A Phase II, Single-arm Study of Combination Pembrolizumab and Olaparib in the Treatment of Patients with Advanced Cholangiocarcinoma
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TITLE: A Phase II, Single-arm Study of Combination Pembrolizumab and Olaparib in the Treatment of Patients with Advanced Cholangiocarcinoma

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1.0 TRIAL SUMMARY

Abbreviated Title	Combination Pembrolizumab and Olaparib in the Treatment of Patients with Advanced Cholangiocarcinoma
Trial Phase	*II*
Clinical Indication	Advanced cholangiocarcinoma who have failed or cannot tolerate 1st line systemic therapy
Trial Type	Single arm, single-site
Type of control	None
Route of administration	Oral and intravenous
Trial Blinding	None
Treatment Groups	Olaparib plus pembrolizumab
Number of trial participants	36
Estimated enrollment period	*24*
Estimated duration of trial	*36*
Duration of Participation	12
Estimated average length of treatment per patient	12

2.0 TRIAL DESIGN

2.1 Trial Design

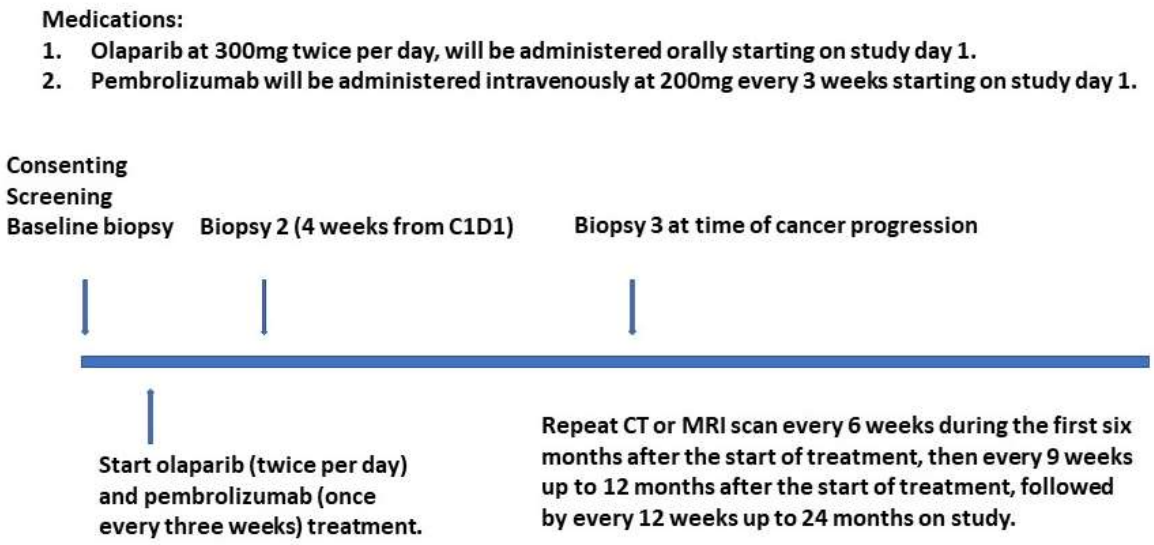
We propose an open label, one-arm study to assess the safety and efficacy of olaparib and pembrolizumab in patients with cholangiocarcinoma who have progressed on or cannot tolerate gemcitabine-based therapy.

The primary objective of the study is to assess the ORR of patients with advanced cholangiocarcinoma receiving a combination of pembrolizumab and olaparib. It is hypothesized that the addition of olaparib will improve the response rate of second line systemic therapy from 17.5% to 35% in patients with advanced cholangiocarcinoma.

The study is designed to enroll 33 subjects (for 85% power) with advanced stage cholangiocarcinoma to test the hypothesis that the combination of olaparib and pembrolizumab will increase the ORR in comparison with the ORR from second line systemic chemotherapy (historical control) in this patient population. As our primary study endpoint, which is also being used to determine the sample size of the study, we propose that the combination of olaparib and pembrolizumab will increase the ORR to 35% from 17.5% (achieved with systemic cytotoxic chemotherapy including mFOLFOX—historical control). To allow a 10% patient drop off rate, we expect to enroll a total of **36** subjects into this study. In addition, as secondary study endpoints we expect to see an increase in the PFS and OS of patients receiving combination therapy compared to cytotoxic chemotherapy.

In this study, we propose the collection of three biopsies—one at baseline prior to the start of treatment, one at the beginning of week 4, three weeks after the administration of combination olaparib and pembrolizumab, and one at the time of cancer progression—for the elucidation of exploratory study endpoints. Patients will have a CT or MRI scan at the beginning of treatment and then every 6 weeks thereafter for the first six months of study treatment administration, then every 9 weeks for up to 12 months after the start of treatment, followed by every 12 weeks up to 24 months on study. All patients will continue to receive olaparib and pembrolizumab combination treatment as tolerated unless unacceptable toxicities or cancer progression occur, at which time therapy will cease. In the absence of any problems, the planned study duration is 20-36 months.

2.2 Trial Diagram



3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) Objective:

Assess the objective response rate (ORR) of patients receiving pembrolizumab and olaparib combination therapy.

(2) Hypothesis:

The combination of olaparib and pembrolizumab regimen will improve the response rate of second line systemic therapy from 17.5% to 35% in patients with advanced cholangiocarcinoma, based on RECIST1.1.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) Objective:

1. Assess the duration of response (DOR) of patient receiving pembrolizumab and olaparib, taking best overall response to progression.

2. Assess progression free survival (PFS) of patients receiving pembrolizumab and olaparib taking best overall response to progression or death from any cause, whichever occurs first.

3. Assess overall survival (OS) of patients receiving pembrolizumab and olaparib from baseline to date of death or last follow up.

4. Assess the safety and tolerability of combined pembrolizumab and olaparib therapy.

(2) Hypothesis:

We propose that a PFS of 24 weeks and an OS of 40 weeks is clinically meaningful in patients who receive the combination of pembrolizumab and olaparib following failure on frontline therapy (due to cancer progression or intolerance of treatment).

3.3 Exploratory Objective

(1) Objective:

1. To correlate in tumor samples the baseline density of CD3 and CD8 in the tumor interior and invasive margin, the expression of PD-L1, and the clonality of the T-cell repertoire with ORR, DOR, PFS, and OS.

2. To assess in tumor samples the baseline density of CD3 and CD8 in the tumor interior and invasive margin, the expression of PD-L1, and the clonality of the T-cell repertoire at baseline and after three weeks of treatment, and then correlate these assessments with ORR, DOR, PFS, and OS.

3. To compare in tumor samples the density of CD3 and CD8 in the tumor interior and invasive margin, the expression of PD-L1, and the clonality of the T-cell repertoire at three time points: at the time of disease progression, after three weeks of treatment, and at baseline.

4. To correlate in the cholangiocarcinoma tissue the baseline expression of ERCC (DRCC+/-) or the baseline mutation status of IDH1 or 2 (mutant or non-mutant) with ORR, DOR, PFS, and OS.

(2) Hypothesis:

Given the low expression of the ERCC1 protein in the majority of cholangiocarcinomas, together with relative frequent IDH1/2 mutations found in these tumor types, we hypothesize that the combination of PARP inhibition and immune checkpoint blockade will produce a durable anti-tumor response against cholangiocarcinoma by synergistically inducing DNA damage, increasing tumor antigen number and producing durable immune response against cholangiocarcinoma. Therapies that target the programmed death-1 (PD-1) receptor have shown unprecedented rates of durable clinical responses in a sub-group of patients with various cancer types [1-5]. Biomarkers in patient tumor that will predict response to anti-PD-1 therapy are being actively investigated. One mechanism by which cancer tissues limit the host immune response is via upregulation of PD-1 ligand (PD-L1) and its ligation to PD-1 on antigen-specific CD8+ T cells [6, 7]. Recent research has reported that tumor regression after therapeutic PD-1 blockade requires pre-existing CD8+ T cells that are negatively regulated by PD-1/PD-L1-mediated adaptive immune resistance [8].

We propose that olaparib will increase the response of pembrolizumab by inducing DNA damage, increasing tumor antigen number, and producing durable immune response against cholangiocarcinoma. We expect that cancer cells with low expression of the ERCC1 proteins or with IDH1/2 mutations will have more DNA damage upon olaparib treatment than cancer cells that have normal expression of the ERCC1 protein, or are without IDH1/2 mutations.

In this study, we will first test whether the effect of olaparib and pembrolizumab treatment on tumor infiltrating lymphocytes, the level of PD-1 and PD-L1 expression, and clonality of the T-cell repertoire differs between low ERCC1/IDH1/2 mutant and normal ERCC1/non IDH1/2 mutant tumor cells. Then we will examine whether the change of tumor infiltrating lymphocytes and the level of PD-1 and PD-L1 expression correlates with clinical response in patients treated with pembrolizumab and olaparib combination therapy.

4.0 BACKGROUND & RATIONALE

4.1 Cholangiocarcinoma

Cholangiocarcinoma has been steadily increasing in incidence worldwide over the last decade [1]. It is difficult to establish the diagnosis of early stage cholangiocarcinoma as symptoms are not prominent until the disease is far advanced. Patients with unresectable tumors have a dismal prognosis, with a median survival time of nine months [2,3]. Surgical resection is considered to be the most viable approach to attempting a “cure” for cholangiocarcinoma but even after surgery, five-year survival rates range from only 25% to 48% due to incomplete resection and a subsequent high recurrence rate (~50%) [4-6]. New approaches are urgently needed to prevent tumor recurrence after surgical resection in an attempt to further improve patient survival.

4.1.1 Chemotherapy and Cholangiocarcinoma

A recent randomized, controlled trial (ABC-02 study) proved that gemcitabine combined with cisplatin (GC-therapy) performed better than gemcitabine monotherapy for cholangiocarcinoma [7]. However the benefits of GC-therapy were shown to be modest with a progression free survival (PFS) of 8.1 months and overall survival (OS) of 11.7 months [7]. Furthermore there is no effective

second line therapy for patients with advanced cholangiocarcinoma. In a Phase II study of second line gemcitabine monotherapy for cholangiocarcinoma in patients refractory to 5-fluorouracil treatment, the median time to progression (TTP) was 1.6 months (95% CI: 1.3-1.9 months), and the median OS was 4.1 months (95% CI: 2.7-5.5 months) [8]. A retrospective analysis of patients with metastatic gallbladder cancer and cholangiocarcinoma who were treated with second-line FOLFOX4 chemotherapy after disease progression on gemcitabine-based first-line chemotherapy demonstrated stable disease in 22% of patients, a median disease free survival (DFS) of 96 days (13 weeks), and an OS of 138 days (19 weeks)[9].

4.2 Pembrolizumab

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

4.2.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [10]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [11, 12].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [13, 14].

The structure of murine PD-1 has been resolved [15]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-

based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [14,16-18]. The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [19, 20]. As a consequence, the PD 1/PD-L1 pathway is an attractive target for therapeutic intervention in [disease under study].

4.2.1.1 Preclinical and Clinical Trial Data

4.2.1.2 Non-Clinical Toxicology Summary of Results

In the 1-month and 6-month toxicology study in cynomolgus monkeys, pembrolizumab, intravenously administered once a week and once every other week respectively up to a dose of 200 mg/kg, resulted in no adverse treatment-related effects. In tissue cross-reactivity studies of pembrolizumab in human and monkey tissues, the expected on-target staining of mononuclear leukocytes membranes was demonstrated in both species. Off-target cross-reactivity staining was also noted in both species but was limited to the cytoplasm of various cell types/tissues and the stroma (extracellular connective tissue matrix), and was considered related to experimental methodological artifacts, i.e. tissue processing for IHC, which are well recognized limitations of tissue cross-reactivity studies and, thus not considered toxicologically relevant. No reproductive or developmental toxicity studies are planned with pembrolizumab. Therefore, inclusion of women of childbearing potential in clinical trials should be avoided in accordance with the study protocol and applicable regulatory guidance (e.g., ICH M3(R2): Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals).

4.2.1.2.1 Clinical Summary of Results

Clinical Pharmacology Summary

The PK profile of pembrolizumab, with low clearance and limited volume of distribution, is typical for therapeutic antibodies. Exposure to pembrolizumab is approximately linear in the dose range of clinical relevance (1 to 10 mg/kg and at 200 mg). Furthermore, pembrolizumab has a low potential of eliciting the formation of ADAs.

Efficacy Summary

For the treatment of unresectable or metastatic melanoma, pembrolizumab demonstrated superior efficacy over available treatment options (IPI, Investigator's choice chemotherapy) in participants with advanced melanoma who were treatment-naïve, as well as those who progressed on prior therapy, including IPI.

Pembrolizumab provided substantial, clinically meaningful benefits in OS, PFS, and ORR in participants with NSCLC who progressed after platinum-containing chemotherapy and whose tumor cells expressed PD-L1. In previously treated participants with PD-L1 TPS ≥1% and disease progression following platinum-containing chemotherapy, pembrolizumab provided a statistically significant and clinically meaningful OS benefit compared to standard docetaxel chemotherapy. For participants with previously untreated metastatic NSCLC whose tumors express high levels of PD-L1, pembrolizumab demonstrated significant improvements in PFS and OS over standard of care chemotherapy.

Pembrolizumab in combination with pemetrexed/carboplatin for the first-line treatment of metastatic nonsquamous NSCLC demonstrated both a statistically significant and clinically meaningful difference in ORR and a statistically significant benefit in PFS compared with pemetrexed/carboplatin alone.

For the treatment of advanced HNSCC in a heavily pretreated population, pembrolizumab demonstrated a clinically meaningful response rate and a prolonged duration of response that is substantially distinct from what is expected with standard of care in previously treated participants with HNSCC, and points to the meaningful clinical benefit of pembrolizumab.

Pembrolizumab for the treatment of relapsed or refractory cHL, has demonstrated durable, robust, clinically meaningful responses in this heavily pretreated population that generally included standard front-line therapies, salvage therapies, auto-SCT if eligible with chemosensitive disease, other single agent or combination chemotherapy regimens as needed, and with or without BV.

For the treatment of urothelial cancer (UC) in participants who have not received prior chemotherapy and are cisplatin-ineligible, pembrolizumab demonstrated a clinically meaningful ORR in participants with locally advanced or metastatic UC. In participants with locally advanced or metastatic UC who have received platinum-containing chemotherapy, treatment with pembrolizumab demonstrated a significant improvement in OS and a clinically meaningful benefit in durable responses compared with standard of care therapies.

In participants with MSI-H tumors, pembrolizumab provided evidence of clinically meaningful benefit over standard treatments, regardless of tumor histology.

For the treatment of gastric or GEJ adenocarcinoma, pembrolizumab administered as a third line or later treatment to participants with PD-L1 positive tumors demonstrated durable response, as assessed by a median ORR and DOR that exceeded the historic data.

Safety Summary

Pembrolizumab has a positive benefit-risk profile and is well tolerated in the approved indications, as evidenced by a low rate of toxicity Grade 3 to 5 drug-related AEs (13.8%), discontinuations due to AEs (11.9%), and deaths due to drug-related AEs (0.4%) in the RSD.

Furthermore, the frequency of immune-mediated Adverse Events of Special Interest (AEOSI) is low, and these events are readily managed in the clinical setting (see package insert] for guidance on management of immune and non-immune-mediated events of interest). Overall, the safety profile of pembrolizumab as defined by the RSD has remained generally consistent with accrual of additional data and participant exposure as represented by the RCSD.

Conclusion

Participants with a broad range of advanced cancers benefit from pembrolizumab therapy, which can induce high rates of durable responses and benefits in OS that are superior to those seen with standard therapies.

Pembrolizumab has a positive benefit-risk profile and is well tolerated in the approved indications. Furthermore, most AEOSIs are mild to moderate in severity, and are generally readily manageable with appropriate care in the clinical setting (see package insert and section 6.1 for guidance on management).

The safety and efficacy data generated to date provide a favorable benefit-risk assessment for the use of pembrolizumab as a treatment for patients in the approved indications.

4.2.1.3 Dosage and Administration

Pembrolizumab is provided as a white to off white lyophilized powder (50 mg/vial) or as a liquid solution (100 mg/vial) in Type I glass vials intended for single use only. Pembrolizumab Powder for Solution for Infusion, 50 mg/vial, is reconstituted with sterile water for injection prior to use. Pembrolizumab is formulated with L-histidine as buffering agent, polysorbate 80 as surfactant, sucrose as stabilizer/tonicity modifier, and hydrochloric acid (HCl) and/or sodium hydroxide (NaOH) for pH adjustment (if necessary). The drug product is stored as a stable lyophilized powder or liquid solution under refrigerated conditions (2°C - 8°C). The product after reconstitution with sterile water for injection and the liquid drug product is a clear to opalescent solution, which may contain extraneous and proteinaceous particulates. The reconstituted product and liquid product is intended for IV administration. The reconstituted drug product solution and liquid drug product can be further diluted with normal saline in IV containers made of polyvinyl chloride (PVC) or non-PVC material. Reconstituted vials should be immediately used to prepare the infusion solution in the IV bag and the infusion solution should be immediately administered. If not used immediately, vials and/or IV bags may be stored at 2-8 °C for up to a cumulative time of 20 hours. If refrigerated, the vials and/or IV bags should be allowed to equilibrate to room temperature prior to subsequent use. Pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of reconstituted drug product solution and liquid drug product in vials, room temperature storage of infusion solution in the IV bag and the duration of infusion.

4.3 Olaparib

A PARP inhibitor is a DNA repair inhibitor, and when applied to a tumor that has a DNA repair defect, there is a synergistic effect between the defect and the inhibitor in a process known as "synthetic lethality", leading to tumor cell death. Development of therapeutics based on this approach is shown to be effective in the treatment of hereditary breast and ovarian cancers, and the U.S. food and Drug Administration has approved two PARP inhibitors—olaparib and rucaparib—to treat certain BRCA-mutant ovarian cancers.

4.3.1 Non-clinical pharmacology

Olaparib is a new chemical entity that is a potent inhibitor of mammalian PARP-1, PARP-2 and PARP-3 and inhibits selected tumor cell lines in vitro and xenograft tumor growth in vivo, either as a stand-alone treatment or in combination with established chemotherapies. Olaparib has an IC50 against the PARP-1 enzyme of 5 nM, an IC50 against the PARP-2 enzyme of 1 nM, and an IC50 against the PARP-3 enzyme of 4 nM. The main target of olaparib that is responsible for the induction of synthetic lethality in HRD cancer cells is PARP-1. In cells cultured in vitro, 50% inhibition of PARP-1 activity, as measured by the formation of PAR, occurs at concentrations of 6-8 nM, with greater than 90% PAR formation being inhibited between 30-100 nM and complete inhibition of PARP-1 activity occurring between 100-300 nM. In vivo, the PARP-1 IC50 was 120 nM (standard error ±33 nM) and the IC90 was 576 nM (standard error not calculated). Olaparib doses leading to tumor regression in a BRCA2 mutant PDX model resulted in PARP-1 inhibition of >50% for more than 10 hours and inhibition of >90% for more than 4 hours. Analysis of a panel of cancer cell lines identified those deficient in homologous recombination repair factors, notably BRCA1 and BRCA2, as being particularly sensitive to treatment with olaparib.

The sensitivity of tumor cell lines and PDX models to Olaparib correlates with their sensitivity to platinums, which suggests that the latter can be used as a potential surrogate marker for the former. In sensitive *BRCA*-mutant in vivo models, olaparib extended the anti- tumor activity of platinum agents when given sequentially, suggesting the potential for olaparib to be given as a maintenance treatment following treatment with platinum. Olaparib showed no significant activity when screened in vitro against a diverse panel of molecular targets including enzymes, receptors, transporters and ion channels. Olaparib inhibited the hERG encoded potassium channel in vitro, with an IC_{50} of 226 μM. Olaparib showed no significant effects in vivo in dog cardiovascular/respiratory and rat Irwin (behavioral) tests.

4.3.1.1 Pharmacokinetics and drug metabolism in animals

The absolute bioavailability of olaparib following oral solution dosing to mice, rats and dogs was approximately 60%, 20% and 80%, respectively. Absorption was rapid, exposure increased less than proportionally with dose in mice, more than proportionally with dose in rats and approximately proportionately in dogs. In mice and rats, exposure dropped on multiple dosing. In dogs, little/no change in PK occurred on multiple dosing. Gender differences in exposure were seen in the rat, with female animals having consistently higher circulating concentrations of olaparib than male animals. This gender difference was not seen in the mouse or dog. Plasma

clearance was low in mice and in dog (1.3-1.7 L/h/kg and 0.39 L/h/kg, respectively) while volume of distribution was low in the mouse and moderate in the dog (<0.5 L/kg and 0.93 L/kg, respectively). These parameters could not be accurately determined in the rat. Olaparib plasma protein binding, in vitro, showed some variation between species. Olaparib bound to HSA and α1AGP although with higher affinity for HSA. Distribution of drug-related material in the rat was rapid and extensive but with little/no distribution seen to the brain, spinal cord or the lens of the eye. In pigmented animals, material was associated with the melanin containing tissues although the association was only transient. In a quantitative whole-body autoradiography analysis of xenograft bearing nude mice, concentrations of radioactivity were higher in the tumor than those in the blood and were cleared more slowly. Metabolism was more extensive in the male rat than in the female rat or in the dog. The majority of the metabolism of olaparib was the result of oxidation and hydroxylation processes with the main site of metabolism being the piperazine carboxycyclopropyl part of the molecule; both the fluorophenyl and phathalazinone ring systems are also subject to metabolism but to a lesser extent. In vitro, CYP3A4/5 were shown to be the major isozyme responsible for the metabolism of olaparib. In vitro, olaparib was a direct inhibitor of CYP3A and a time dependent inhibitor of CYP3A. Using human hepatocyte cultures, olaparib was able to induce expression of messenger RNA for CYPs 1A2, 2B6 and 3A4. Olaparib was able to inhibit the Phase II metabolism enzyme UGT1A1 but had no appreciable effect against UGT2B7 in vitro. In vitro studies showed that olaparib was subject to active uptake by isolated human hepatocytes but that it was not a substrate for OATP1B1, OATP1B3 or OCT1 hepatic uptake transporters. Olaparib was a substrate for the efflux transporter MDR1 Pgp, but not for BCRP or MRP-2 efflux transporters. Olaparib was an inhibitor of OATP1B1 and OCT1; it caused no significant inhibition of OATP1B3 and was a very weak inhibitor of NTCP. Olaparib was shown to inhibit MDR1 and very weakly inhibit BCRP. Olaparib did not inhibit MRP-2. Olaparib was able to inhibit OCT2, OAT3, MATE1 and MATE2K. Olaparib had no significant effect on OAT1. Drug-related material was predominantly excreted via the faces in both species.

Pharmacokinetics:

Absorption:

Following oral administration of olaparib via the capsule formulation, absorption is rapid with peak plasma concentrations typically achieved between 1 to 3 hours after dosing. On multiple dosing there is no marked accumulation (accumulation ratio of 1.4- 1.5 for twice daily dosing), with steady state exposure achieved within 3 to 4 days.

Co-administration with a high fat meal slowed the rate (Tmax delayed by 2 hours) of absorption, but did not significantly alter the extent of olaparib absorption (mean AUC increased by approximately 20%). Therefore there is no restriction with diet while olaparib is administered.

Drug interactions:

In vitro, olaparib was an inhibitor of CYP3A4 and an inducer of CYP2B6, but these activities occurred at higher concentrations than are clinically achieved. Olaparib produced little/no

inhibitions of other CYP isozymes. In vitro studies have shown that olaparib is a substrate of CYP3A4.

Based on the data from a drug-interaction trial (N=57), the AUC and Cmax of Olaparib increased by 2.7- and 1.4-fold, respectively, when Olaparib was administered in combination with itraconazole, a strong CYP3A inhibitor. Simulations using physiologically-based pharmacokinetic (PBPK) models suggests that a moderate CYP3A inhibitor (fluconazole) may increase the AUC and Cmax of Olaparib by 2- and 1.1-fold, respectively.

Based on the data from a drug-interaction trial (N=22), the AUC and Cmax of Olaparib decreased by 87% and 71%, respectively, when Olaparib was administered in combination with rifampicin, a strong CYP3A inducer. Simulations using PBPK models suggested that a moderate CYP3A inducer (efavirenz) might decrease the AUC and Cmax of Olaparib by 50-60% and 20-30%, respectively.

4.3.1.2 Toxicology

In repeat dose oral toxicity studies of up to 6 months duration in rats and dogs, the principal target organ for toxicity was the bone marrow, with associated changes in peripheral hematology parameters, which may be related to the primary pharmacology of olaparib. All changes showed full or partial recovery following withdrawal of olaparib. Olaparib was not mutagenic in an Ames bacterial mutation test, but was clastogenic in a CHO chromosome aberration test in vitro. When dosed orally, olaparib also induced micronuclei in bone marrow of rats. These findings are consistent with genomic instability resulting from the primary pharmacology of olaparib. In reproductive toxicology studies in rats, oral dosing of olaparib prior to mating produced no adverse effects on male fertility. In female rats, although conception rates were unaffected by pre- and peri-conception dosing, embryofetal survival was decreased. Administration of olaparib during organogenesis had an adverse effect on embryofetal survival and also increased major fetal malformations at dose levels that were not maternally toxic. The effects on embryofetal development are considered to be related to the primary pharmacology of olaparib. Exposures in the repeat dose and reproductive toxicology studies were below those achieved at the clinical therapeutic doses of 400 mg daily olaparib (capsule) and 300 mg bid (tablet).

Combination studies in rats suggest potential for olaparib to exacerbate the effects of TMZ and topotecan, although combination of olaparib with these anti-cancer agents did not induce any additional target organ toxicities to those seen with single agent administration.

4.3.2 Clinical experience

The olaparib capsule formulation was registered for use in the EU and US in December 2014.

The recommended olaparib monotherapy capsule dose is 400 mg daily

The Phase III registration studies and most new clinical studies are investigating the tablet formulation, which delivers the therapeutic dose of olaparib in fewer dose units than the capsule.

The tablet formulation was registered for use in the US in August 2017 for ovarian cancer and in January 2018 for breast cancer. In January 2018, the tablet formulation was also registered for use in Japan for ovarian cancer. The recommended olaparib monotherapy tablet dose under investigation is 300 mg b.i.d.

4.3.2.1 Safety in humans

Monotherapy
Data from the development program indicate that olaparib is generally well tolerated at monotherapy doses up to 400 mg daily (capsule formulation) and 300 mg bid (tablet formulation) in patients with solid tumors. Administration of olaparib monotherapy has been associated with adverse reactions generally of mild or moderate severity (CTCAE Grade 1 or 2) and generally not requiring treatment discontinuation (package insert).

Combination studies
Studies of olaparib in combination with various chemotherapy agents indicate an increase in bone marrow toxicity (anemia, neutropenia, thrombocytopenia) greater than expected if the agents had been administered alone. The effects are generally transient but treatment delays are common and alternative administration schedules/toxicity management processes have been evaluated within some of these studies. When this type of toxicity has occurred it has been managed by routine clinical practice including dose delays, dose reductions, intermittent dosing and/or the use of supportive care measures, including G-CSF.

4.3.2.2 Effect of other drugs on olaparib

CYP3A4/5 are the isozymes predominantly responsible for the metabolic clearance of olaparib. Clinical studies conducted with a tablet formulation to evaluate the impact of known CYP3A inhibitors and inducers have shown that co-administration of a potent CYP3A inhibitor, itraconazole, increased olaparib Cmax by 142% (90% CI: 1.33-1.52) and increased mean AUC by 270% (90% CI: 2.44-2.97) and that co-administration of a potent CYP inducer, rifampicin, decreased Cmax by 71% (treatment ratio: 0.29; 90% CI: 0.24-0.33) and mean AUC by 87% (treatment ratio: 0.13; 90% CI: 0.11-0.16). Moderate inhibitors and inducers of CYP3A are also predicted to significantly alter the exposure of olaparib. It is therefore recommended that known strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) should not be taken with olaparib.

If there is no suitable alternative concomitant medication then the dose of olaparib or study treatment should be reduced for the period of concomitant administration. With strong CYP3A inhibitors, the dose of olaparib tablet formulation should be reduced from 300 mg bid to 100 mg bid for the duration of concomitant therapy with the strong inhibitor and for 5 half-lives of the concomitant medication after stopping its treatment. With moderate CYP3A inhibitors, the dose of the tablet formulation should be reduced from 300 mg bid to 150 mg bid for the duration of concomitant therapy with the moderate inhibitor and for 3 half-lives of the concomitant medication

after stopping its treatment. After the washout of the inhibitor is complete, the olaparib dose can be re-escalated.

Strong (e.g., phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort) and moderate CYP3A inducers (e.g., bosentan, efavirenz, modafinil) of CYP3A should not be taken with olaparib. If the use of any strong or moderate CYP3A inducers is considered necessary for the patient's safety and welfare this could diminish the clinical efficacy of olaparib. If a patient requires use of a strong or moderate CYP3A inducer or inhibitor then they must be monitored carefully for any change in efficacy of olaparib or study treatment.

4.3.2.3 Effect of olaparib on other drugs

Olaparib can inhibit CYP3A4 and UGT1A1 in vitro. Using basic models these findings suggest that olaparib has the potential to cause clinically significant interactions with other CYP3A4 and UGT1A1 substrates in the liver or GI tract. However, PBPK modeling predicted olaparib to be a weak CYP3A inhibitor in vivo and did not predict olaparib to be a UGT1A1 inhibitor in vivo. Therefore, caution should be exercised when substrates of CYP3A4 are combined with olaparib, in particular those with a narrow therapeutic margin (e.g., simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine). Substrates of UGT1A1 should also be given with caution in combination with olaparib (e.g., irinotecan, nintedanib, ezetimibe, raltegravir or buprenorphine).

Induction of CYP1A2, 2B6 and 3A4 has been shown in vitro with CYP2B6 being most likely to be induced to a clinically relevant extent. It cannot be excluded that olaparib upon co-administration may reduce the exposure to substrates of these metabolic enzymes.

In vitro, olaparib has been shown to be an inhibitor of Pgp, OATP1B1, OCT1, OCT2, OAT3,

MATE1 and MATE2K and is a weak inhibitor of BRCP. Olaparib is predicted by PBPK modeling not to be a Pgp inhibitor in vivo. However, it cannot be excluded that olaparib may modulate the exposure to substrates of OATP1B1 (e.g., bosentan, glibenclamide, repaglinide, statins and valsartan), OCT1 (e.g., metformin), OCT2 (e.g., serum creatinine), OAT3 (furosemide, methotrexate), MATE1 and MATE2K (metformin). In particular, caution should be exercised if olaparib is administered in combination with any statin.

4.3.2.4 The effect of food on exposure to olaparib

The effect of food on olaparib tablet has been investigated. Co-administration with food slowed the rate of absorption (tmax delayed by 2.5 hours and Cmax reduced by 21%), however food did not significantly affect the extent of absorption (AUC), therefore olaparib tablet formulation can be given without regard to food.

4.4 Overall Rationale

4.4.1 Rationale for the combination of olaparib with pembrolizumab:

Studies reveal a direct causal relationship between cancer and immune dysfunction, whereby tumor cells and their microenvironment are able to evade immune attack by exploiting various immunoregulatory mechanisms in a process termed cancer immunoediting [21). Regulatory pathways that limit the immune response to cancer are becoming increasingly well characterized and provide new strategies in cancer therapy. Monoclonal antibodies targeting PD-1 that boost the immune system are being developed for the treatment of a number of cancers. On September 4, 2014, the U.S. Food and Drug Administration granted accelerated approval to pembrolizumab (KeytrudaTM, Merck Sharp & Dohme Corp.) for the treatment of patients with unresectable or metastatic melanoma [22]. In May of 2017, the FDA approved pembrolizumab for use in patients who fit these disease criteria and are microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with ligands PD-L1 and PD-L2, thereby releasing PD-1 pathway-mediated inhibition of the immune response, including anti-tumor immune response. The response rate of pembrolizumab in patients with advanced cholangiocarcinoma was 17% in a phase I study [23].

There has been much interest in the combination of PARP inhibitors and immunotherapy, based on preclinical data that support the association of BRCA1/2 mutational status with neoantigen load, tumor infiltrating lymphocytes, and the expression of PD-1/PD-L1 or CTLA-4, thus forming the rationale for combination therapy. There have been data indicating that BRCA1/2 deficient cancers express higher levels of neoantigens and are therefore likely to be more immunogenic. In addition, preclinical studies showed that a combination of PARP inhibition with a CTLA-4 antibody had synergistic activity against BRCA1/2 mutant ovarian cancer [24]. A crosstalk between PARPi and tumor-associated immunosuppression, and provides evidence to support the combination of PARPi and PD-L1 or PD-1 immune checkpoint blockade [25]. PARPi-related upregulation of PD-L1 expression in breast cancer cell lines and animal models appeared to occur via an induction of high GSK3β Ser9 phosphorylation (the inactive form of GSK3β). Thus, knocking out GSK3Bβ activity significantly increased PD-L1 expression. However, PD-L1 expression in GSK3β-knockout cells was no longer enhanced by PARPi (olaparib) treatment. These results suggested that inactivation of GSK3β is required for the PARPi-induced PD-L1 upregulation. PARPi attenuated anticancer immunity via upregulation of PD-L1 increased PD-1 binding, which was resistant to activated T-cell killing. Blockade of PD-L1 acted to resensitize PARPi-treated cancer cells to T-cell killing. The data supports the hypothesis that the combination of a PARPi and an immune checkpoint inhibitor is a potential therapeutic approach to cancer treatment.

4.4.1.1 Rationale for the combination of olaparib and pembrolizumab in cholangiocarcinoma:

Research into the molecular pathogenesis of cholangiocarcinoma has revealed potential mechanisms contributing to tumorigenesis. Low expression of excision repair cross complementation group 1 (ERCC1) is found in 74% of cholangiocarcinomas, and this is associated

with susceptibility to PARP inhibition [26]. In addition, mutations in isocitrate dehydrogenase-1 or -2 (IDH1/2) are found in 25% of cholangiocarcinomas. [27].

It was recently reported that tumors with mutations in isocitrate dehydrogenase-1 or -2 (IDH1/2) proteins exhibit features similar to BRCA-mutant tumors and are more likely to respond better to PARP inhibitors than to IDH inhibitors [28]. IDH is an enzyme that plays a role in the citric acid cycle, the energy-producing unit of the cells, and IDH mutations are found in about 25% of cholangiocarcinomas. The oncometabolites, 2-hydroxyglutarate (2-HG), produced by IDH mutations, induce a state in the cells where DNA repair is profoundly inhibited. This essentially makes them quite similar to breast and ovarian cancers which harbor mutations in key DNA repair genes such as BRCA1 and BRCA2. Furthermore, IDH-mutant patient-derived glioma cells, bone-marrow cultures of IDH-mutant acute myeloid leukemia, and mice bearing IDH-mutant human tumor cells were all susceptible to PARP inhibition [29].

Given the low expression of the ERCC1 protein in the majority of cholangiocarcinomas, together with relative frequent IDH1/2 mutations found in these tumor types, we hypothesize that the combination of PARP inhibition and immune checkpoint blockade will produce a durable anti-tumor response against cholangiocarcinoma by synergistically inducing DNA damage, increasing tumor antigen number and producing durable immune response against cholangiocarcinoma.

4.4.2 Rationale for pembrolizumab dose selection

Support for 200 mg q3w fixed-dose across cancer types:

Because the antitumor effect of pembrolizumab is driven through reactivation of adaptive immune response by blocking PD-1 expressed on T-cells and not direct binding to cancer cells, once the PD-1 on T-cells are fully saturated by pembrolizumab, the shape of the exposure-response relationship across cancer types is expected to be similar [30]. This is supported by exposure-response analysis in multiple indications (Rationale to Change the Dose of Pembrolizumab to a 200-mg Fixed Dose in Various Tumor Indications, 2015). A flat exposure-response relationship was demonstrated between pembrolizumab exposure (or dose) and efficacy or safety within the dose range of 2 to 10 mg/kg or 200 mg to 10 mg/kg (exposure at 2 mg/kg Q3W is similar to exposure at 200 mg Q3W). The similarity in efficacy between the tested dose regimens is further supported by comparisons of ORR/survival outcomes for the tested dose regimens in the melanoma and NSCLC indications. Available PK results in participants with various indications (melanoma, NSCLC, HNSCC, and MSI-H) support a lack of meaningful difference in PK among tumor types [30]. Therefore, the selection of the 200 mg Q3W dosing for pembrolizumab was supported as an appropriate dose for multiple indications, providing exposures which are within the flat therapeutic range of 2 mg/kg Q3W - 10 mg/kg Q2W associated with near maximal efficacy for pembrolizumab and close to the exposure at 2 mg/kg Q3W. On this basis, the approved doses were 2 mg/kg Q3W or 200 mg Q3W in multiple indications.

4.4.3 The safety of combining pembrolizumab and olaparib

There are ongoing trials of combined PARP inhibitors and immune checkpoint inhibitors. Four trials (NCT02571725, NCT02734004, NCT02953457, and NCT02484404) are assessing the combination of olaparib and durvalumab and/or tremelimumab as salvage treatment of BRCA1 or BRCA2 mutation carriers with recur-rent platinum-sensitive or platinum- resistant or refractory epithelial ovarian cancer. One trial (NCT02657889) is evaluating niraparib in combination with pembrolizumab in patients with recurrent, platinum-resistant epithelial ovarian cancer. In addition, in a Study of Pembrolizumab (MK-3475) Combination Therapies in Metastatic Castration-Resistant Prostate Cancer (MK-3475-365/KEYNOTE-365), olaparib at 300 mg bid has been combined with Pembrolizumab (NCT02861573). From the preliminary data from multiple clinical trials, Pembrolizumab at 200 mg every three weeks and Olaparib at 300 mg bid have been well tolerated when the combination of Pembrolizumab and Olaparib have been administered to patients.

In this current phase II study, the dosage of pembrolizumab and olaparib are selected based on the data from the NCT02861573 study. Pembrolizumab will be administered at 200 mg every 3 weeks; olaparib will be administered at a dose of 300 mg by mouth twice per day.

4.5 Rationale for Endpoints

After first-line treatment with a gemcitabine-based regimen, there is no recommended, standard second-line chemotherapy for patients with metastatic gallbladder cancer and cholangiocarcinoma. A multicenter survey and pooled analysis with published data showed that response rates (RRs) to second-line chemotherapy were low (3.4 %), with median PFS and OS of 3.0 months and 6.6 months, respectively [8]. Immune checkpoint inhibitors have shown durable disease control in multiple types of cancer, e.g., melanoma, renal cell carcinoma, non-small cell lung cancer, etc. We propose that an improvement in overall response rate of 35% in patients who receive the combination of pembrolizumab and olaparib after cancer progression or intolerance to frontline treatment (compared to a response rate of 17.5% in patients who received second line systemic chemotherapy per historical control) will be considered clinically meaningful.

4.5.1 Primary Endpoints

The primary study endpoints are (1) the overall response rate (ORR) of patients with advanced cholangiocarcinoma receiving a combination of pembrolizumab and olaparib, which directly assesses whether this drug combination yields a clinically meaningful result in this group of patients—as per the rationale stated in the paragraph above; and (2) the safety and tolerability of combined pembrolizumab and olaparib in patients with advanced cholangiocarcinoma as measured by adverse events, which will help to rationally validate any apparent clinical improvement observed.

4.5.2 Secondary Endpoints

The secondary study endpoints are the duration of response (DOR), progression free survival (PFS), and overall survival (OS) in patients receiving the combination therapy. All of these endpoints are part of the clinical response assessment.

Primary Endpoint Definition

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

Secondary Endpoint Definition

1. PFS is defined as the duration from the date of registration until disease progression (as defined above; using RECIST 1.1) or death occurs. Subjects who have not progressed will be right-censored at the date of the last disease evaluation.

2. OS is defined as the time of registration until death as a result of any cause.

3. Overall response rate (ORR) is defined as the sum of complete response (CR) + confirmed partial response (PR) and will be determined using the immune-related response criteria (iRECIST).

4. Grade 3 and 4 toxicities as defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.

4.5.3 Rationale for Exploratory (Biomarker) Endpoints

Given the low expression of the ERCC1 protein in the majority of cholangiocarcinomas, together with relative frequent IDH1/2 mutations found in these tumor types, we hypothesize that the combination of PARP inhibition and immune checkpoint blockade will produce a durable anti-tumor response against cholangiocarcinoma by synergistically inducing DNA damage, increasing tumor antigen number and producing durable immune response against cholangiocarcinoma. Therapies that target the programmed death-1 (PD-1) receptor have shown unprecedented rates of

durable clinical responses in a sub-group of patients with various cancer types [1-5]. Biomarkers in patient tumor that will predict response to anti-PD-1 therapy are being actively investigated. One mechanism by which cancer tissues limit the host immune response is via upregulation of PD-1 ligand (PD-L1) and its ligation to PD-1 on antigen-specific CD8+ T cells [6, 7]. Recent research has reported that tumor regression after therapeutic PD-1 blockade requires pre-existing CD8+ T cells that are negatively regulated by PD-1/PD-L1-mediated adaptive immune resistance [8].

We propose that olaparib will increase the response of pembrolizumab by inducing DNA damage, increasing tumor antigen number, and producing durable immune response against cholangiocarcinoma. We expect that cancer cells with low expression of the ERCC1 proteins or with IDH1/2 mutations will have more DNA damage upon olaparib treatment than cancer cells that have normal expression of the ERCC1 protein, or are without IDH1/2 mutations.

In this study, we will first test whether the effect of olaparib and pembrolizumab treatment on tumor infiltrating lymphocytes, the level of PD-1 and PD-L1 expression, and clonality of the T-cell repertoire differs between low ERCC1/IDH1/2 mutant and normal ERCC1/non IDH1/2 mutant tumor cells. Then we will examine whether the change of tumor infiltrating lymphocytes and the level of PD-1 and PD-L1 expression correlates with clinical response in patients treated with pembrolizumab and olaparib combination therapy.

5.0 METHODOLOGY

5.1 Study Population

This trial is a single institution study, enrolling patients with cholangiocarcinoma, biliary cancers manifesting as either intrahepatic, extrahepatic or gallbladder cancer, that is unresectable, metastatic, or has either failed to respond to or demonstrated progression despite prior 1st line therapy. Patients with ampullary cancers are excluded. Patients must be, in the opinion of the site investigator, appropriate candidates for experimental therapy. Patients should be evaluated for the need to undergo biliary drainage by stent placement prior to study participation. Patients should have adequate biliary drainage with no unresolved biliary obstruction.

The target recruitment for this study is 36 patients. As the trial is opening at several centers, recruitment is anticipated to take 21 months, and the anticipated time to complete follow-up of all patients will be 36 months.

5.2 Inclusion Criteria

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

1. Be willing and able to provide written informed consent/assent for the trial.

2. Be ≥ 18 years of age on day of signing informed consent.

3. Patients must have received 1 line of prior systemic therapy for metastatic or resectable disease (i.e. patients may have received adjuvant gemcitabine and then later platin-based therapy for recurrent metastatic disease)

4. Histological confirmation of cholangiocarcinoma manifesting as either intrahepatic, extrahepatic or gallbladder cancer. Patients with ampullary cancer are excluded.

5. Have measurable disease based on RECIST 1.1.

6. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. Newly obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1. Subjects for whom newly obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the sponsor-investigator. Subjects from whom a biopsy is not medically possible or safe may be enrolled on the study upon agreement from the principal investigator.

7. Have a performance status of 0 or 1 on the ECOG Performance Scale.

8. Demonstrate adequate organ function as defined in Table 1. All screening labs will be performed within 28 days of registration.

Table 1: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥ 1,500 /μL
Platelets	≥ 100,000 / μL
Hemoglobin	≥ 9 g/dL or ≥ 5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤ 1.5 X upper limit of normal (ULN) **OR** ≥ 50 mL/min for subject with creatinine levels > 1.5 x institutional ULN
Hepatic	

Serum total bilirubin	≤ 2.0 X ULN
AST (SGOT) and ALT (SGPT)	≤ 3.0 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥ 2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤ 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

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

10. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section in Appendix 3). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

11. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

5.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. A history of anaphylaxis to olaparib

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

3. A woman of childbearing potential (WOCBP) who has a positive urine pregnancy test within 72 hours prior to 1st dose of treatment (see Appendix 3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

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

5. Has known hypersensitivity to pembrolizumab or any of its excipients.

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

7. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

   NOTE: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

   NOTE: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

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

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

10. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

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

12. Has an active infection requiring systemic therapy.

13. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full

duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the site investigator.

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

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

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

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.

18. Has known active Hepatitis B without HBV treatment (HBV infection with ongoing HBV treatment is allowed); chronic Hepatitis C infection is allowed. Any patient receiving treatment for HCV should wait at least 14 days after completion of HCV treatment before beginning study treatment. No patient should receive HCV treatment while receiving study treatment. Note: no testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

19. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

5.3.1 Lifestyle Restrictions

5.3.1.1 Meals and Dietary Restrictions

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

5.3.1.2 Contraception

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

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

5.3.2 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study treatment. 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 (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to Merck and followed as described in Section 7.2.2.

5.3.3 Use in Nursing Women

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

5.4 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
Olaparib	300 mg	bid	Oral tablet	continuously	Experimental

5.4.1 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis. There are no pre-medications for olaparib or pembrolizumab.

Patient will be treated with olaparib at 300 mg by mouth twice per day continuously in combination with pembrolizumab at 200 mg administered intravenously every three weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

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

5.4.2 Dose Modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 3. NOTE: During management of any irAEs, Olarparib treatment may continue subject to physician discretion.

Table 3 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered to ≤10 mg prednisone or equivalent per day for a full week without worsening signs and symptoms. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.
4. During management of any irAEs, Olaparib treatment may continue subject to physician discretion.

Immune-related AEs	**Toxicity grade or conditions (CTCAE v4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus).

	Grade 4	Permanently discontinue		• Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	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	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g., levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.

Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

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

NOTE:

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

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 4.

Table 4 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5 h (± 30 minutes) prior to infusion of _____ 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 (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.
For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov

Dose Modification of Olaparib

Patients who experienced grade 3 or 4 toxicities attributable to Olaparib will temporarily hold Olaparib treatment until the side effects have improved to grade 1 or baseline, then restart Olaparib the next lower dose level.

Table 5: Olaparib Dose Modifications

Dose level -1	200 mg bid
Dose level -2	100 mg bid

5.4.3 Other allowed dose interruptions for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 6 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

5.4.3.1 Second Course *

All participants who stop study treatment with SD or better may be eligible for up to an additional 17 cycles (approximately 1 year) of pembrolizumab treatment if they progress after stopping study treatment from the initial treatment phase. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the participant meets the following conditions:

Either

- Stopped initial treatment with study treatment after attaining an investigator-determined confirmed CR based on RECIST 1.1, and
    - Was treated with at least 8 cycles of study treatment before discontinuing treatment, and
    - Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared

OR

- Had SD, PR, or CR and stopped study treatment after completion of 35 administrations (approximately 2 years) of study treatment for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined radiographic disease progression by RECIST 1.1 after stopping initial treatment, and
    - No new anticancer treatment was administered after the last dose of study treatment, and
    - The participant meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
    - The study is ongoing

An objective response or disease progression that occurs during the Second Course Phase for a participant will not be counted as an event for the primary analysis of either endpoint in this study.

**Note: patients must have measurable disease at the start of protocol treatment to be eligible for this provision.*

5.4.3.2: Re-challenge with Pembrolizumab treatment

If patient's pembrolizumab treatment is discontinued for immune mediated AEs, when patient's immune mediated AEs have resolved or improved to grade 1, if patient will likely benefit from the treatment and it is safe to restart Pembrolizumab treatment per treating physician's assessment, patient is allowed to resume pembrolizumab treatment and follow the procedures per protocol.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

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

5.5.1 Acceptable Concomitant Medications

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.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

Considering olaparib treatment, avoid concomitant use of strong and moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. If the inhibitor cannot be avoided, reduce the olaparib dose to 150 mg twice daily for a strong CYP3A inhibitor or 200 mg twice daily for a moderate CYP3A inhibitor. (see FDA package insert of Olaparib).

5.5.2 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
  - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

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

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

5.5.3 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in

Section 5.2.2, [Table 3]. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to [Table 3] in Section 5.2.2 for guidelines regarding dose modification and supportive care.

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

5.6 Participant Withdrawal/Discontinuation Criteria

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor 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 study treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

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

- The participant or participant's legally acceptable representative requests to discontinue study treatment
- Confirmed radiographic disease progression outlined in Section 7.1.2.6
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Unacceptable adverse experiences as described in Section 5.2.2.
- The participant has a medical condition or personal circumstance that, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test
- Noncompliance with study treatment or procedure requirements

- Recurrent Grade 2 pneumonitis
- Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving 2 doses of pembrolizumab and at least 80% of the planned doses of olaparib beyond the date when the initial CR was declared. These participants may be eligible for second course treatment described in Section 5.2.3.
- The participant is lost to follow-up
- Completion of 35 treatments (approximately 2 years) with pembrolizumab

  Note: The number of treatments is calculated starting with the first dose. Participants who stop the combination or pembrolizumab after receiving 35 doses may be eligible for retreatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 5.2.3. Participants may be retreated in the Second Course Phase (Retreatment) for up to an additional 17 cycles (approximately 1 year).

- Administrative reasons

5.7 Participant Replacement Strategy

Subjects who have not completed the 1st cycle of combination therapy can be replaced.

5.8 Clinical Criteria for Early Trial Termination

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

1. Quality or quantity of data record is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to participants
4. Plans to modify or discontinue the development of the study drug

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

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Study Evaluation Cycle = 21 days	Screening ≤ 28 days	On Treatment Cycle 1-n Day 1	Follow Up Visit (1) 30 days post last dose ± 7 days	Follow Up Visit (2) 6 weeks after Visit 1 ± 7 days	Long Term Follow Up [10] Every 12 weeks after Visit 2	Survival Follow Up [11] Every 12 weeks after Visit 2
REQUIRED ASSESSMENTS						
Informed Consent	X					
Medical History[1]	X					
Diagnosis and Staging[2]	X					
Physical Exam	X	X[9]	X	X		
Vital signs and ECOG Performance Status[3]	X	X[9]	X	X		
AEs & concomitant medications	X	X[9]	X	X		
LABORATORY ASSESSMENTS						
Complete Blood Cell Count with diff (CBC)	X	X[9]	X	X		
Comprehensive Metabolic Profile (CMP) and amylase	X	X[9]	X	X		

Study Evaluation Cycle = 21 days	Screening ≤ 28 days	On Treatment Cycle 1-n Day 1	Follow Up Visit (1) 30 days post last dose ± 7 days	Follow Up Visit (2) 6 weeks after Visit 1 ± 7 days	Long Term Follow Up [10] Every 12 weeks after Visit 2	Survival Follow Up [11] Every 12 weeks after Visit 2
PT/INR and aPTT	X	X[9]	X	X		
Thyroid Function (TSH, free T4, T3)	X	X[9]	X	X		
Urinalysis	X	X[9]	X	X		
Pregnancy test (serum or urine) (WOCBP)[4]	X					
Carbohydrate antigen (CA) 19-9		X[10]	X	X		
DISEASE ASSESSMENT						
CT of chest[5]	X		X	X	X	
CT or MRI of abdomen and pelvis[5]	X		X	X	X	
MRI Brain[5]	X		X	X	X	
TREATMENT EXPOSURE						
Olaparib[6]		X				
Pembrolizumab[6]		X				
SPECIMEN COLLECTION						

Study Evaluation Cycle = 21 days	Screening ≤ 28 days	On Treatment Cycle 1-n Day 1	Follow Up Visit (1) 30 days post last dose ± 7 days	Follow Up Visit (2) 6 weeks after Visit 1 ± 7 days	Long Term Follow Up [10] Every 12 weeks after Visit 2	Survival Follow Up [11] Every 12 weeks after Visit 2
Archival or Newly Obtained Tumor Tissue[7]	X	X[8]				
Blood Samples[8]	X	X	X			
FOLLOW-UP						
Survival Status, Subsequent Therapy					X	X

KEY TO FOOTNOTES

[1] **MEDICAL HISTORY SHOULD INCLUDE SMOKING AND ALCOHOL/CARBONATED BEVERAGE HISTORY AS WELL AS HOW THE SUBJECT LEARNED ABOUT THIS STUDY.**

[2] **DIAGNOSES AND STAGING TO INCLUDE: REVIEWING PATHOLOGY REPORT AND SCREENING SCANS.**

[3] **VITAL SIGNS TO INCLUDE BLOOD PRESSURE, WEIGHT, AND HEIGHT (SCREENING ONLY) AND ECOG PERFORMANCE STATUS**

[4] **FOR WOMEN OF CHILDBEARING POTENTIAL (WOCBP): URINE OR SERUM BHCG, WITHIN 28 DAYS OF REGISTRATION AND ONLY IF CLINICALLY APPROPRIATE. IF A URINE TEST IS DONE AND IT IS POSITIVE OR CANNOT BE CONFIRMED AS NEGATIVE, A SERUM PREGNANCY TEST WILL BE REQUIRED.**

[5] **RADIOLOGY IMAGING FOR DISEASE ASSESSMENT WILL BE PERFORMED AT THE FOLLOWING TIME POINTS: SCREENING, EVERY SIX WEEKS WITHIN THE 24 WEEKS FROM THE START OF TREATMENT, THEN EVERY NINE WEEKS UP TO 12 MONTHS FROM THE START OF TREATMENT, THEN EVERY TWELVE WEEKS UP TO 24 MONTHS. FOR PATIENTS WHO DO NOT HAVE RADIOGRAPHIC PROGRESSION: RADIOLOGY IMAGING OR REPORT SHOULD BE OBTAINED EVERY 12 WEEKS THEREAFTER UNTIL DISEASE (RADIOGRAPHIC) PROGRESSION IF POSSIBLE. MRI OF THE BRAIN SHOULD ONLY BE DONE IF THE PATIENT IS SUSPECTED TO HAVE A BRAIN LESION.**

[6] OLAPARIB WILL START ON C1D1 AND CONTINUE TWICE DAILY. PEMBROLIZUMAB WILL START C1D1 AND CONTINUE EVERY 3 WEEKS. PLEASE SEE SECTION 5 FOR DETAILS REGARDING OLAPARIB AND PEMBROLIZUMAB ADMINISTRATION.

[7] ALL SUBJECTS WILL HAVE A BIOPSY PERFORMED OF A SAFELY ACCESSIBLE TUMOR BEFORE STARTING TREATMENT (WITHIN 42 DAYS OF STARTING TREATMENT ON THIS PROTOCOL) AND THE 3RD WEEK PRIOR TO 2ND DOSE OF PEMBROLIZUMAB, AND AT THE TIME OF CANCER PROGRESSION. SUBJECTS FOR WHOM NEWLY OBTAINED SAMPLES CANNOT BE PROVIDED (E.G. INACCESSIBLE OR SUBJECT SAFETY CONCERN) MAY SUBMIT AN ARCHIVED SPECIMEN ONLY UPON AGREEMENT FROM THE SPONSOR-INVESTIGATOR. SUBSEQUENT BIOPSIES CAN BE WAIVED BY SPONSOR-INVESTIGATOR FOR SAFETY CONCERNS OF THE BIOPSY PROCEDURE.

[8] SERIAL BLOOD SAMPLES WILL BE COLLECTED TO SUPPORT BIOMARKER RESEARCH AT THE FOLLOWING TIME POINTS: PRIOR TO TREATMENT (1) C1D1, (2) C2D1, (3)C3D1 AND (5) FOLLOW UP VISIT 1. SEE CLM FOR ADDITIONAL DETAILS.

[9] THIS TESTING IS TO BE DONE PRIOR TO EACH PEMBROLIZUMAB TREATMENT.

[10] CARBOHYDRATE ANTIGEN (CA) 19-9 WILL BE DRAWN EVERY OTHER CYCLE STARTING AT CYCLE 1 (E.G. CYCLE 1, CYCLE 3, CYCLE 5, ETC).

[11] FOLLOW UP FOR PATIENTS THAT HAVE NOT EXPERIENCED PROGRESSION WILL OCCUR EVERY 12 WEEKS ± 7 DAYS; THIS MAY BE DONE BY PHONE CALL OR OTHER AVENUES, AS APPROPRIATE. EVERY EFFORT SHOULD BE MADE TO OBTAIN INFORMATION ON RADIOLOGY SCANS OR OTHER TYPES OF DISEASE ASSESSMENT DOCUMENTATION.

[12] ONCE A SUBJECT EXPERIENCES CONFIRMED DISEASE PROGRESSION OR STARTS A NEW ANTI-CANCER THERAPY, THE SUBJECT MOVES INTO THE SURVIVAL FOLLOW-UP PHASE AND SHOULD BE CONTACTED BY TELEPHONE EVERY 12 WEEKS ± 7 DAYS TO ASSESS FOR SURVIVAL STATUS UNTIL DEATH, WITHDRAWAL OF CONSENT, OR THE END OF THE STUDY, WHICHEVER OCCURS FIRST.

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Total protein	Microscopic exam *(If abnormal)*	Total triiodothyronine (T3)

Hematology	Chemistry	Urinalysis	Other
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free thyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or bicarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Sodium		Blood for correlative studies
	Calcium		
	Chloride		
	Glucose		
	Phosphorus		
	Potassium		
	Blood Urea Nitrogen		
	creatinine		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	amylase		
† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. ‡ If considered standard of care in your region.			

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or Merck for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential participant prior to participating in a clinical trial.

7.1.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the IRB/ERC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the trial.

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the trial. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

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

7.1.1.5.2 Prior Treatment Details

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

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the participant will move into survival follow-up.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Appendix 2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

7.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

Computed tomography (CT) is the strongly preferred method of tumor imaging. For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when local practice mandates it. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing

and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

7.1.2.6.1 Initial Tumor Imaging

Initial tumor imaging for screening purposes must be performed within 28 days prior to Cycle 1, Day 1 of treatment. The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1.

For confirmation of measurable disease by RECIST 1.1—for eligibility prior to C1D1 of treatment—the screening images must be reviewed by the PI as well as another radiologist (one who did not perform the imaging).

In subjects being treated for a brain metastatic lesion, brain imaging—if performed to document the stability of existing metastases—should be by MRI if possible. If MRI is medically contraindicated, CT with contrast is an acceptable alternative.

7.1.2.6.2 Tumor Imaging During the Study

The first on-study imaging assessment should be performed at six weeks (42 days ±7 days]) from the date of C1D1. Subsequent tumor imaging should be performed every six weeks (42 days ±7 days) or more frequently if clinically indicated. After 24 weeks, participants who remain on treatment will have imaging performed every nine weeks (63 days ±7 days). After 48 weeks, participants who remain on treatment will have imaging performed every twelve weeks (84 days ±7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until the Investigator identifies disease progression.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging every twelve weeks, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per iRECIST (Section 9.2.1.6), disease progression should be confirmed 4 to 8 weeks after first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the Investigator until the site confirms progression, provided the conditions detailed in Section 9.2.1.6 have been met. Participants who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable. Participants, who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study treatment. Exceptions are detailed in Section 9.2.1.6.

7.1.2.6.3 End of Treatment and Follow-up Tumor Imaging

In participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. In participants who discontinue study treatment due to the documented disease progression and the Investigator elects not to implement iRECIST, this is the final required tumor imaging.

In participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every nine weeks in Year 1 or every twelve weeks after Year 1) to monitor disease status until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.2.6.4 Second Course (Retreatment) Tumor Imaging

Tumor imaging must be performed within 28 days prior to restarting treatment with pembrolizumab. Local reading (Investigator assessment with site radiology reading) will be used to determine eligibility.

The first on-study imaging assessment should be performed at six weeks (42 days ±7 days) after the restart of treatment. Subsequent tumor imaging should be performed every 6 weeks (42 days ±7 days) or more frequently, if clinically indicated. After 24 weeks, participants who remain on treatment will have imaging performed every nine weeks (63 days ±7 days). After 48 weeks, participants who remain on treatment will have imaging performed every twelve weeks (84 days ±7 days).

Per RECIST 1.1 (Section 9.1.2.6), if tumor imaging shows initial PD, tumor assessment should be repeated 4 to 8 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. Participants who obtain confirmatory imaging do not need to undergo scheduled tumor imaging if it is less than 4 weeks later and may wait until the next scheduled imaging time point, if clinically stable.

Imaging should continue to be performed until disease progression, the start of a new anticancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. Disease progression may be confirmed 4 to 8 weeks after the first tumor imaging indicating PD, by the Investigator using iRECIST, in clinically stable participants.

In participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. In participants who discontinue study treatment due to documented disease progression, this is the final required tumor imaging.

In participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every twelve weeks (84 days ±7 days) until either the start of a new anticancer treatment, disease progression, pregnancy, death, or the end of the study, whichever occurs first.

7.1.2.6.5 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of study treatment).

7.1.2.6.6 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. When clinically stable, participants should not be discontinued from the study until disease progression is confirmed by the Investigator, working with the local radiology team according to the rules below. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response.

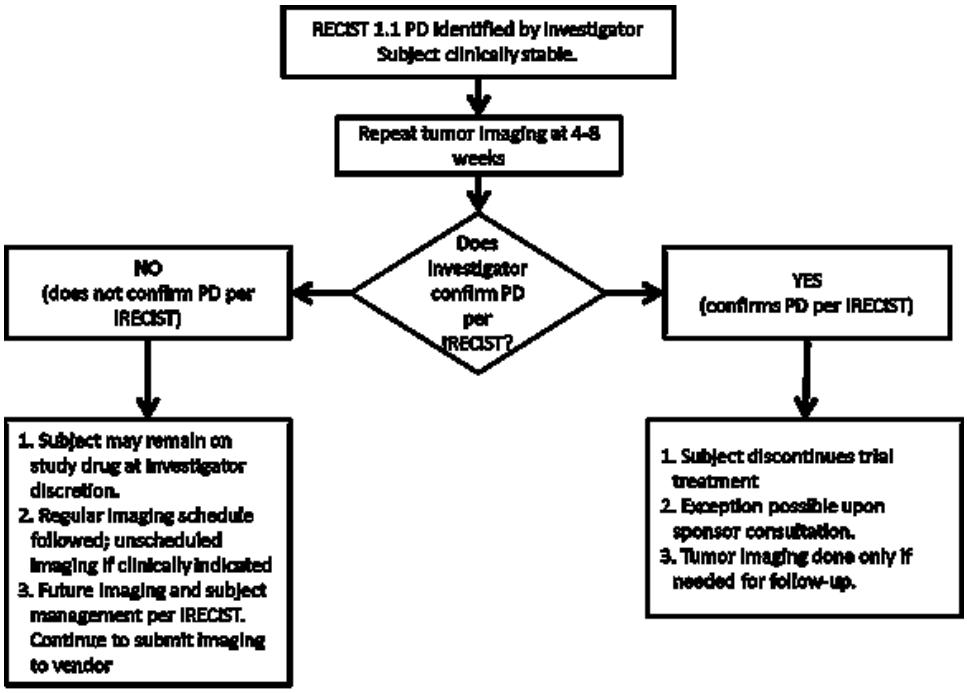
A description of the adaptations and iRECIST process is provided in Appendix 4, with additional detail in the iRECIST publication [Seymour et al, 2017]. iRECIST will be used by the Investigator to assess tumor response and progression, and make treatment decisions.

Table 5 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per Investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per Investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the Investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per Investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the Investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor image should occur according to the regular imaging schedule.

iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1..

Figure 1: Imaging and Treatment for Clinically Stable Participants after First Radiologic Evidence of PD Assessed by the Investigator



7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

7.1.2.7.1 Biospecimen studies and Procedures

We propose that olaparib will increase the response of pembrolizumab by inducing DNA damage, increasing tumor antigen number and producing durable immune response against cholangiocarcinoma. The cancer cells with low expression of the ERCC1 proteins or with IDH1/2 mutations will have more DNA damage upon olaparib treatment compared to that with normal expression of the ERCC1 protein, or without IDH1/2 mutations.

In this study, we will first test the effect of olaparib and pembrolizumab treatment on tumor infiltrating lymphocytes, the level of PD-1 and PD-L1 expression, and clonality of the T-cell repertoire differ between low ERCC1/IDH1/2 mutant and normal ERCC1/no IDH1/2 mutant. Then we will examine whether the change of tumor infiltrating lymphocytes, the level of PD-1 and PD-L1 expression correlates with clinical response in patients treated with pembrolizumab and olaparib combination therapy.

Immunohistochemical (IHC) staining: The level of PD-1 and PD-L1 expression in tumor biopsy will be measured by immunohistochemical (IHC) staining at Merck laboratories.

Immunohistochemical (IHC) staining, Digital image acquisition and analysis: The density of intratumoral total (CD3+) and cytotoxic (CD8+) T lymphocytes will be measured in the tumor interior (TI) and in the invasive margin (IM) of the three biopsied tumor samples. Immune cell densities will be obtained by immunohistochemistry and quantified using a biomarker imaging system in tandem with Image J processing software at Lombardi Comprehensive Cancer Center. Immune cell density in the TI and IM was converted to a binary score (0 as Low, 1 as High), with a cutoff threshold determined by the median density of CD3+ and CD8+ cells. We previously carried out a study on the association of intratumoral CD3 and CD8 cell density with recurrence free survival in patients with surgically resected Hepatocellular Carcinoma.

Next Generation Sequencing for T-cell receptor clonality: TCR sequencing and clonality quantification was performed as previously described [29,30] from tumor samples preserved using RNAlater (Qiagen) and stored at −80°C. DNA was isolated by mincing followed by extraction utilizing a DNeasy kit (Qiagen). TCRβ CDR3 regions were amplified and sequenced using the survey ImmunoSeq assay in a multiplexed PCR method using 45 forward primers specific to TCR Vβ gene segments and 13 reverse primers specific to TCR Jβ gene segments. The experiments of measuring T-cell receptor clonality will be carried out at Lombardi Comprehensive Cancer Center.

PCR template abundance estimation: In order to estimate the average read coverage per input template in our multiplex PCR and sequencing approach, we will employ a set of approximately 850 unique types of synthetic TCR analog, comprising each combination of Vβ and Jβ gene segments.[30] These molecules will be included in each PCR reaction at very low concentration so that most unique types of synthetic template are not observed in the sequencing output. Using the known concentration of the synthetic template pool, we will

simulate the relationship between the number of observed unique synthetic molecules and the total number of synthetic molecules will be added to reaction (this is very nearly one-to-one at the low concentrations we employed). These molecules then will allowed us to calculate for each PCR reaction the mean number of sequencing reads obtained per molecule of PCR template, and thus to estimate the number of rearranged T cell receptors per diploid genome (i.e., level of TIL infiltration) in the input material. The PCR analysis will be carried out in Lombardi Comprehensive Cancer Center.

All correlatives samples should be stored and batch shipped. All analyses will be completed after all samples are collected. Please see lab manual for instructions.

7.1.2.7.2 Tumor Biopsies

All patients will have biopsies performed of safely accessible tumors before starting treatment (within 42 days of starting treatment on this protocol), the 3rd week since the start of treatment and at the time of disease progression. Preferred biopsy is a core biopsy; five 20-gauge core needle biopsies (diameter about 2 mm) with a throw length of approximately 2 cm will provide adequate tissue for study. Available paraffin embedded tumor tissue from prior biopsies or excisions may also be collected as pre-treatment comparator samples, so long as the patient provides consent for use in this study. Preferred archival material includes tissue obtained in the same manner as specified in this trial and with no systemic anti-tumor treatment received by the patient between the biopsy and their enrollment on this protocol. However, other archival tissue may also be collected.

Each set of core biopsies will be divided into 5 portions and processed as below for later analysis:

1.1) FFPE for histology and IHC (20% of the specimen, or 1 core biopsy)

2.2) Quick-frozen in OCT for immunohistology and protein studies (20% of the specimen, or 1 core biopsy): embedded in optimum cutting temperature (OCT) solution, frozen in liquid nitrogen, and then stored at -80° C.

3.3) Placed in RPMI with serum and processed for single cell suspensions of TIL and tumor (40% of the specimen, or 2 core biopsies)

4.4) Placed in RNA-later for RNA and RT-PCR (20% of the specimen, or 1 core biopsy).

Of note, patients who are on chronic anticoagulation will be required to hold anticoagulation prior to the biopsies being performed. Patients on warfarin must hold treatment for 5 days, but will be on low-molecular weight heparin (LMWH), 1 mg/kg subcutaneously twice a day. The LMWH will continue until the last biopsy is complete. Patients may then resume warfarin the day after the last biopsy. Additionally, patients on LMWH will hold (i.e., not receive) the dose of LMWH the morning of the procedure, but will resume the LMWH the evening of the day of the biopsy.

7.1.2.7.3 Blood Collections

Plasma, serum, and peripheral blood for PBMCs will be collected at the five scheduled time points. PBMCs will be isolated by Ficoll gradient centrifugation and cryopreserved in 10% DMSO at -80°C for subsequent evaluation.

7.1.2.7.4 Storage of Biospecimens

Remaining specimens will be stored for future research once protocol described biospecimen-based studies is complete. This option will be presented to subjects in the informed consent.

7.1.2.7.5 Confidentiality of Biospecimens

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

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 6.

Table 6 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count		Microscopic exam *(If abnormal)*	Total triiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free thyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or bicarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
			PK
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

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

‡ If considered standard of care in your region.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a participant discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events, which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Participants who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 5.2.3. After discontinuing treatment following assessment of CR, these participants should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.3.2).

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of study treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Participants with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Participants who are eligible for retreatment/crossover with pembrolizumab (as described in Section 5.2.3) may have up to two safety follow-up visits, one after the Initial Treatment Period and one after the Second Course Treatment.

7.1.5.2 Disease Status Follow-up Visits

Participants who discontinue study treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 6 weeks (42 ± 7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 9 weeks (± 7 days). Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of the study or if the participant begins retreatment with pembrolizumab as detailed in Section 5.2.3.

Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 5.2.3 will move from the follow-up phase to the Second Course Phase when they experience disease progression.

7.1.5.3 Survival Follow-up

Participants who experience confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-Up Phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product, is also an adverse event.

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

Adverse events may occur during the course of the use of Merck product in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before treatment is started must be reported by the investigator if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

● All AEs from the time of treatment through 30 days following cessation of study treatment must be reported by the investigator.

● All AEs meeting serious criteria, from the time of treatment through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the

participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.

● All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.

● Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately by the investigator if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify Merck.

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck

For purposes of this study, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX [redacted])

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

Although pregnancy and infant exposure during breast-feeding are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a participant (spontaneously reported to them) that occurs during the study.

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

Pregnancies and infant exposures during breastfeeding that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor'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 Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229

7.2.3 Immediate Reporting of Adverse Events to the Sponsor and to Merck

7.2.3.1 Serious Adverse Events

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event
- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

Refer to Table 7 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any participant must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization 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 serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to Merck Global Safety.

All participants with serious adverse events must be followed up for outcome.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +[redacted]

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

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX [redacted]).

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any participant must be reported within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization 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 2 working days to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

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

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

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. 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.

Table 7 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the participant, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of participant taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor and to Merck within 2 working days..	

	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause Merck product to be discontinued?	
Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the participant was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the participant re-exposed to Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY MERCK PRODUCT, OR IF RE-EXPOSURE TO MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).**
Yes, there is a reasonable possibility of Merck product relationship.		There is evidence of exposure to Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.
No, there is not a reasonable possibility of Merck product relationship		Participant did not receive the Merck product OR temporal sequence of the AE onset relative to administration of Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a participant with overdose without an associated AE.)

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

8.1.1 Statistical Methods

8.1.1.1 Study Design

This is an open-label, single-arm, Phase II safety and efficacy study of combination therapy with pembrolizumab and olaparib in patients with advanced cholangiocarcinoma who have progressed on or cannot tolerate frontline chemotherapy.

8.1.1.2 Endpoints

1. Definition of Primary Endpoint

    a. Efficacy endpoint: overall response rate (ORR): defined as the proportion of subjects who achieve the best response (CR and PR) determined by RECIST1.1.

2. Definition of Secondary Endpoints

    a. PFS: defined as time from registration till the patient's disease progression or death from any cause whichever occurs first (those for whom event of progression or death not observed will be censored).

    b. OS: defined as time from registration till the patient's death from any cause (patient who are still alive at the end of the study will be censored).

    c. Overall response rate: defined as the proportion of subjects who achieve the best response (CR and PR) determined by irRC.

    d. To assess duration of response (DOR) of patients with advanced cholangiocarcinoma receiving a combination of pembrolizumab and olaparib.

    e. Safety endpoint: patients' toxicity profile, adverse event, serious adverse event, serious adverse even leading to discontinuation of the treatment, death. Safety and tolerability of the combination of olaparib and pembrolizumab is assessed by CTCAE v4.

3 Definition of Exploratory Endpoints

a. To correlate the baseline density of CD3 and CD8 in the tumor interior and invasive margin of the tumor, the expression of PD-L1, and the clonality of the T-cell repertoire with ORR, DOR, PFS, and OS.

b. To correlate the difference between the baseline density of CD3 and CD8 in the tumor interior and invasive margin of the tumor, the expression of PD-L1, and the clonality of the T-cell repertoire and the same assessments after three weeks of treatment with ORR, DOR, PFS, and OS.

c. To compare the density of CD3 and CD8 in the tumor interior and invasive margin of the tumor, the expression of PD-L1, and the clonality of the T-cell repertoire at three time points: at the time of disease progression, after three weeks of treatment, and at baseline.

d. To correlate in the cholangiocarcinoma tissue the baseline expression of ERCC (DRCC+/-) or the baseline mutation status of IDH1 or 2 (mutant or non-mutant) with ORR, DOR, PFS, and OS.

8.1.1.3 Sample Size and Accrual

The primary objective of the study is to assess the ORR of patients with advanced cholangiocarcinoma receiving a combination of pembrolizumab and olaparib. It is hypothesized that the combination of olaparib and pembrolizumab will improve the overall response rate (ORR) from 17.5% (historical control) to 35% in patients with advanced cholangiocarcinoma. The sample size is based on the number of patients that are anticipated to complete the primary objective.

Simon's two-stage Optimum design will be used to test the null hypothesis of P <= 0.05 versus the alternative hypothesis of P >= 0.25. At the first stage, 13 patients will be treated with the combination of olaparib and pembrolizumab. The trial will be terminated if 2 or fewer patients respond. If there are more than 2 responses, the trial will go on to the second stage and 20 more patients will be enrolled to a total of 33 patients. If the total number responding among the 33 patients is <= 8, the null hypothesis will not be rejected and the combination of olaparib plus pembrolizumab will not be investigated further. Using this statistical method, there is a 0.092 (9.2%) probability of erroneously concluding that this drug combination is effective when it actually is not (targeted value of 0.1). If the drug is actually effective, there is a 0.192 probability of concluding that it is not (targeted value of 0.2). The power of the design is 85% with a one-sided significance level of 0.05. If we assume a 10% patient dropout rate, then a total of 36 patients will be needed for the trial.

8.1.1.4 Analysis Datasets

Population:

Enrolled: This will comprise all subjects who meet the eligibility criteria and are registered onto the study.

Evaluable: This will comprise all subjects who receive at least one dose of olaparib and pembrolizumab trial drug and either undergo at least one post-baseline assessment or die before any evaluation. Non-evaluable patients will be replaced.

Intention-to-treat (ITT): This will comprise all subjects who meet the eligibility criteria and are registered onto the study irrespective of their compliance to the planned course of treatment. (See ITT principle below*)

Per Protocol Set (Valid Cases, Efficacy Sample, Evaluable Subjects Sample): This will comprise all subjects who complied with the protocol sufficiently to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of major protocol violations. This population should be specifically defined in the protocol.

Safety: This will comprise all subjects who have received at least one dose of olaparib and one dose of pembrolizumab that contribute data to the safety analysis.

Treated: This will comprise all subjects who have been exposed to the planned course of treatment to any extent.

8.2 Statistical Analysis Plan

8.2.1 Analysis Plans for Primary Objective

The overall response rate will be estimated with its 95% exact confidence interval. Safety summaries will be presented by the severity of the adverse event and by relationship to study drug. Descriptive statistics (minimum, maximum, mean median, standard deviation for continuous variables; counts, percentages for categorical variables) will be used in summarizing of all laboratory and safety parameters (adverse events, serious adverse events, adverse events leading to discontinuation, deaths) for all treated subjects.

8.2.2 Analysis Plans for Secondary Objectives

Progression free survival (PFS) and overall survival (OS) will be evaluated using the methods of Kaplan and Meier (1958). 95% confidence interval will be constructed for the estimated median PFS and OS. The exploratory overall response rate will be estimated with its 95% exact confidence interval.

8.2.3 Analysis Plans for Exploratory Objectives

The biomarkers which are of interest are programmed death ligand-1 (PD-L1) levels, immune score as determined by the density of CD3 and CD8 in the tumor interior and invasive margin(s) of the tumor, the clonality of the T-cell repertoire in the tumors, the expression of ERCC, and the mutation status of IDH1 or 2 in the same cholangiocarcinoma tissue. We will assess the biomarker levels at baseline, after four weeks of combination olaparib and pembrolizumab therapy, and at the time of cancer progression. The expression of ERCC and the mutation status of IDH1 or 2 in

the same cholangiocarcinoma tissue will only be assessed at baseline. For different levels of biomarkers at baseline or change between different time points, we are interested in correlating them with patients' response, PFS, OS, and DOR

The density of CD8+ cells, CD3+ cells, and the expression of PD-1 and PD-L1 in the same cholangiocarcinoma tissue at baseline, after four weeks of combination olaparib and pembrolizumab therapy, at the time of cancer progression, and the changes between different time points will be summarized using descriptive statistics (N, Range, Median, Mean, STD). The paired t-test will be used to examine the changes in each biomarker level from the same tumor prior to any treatment at four weeks after the combination of olaparib and pembrolizumab, and at the time of cancer progression. These biomarkers levels and changes may be categorized into high or low levels based on the distribution of the data collected. The response of different biomarker levels (high vs. low) at baseline, at 4 weeks after combination treatment with olaparib and pembrolizumab, or at the time of cancer progression will be compared via Chi-Square test or Fisher's Exact test when appropriate. The relationship between these biomarker levels, their changes, and the DOR and PFS will be explored via Kaplan-Meier methodology and Log-rank test.

Similar analyses will be done for the Shannon Diversity Index (SDI) of T cell clonality in tumor samples.

The expression of ERCC (DRCC+/-), and the mutation status of IDH1 or 2 (mutant or non-mutant) in the same cholangiocarcinoma tissue at baseline will be summarized using descriptive statistics (N, frequency). The response of ERCC- or IDH1/2 wild type tumors at baseline will be compared with the response of ERCC+ or IDH1/2 mutant tumor using Chi-Square test or Fisher's exact test when appropriate. The relationship between these biomarker levels and the DOR and PFS will be explored via Kaplan-Meier methodology and Log-rank test.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

9.1.1 Drug Information

9.1.1.1 Pembrolizumab (Keytruda®)

Pembrolizumab is a potent and highly selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of subjects with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor. It is also approved for the treatment of subjects with PD-L1 positive metastatic NSCLC who have disease progression on or after platinum chemotherapy. Please refer to the current version of the Keytruda® prescribing information and the pembrolizumab Investigator's Brochure (IB) for additional information regarding this drug.

9.1.1.1.1 Supplier/How Supplied

Merck will supply pembrolizumab at no charge to subjects participating in this clinical trial, as summarized in the table below.

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/ 4 mL	Solution for Injection

9.1.1.1.2 Preparation

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

9.1.1.1.3 Storage and Stability

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

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

9.1.1.1.4 Handling and Disposal

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.

9.1.1.1.5 Dispensing, 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 subjects and the amount remaining at the conclusion of the trial.

9.1.1.1.6 Use in Pregnancy and Nursing Women

Based on its mechanism of action, pembrolizumab can cause fetal harm when administered to a pregnant woman. Subjects who are pregnant or planning to become pregnant are not eligible for enrollment. It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

9.1.1.1.7 Adverse Events

Please refer to the current Investigator's Brochure for a complete list of adverse events.

Pembrolizumab is generally well tolerated and demonstrates a favorable safety profile in comparison to chemotherapy. Pembrolizumab is an immunomodulatory agent, and based on this mechanism of action, immune mediated adverse events are of primary concern. Important identified risks for pembrolizumab are of an immune mediate nature, including: pneumonitis, colitis, hypophysitis (including hypothryoidism/hyperthyroidism), hepatitis, Type I diabetes mellitus, uveitis, and nephritis, myositis, Guillain-Barre syndrome, pancreatitis, and severe skin reaction toxic epidermal necrolysis (TEN), some with fatal outcome). A new important risk of myocarditis has been identified; cases with fatal outcome have been reported.

Most immune-mediated adverse events were mild to moderate in severity, were manageable with appropriate care, and rarely required discontinuation of therapy.

In addition to the previously noted identified risks, infusion-related reactions are a risk but are not considered immune mediated; these are also further described in the current IB.

9.1.1.2 Olaparib

Olaparib is an inhibitor of the mammalian polyadenosine 5'-diphosphoribose polymerase (PARP) enzyme. The chemical name [redacted].

The empirical molecular formula for olaparib is [redacted]

Olaparib is a crystalline solid, is non-chiral and shows pH-independent low solubility of approximately 0.1 mg/mL across the physiological pH range.

Olaparib is available in 100mg and 150mg tablets for oral administration. Each capsule contains olaparib as the active ingredient and following inactive ingredients: lauroyl polyxylglycerides in capsule content, hypromellos, titanium dioxide, gellan gum, potassium acetate in capsule shell, shellac and ferrosoferric oxide in capsule printing ink.

9.1.1.2.1 Supplier/How Supplied

Merck will supply Olaparib at no charge to subjects participating in this clinical trial, as summarized in the table below.

Product Name & Potency	Dosage Form
Olaparib	100 and 150 mg tablets

9.1.1.2.2 Storage and Stability

Olaparib should be stored at 25°C to 25°C (68°F to 77°F); excursions permitted to 15°-30°C (59-86°F) [see USP Controlled Room Temperature]. Olaparib should be stored in original bottle to protect from moisture.

9.1.1.2.3 Handling and Disposal

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.

9.1.1.2.4 Dispensing, 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 subjects and the amount remaining at the conclusion of the trial.

9.1.1.2.5 Use in Pregnancy and Nursing Women

Based on findings in animals and its mechanism of action, Olaparib can cause fetal harm.

It is not known whether the components of olaparib are excreted in human milk. Because of the potential for adverse reactions from the drug in nursing infants, a decision must be made whether to discontinue nursing or discontinue the olaparib treatment, taking into account the importance of the therapy to the mother.

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

9.1.1.2.6 Adverse Events

Monotherapy

Data from the development program indicate that olaparib is generally well tolerated in patients with solid tumors at monotherapy doses up to 400 mg daily if in capsule formulation and 300 mg bid if in tablet formulation. Administration of olaparib monotherapy has been associated with generally mild or moderately severe adverse reactions (CTCAE Grade 1 or 2), which generally do not require treatment discontinuation (package insert).

Combination studies

Studies of olaparib in combination with various chemotherapy agents indicate an increase in bone marrow toxicity (anemia, neutropenia, thrombocytopenia) that is greater than expected from the agents when administered alone. The effects are generally transient but treatment delays are common and alternative administration schedules and/or toxicity management processes have been evaluated within some of these studies. When this type of toxicity has occurred it has been managed by routine clinical practice, including dose delays, dose reductions, intermittent dosing and/or the use of supportive care measures, including G-CSF.

Packaging and Labeling Information

Supplies will be labeled in accordance with regulatory requirements.

9.2 Clinical Supplies Disclosure

This trial is open-label; therefore, the participant, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.3 Storage and Handling Requirements

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.

9.4 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.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Study Management

10.1.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by Georgetown University. All investigators will follow the University conflict of interest policy.

10.1.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the Georgetown IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient, and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

10.1.3 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Research Office:

- A copy of the official IRB approval letter for the protocol and informed consent
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- A copy of the IRB approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

10.1.4 Data Management and Monitoring/Auditing

Data safety monitoring committee (DSMC) The Georgetown Lombardi Comprehensive Cancer Center (LCCC) will be responsible for the data and safety monitoring of this trial. As this study is an investigator initiated Phase II study it is considered a Moderate risk study which requires real-time monitoring by the PI and study team and Semi-annual reviews by the LCCC Data and Safety Monitoring Committee (DSMC).

Progress on the trial and the toxicities experienced will be reviewed by the LCCC Data and Safety Monitoring Committee every six (6) months from the time the first patient is enrolled on the study. Results of the DSMC meetings will be forwarded to the IRB with recommendations regarding need for study closure.

DSMC recommendations will be based not only on results for the trial being monitored but also on data available to the DSMC from other studies. It is the responsibility of the Principal Investigator (PI) to ensure that the DSMC is kept apprised of relevant study data as well as non-confidential results from related studies that become available, for review per the monitoring schedule. It is the responsibility of the DSMC to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

A written copy of the DSMC recommendations will be given to the trial Principal Investigator and the IRB. If the DSMC recommends a study change for patient safety or efficacy reasons the PI must act to implement the change as expeditiously as possible. In the unlikely event that the PI does not concur with the DSMC recommendations, then the LCCC Associate Director (AD) of Clinical Research must be informed of the reason for the disagreement. The PI, DSMC Chair, and the LCCC AD for Clinical Research will be responsible for reaching a mutually acceptable decision about the study and providing details of that decision to the IRB. Confidentiality must be preserved during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and staff to seek advice to assist in reaching a mutually acceptable decision.

If a recommendation is made to change a trial for reasons other than patient safety or efficacy the DSMC will provide an adequate rationale for its decision. If the DSMC recommends that the trial be closed for any reason, the recommendation will be reviewed by the Associate Director for Clinical Research at GULCCC. Authority to close a trial for safety reasons lies with the IRB, with the above described input from DSMC and the AD for Clinical Research.

10.1.5 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.1.6 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

10.1.7 Data Collection and Management

Patient data will be entered into the on-line accessible database. This database is housed at Lombardi-Georgetown, but is accessible anywhere there is internet access. The data manager and research coordinator at each site will attend an on-line training session so that they can learn how to enroll data into the database. All screening data should be entered prior to starting therapy, and all ongoing patient data should be entered within one week of each patient visit.

11.0 ETHICS AND GCP COMPLIANCE

This study will be conducted in compliance with the protocol, GCP, HIPAA and all applicable regulatory requirements:

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and well being of trial patients are protected; consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. For detailed information on an Investigator's and a Sponsor's obligation, see www.fda.gov/oc/gcp/ and www.ich.org/

11.1 ETHICAL CONSIDERATIONS

11.2 Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IRB. IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to the study site. Any amendments to the protocol will require IRB approval prior to implementation of any changes made to the study design. Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to the IRB. During the conduct of the study, the investigator should promptly provide written reports to the IRB of any changes that affect the conduct of the study and/or increase the risk to subjects.

11.3 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical Principals that have their origin in the Declaration of Helsinki.

11.4 Subject Information and Consent

Prior to the initiation of any screening or study-specific procedures, the investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. A separate informed consent is also required from subjects who provide blood for genetic testing or fresh biopsy tissue samples for analyses. Each informed consent will be reviewed, signed and dated by the subject and the person who administered the informed consent. A copy of each informed consent will be given to the subject and each original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy. Tissue sample collection for analysis will only be performed if the subject has voluntarily consented to participate after the nature of the testing has been explained and the subject has had the opportunity to ask questions. If the subject does not consent to the tissue sample collection, it will not impact the subject's participation in the study.

11.5 Ethical Consideration for Enrollment

Only patients with advanced cancer, for whom no curative therapy exists, will be considered for enrollment. The only treatment options for these patients are enrollment in a Phase II clinical trial, or treatment off protocol, with a non-standard therapy. As described above, the combination of olaparib and pembrolizumab is a rational and promising combination for such patients

11.6 Protection of Patient Confidentiality

All patient records, questionnaires, and tissue specimens will be de-identified using a letter and number assigned to their case at the time of enrollment on study. No record or specimen will

contain information that could identify the patient. The key that connects patient identifiable information with this assigned number will be held by the Principal investigator. For computer records, the key will be protected by a double password protection system. Any paper records will be contained in a locked cabinet within a locked office to ensure patient's privacy is protected.

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13.0 APPENDICES

Appendix 1: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix 2: Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

Appendix 3: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (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:

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

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol-defined time frame in section X:

- 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 9 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
  - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception that has a low user dependency consistently and correctly as described in Table 9 during the protocol-defined time frame in Section X.

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 10 during the protocol-defined time frame in Section X.

Table 10 Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b, c] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b, c] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The

reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least [X 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 that inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test and in accordance with local requirements. When applicable this test should be repeated a maximum of 24-hours before the first dose/vaccination.

Following initiation of treatment additional pregnancy testing will be performed at monthly intervals during the treatment period and at [X days] after the last dose of study treatment and as required locally.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

Appendix 4: Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

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

Assessment and Decision at RECIST 1.1 Progression

In participants who show evidence of radiological PD by RECIST 1.1 the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management (see Table 5 and Figures 1 and 3). This decision by the Investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed clinically unstable should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

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. I

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

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

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

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

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

Assessment at the Confirmatory Imaging

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

Confirmation of Progression

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

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

Persistent iUPD

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

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

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

Resolution of iUPD

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

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

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

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 6.

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 [Seymour et al, 2017].