival advantage with nab-paclitaxel and gemcitabine combination in metastatic PDA.[9] Expansion is ongoing but the regimen is active and well-tolerated. Six patients have been treated on the nab-paclitaxel 80mg/m2 level on the every other week schedule. The median PFS is 10.3 months and the median OS is 15.7 months. A low dose regimen is more inclusive of symptomatic patients with metastatic pancreatic cancer and is better tolerated than the current standard of care platinum-containing standard of care regimen, FOLFIRINOX. Moreover, this regimen enables the administration of platinum containing (DNA damaging) chemotherapy in an unselected population.

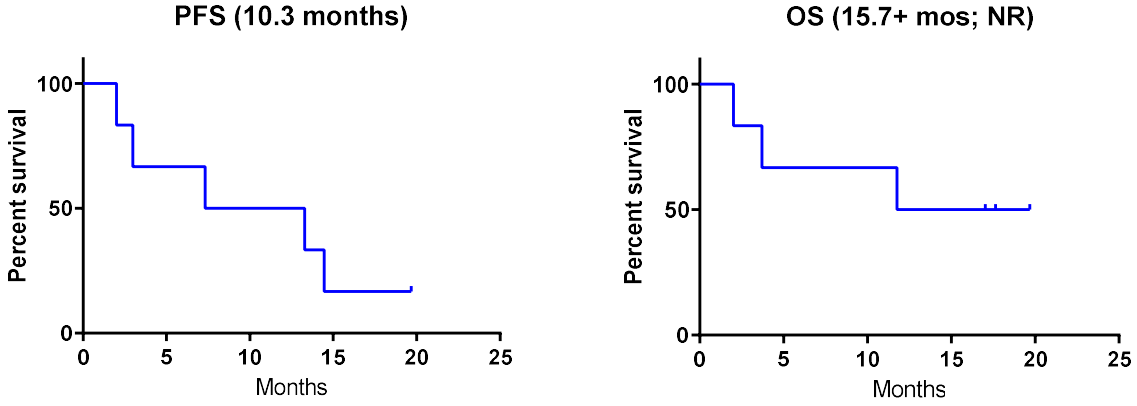


Figure 2. GAX-CI Progression Free Survival and Overall Survival of Nab-Paclitaxel 80mg/m2 Cohort (N=6)

Homologous recombination repair deficiency in PDA

A proportion of patients with PDA harbor defects in the canonical homologous recombination (HR) genes such as *BRCA1*, *BRCA2*, and *PALB2*.[18] Tumors with defects in homologous recombination repair lead to an enhanced sensitivity to DNA damaging chemotherapy and to the synthetic lethality of PARP inhibition.[24] Many more patients with PDA may exhibit a "BRCAness" phenotype that is not captured by these canonical mutations. According to one series, 45% of the double strange break repair cases lacked germline or somatic mutations in canonical HR repair genes. This same subset was associated with increased CD8 T cells and immune checkpoints indicating a potential synergistic effect of immunotherapy and PARP-inhibition.[25] Defects in homologous recombination repair can be exploited to enhance efficacy of DNA

damaging agents including chemotherapy and PARP inhibition. Given that a large proportion of patients may exhibit a "BRCAness" phenotype and preclinical models have demonstrated response in both HR proficient and deficient tumors, administering DNA damaging chemotherapy in an unselected population may lead to a survival advantage.

Rationale for Dual Inhibition of PARP and PD-1 Inhibition

In some diseases, tumors with DNA damage response-deficiency are thought to express immune checkpoints, have increased immune infiltration, and higher mutational load. Preclinical models have demonstrated a potential immunomodulatory effect of PARP inhibitors, with upregulation of PD-L1 expression and increased CD8 and NK cell infiltration in the tumor microenvironment.[26] A report evaluating the mechanism of the immunomodulatory effects of PARP inhibitors, showed PARP inhibitor-treated tumors to upregulate interferon beta (*IFNB1*) expression via activation of the cGAS-STING pathway and mediation of type I interferon inflammatory responses. These investigators found the combination of PARP and PD-1 inhibition showed activity in both homologous recombination repair deficient and proficient models.[27] A phase 1b trial of pamiparib (PARP inhibitor) plus tislelizumab (PD-1 inhibitor), demonstrated a response rate of 20% with similar response rates in germline BRCA wildtype and mutated cancers of multiple tumor types.[21,27]

3. PATIENT SELECTION

3.1. Eligibility Criteria for GAX-CI

3.1.1. Ability to understand and the willingness to sign a written informed consent document

3.1.2. Age ≥ 18 years

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

3.1.4. Metastatic histologically or cytologically confirmed pancreatic ductal adenocarcinoma. Subjects with islet cell neoplasms and mixed histology will be excluded.

3.1.5. Patients must not have received prior treatment for pancreatic cancer

3.1.6. Have measurable disease based on RECIST 1.1.

3.1.7. Patient agreeable to a biopsy of an accessible lesion post 6 cycles of GAX-CI chemotherapy and after one cycle of maintenance pembrolizumab and olaparib. Biopsy will only be obtained if lesion is accessible and felt to be reasonably safe to biopsy.

3.1.8. Patient 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 upper limit of normal (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) ≥ 60 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 4.7.2**), not breastfeeding, and at least one of the following conditions applies:

a) Not a woman of childbearing potential (WOCBP) as defined in **Section 4.6**

OR

b) A WOCBP who agrees to follow the contraceptive guidance in **Section 4.7.2** 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 4.7.1** 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. Participant 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 AE, understand the drug dosing schedule and use of medications to control AE.

3.2. Exclusion Criteria

3.2.1. Patients who will be considered for surgery are ineligible.

3.2.2. Subjects who have had prior chemotherapy for pancreatic cancer or prior chemotherapy within 5 years of enrollment for other cancer diagnoses.

3.2.3. Subjects who are receiving or have received any investigational agents within 28 days prior to Day 1 of treatment in this study.

3.2.4. Subject has undergone major surgery, other than diagnostic surgery (i.e. surgery done to obtain a biopsy for diagnosis or an aborted Whipple), within 28 days prior to Day 1 of treatment in this study

3.2.5. Has history of central nervous system (CNS) metastases and/or carcinomatous meningitis.

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

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

3.2.8. Has received prior therapy with gemcitabine, nab-paclitaxel, capecitabine, cisplatin, irinotecan, or PARP inhibitor.

3.2.9. History of severe hypersensitivity reaction to gemcitabine, nab-paclitaxel, capecitabine, cisplatin, irinotecan, PARP inhibitor or related compounds and/or to any of their components.

3.2.10. Is taking a moderate or strong CYP3A4 or CYP2C9 inhibitor (see **Appendix B**).

3.2.11. Has uncontrolled acute or chronic medical illness.

3.2.12. Has known additional malignancy that is progressing and requires active treatment.

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.

3.2.13. Has received radiotherapy for pancreatic cancer.

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

3.2.15. 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.

3.2.16. Has active autoimmune disease. Subjects with Graves or Hashimoto's disease, vitiligo, type I diabetes mellitus, psoriasis or other conditions not requiring systemic treatment are permitted to enroll. Subjects requiring systemic treatment for autoimmune disease in the past must be approved by the PI.

3.2.17. 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.

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

3.2.19. 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.

3.2.20. Requirement for daily supplemental oxygen.

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

3.2.22. Subject with clinically significant wound.

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

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

3.2.25. Has known active Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active 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.

3.2.26. Has uncontrolled infection

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

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

3.2.29. 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.

3.2.30. 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. In the case of a positive serum 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. Please see **Section 7** for detailed information on drug preparation and administration. Appropriate dosing delays are described in **Section 5.** Reported adverse events and potential risks are described in **Section 6.** No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Subjects that are required to stop treatment with either chemotherapy, olaparib, 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 or a new baseline. The relationship to the drug causing toxicity should be well documented in the source documents and permission from the PI needs to be obtained prior to continuation with drug therapy.

Suggested order of intravenous agent administration during GAX-CI phase is as follows: 1) nab-paclitaxel 2) gemcitabine 3) cisplatin 4) irinotecan. Complete details of agent administration and preparation can be found in **Section 7.**

Table 1: GAX-CI Treatment Regimen

Agent	Suggested pre and/or post medications and hydration	Dose	Route[a]	Schedule[b]
Nab-paclitaxel	**Pre-Medications:** - 5-HT3 antagonist IV - Fosaprepitant IV - Dexamethasone (Dex) 12 mg IV **Post-Medications**: - Dex 8mg BID PO on Day 2 & 3 - 5-HT3 antagonist PO on evening of Day 1, BID on Day 2 & 3	80 mg/m2	IV infusion over 30 min	Day 1 and Day 15
Gemcitabine	See Nab-paclitaxel	500 mg/m2	IV infusion over 30 min	Day 1 and Day 15
Cisplatin[c]	Pre: Normal saline 500cc IV Post: Normal saline 500cc IV	20 mg/m2	IV infusion over 60 min	Day 1 and Day 15
Irinotecan	**Atropine** should be immediately available for anti-cholinergic reactions	20 mg/m2	IV infusion over 30 min	Day 1 and Day 15
Capecitabine[d]	Oral 5-HT3 antagonist or prochlorperazine as needed	500 mg	Oral BID	Days 1-7 and Days 15-21

a. Infusion times are approximate (+/- 15 minutes) and may be adjusted based on subject tolerability
b. Cycle Length during the GAX-CI phase of the trial is **28 days**
c. The hydration for cisplatin should occur pre and post infusion as standard of care
d. The subject will be requested to maintain a medication diary of each dose of capecitabine. The medication diary will be returned to the study team at the end of each cycle

Table 2: Pembrolizumab and Olaparib Treatment Regimen

Agent	Suggested pre and/or post medications	Dose	Route[a]	Schedule[b]
Pembrolizumab	None, unless indicated by previous experience in an individual subject per **Table 3**	400 mg	IV infusion over 30 (-10/+15) min[b]	Day 1 every other cycle (every 6 weeks)
Olaparib[c]	None	300 mg	Oral BID	Days 1-21

a. Infusion times are approximate and may be adjusted based on subject tolerability
b. Cycle length during the Pembrolizumab/Olaparib phase of the trial is **21 days**
c. The subject will be requested to maintain a medication diary of each dose of olaparib. The medication diary will be returned to the study team at the end of each cycle.

4.1.1 Other Considerations for Oral Drugs

Capecitabine

Capecitabine tablets should be swallowed whole with water within 30 minutes after eating. Do not crush, chew, or dissolve them.

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. Subjects will make note in the comments of the pill diary if a dose is vomited.

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.

4.2. General Concomitant Medication and Supportive Care Guidelines

The concurrent use of all other drugs, over-the-counter medications, or alternative therapies must be documented. The PI should be alerted if the subject is taking warfarin, or phenytoin. These drugs are not contra-indicated but should be monitored closely while on treatment.

Subjects may not enroll in any other therapeutic clinical protocol or therapeutic investigational trial while enrolled in this study. Irradiation may be allowed during the study. Administration of other chemotherapy, immunotherapy, or anti-tumor hormonal therapy during the study is not allowed. Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the PI or Co-Investigators. Concurrent treatment with bisphosphonates is allowed.

All concomitant treatments, including blood and blood products, must be reported on the case report form (CRF). Erythropoietin, G-CSF, may be administered at the discretion of the PI or Co-Investigators.

Since pembrolizumab contains only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce an infusion or hypersensitivity reaction. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other allergic-like reactions. Infusion reactions should be graded according to The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 guidelines. Treatment recommendations are provided in **Table 3** and may be modified based on local treatment standards and guidelines as appropriate.

Table 3: 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 hours	**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. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	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).
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 Grade 4: Life-threatening; vasopressor 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, Vasopressors, 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.	No subsequent dosing

	**In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	

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 as described in **Section 4.4.**
- Live vaccines within 30 days prior to the first dose of study treatment as outlined in **Section 3.5.14** and while participating in the study
- Systemic glucocorticoids for any purpose other than to modulate symptoms from chemotherapy or from an event of clinical interest of suspected immunologic etiology or as specified in **Sections 4.2** and **Table 3.** Premedication for infusion and/or tumor assessments are allowed. If systemic steroids for other reasons are required, continuation of pembrolizumab should be approved by the PI. The use of physiologic doses of corticosteroids may be approved after consultation with the PI.
- Strong inhibitors or inducers of CYP3A4 or CYP2C9 (**Appendix B)**

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management might 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 PI 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 Serious Adverse Events (SAEs) and Events of Clinical Interest (ECI) as defined in **Section 6.**

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 adverse events, 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 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.

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 PI must be consulted prior to re-initiating treatment.

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 (≥2.5 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 PI and within 2 working days to Merck Global Safety. Merck contact information can be found in **Section 6.3.1.**

4.6. WOCBP

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:

- Premenopausal female with 1 of the following: Documented hysterectomy, bilateral salpingectomy, or 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 question 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.

4.7. Contraception

4.7.1. Male Participants

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 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 3.1.10:**

- 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 4** 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.

4.7.2. 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 4** during the protocol-defined time frame in **Section 3.1.9.**

Table 4: Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] :
● 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 Dependence :

- 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.

a. Failure rate of <1% per year when used consistently and correctly. 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.

**Note*: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.

4.8. 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 (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**).

4.9. Use in Nursing

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.

4.10. Duration of Therapy

Subjects in Cohort 1 who are clinically stable and meet dosing requirements (per **Section 5**) may continue to receive maintenance treatment for up to a maximum of 2 years. Subjects in cohort 1 who are eligible for retreatment with GAX-CI may continue retreatment with GAX-CI until confirmed disease progression. Subjects in Cohort 2 (Exploratory cohort) may continue treatment with olaparib and pembrolizumab for up to 2 years.

4.11. Criteria for Removal from Treatment

Participants may discontinue study treatment at any time for any reason or be removed from the study treatment at the discretion of the investigator. A participant may be discontinued from study treatment by the investigator or the PI 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)**.

The reason for study removal and the date the subject was removed will be documented in the eCRF. A subject must be discontinued from the trial for any of the following reasons:

A subject must be discontinued from treatment (but may continue to be monitored in the post-treatment follow-up portion of the trial) for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent for treatment,
- Confirmed radiographic disease progression using iRECIST in cohort 1 patients re-treated with GAX-CI and cohort 2 patients treated with pembrolizumab and olaparib
- Unacceptable adverse experiences as outlined in **Section 4.11.2,**
- Dose delay >6 weeks during the pembrolizumab and olaparib treatments (exceptions in **Section 4.11.2**)
- Intercurrent illness that prevents further administration of treatment,

- If in the opinion of the Investigator, a change or temporal or permanent discontinuation of therapy would be in the best interest of the patient (The IND Sponsor should be included in this decision),
- Participant has medical condition or personal circumstance placed the participant at unnecessary risk from continued administration of the study treatment,
- Participant becomes pregnant,
- Major noncompliance with study treatment or procedure requirements,
- Discontinuation of treatment may be considered for participants who have attained confirmed complete response (CR) and have been treated for at least 2 years,
- Participant is lost to follow-up, or
- Administrative reasons.

4.11.1. Disease Progression:

Pembrolizumab is expected to trigger immune-mediated responses which require activation of the immune system prior to clinical response and may take weeks to months to become evident. Some subjects may have objective volume increase of tumor lesions or other disease parameters within weeks after 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, this would constitute disease progression and lead to a discontinuation of therapy. Immune- mediated responses should be considered when evaluating disease progression.

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

- Subject is tolerating study drug.
- 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 PI and documented in the study records.

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment.

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

4.11.2. Pembrolizumab and Olaparib Related Adverse Events

Permanent discontinuation of study treatment should be considered as outlined below.

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

- 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 6.3.6)**

    - 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 <u>not</u> 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 PI.

- 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 PI 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 PI. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the PI 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 GAX-CI, pembrolizumab, olaparib dosing.

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

4.12. End of Treatment Visit

All subjects will have an End-of Treatment (EOT) visit 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). Procedures and assessments performed at this visit and beyond should follow the respective guidelines described in **Section 4.13** and **Section 9.0** as appropriate.

4.13. Duration of Follow Up

4.13.1. Safety Follow-Up

Subjects who receive chemotherapy only and discontinue treatment should be contacted by telephone or email at 30 days (+ 14-day reporting window) or within 7 days before initiation

of a new antineoplastic treatment (whichever comes first) to assess for treatment related toxicities. Subjects who receive immunotherapy and discontinue treatment should be contacted by telephone or email at 90 days (+14 day reporting window) 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.

4.13.2. Clinical Follow-Up

Subjects who discontinue Olaparib/Pembrolizumab Phase of 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 every 8 weeks (± 4 weeks) 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 9.0** for the schedule of assessments that should be performed at each visit.

Subjects who discontinue GAX-CI retreatment without disease progression will also enter the clinical follow-up portion of the trial where scans and information on other cancer therapies after discontinuation from the study treatment will be collected. Frequency of scans will be determined by each subject's treating oncologist per SOC.

After disease progression or start of a new antineoplastic therapy, subjects will enter the survival follow-up portion of the trial.

4.13.3. Survival Follow-Up

Subjects who discontinue treatment and have disease progression will enter the survival follow-up portion of the trial. Subjects should be contacted every 8 weeks (± 1 month) to monitor overall survival (medical record searches may be used as well). Information of other cancer therapies after discontinuation from the study treatment will be collected as well.

5. DOSING DELAYS AND MODIFICATIONS

Subjects will be monitored continuously for AEs while on study drug. Subjects will be instructed to notify their physician for any and all AE. Dose reductions for toxicities are permitted as per **Table 5 and Table 6**. 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.

5.1. Dose Delay Criteria for GAX-CI

Dosing of study therapy (including initiation of retreatment with GAX-CI for patients who progress in Cohort 1) may be delayed for the following laboratory criteria on Day 1 and Day 15 during the GAX-CI phase:

- ANC < 1000/mcL
- Platelets < 70 x 10^9/L
- Hemoglobin < 7g/dL
- Total bilirubin > 2x ULN
- AST(SGOT)/ALT (SGPT) > 5x ULN
- Creatinine > 1.5x ULN

* *Note:* if creatinine clearance ≥ 30mL/min/1.73m^2 for subjects with creatinine levels > 1.5 x ULN then agents other than cisplatin may be administered)

Discretion is left up to the investigator to determine whether longer treatment delays may be warranted for patients who are doing exceptionally well or may need a little extra time for clinical and laboratory status to recover and request approval from the PI for a longer break from therapy during the GAX-CI retreatment phase of the study.

5.2. Suggested Dose Modifications for GAX-CI

Suggested dose reductions are provided in **Table 5.** Additional dose reductions are left up to the discretion of the PI.

Table 5: Suggested Dose Modifications for GAX-CI

Study drug	Level 0	Level -1	Level -2
Gemcitabine	500 mg/m2	500 mg/m2	500 mg/m2
Nab-paclitaxel	80 mg/m2	60 mg/m2	40 mg/m2
Capecitabine	500mg BID	300mg BID	150mg BID
Cisplatin	20 mg/m2	Hold	Hold
Irinotecan	20mg/m2	Hold	Hold

Note: Dose reduction suggestions are for individual drugs based on each toxicity

5.2.1. Suggested Modifications for GAX-CI Hematologic Toxicity

Laboratory values are measured on Day 1 and Day 15 (±3 days) of every cycle during the GAX-CI phase.

Event Name	**Neutropenia**
Laboratory Value	**Management/Next Dose**
ANC <1000/mcL	Hold until ≥ 1000, no change in dose. Resume at one dose level lower, if indicated. Transient grade 3 neutropenia may occur
Recommended management: consider growth factor as indicated	

Event Name	**Thrombocytopenia**

Laboratory Value	Management/Next Dose
Platelets <70 x 10^9/L	Hold until ≥ 70K, no change in dose
Grade 3-4	Hold until ≥ 70K. Resume at one dose level lower, if indicated
A platelet goal of 50K should be considered for those on anticoagulation	

5.2.2. Suggested Modifications for GAX-CI Non-Hematologic Toxicity

Event Name	Nausea
Grade of Event	**Management/Next Dose**
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 3-4	Hold until < Grade 2. Resume at one dose level lower, if indicated
Recommended management: Antiemetics	

Event Name	Vomiting
Grade of Event	**Management/Next Dose**
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 3-4	Hold until < Grade 2. Resume at one dose level lower, if indicated
Recommended management: Antiemetics	

Event Name	Diarrhea
Grade of Event	**Management/Next Dose**
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 3-4	Hold until < Grade 2. Resume at one dose level lower, if indicated
Recommended management: Loperamide anti-diarrheal therapy Dosage scheduled: 4mg at first onset, followed by 2mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16mg/24 hours)	

Event Name	Peripheral Neuropathy
Grade of Event	**Management/Next Dose**
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 3-4	Hold until < Grade 2. Resume at one dose level lower, if indicated
Recommended management: medications for neuropathy (IE duloxetine or gabapentin)	

Event Name	Fatigue

Grade of Event	Management/Next Dose
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 3-4	Hold until < Grade 2. Resume at one dose level lower, if indicated
Recommended management: Antiemetics	

Event Name	Palmar-plantar erythrodysesthesia syndrome
Grade of Event	**Management/Next Dose**
≤ Grade 1	No change in dose
Grade 2	Hold capecitabine until ≤ Grade 1. Resume capecitabine 300mg PO BID. For 2nd occurrence, resume at 150mg BID
Grade 3-4	Hold capecitabine until ≤ Grade 1. Resume capecitabine 300mg PO BID. For 2nd occurrence, resume at 150mg BID
Recommended management: topical moisturizers to intact skin	

5.3. Dose Delay Criteria for Olaparib and Pembrolizumab

Dosing of study therapy may be delayed for the following laboratory criteria on Day 1 during the maintenance (olaparib and pembrolizumab) phase:

- ANC < 1000/mcL
- Platelets < 70 x 10^9/L
- Hemoglobin < 7g/dL
- Total bilirubin > 2x ULN
- AST (SGOT)/ALT (SGPT) > 5x ULN
- Creatinine > 1.5x ULN

  (if creatinine clearance ≥ 30mL/min/1.73m^2 for subjects with creatinine levels > 1.5 x ULN then dosing may continue with pembrolizumab and olaparib dose recommendations in **Table 6**).

5.4. Suggested Dose Modifications for Olaparib

Table 6: Suggested Dose Modifications for Olaparib

Creatinine Clearance*	Initial Dose Level	First Reduction	Second Reduction	Third Reduction
≥ 50 mL/min/1.73 m^2	300mg BID	250 mg BID	200 mg BID	100mg BID
≥ 30-49 mL/min/1.73 m^2	200mg BID	100mg BID	Discontinue	-

* A dose reduction is recommended for patients who develop moderate renal impairment (calculated creatinine clearance between 31 and 50ml/min/1.73m^2) for any reason during the

course of the study.

Patients who require more than two dose reductions will have to discontinue olaparib. 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 PI and must be approved to continue. 100mg and 150mg tablets will be supplied for 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 6**. If the event recurs with the same severity, treatment should be interrupted again and, on resolution, a further dose reduction made.

5.4.1. Suggested Modifications for Hematologic Toxicity of Olaparib

Laboratory values are measured on day 1 (±3 days) during the olaparib and pembrolizumab phase.

Event Name	**Neutropenia**
Laboratory Value	**Management/Next Dose**
ANC <1000/mcL	Hold until ANC ≥ 1000. Resume at one dose level lower once recovered
Recommended management: consider growth factor as indicated	

Event Name	**Thrombocytopenia**
Laboratory Value	**Management/Next Dose**
Platelets <70 x 10^9/L	Hold until ≥ 70K, no change in dose
Grade <50 x 10^9/L	Hold until ≥ 70K. Resume at one dose level lower
A platelet goal of 50K should be considered for those on anticoagulation	

Event Name	**Anemia**
Laboratory Value*	**Management/Next Dose**
Hemoglobin <8 g/dL	Give appropriate supportive treatment and investigate causality. PI discretion to either continue olaparib with supportive treatment or interrupt olaparib dosing
Hemoglobin <7 g/dL	Hold until ≥ 7 g/dL. Resume at one dose level lower, if indicated

5.5. Dose Delays and Modifications for Pembrolizumab

5.5.1. Dose Guidance for Immune Related Adverse Events Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AE (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab. Based on existing clinical study data, most irAEs are

reversible and can be managed with interruption of pembrolizumab, administration of corticosteroids and/or other supportive care. Based on severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modifications and toxicity management guidelines are provided in **Table 7.**

Table 7: Suggested Dose Modification and Toxicity Management for Immune-Related AEs Associated with Pembrolizumab

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the 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. The 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
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

				feasible, fluid and electrolytes should be substituted via IV infusion.
AST or ALT elevation or Increased bilirubin	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 enzyme value returned to baseline or is stable
	Grade 3[b] or 4[b]	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of =β-cell failure	Withhold[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 and Renal dysfunction: 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 and/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 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).

6. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

This study will use the descriptions and grading scales found in the revised national Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 for adverse event 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 (AE)

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.

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 (SAE)

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
  Note: reports of congenital abnormalities/birth defects must also be reported on the Pregnancy Supplemental Form)
- Is an important medical event. Potential drug induced liver injury (DILI) related to pembrolizumab and olaparib is also considered an important medical event
  Note: An important medical event is 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.
- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE
- Is a new cancer
- 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 serious adverse events are hospitalizations for:

- 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
- 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, administrative)
- Admissions for monitoring of treatment-related infusion reactions that do not otherwise meet the criteria for a SAE

6.2. Evaluating Adverse Events (AEs)

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 eCRF. 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 eCRF at the highest level experience by the subject.

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 Investigator's Brochure (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 or package insert 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.

GAX-CI Phase:

All SAEs (including deaths) occurring from the first dose of GAX-CI, throughout the course of treatment, and 30 days after the last dose of GAX-CI (or before initiation of a new antineoplastic treatment, whichever comes first) must be reported to the PI (Dung Le) and Regulatory Specialist (Jennifer Durham) within 24 hours of recognition of the adverse event.

Adverse events that are serious, unexpected, and assessed by the investigator to be related to the study drug will be reported within 24 hours of becoming aware of the event occurrence to the post-marketing departments of the drug manufacturers (contact pharmacy to verify the manufacturer).

Olaparib and Pembrolizumab Phase:

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 PI (Dung Le), Regulatory Specialist (Jennifer Durham), and Merck within 24 hours of recognition of the adverse event using the form found in **Appendix E**. Merck should only receive reports after the pembrolizumab and olaparib period have started and during the SAE reporting period for these agents. 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:

Dung Le: [redacted]
Jennifer Durham: [redacted]
Merck: [redacted]

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 PI 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 PI will reconcile the clinical database SAE cases (case level only) transmitted to the PI and Merck. Frequency of reconciliation should be approximately every 6 months and prior to the database lock or final data summary. Merck will email, upon request from the Investigator or designee, 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 PI determines a case was not transmitted to the PI and Merck, the case should be sent immediately to the PI 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 using the form found in **Appendix F**.

Events of clinical interest for this trial include:

1. An overdose of Merck product, as defined in **Section 4.5**, that is not associated with clinical symptoms or abnormal laboratory results.

2. Potential DILI are addresses in **Sections 6.1.3 and 6.3.6**.

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 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 time of treatment allocation through 120 days following cessation of PI'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 PI and Merck Global Safety. (Attn: Worldwide Product Safety; FAX [redacted]).

6.3.6. Potential Drug-Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, and related to pembrolizumab and olaparib, must be reported as SAEs under the seriousness category checked as 'other medically important event'. Potential drug induced liver injury is defined as:

1) ALT or AST elevation > 3 times upper limit of normal (ULN)
   AND
2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
   AND
3) No other immediately apparent possible causes of AST/ALT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.3.7. Institutional Review Board (IRB)

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

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 PI (or designee) and Merck will notify investigators of all SAEs that are unexpected (i.e., not previously described in the IB), and related to GAX-CI pembrolizumab, olaparib. 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. Nab-paclitaxel

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

Description, Formulation, and Storage:

Nab-paclitaxel (albumin-bound form of paclitaxel) a microtubule inhibitor that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Nab-paclitaxel is a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each single-use vial contains 100 mg of paclitaxel (bound to human albumin) and approximately 900 mg of human albumin (containing sodium caprylate and sodium acetyltryptophanate). Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. Nab-paclitaxel is free of solvents.

Nab-paclitaxel should be stored between 20 and 25°C (68°F-77°F) in a secure and dry place. Retain in the original package to protect from bright light. Neither freezing nor refrigeration adversely affects the stability of the product.

Preparation and Administration:

Nab-paclitaxel reconstitution, preparation, and administration should be completed according to the manufacturer's recommendation.

Nab-paclitaxel may be administered on an outpatient basis. Nab-paclitaxel should be administered on day 1 and 15 of each cycle by intravenous infusion over 30 minutes. Infusion times are approximate and may need to be adjusted based on patient tolerability.

Nab-paclitaxel doses may be rounded to the nearest whole and half-vial size (50 and 100 mg) and within 10% of the patient's ordered dose.

Reconstituted nab-paclitaxel in the vial should be used immediately, but may be refrigerated at 2ºC to 8ºC (36ºF to 46ºF) for a maximum of 8 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion.

The suspension for infusion when prepared as recommended in an infusion bag should be used immediately but may be stored at ambient temperature (approximately 25ºC) and lighting conditions for up to 4 hours. Discard any unused portion.

Toxicities of Nab-Paclitaxel:

Please see the nab-paclitaxel prescription information for more details on the known precautions, warnings, and adverse reactions of nab-paclitaxel. The most common adverse reactions (≥ 20%) in metastatic pancreas cancer patients are neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration. Fetal harm can occur when administered to a pregnant woman. Women of childbearing potential should be advised not to become pregnant when receiving nab-paclitaxel.

Subject Care Implications:

The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering nab-paclitaxel concomitantly with medicines known to inhibit (e.g., ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce (e.g., rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine) either CYP2C8 or CYP3A4.

7.2. Gemcitabine

For complete details on preparation instructions, storage, clinical pharmacology, a comprehensive list of adverse events and the human pharmacokinetics of Gemcitabine, please see the Gemcitabine prescribing information.

Description, Formulation, and Storage:

Gemcitabine (difluorodeoxycytidine) is a pyrimidine antimetabolite, which is an analogue of deoxycytidine. It was initially synthesized as a potential antiviral drug but selected for anticancer development because of its activity in in-vivo and in vitro tumors. Gemcitabine is approved for the treatment of patients with pancreatic cancer and will be obtained commercially. Gemcitabine is commercially supplied as a powder for reconstitution in 200 mg and 1 gm vials.

Intact vials containing sterile powder are stored at room temperature (20° to 25°C) (68° to 77°F). Gemcitabine solutions are stable for 24 hours at controlled room temperature of 20° to 25°C (68° to 77°F). Do not refrigerate as crystallization can occur. The diluted solution should be clear and colorless to light straw-colored solution.

Preparation and Administration:

Reconstitute the 200 mg vial with 5 mL 0.9% NaCl and the 1 g vial with 25 mL 0.9%NaCl. The resulting solution is approximately 38 mg/mL, but the concentration varies. It is suggested that when the desired dose is less than the entire vial, the entire volume be drawn up into a syringe in

order to determine the actual concentration. Then the desired amount should be measured and diluted in 0.9%NaCl for infusion. Reconstituted solution should be further diluted in 100 ml NS for intravenous infusion.

In this study, Gemcitabine may be administered on an outpatient basis. Gemcitabine should be administered on day 1 and 15 of each cycle by intravenous infusion over 30 minutes following the nab-paclitaxel infusion. Infusion times are approximate and may need to be adjusted based on patient tolerability.

Toxicities of Gemcitabine:

Please see the Gemcitabine prescribing information for more details on the known precautions, warnings, and adverse reactions of Gemcitabine. Gemcitabine can suppress bone marrow function as manifested by leukopenia, thrombocytopenia and anemia, and myelosuppression is usually the dose-limiting toxicity. Subjects should be monitored for myelosuppression during therapy.

Hemolytic-Uremic Syndrome (HUS) has been reported rarely with the use of Gemcitabine. Gemcitabine is a Pregnancy Category D drug. Gemcitabine can cause fetal harm when administered to a pregnant woman. Gemcitabine is embryotoxic causing fetal malformations (cleft palate, incomplete ossification) at doses of 1.5 mg/kg/day in mice (about 1/200 the recommended human dose on a mg/m2 basis). Gemcitabine is fetotoxic causing fetal malformations (fused pulmonary artery, absence of gall bladder) at doses of 0.1 mg/kg/day in rabbits (about 1/600 the recommended human dose on a mg/m2 basis). Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. There are no studies of Gemcitabine in pregnant women. If Gemcitabine is used during pregnancy, or if the subject becomes pregnant while taking Gemcitabine, the subject should be apprised of the potential hazard to the fetus.

7.3. Capecitabine

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

Description, Formulation, and Storage:

Capecitabine is a fluoropyrimidinecarbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is converted to 5-fluorouracil. Normal cells, as well as tumor cells metabolize 5- Fluorouracil into 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). Both are metabolites that cause cell injury by two different mechanisms. FdUMP and the folate factor, N5-10-methylenetetrahydrofolate, bind to thymidylate synthase (TS) to inhibit the formation of thymidylate. This deficiency of thymidylate causes cell cycle division to halt. This is because thymidalate is necessary for thymidine triphosphate production, which is essential for DNA synthesis. FUTP works by incorporating itself into transcription in place of uridine triphosphate therefore interfering with RNA transcription and protein synthesis.

Capecitabine is supplied as either 150 mg or 500 mg peach to light peach, oblong, film-coated, biconvex tablets for oral administration.

Capecitabine will be provided as an outpatient prescription. Capecitabine should be stored at 25° C (77° F); excursions permitted to 15° to 30°C (59° to 86°F). Keep bottle tightly closed.

Dosing and Administration of Capecitabine:

Capecitabine will be administered on an outpatient basis. Capecitabine will be given by oral administration twice daily on days 1-7 and 15-21 of each cycle. Capecitabine tablets should be taken within 30 minutes after the end of a meal and swallowed with water.

Toxicities of Capecitabine:

Please see the capecitabine prescribing information for more details on the known precautions, warnings, and adverse reactions of capecitabine. The most common side effects of capecitabine are diarrhea, nausea, vomiting, stomatitis, abdominal pain, upset stomach, constipation, loss of appetite, dehydration, hand-and-foot syndrome (palms of the hands or soles of the feet tingle, become numb, painful, swollen or red), rash, dry, itchy or discolored skin, nail problems, hair loss, tiredness, weakness, dizziness, headache, fever, pain (including chest, back, joint, and muscle pain), trouble sleeping, and taste problems. Capecitabine is a Pregnancy Category D drug. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with capecitabine. If capecitabine is used during pregnancy, or if the subject becomes pregnant while taking capecitabine, the subject should be apprised of the potential hazard to the fetus.

7.4. Cisplatin

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

Description, Formulation, and Storage:

Cisplatin (cis-diamminedichloroplatinum) is a heavy metal complex containing a central atom of platinum surrounded by two chloride atoms and two ammonia molecules in the cis position. Cisplatin inhibits DNA synthesis by forming inter- and intra-strand crosslinks. Other possible mechanisms include chelation of DNA and binding to cell membranes thereby stimulating immune mechanisms.

Cisplatin Injection is a sterile aqueous solution, available commercially in 50, 100 and 200 mL multiple dose vials, each mL containing 1 mg of cisplatin and 9 mg sodium chloride in water for injection. HCl and/or sodium hydroxide added to adjust pH to 3.5 to 4.5.

Intact vials should be stored at room temperature and be protected from light. Solutions diluted in 0.9% or 0.45% NaCl to a concentration of 0.05-2mg/mL are stable for up to 72 hours at room temperature and protected from light.

Preparation and Administration:

Unopened vials of dry powder are stable for the lot life indicated on the package when stored at room temperature (25° C, 77° F). The reconstituted solution is stable for 20 hours at room temperature (25° C, 77° F). Solution removed from the amber vial should be protected from light if it is not to be used within six hours. Once reconstituted, the solution should be kept at room temperature (25° C, 77° F). If the reconstituted solution is refrigerated a precipitate will form.

Cisplatin may be administered on an outpatient basis. Cisplatin should be administered on day 1 and 15 of each cycle by intravenous infusion over 60 minutes following the gemcitabine infusion. Infusion times are approximate and may need to be adjusted based on patient tolerability. Cisplatin should be administered in 250 mL NaCl, following intravenous hydration with at least 500 ml of normal saline. 500ml of normal saline may also be administered after cisplatin. Needles, syringes, catheters, or IV administration sets containing aluminum parts should not be used, as contact with cisplatin yields a black precipitate.

Toxicities of Cisplatin:

Please see the Cisplatin prescribing information for more details on the known precautions, warnings, and adverse reactions of Cisplatin. Common side effects include myelosuppression, nausea, vomiting, anorexia, elevation of BUN and creatinine, hyperuricemia, renal tubular damage, rare cardiac abnormalities, taste alteration, peripheral neuropathy, seizures, anaphylactoid and urticarial reactions (acute), rash, fatigue, ototoxicity including hearing loss or tinnitus, and loss of muscle function. Cisplatin can cause fetal harm when administered to a pregnant woman. Cisplatin is mutagenic in bacteria and produces chromosome aberrations in animal cells in tissue culture. In mice, cisplatin is teratogenic and embryotoxic. If this drug is used during pregnancy or if the subject becomes pregnant while taking this drug, the subject should be apprised of the potential hazard to the fetus. Subjects should be advised to avoid becoming pregnant.

7.5. Irinotecan

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

Description, Formulation, and Storage:

Irinotecan is a derivative of camptothecin. Camptothecins interact specifically with the enzyme topoisomerase I, which relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase IDNA complex and prevent re-ligation of these single-strand breaks. Current research suggests that the cytotoxicity of irinotecan is due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either irinotecan or SN-38. Mammalian cells cannot efficiently repair these double-strand breaks.

Irinotecan is a sterile, pale yellow, clear, aqueous solution. It is available in three single-dose sizes in brown glass vials: 2 mL-fill vials contain 40 mg irinotecan hydrochloride, 5 mL-fill vials contain 100 mg irinotecan hydrochloride, and 15 mL-fill vials contain 300 mg irinotecan hydrochloride.

Each milliliter of solution contains 20 mg of irinotecan hydrochloride (on the basis of the trihydrate salt), 45 mg of sorbitol, NF, and 0.9 mg of lactic acid, USP. The pH of the solution has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light. It is recommended that the vial should remain in the carton until the time of use.

Preparation and Administration:

Dilute irinotecan with 5% Dextrose Injection, USP (D5W), or 0.9% Sodium Chloride Injection, USP, prior to intravenous infusion. The solution is physically and chemically stable for up to 24 hours at room temperature and in ambient fluorescent lighting. Solutions diluted in 5% dextrose injection, USP, and stored at refrigerated temperatures (approximately 2° to 8°C, 36° to 46°F), and protected from light are physically and chemically stable for 48 hours. Refrigeration of admixtures using 0.9% Sodium Chloride Injection, USP, is not recommended due to a low and sporadic incidence of visible particulates. Freezing irinotecan and admixtures of irinotecan may result in precipitation of the drug and should be avoided.

The irinotecan injection solution should be used immediately after reconstitution as it contains no antibacterial preservative. Irinotecan may be administered on an outpatient basis and should be administered on day 1 and 15 of each cycle by intravenous infusion over 30 minutes following the Cisplatin infusion. Infusion times are approximate and may need to be adjusted based on patient tolerability.

Toxicities of Irinotecan:

Please see the Irinotecan prescribing information for more details on the known precautions, warnings, and adverse reactions of Irinotecan. Common adverse reactions (≥30%) observed in combination therapy clinical studies are: nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia, mucositis, neutropenia, leukopenia (including lymphopenia), anemia, thrombocytopenia, asthenia, pain, fever, infection, abnormal bilirubin, alopecia.

Subject Care Implications:

Irinotecan and its active metabolite, SN-38, are metabolized via the human cytochrome P450 3A4 isoenzyme (CYP3A4) and uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1), respectively. Patients receiving concomitant ketoconazole, a CYP3A4 and UGT1A1 inhibitor, have increased exposure to irinotecan and its active metabolite SN-38. Co-administration of Irinotecan with other inhibitors of CYP3A4 (e.g., clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole) or UGT1A1 (e.g., atazanavir, gemfibrozil, indinavir) may increase systemic exposure to irinotecan or SN-38. Discontinue strong CYP3A4 inhibitors at least 1 week prior to starting Irinotecan therapy. Do not administer strong CYP3A4 or UGT1A1 inhibitors with Irinotecan unless there are no therapeutic alternatives.

7.6. Pembrolizumab

Agent Accountability:

The PI or the PI'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.

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.

Description:

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

Packaging and Labeling Information:

Clinical supplies will be labeled in accordance with regulatory requirements.

Preparation and Administration:

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.

Pembrolizumab is to be administered as a 30 (-10/+15) minute IV infusion on day 1 the maintenance phase. Pembrolizumab will be given every other cycle (every 6 weeks) during the maintenance phase.

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.

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.

Subject Care Implications:

Based on results from nonclinical studies, there are currently no specific safety considerations. Pembrolizumab is a humanized monoclonal antibody. 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 adverse events 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 (hypothyroidism/ hyperthyroidism), hepatitis, hypophysitis, Type I diabetes mellitus, uveitis, and nephritis. After a recent review of data, events newly characterized as identified risks also include pancreatitis, myositis, and severe skin reaction.

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.

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.

7.7. Olaparib

Agent Accountability:

The PI 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.

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 subsequent cell death.

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.

Packaging and Labeling Information:

Clinical supplies will be labeled in accordance with regulatory requirements.

Dispensing:

An initial bulk supply of olaparib will be provided to sites prior to Cycle 1, Day 1 of the maintenance phase 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 drug accountability log.

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.

Dosing and Route of Administration:

Olaparib will be administered orally BID every 12 hours without regard to food at the dose specified. 100mg and 150mg tablets will be supplied.

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.

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.

8. CORRELATIVE/SPECIAL STUDIES

Research samples will be collected at the discretion of the PI based on availability of supplies and safety of patient and staff. Sample collection, processing, storage, and shipment instructions will be provided in the Laboratory Manual for all specimens collected. Tissue, fluid, or blood may be collected from standard of care procedures used to treat or diagnoses immune related toxicities.

8.1. Serum and Plasma Marker Studies

Sera and plasma will be collected 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.

Samples will be collected at the following time points: at baseline, after 6 cycles of GAX-CI, and after two cycles of maintenance therapy. An optional EOT sample may be collected.

8.2. Whole Blood Studies

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.

Whole blood will be collected at baseline. An optional EOT sample may be collected.

8.3. Peripheral Blood Mononuclear Cells (PBMCs)

PBMCs will be collected to assess baseline characteristics of the subjects enrolled and to assess dynamics of effector, helper, and regulatory T cells, NK cells and macrophages during treatment. This will be assessed through cell phenotyping analysis and by measuring gene expression profiling. Post-treatment expression of PD-1 and other lymphocyte activation markers will be measured. T cells will be isolated and co-cultured with synthetic peptide neo-antigens and will undergo TCR sequencing to assess for clonal expansion as previously describe.

Samples will be collected at baseline, after 6 cycles of GAX-CI, and after two cycles of maintenance therapy. An optional EOT sample may be collected.

8.4. Tumor Tissue Studies

Attempts will be made to obtain archival tumor samples (slides and/or blocks) from all subjects if eligibility criteria are met. Tumor biopsies will be collected prior to initiation of maintenance phase and after two cycles of maintenance therapy (4-6 cores per time point). Additional biopsies may be obtained later in course of therapy.

To explore the association of the tumor microenvironment and clinical responses, archived tumor tissue, tumor tissue following 6 cycles of GAX-CI and tumor tissue after two cycles of maintenance immunotherapy will be compared. 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).

8.5. 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, neo-epitope prediction, mutation burden, 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 FASTQ files, BAM files and VCF files will be generated and analyzed.

Genomic sequencing data will be stored and computations conducted using a Johns Hopkins Information Technology managed subscription of Azure.

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. 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

		GAX-CI Phase (Cycle Length: 28 days)[19]						Olaparib and Pembrolizumab Phase (Cycle Length: 21 Days)[20]				EOT[22]	Safety Follow up [23]	Clinical Follow up[24]	Survival Follow up[25]
		Cycles 1-6						Cycle 1, 3, 5...		Cycle 2, 4, 6...					
Study Procedures	**Pre-Study (Baseline)**	**Day 1[18]**	**Days 2-7**	**Days 8-14**	**Day 15**	**Days 16-21**	**Days 22-28**	**Day 1**	**Days 2-21**	**Day 1**	**Days 2-21**				
Visit Window (days)[1]	-28 to 0	±3	-	-	±3	-	-	±7[25]	-	±7	-	±7	±14	±14	±14
Nab-paclitaxel		X			X										
Gemcitabine		X			X										
Cisplatin		X			X										
Irinotecan		X			X										
Capecitabine		X →			X →										
Olaparib								X →							
Pembrolizumab[21]								X							
Informed Consent	X														
Eligibility Criteria	X														
Demographics	X														
Medical History[2]	X														
Medications[3]	X	X			X			X		X		X			
Physical Exam[4]	X	X			X			X		X		X		X^A	
Height[5]	X														
Weight	X	X			X			X		X		X		X^A	
Vital Signs[6]	X	X			X			X		X		X		X^A	
Performance Status[7]	X	X			X			X		X		X		X^A	
Hematology[8, 9]	X	X			X			X		X		X		X^A	
Chemistry[9, 10]	X	X			X			X		X		X		X^A	
Endocrine [9,11]								X				X			
CA 19-9/CEA[9,12]	X	X						X		X		X		X^A	
Pregnancy Test [9,13]	X							X							

		GAX-CI Phase (Cycle Length: 28 days)[19]						Olaparib and Pembrolizumab Phase (Cycle Length: 21 Days)[20]				EOT[22]	Safety Follow up[23]	Clinical Follow up[24]	Survival Follow up[25]
		Cycles 1-6						Cycle 1, 3, 5+		Cycle 2,4,6 +					
Study Procedures	**Pre-Study (Baseline)**	**Day 1[18]**	**Days 2-7**	**Days 8-14**	**Day 15**	**Days 16-21**	**Days 22-28**	**Day 1**	**Days 2-21**	**Day 1**	**Days 2-21**				
Radiologic Evaluation RECIST/iRECIST[14]	X	X						X		X		X		X[A,B]	
AE Evaluation	X	X			X			X		X		X	X	X[A]	
Whole Blood Sample (up to 10cc)[15, 27]		X													
PBMC Sample (up to 100 cc)[16, 27]		X						X				X			
Serum (up to 5 cc)[16, 27]		X						X				X			
Plasma (up to 20 cc)[16, 27]		X						X				X			
Tumor Biopsy[17, 27]								X							
Archival Tissue[26]		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 by the investigator and to minimize participant 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. Longer delays may be approved by the PI
2. Medical History: Includes patient's personal and family history of cancer. 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, and tumor mutation testing.

3. Concurrent Medications should be reviewed at every treatment visit with a particular focus on medication interactions. Can occur within 3 days of treatment.
4. Complete physical exam will be performed at baseline. Focused physical exam will be conducted at every treatment visit. Can occur within 3 days of treatment.
5. Prior documented height may be utilized
6. Blood pressure, heart rate, oxygen saturation and temperature will be obtained at baseline and at every treatment visit. Vitals will be collected prior to and at the end of pembrolizumab infusion (+ 15/ -5 minutes).
7. Eastern Cooperative Oncology Group (ECOG) Performance Status will be performed at baseline and at every treatment visit. Can occur within 3 days of treatment.
8. Hgb, HCT, RBC count, WBC with differential, ANC, ALC, AEC, and platelet count.
9. Labs may be collected within 3 days of dosing and treatment visit (including tumor markers, pregnancy tests, etc).
10. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, magnesium.
11. TSH (Total T3 and free T4 if TSH abnormal and clinically indicated) will be collected during the olaparib and pembrolizumab phase with odd cycles only (i.e. cycles 1, 3, 5, 7) and at the EOT visit.
12. Tumor markers will be obtained at baseline and on Day 1 of every cycle during the GAX-CI phase and the olaparib and pembrolizumab phase. Tumor markers may be discontinued by the PI.
13. Pregnancy tests will be administered to WOCBP. Pregnancy test will be obtained at screening, and prior to cycle 1, day 1 of maintenance therapy (prior to first dose of pembrolizumab).
14. CT scan (chest/abdomen/pelvis) with intravenous contrast or MRI (if patient has contrast allergy). The baseline scan must be within 28 days of the first dose of treatment. On study scans should be assessed at the following timepoints: 1. every 8 weeks (±1 week) during the GAX-CI phase (end of cycle 2 and 4), 2. prior to the first dose of pembrolizumab/olaparib (GAXCI Cycle 6 Day 16 through Cycle 1 Day 1 pembro/olaparib), and 3. every 9 weeks (±1 week) during the olaparib and pembrolizumab phase. Weeks are in reference to calendar week and should not be adjusted due to dosing delays. However, if a scan is performed for clinical reasons, the investigator can re-start the 8 week count as to not overuse imaging. CT scan assessment at EOT will occur 30 days (± 4 weeks) after the final dose. The EOT scans do not need to be repeated if one has been done within the past 6 weeks. On-study radiologic evaluation and tumor assessments will be performed utilizing RECIST and iRECIST per **Appendix C and D.**
15. Whole blood will be collected at baseline only (any time prior to first dose after eligibility is met).
16. Plasma, serum and PMBC samples will be collected at baseline (any time prior to first dose after eligibility is met), after 6 cycles of GAX-CI (C1D1 of maintenance therapy), and after 2 cycles of maintenance therapy (C3D1). Optional EOT sample may be collected at the discretion of the PI.
17. Tumor Biopsies will be obtained if subject tumor is thought to be reasonably safe and accessible to biopsy. 4-6 cores will be taken, Fine Needle Aspiration (FNA) is not acceptable. Biopsy should be obtained within 7 days of initiation of the maintenance phase (C1D1)

and within 7 days of cycle 3 of the maintenance phase. Additional biopsies may be obtained later in course of therapy if tumor is thought to be reasonably safe and accessible to biopsy.

18. Cycle 1, Day 1 evaluations do not need to be repeated if they were conducted within 3 days of the pre-study evaluations.
19. Patients will be placed into two cohorts during the GAX-CI phase. Cohort 1 will include patients whose disease demonstrates stability after 6 cycles of GAX-CI. Patients in Cohort 1 who have clinical or radiographic progressive disease during the maintenance phase, or those who become intolerant of treatment with either pembrolizumab or olaparib, may be eligible for retreatment with GAX-CI if the PI believes they will derive benefit from retreatment. Those eligible for retreatment will follow the same treatment schedule as the initial GAX-CI phase. Retreatment with GAX-CI may continue until confirmed disease progression. Cohort 2 will be an exploratory and will include patients who have progressive disease prior to completing 6 cycles of GAX-CI.
20. The olaparib and pembrolizumab phase should begin within 7-28 days of last dose of oral capecitabine. Combination olaparib and pembrolizumab therapy may continue for a maximum duration of 2 years.
21. Pembrolizumab will be given every other cycle during the maintenance phase (cycle 1, 3, 5, 7…).
22. 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). If the EOT visit occurs early and the patient cannot return due to disease progression, an assessment for AEs should be made by telephone or email on day 30 (±1) after last study dose in place of the PE/PS/vitals (clinical laboratory values should still be collected).
23. 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.
24. [A] Subjects who discontinue Olaparib/Pembrolizumab Phase of treatment without disease progression will enter the clinical follow-up portion of the trial (**Section 4.13.2**). Clinical follow-up visits will occur every 8 weeks (± 4 weeks) until progression. After disease progression, subjects will enter the survival follow up portion of the trial. [B] Subjects who discontinue GAX-CI retreatment without disease progression will also enter the clinical follow-up portion of the trial where scans (frequency determined by each subjects treating oncologist per SOC) and information on other cancer therapies after discontinuation from the study treatment will be collected.
25. Subjects who discontinue treatment and have disease progression will enter the survival follow-up portion of the trial (**Section 4.13.3**). Subjects should be contacted every 8 weeks (± 1 month) to monitor overall survival (medical record searches may be used as well). Information of other cancer therapies after discontinuation from the study treatment will be collected.
26. If eligibility criteria are met, every effort will be made to obtain archived tissue sample for correlative analyses
27. 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 6 month progression free survival on maintenance therapy with olaparib and pembrolizumab per RECIST 1.1 of patients with metastatic PDA whose disease has stabilized with GAX-CI (Cohort 1).

10.2. Secondary Endpoints

Safety assessments will include the following:

- Number of patients who have grade 3 or higher drug-related toxicities
- Frequency of drug-related toxicity by grade
- Infusion reactions
- Immune-related AEs
- Unacceptable toxicities
- Physical exam including vital signed (BP, pulse, temperature)
- Clinical hematology: complete blood count (CBC) with differential, and platelet count
- Clinical chemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, total protein, albumin, calcium, magnesium, and phosphate
- TSH, T3, Free T4

10.3. Exploratory Endpoints

Exploratory endpoints are as follows:

- For Cohort 1, Progression free survival (PFS), objective response rate (ORR), disease control rate (DCR), overall survival (OS) on maintenance therapy of pembrolizumab and olaparib, measured by RECIST 1.1 and iRECIST.
- For Cohort 1, PFS, ORR, DCR, OS, on retreatment with GAX-CI, per RECIST 1.1 and iRECIST
- For Cohort 1, PFS, ORR, DCR, OS, from the start of initial GAX-CI, per RECIST 1.1 and iRECIST.
- For Cohort 2, PFS, ORR, DCR, OS on second-line treatment of pembrolizumab and olaparib, measured by RECIST 1.1 and iRECIST
- For all patients in Cohort 1 and 2 combined, PFS, ORR, DCR, OS, from the start of initial GAX-CI, per RECIST 1.1 and iRECIST.

    - Progression-free survival (PFS) is defined as the duration of time from the start of study treatment to the date of first documented disease progression or death, whichever occurs first.
    - Objective Response Rate (ORR) is defined as the percentage of subjects achieving a PR or CR on study treatment.

- Disease Control Rate (DCR) is defined as the percentage of subjects achieving stable disease or better (SD + PR + CR) on study treatment
- Overall Survival (OS) is defined as the duration of time from study treatment to time of death

- Immune subset analysis by Immunohistochemistry (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 but not limited to 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
- 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 6.0.**

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 PI.

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 eCRFs. Before or between visits, the PI, 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 PI, 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, 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

The SKCCC Compliance Monitoring Program will provide external monitoring for JHU-affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee will

determine the level of patient safety risk and level/frequency of monitoring. The PI shall internally monitor the progress of the trial, including review and confirmation of all safety/treatment-related outcomes, response assessments, safety reports and/or any related source documentation. The protocol will be monitored 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 Informed Consent Form (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 PI 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 PI 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 PI correspondence will be kept on-site in study site-specific binders.

The PI 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 PI 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 PI (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 PI 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 PI. 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 PI 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 PI 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, PI or their representative.

12. STATISTICAL CONSIDERATIONS

12.1. Study Design/Endpoints

This is an open-label, single-arm phase 2 study to evaluate the safety and clinical activity of maintenance olaparib and pembrolizumab following low dose multi-agent chemotherapy with GAX-CI in untreated metastatic PDA.

The primary endpoint is to determine the 6 month progression-free survival (PFS) rate of patients treated with maintenance pembrolizumab and olaparib following multi-agent low dose chemotherapy (Cohort 1), defined as the time from cycle 1, day 1 of maintenance therapy to the date of disease progression per RECIST 1.1 or death, whichever occurs first.

Secondary endpoints will include safety. Exploratory endpoints include will include PFS, ORR, and DCR per RECIST 1.1 and iRECIST. For Cohort 1, these endpoints will be calculated from cycle 1, day 1 of maintenance therapy, from cycle 1, day 1 of GAX-CI, and from cycle 1, day 1 of re treatment with GAX-CI following progression on maintenance therapy, when applicable.

Cohort 2 is an exploratory cohort which includes patients with disease progression prior to receiving 6 cycle of GAX-CI. This cohort will receive pembrolizumab and olaparib as second-line therapy. PFS, ORR, DCR, and OS per RECIST 1.1 and iRECIST will be calculated from cycle 1, day 1 of olaparib and pembrolizumab.

Additionally, PFS, ORR, DCR, and OS per RECIST 1.1 and iRECIST will be calculated for all patients (Cohort 1 and Cohort 2) from cycle 1, day 1 of GAX-CI.

12.2. Sample Size Determination

The regimen will be considered to be inactive and of no interest for further evaluation if the 6 month PFS is less than 10% (half of the 6 month PFS rate of BRCA germline patients on the control arm of the olaparib maintenance study).[1] The regimen is considered active if the 6 month PFS after treatment with maintenance pembrolizumab and olaparib is higher than 10%. We expect the treatment will result in a 6 month PFS of at least 30%.

The trial plans to have 18 patients receiving maintenance treatment and evaluable for the primary endpoint of 6-month PFS rate. A sample size of 18 gives 84% power to reject the null hypothesis of 6 months PFS rate of 10% and detect a PFS of 30%, based on a one-sided binomial exact test with type I error of 0.1. If 4 or more patients out of 18 are free of progression at 6 months, the effect of the therapy is considered desirable. Subjects will be considered evaluable if they receive at least one dose of maintenance therapy after disease stabilization with 6 cycles of GAX-CI and an assessment of progression status can be made at 6 months. Those who do not have radiological assessment of disease due to clinical progression within 6 months of therapy are considered evaluable as having disease progression by 6 months. Up to 36 patients could be enrolled to account for the possibility that 50% may not start maintenance therapy.

Sample size of the exploratory Cohort may vary depending number of patients with disease progression prior to 6 cycles of GAX-CI.

12.3. 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.

For Cohort 1, the primary outcome 6-month progression free survival will be estimated as among the patients with stable disease after 6 cycles of GAX-CI, the proportion who are free of disease progression at 6 months after maintenance therapy, with corresponding 95% binomial confidence interval. For the exploratory outcomes with maintenance therapy, we will estimate the rate of objective response (ORR), defined as the proportion of patients who have complete response (CR) or partial response (PR) with maintenance therapy 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 from cycle 1, day 1 of maintenance therapy, will be estimated. Progression-free survival and overall survival (OS), both starting from day 1 cycle 1 of maintenance therapy, will be summarized using Kaplan-Meier method. Analyses will be performed based on RECIST 1.1 criteria and iRECIST, respectively. These endpoints will also be estimated from day 1 cycle 1 of GAX-CI

The analysis for Cohort 2 with second line pembrolizumab and olaparib will use the same method as described above.

Additionally, we will estimate OS, defined as the time from day 1, cycle 1 of multi-agent chemotherapy to death due to any cause, for all patients who receive at least one treatment of chemotherapy in all patients of cohort 1 and 2. OS times will be censored for patients who are alive at the time of analysis. PFS, defined as the time from cycle 1 day 1 of chemotherapy to disease progression on pembrolizumab and olaparib following chemotherapy, will be estimated for all patients in cohort 1 and cohort 2.

For correlative studies, plots will be used to show the changes in immune response over time for each individual. Changes from 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 quantified using 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.

Genomic sequencing library construction, whole genome/exome sequencing, whole transcriptome sequencing, microbial sequencing, neoepitope prediction, mutation burden, 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 FASTQ files, BAM files and VCF files will be generated and analyzed.

Genomic sequencing data will be stored and computations conducted using a JH IT managed subscription of Azure.

12.4. Analysis Sets

Since the focus of this study is on investigating the efficacy of the maintenance therapy, all efficacy outcomes of Cohort 1 will be assessed using the patients who receive at least one dose of the maintenance combination treatment as the primary population for analysis. The analysis of overall survival will also be conducted with all patients who receive at least one dose of chemotherapy. The analysis for Cohort 2 will include the patients who receive at least one dose of pembrolizumab and olaparib as second-line therapy.

The safety population includes all subjects who received at least one dose of maintenance treatment. A separate safety assessment will be performed for the induction chemotherapy phase among the patients who receive at least one dose of GAX-CI. 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.

12.5. Safety Analysis

The safety analysis will be performed in all subjects receiving maintenance therapy. A separate safety assessment will be performed for the induction chemotherapy phase. 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 monitoring and stopping guidelines: The study will be continually monitoring for adverse events in the maintenance phase. We will temporarily halt the enrollment pending safety evaluations if we observe > 33% unacceptable toxicities at any time starting from the 6th treated patients. We will stop if:

Number of patients with AE > 33%	2	3	4	5	6	7	8	9
Number of patients between	6	7-9	10-12	13-15	16-18	19-21	22-24	25

The operating characteristics of the stopping rule for toxicity based on 5000 simulations are shown below:

Risk of AE	0.1	0.2	0.25	0.3	0.33	0.4	0.45
% of time study halts	12.7%	43.2%	62.2%	75.5%	82.3%	93.8%	97.3%
Expected sample size	22.64	17.37	14.04	11.84	10.63	8.4	7.4

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14. APPENDICES

APPENDIX A: PERFORMANCE STATUS CRITERIA

Eastern Cooperative Oncology Group (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 CYP3A4 AND CYP2C9 INHIBITORS

Examples 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

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

Examples 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

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/ pneumonitis, 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 PI).

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.

APPENDIX D: DESCRIPTION OF iRECIST PROCESS

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 4.11.1**.

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

  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 (i.e., 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.

Table 8: 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 9: 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.

APPENDIX E: SERIOUS ADVERSE EVENT REPORTING FORM

Dung Le, MD
[redacted]

JOHNS HOPKINS
MEDICINE
THE SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER

FAX

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

Study:

Multi-agent low dose chemotherapy (gemcitabine, nab-paclitaxel, capecitabine, cisplatin, irinotecan) followed by maintenance olaparib and pembrolizumab in untreated metastatic pancreatic ductal adenocarcinoma (J2112, #59686)

Comments:

Please confirm receipt to:

Serious Adverse Event Reporting Form

Please notify: Dr. Le within 24 hours (email: [redacted])
Jennifer Durham within 24 hours (email: [redacted])
Merck within 24 hours (fax: [redacted])

<table>
<tr><td>Protocol Title:</td><td colspan="3">Multi-agent low dose chemotherapy (gemcitabine, nab-paclitaxel, capecitabine, cisplatin, irinotecan) followed by maintenance with olaparib and pembrolizumab in untreated metastatic pancreatic ductal adenocarcinoma</td></tr>
<tr><td>Protocol Number:
J2112
Merck #59686</td><td>Principal Investigator:
Dung Le</td><td>Signature of PI:</td><td>Date of Report:</td></tr>
<tr><td rowspan="2">Report Type:
☐ Initial
☐ Follow-up
☐ Final Follow-up
☐ Death
☐ Addendum to:</td><td rowspan="2">Serious Criteria (check all that apply):
☐ Death
☐ Life-threatening
☐ Hospitalization or Elongation Hospitalization
☐ Other Important Medical Event
☐ Cancer
☐ Overdose
☐ Other:_____</td><td>Hospital Admission Date:</td><td>SAE ID:</td></tr>
<tr><td>Hospital Discharge Date:</td><td>Date Event Discovered:</td></tr>
<tr><td colspan="4">Section A: Subject Information</td></tr>
<tr><td colspan="2">Subject ID:</td><td>Subject Gender:
☐ Male
☐ Female</td><td>Subject Age:</td></tr>
<tr><td colspan="4">Section B: Event Information</td></tr>
<tr><td colspan="2">Event diagnosis or symptoms:</td><td>Event Grade:</td><td>Cause of death (if applicable):</td><td>Event Outcome:
☐ Not Recovered
☐ Recovering
☐ Recovered
☐ Recovered with sequelae
☐ Death
☐ Unknown</td></tr>
<tr><td colspan="2">Event Onset Date (or Date of Death):</td><td colspan="2">Event End Date:</td></tr>
</table>

Section C: Study Drug Information:

Investigational Product: Pembrolizumab (400mg, IV infusion), Olaparib (100mg or 300mg, Oral), Gemcitabine (500mg/m2, IV infusion), Nab-paclitaxel (80mg/m2, IV infusion), Cisplatin (20mg/m2, IV infusion), Irinotecan (20mg/m2, IV infusion), Capecitabine (500mg, Oral)
Indication: Metastatic Pancreatic Ductal Adenocarcinoma

Number of Total Cycles:						**Action Taken with Study Drug:**		
Date of First Dose:			**Date of Last Dose Prior to Event:**			☐ None ☐ Interrupted ☐ Delayed ☐ Discontinued		
Relationship to:	**Gem-citabine**	**Nab-paclitaxel**	**Cisplatin**	**Irinotecan**	**Cape-citabine**	**Olaparib**	**Pembro-lizumab**	**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: Dr. Le within 24 hours (email: [redacted]
Jennifer Durham within 24 hours (email: [redacted])
Merck within 24 hours (fax: [redacted])

Protocol Title:	Multi-agent low dose chemotherapy (gemcitabine, nab-paclitaxel, capecitabine, cisplatin, irinotecan) followed by maintenance with olaparib and pembrolizumab in untreated metastatic pancreatic ductal adenocarcinoma		
Protocol #: J2112 Merck 59686	**Principal Investigator:** Dung Le, MD	**Signature of PI:**	**Date of Report:**
Report Type: ☐ **Initial** ☐ **Follow-up** ☐ **Final Follow-up** ☐ **Addendum to:**			

Section A: Subject Information

Subject ID:	**Subject Age:**	**Subject Gender:** ☐ **Male** ☐ **Female**

Section B: Event Information

Event diagnosis or symptoms:	**Date of first dose of study drugs:**	**Action taken with the study drugs:** ☐ **None** ☐ **Interrupted** ☐ **Delayed** ☐ **Discontinued**
	Date of last dose of study drugs prior to event:	
Event Grade:	**Number of total doses study drug:**	
Event Onset Date:	**Event End Date:**	**Date Event Discovered:**

Relationship to:	**Gem-citabine**	**Nab-paclitaxel**	**Cisplatin**	**Irinotecan**	**Cape-citabine**	**Olaparib**	**Pembro-lizumab**	**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