Olaparib in Combination with Pembrolizumab and Carboplatin as First-Line Treatment of Recurrent or Metastatic Head and Neck Squamous-Cell Carcinoma: A Single-Arm, Phase 2 Trial

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Protocol Revision History

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

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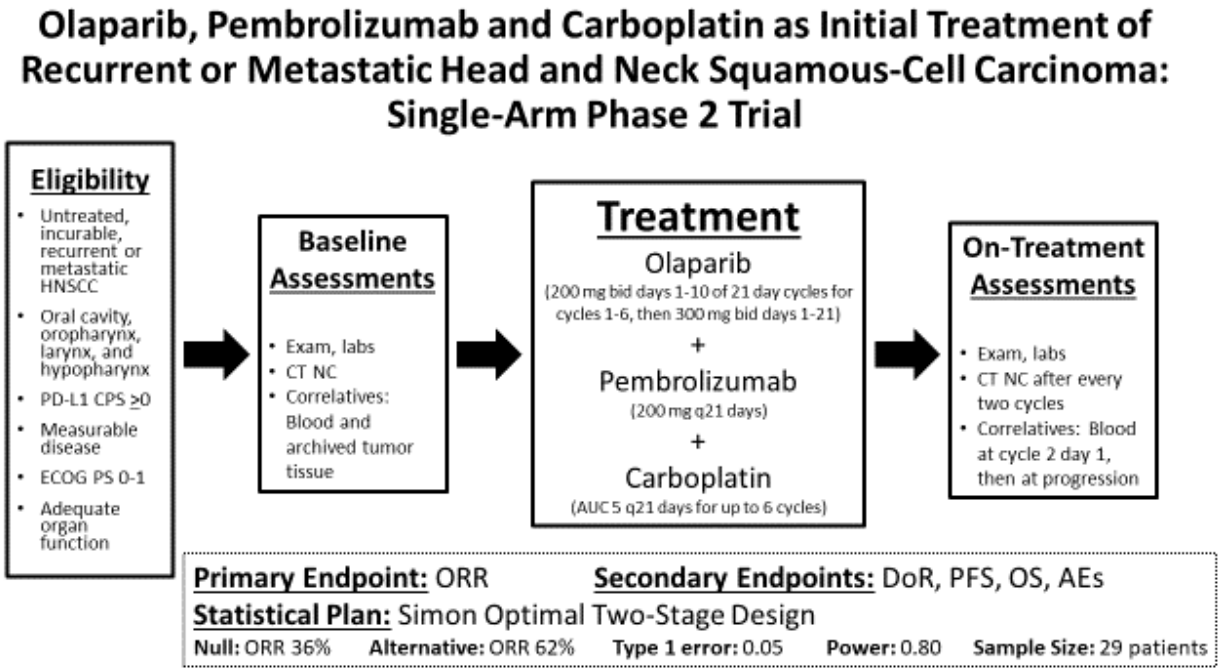
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PROTOCOL SUMMARY

Title:	Olaparib in Combination with Pembrolizumab and Carboplatin as First-Line Treatment of Recurrent or Metastatic Head and Neck Squamous-Cell Carcinoma: A Single-Arm, Phase 2 Trial
Study Description:	In this study, patients with recurrent or metastatic head and neck squamous cell carcinoma will receive first line treatment with olaparib, pembrolizumab, and carboplatin. The primary hypothesis is that olaparib, pembrolizumab and carboplatin will result in an objective response rate (ORR) higher than the historical ORR observed with pembrolizumab, platinum and 5-FU reported in the KEYNOTE-048 trial.
Objectives:	Primary Objective: To establish the proportion of patients with recurrent or metastatic head and neck squamous cell carcinoma who achieve an objective tumor response to first-line treatment with olaparib, pembrolizumab, and carboplatin. Secondary Objectives: 1. To determine duration of response (DoR), progression-free survival (PFS), and overall survival (OS) of patients with recurrent or metastatic head and neck squamous cell carcinoma who are treated with olaparib, pembrolizumab, and carboplatin. 2. To determine the safety and tolerability of the combination of olaparib, pembrolizumab, and carboplatin in patients with recurrent or metastatic head and neck squamous cell carcinoma. 3. To determine the association between HR and *PTEN* gene status, PD-L1 CPS status, or HPV status with efficacy endpoints. Tertiary Objectives: 1. Evaluate baseline and changes in peripheral blood lymphocytes with therapy.
Endpoints:	Primary Endpoint: Objective response rate (ORR) Secondary Endpoints: 1. DoR 2. PFS 3. OS 4. Adverse events (AEs) 5. HR and PTEN gene status 6. PD-L1 CPS status 7. HPV status Tertiary Endpoints;

	1. T and NK subsets
Study Population:	Twenty-nine patients with incurable recurrent or metastatic HNSCC of the oral cavity, oropharynx, larynx or hypopharynx who have not received any prior systemic therapy for recurrent or metastatic disease will be enrolled in this study.
Phase:	Phase 2
Description of Sites / Facilities Enrolling:	This study will be open at and coordinated by Siteman Cancer Center at Washington University School of Medicine
Description of Study Intervention:	This is an open-label, single-arm phase 2 trial. Patients enrolled in this study will receive olaparib, pembrolizumab and carboplatin in three-week cycles for six cycles, followed by maintenance therapy with three-week cycles of olaparib and pembrolizumab. Treatment will continue until disease progression, intolerable toxicity, patient or physician decision to stop therapy, or after 35 cycles, whichever occurs first. Drug dosing for each cycle is as follows: a. Olaparib 200 mg bid po Days 1-10 for the first six cycles (when given with carboplatin), followed by 300 mg bid po Days 1-21 of subsequent cycles. b. Pembrolizumab 200 mg IV Day 1. c. Carboplatin AUC 5 IV on Day 1 for up to six cycles.
Study Duration:	24 months (enrollment) + 24 months (maximum treatment) + 12 months (average follow-up) + 12 months (analysis) = 72 months
Participant Duration:	Participants will receive treatment on study for up to 35 cycles (2 years) or until disease progression, unacceptable toxicity, patient withdrawal, or death, after which participants will be followed until death or the study is closed.

SCHEMA


Olaparib, Pembrolizumab and Carboplatin as Initial Treatment of Recurrent or Metastatic Head and Neck Squamous-Cell Carcinoma: Single-Arm Phase 2 Trial
Eligibility
Untreated, incurable, recurrent or metastatic HNSCC
Oral cavity, oropharynx, larynx, and hypopharynx
PD-L1 CPS ≥0
Measurable disease
ECOG PS 0-1
Adequate organ function
Baseline Assessments
Exam, labs
CT NC
Correlatives: Blood and archived tumor tissue
Treatment
Olaparib
(200 mg bid days 1-10 of 21 day cycles for cycles 1-6, then 300 mg bid days 1-21)
+
Pembrolizumab
(200 mg q21 days)
+
Carboplatin
(AUC 5 q21 days for up to 6 cycles)
On-Treatment Assessments
Exam, labs
CT NC after every two cycles
Correlatives: Blood at cycle 2 day 1, then at progression
Primary Endpoint: ORR
Secondary Endpoints: DoR, PFS, OS, AEs
Statistical Plan: Simon Optimal Two-Stage Design
Null: ORR 36%
Alternative: ORR 62%
Type 1 error: 0.05
Power: 0.80
Sample Size: 29 patients

SCHEDULE OF ACTIVITIES

Screening evaluations to be conducted within 28 days prior to start of protocol treatment.

	Screening	Cycle 1 Day 1	Day 1 of each subsequent cycle[f]	EOT	30-day F/U[f]	Long term F/U[g]
Informed consent	X					
Physical exam, VS, PS	X	X	X	X		
AE assessment		X ---------- X				
CBC	X[m]	X	X	X		
Chemistry panel, LFTs[a,b]	X[m]	X	X	X		
Thyroid function tests[c]	X		X[c]	X[c]		
Pregnancy test[e]	X					
Urinalysis macro/micro	X					
PT/INR; PTT	X[m]					
EKG	X					
Tumor assessment	X		Q2-4 cycles[d]	X		X[g]
Olaparib		X[h]	X[h, i]			
Pembrolizumab		X	X[i]			
Carboplatin		X	X[j]			
Archival tumor tissue for research	X[l]					
Peripheral blood for research		X	X[k]	X[k]		
Survival and disease status						X

[a] Chemistry includes Ca, K, Na, glucose, albumin, urea, and creatinine.
[b] LFTs include ALT, AST, alkaline phosphatase, and total bilirubin.
[c] TSH, Free T4. Screening, Day 1 of cycles 3 and 5, then every fourth cycle.
[d] All patients must have neck and chest CT; patients with liver metastases also require abdominal CT. Scans to occur on Day 14-21 of cycles 2, 4, and 6, then every fourth cycle. Confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.
[e] Women of childbearing potential only; must be done no more than 72 hours prior to 1st dose of pembrolizumab
[f] +/- 2 days
[g] Every 3 months +/- 1 month. Patients who come off study for a reason other than disease progression (if coming off for AEs, etc.) will be assessed every 6 weeks (42 ± 7 days) by radiologic imaging if in Cycles 1-6 or every 12 weeks (+/- 1 week) if in Cycles 7-35 to monitor disease status. Patients who come off study because they completed all 35 cycles of treatment will be assessed every 3 months (12 weeks +/- 1 week) by radiologic imaging to monitor disease status.
[h] 200 mg bid po Days 1-10 for first 6 cycles (when given with Carboplatin), then 300 mg bid po Days 1-21 of subsequent cycles.
[i] Max 35 cycles.
[j] Starting dose AUC5. Dosing for up to 6 cycles.
[k] Cycle 2 Day 1 and disease progression only
[l] Tempus-xT648 genome sequencing, RNASeq and PD-L1 CPS.
[m] Within 10 days prior to the start of study treatment.

1.0 INTRODUCTION

1.1 Background and Rationale

1.1.1 Recurrent and Metastatic Head and Neck Squamous Cell Carcinoma

In 2018, over 800,000 new cases of HNSCC occurred worldwide.[1] Half of these patients will develop recurrent or metastatic disease. The KEYNOTE-048 trial established the standard first-line treatment of recurrent or metastatic HNSCC: pembrolizumab in patients with a PD-L1 combined proportional score (CPS) $\geq$1 or pembrolizumab in combination with chemotherapy (a platinum and 5-FU) in patients with a PD-L1 CPS $\geq$0.[2] KEYNOTE-048 was a three-arm randomized trial that compared pembrolizumab or pembrolizumab with chemotherapy versus cetuximab with chemotherapy. Of the total population, 85% of patients had PD-L1 CPS $\geq$1. In patients with PD-L1 CPS $\geq$1, pembrolizumab improved overall survival (OS) versus cetuximab with chemotherapy (median 12.3 vs 10.3 months, HR 0.78 [95%CI 0.64-0.96], p=0.0086). In the total population (PD-L1 CPS $\geq$0), pembrolizumab with chemotherapy improved OS versus cetuximab with chemotherapy (median OS 13.0 vs 10.7 months, HR 0.77 [95%CI 0.63-0.93], p=0.0034). Although the objective response rates (ORRs) were higher in patients treated with pembrolizumab plus chemotherapy or cetuximab plus chemotherapy compared to pembrolizumab monotherapy (36 vs 35 vs 19%), the median duration of response (DoR) with pembrolizumab monotherapy was much longer than pembrolizumab plus chemotherapy or cetuximab plus chemotherapy (23.4 vs 6.7 vs 4.5 months). Based on these data, strategies to improve the tumor response to pembrolizumab should focus on immune-based approaches.

The results of the KEYNOTE-048 trial demonstrated that tumor responses to pembrolizumab are durable; however, the ORR with pembrolizumab was low. Also, the addition of chemotherapy (a platinum and 5-FU) to pembrolizumab did not result in a median DoR comparable to that seen with pembrolizumab monotherapy.

Chemotherapy may enhance the benefit of immunotherapy by increasing tumor-specific neoantigen expression; however, chemotherapy may reduce the benefit of immunotherapy by enhancing immunosuppression. The relative balance of these opposing effects depends on the chemotherapy drug being used. 5-FU is an anti-metabolite, which as a class are widely regarded to be potent immunosuppressive agents, by impairing T-cell proliferation and function. In contrast, carboplatin, a platinum agent, is a potent inducer of tumor neoantigen expression with little immunosuppressive effect. These observations point to potential benefits of carboplatin in combination with pembrolizumab, and the potential lack of benefit of 5-FU in combination with pembrolizumab.

1.1.2 Rationale for PARP Inhibitors in combination with Pembrolizumab and Carboplatin in HNSCC

The HR-deficient phenotype ("BRCAness") is common in HNSCC and sensitizes HNSCC to PARP inhibition: Collectively, somatic mutations in DNA repair genes, including homologous recombination (HR), are common events in HNSCC. Mutations occur in ATM (16%), ATR (10%), BRCA2 (7%), BRCA1 (6%), along with inactivation of Fanconi Anemia/BCRA1 pathway via promoter hypermethylation of FANCF (15%).[3-6] Also, homozygous deletion of PTEN occurs in 12% of HNSCC cases.[5] Mutation in PTEN is another mechanism of HR deficiency, which sensitizes cell lines and xenografts to PARP inhibitors.[7] These somatic events result in a HR-deficient phenotype ("BRCAness") that sensitize HNSCC cells to PARP inhibition.[8] In vitro studies showed HR-deficient HNSCC cells are hypersensitive to PARP inhibitors.[9]

PARP inhibitors sensitize HR-deficient HNSCC to platinum agents: Fanconi anemia (FA) results from germ-line mutations in one of sixteen genes that participate in DNA repair, which causes a reduced capacity for HR. Patients with FA have a high risk for development of HNSCC, particularly oral cavity cancers. Induction of inter-strand crosslinks (ISC) in FA-deficient cells resulted in increased DNA damage sensing and repair by poly(ADP-ribose) polymerase (PARP).[8] Human FA HNSCC cells are hypersensitive to PARP inhibition.[10] The FA model shows that HNSCC cells with reduced capacity for HR are dependent on PARP-mediated mechanisms for DNA repair, and this reliance results in relative resistance to drugs (such as platinum agents) that cause ISC. These data suggest that PARP inhibition may be a strategy to reverse resistance to platinum agents.

Inhibitors of PARP and PD-1 are Synergistic: PARP inhibitors induce IFN Type 1 regulated genes, which may improve the efficacy of immunotherapy.[11] PARP inhibitors also upregulate PD-L1 expression. Pre-clinical models showed synergistic antitumor activity of PARP inhibitors and anti-PD-1 antibodies.[12-14]

1.1.3 Olaparib

Olaparib (AZD2281, KU-0059436) is a potent Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerization (PARP) inhibitor (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents.

Olaparib is a highly selective PARP 1/2 inhibitor[15] that inhibits tumor growth and induces synthetic lethality in models with loss of BRCA.[16] Regimens that include olaparib in combination with carboplatin or pembrolizumab are safe and tolerable. Preliminary reports showed promising activity of these combinations in several cancer types (CRC, PCa, Ovarian cancer, lung cancer and cholangiocarcinoma) and trials are in progress to assess the efficacy of these combinations (KEYNOTE-365; ENGOT-OV43/KEYLYNK-001; KEYLYNK-006; KEYLYNK-009).[17,18]

Investigators should be familiar with the current olaparib (AZD2281) Investigator Brochure (IB).

PARP inhibition is a novel approach to targeting tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HR). Tumors with HR deficiencies (HRD), such as ovarian cancers in patients with BRCA1/2 mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumor types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

1.1.3.1 Justification for Dose

Olaparib 200 mg bid for 10 days every 21 days, when given with carboplatin and pembrolizumab, was selected because this dose schedule is consistent with Astrazeneca's IIT program when olaparib is used in combination with chemotherapy. Olaparib 300 mg bid, when given with pembrolizumab, was selected because this this dose schedule is consistent with the package insert when administering olaparib monotherapy and is safe and tolerable when administered in combination with the PD-L1 inhibitor durvalumab (Journal of Thoracic Oncology 14: 1847-57, 2019).

1.1.4 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.

1.1.4.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades.[19] 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.[20,21]

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).[22,23]

The structure of murine PD-1 has been resolved.[24] 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.[23,25-27] 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 [Parry et al., 2005; Francisco, 2010].[28,29] As a consequence, the PD 1/PD-L1 pathway is an attractive target for therapeutic intervention in head and neck cancer.

1.1.4.2 Justification for Dose

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

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg

every 2 weeks (Q2W),

- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5 fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across pembrolizumab protocols.

1.1.5 Correlative Studies Background

Routine standard-of-care tailored genome sequencing and PD-L1 CPS will be performed on archived tumor tissue (preferably obtained at recurrence or metastasis) using the Tempus platform. The correlation of HR and *PTEN* gene status, PD-L1 CPS status, or HPV status and efficacy endpoints will be assessed.

In an exploratory analysis, peripheral blood will be collected at baseline, after cycle 2 and at progression with possible plans to perform immunologic tests to evaluate changes over time and to correlate with efficacy endpoints.

1.2 Study Design

1.2.1 Overall Design

This is an open-label, single-arm phase 2 trial. All the enrolled patients with recurrent or metastatic HNSCC receive olaparib, pembrolizumab, and carboplatin. The primary aim is to establish the proportion of patients with recurrent or metastatic HNSCC who achieve an objective tumor response to first-line treatment with olaparib, pembrolizumab and carboplatin. The primary endpoint is ORR, with tumor response assessed by iRECIST. Simon's two-stage design[31] will be used for the primary objective.

1.3 Risk/Benefit Assessment

1.3.1 Known Potential Risks

1.3.1.1 Olaparib

Very common:

- Feeling sick (nausea)
- Being sick/throwing up (vomiting)
- Tiredness/weakness
- Indigestion/heartburn (dyspepsia)
- Loss of appetite
- Headache
- Changes in taste of foods (dysgeusia)
- Dizziness
- Diarrhea.
- Cough
- Shortness of breath (dyspnea)
- Decrease in the number of red blood cells (anemia) which can be associated with symptoms of shortness of breath, fatigue, pale skin, or fast heartbeat.

- Decrease in the total number of white blood cells (leukopenia) and in certain white blood cells (neutropenia) that protect from infection, which can be associated with symptoms of fever
- Decrease in the number of platelets in blood (thrombocytopenia), which can be associated with symptoms of bruising or bleeding for longer if injured

Common:
- Sore mouth (stomatitis)
- Rash
- Pain in the stomach area under the ribs (upper abdominal pain)
- Decrease in the number of white blood cells that support the immune system (lymphopenia), which can be associated with increased susceptibility to infection
- Increase in blood creatinine.

Uncommon:
- Allergic reactions
- Itchy rash on swollen, reddened skin (dermatitis)
- Increase in the size of red blood cells (not associated with any symptoms)

1.3.1.2 Pembrolizumab

Very Common:
- itching of the skin
- loose or watery stools
- cough

Common:
- joint pain
- rash
- fever
- back pain
- pain in abdomen
- loss of skin color
- hypothyroidism
- hyponatremia

Uncommon:
- inflammation of the lungs, intestine or skin.
- hyperthyroidism
- infusion reaction

Rare:

- inflammation of the nerves, muscles, pancreas, eyes, liver, pituitary or adrenal glands, heart, kidneys, or brain.
- Type 1 Diabetes

1.3.1.3 Carboplatin

Common:

- Infection, especially when white blood cell count is low
- Bruising, bleeding
- Anemia which may cause tiredness or may require blood transfusions
- Vomiting
- Nausea
- Pain
- Hair loss

Occasional:

- Visual loss
- Diarrhea
- Constipation
- Belly pain
- Changes in taste
- Numbness and tingling in fingers and toes

Rare and serious:

- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

1.3.2 Known Potential Benefits

It is not known if olaparib will benefit patients with RM-HNSCC. Similarly, it is not known if carboplatin and pembrolizumab with olaparib will benefit patients. The purpose of the trial is to determine if this combination of treatment will result in tumor responses in patients with RM-HNSCC.

2.0 OBJECTIVES AND ENDPOINTS

Objectives	**Endpoints**	**Justification for Endpoints**
Primary		
To establish the proportion of patients with recurrent or metastatic HNSCC who	ORR, with tumor response assessed by iRECIST.	ORR is a key signal of efficacy of the study drugs.

achieve an objective tumor response to first-line treatment with olaparib, pembrolizumab and carboplatin.		
Secondary		
1. Determine duration of response, progression-free survival, and overall survival of patients with RM-HNSCC treated with olaparib, pembrolizumab, and carboplatin.	DoR PFS OS	DoR, PFS and OS are additional measures of efficacy of the study drugs.
2. To assess the safety and tolerability of the combination of olaparib, pembrolizumab and carboplatin in patients with RM-HNSCC	AEs by CTCAE v5.0	AEs are clinical measures of safety and tolerability of the study drugs.
3. To determine the association between HR and PTEN gene status, PD-L1 CPS status, or HPV status with efficacy endpoints.	HR-DNA repair, PD-L1 CPS status, HPV status	HR and *PTEN* gene status, PD-L1 CPS, and HPV status are measures of ability to repair DNA and responsiveness to pembrolizumab, respectively.
Tertiary/Exploratory		
1. Evaluate baseline and changes in peripheral blood lymphocytes with therapy.	1. T and NK subsets	Correlate laboratory results with efficacy endpoints.

3.0 STUDY POPULATION

3.1 Inclusion Criteria

1. Histologically or cytologically confirmed recurrent or metastatic HNSCC of the oral cavity, oropharynx, larynx hypopharynx, and p16+ SCC of the neck (unknown primary).

2. Measurable disease per RECIST. Measurable disease defined as lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with CT scan, as ≥ 20 mm by chest x-ray, or ≥ 10 mm with calipers by clinical exam.

3. PD-L1 CPS ≥ 0 on archived tumor tissue. Result not required to enroll and start on study therapy.

4. Incurable disease, or ineligible for (including patient declined) local therapy.

5. At least 18 years of age.

6. ECOG performance status ≤ 1 (see Appendix A)

7. Life expectancy ≥ 16 weeks.

8. Normal bone marrow and organ function as defined below (specimens must be collected within 10 days prior to the start of study treatment):
   a. Hemoglobin ≥ 10.0 g/dL (criteria must be met without erythropoietin dependency and without packed red blood cell transfusion within the last 2 weeks)
   b. Absolute neutrophil count ≥ 1,500/mcL
   c. Platelets ≥ 100,000/mcL
   d. INR or PT ≤ 1.5 x IULN and aPTT ≤ 1.5 x IULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
   e. Total bilirubin ≤ 1.5 x IULN
   f. AST(SGOT)/ALT(SGPT) ≤ 2.5 x IULN unless liver metastases are present (in which case they must be ≤ 5 x IULN)
   g. Serum creatinine <1.5 x ULN or creatinine clearance ≥ 51 mL/min by Cockcroft-Gault or based on a 24-hour urine test

      $$\text{Estimated creatinine clearance} = \frac{(140\text{-age [years]}) \times \text{weight (kg)}}{\text{serum creatinine (mg/dL)} \times 72} \ (\times F)^{a}$$

      [a] where F=0.85 for females and F=1 for males.

9. Known p16 expression, if oropharyngeal primary.

10. Postmenopausal or evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test within 72 hours of Day 1 of study treatment.

    Postmenopausal is defined as:
    a. Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments
    b. Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels in the post-menopausal range for women under 50
    c. radiation-induced oophorectomy with last menses >1 year ago
    d. chemotherapy-induced menopause with >1 year interval since last menses
    e. surgical sterilization (bilateral oophorectomy or hysterectomy)

11. Male patients must use a condom during treatment and for 3 months after the last dose of olaparib when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients should also use a highly effective form of contraception (see Section 5.6) if they are of childbearing potential

12. Ability to understand and willingness to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

3.2 Exclusion Criteria

1. Progression within 6 months of curatively intended **systemic** therapy given for locoregionally advanced disease.

2. Investigational therapy within 28 days of treatment start.

3. Prior systemic therapy for recurrent or metastatic disease.

4. Known CNS metastases/leptomeningeal metastatic disease.

5. Other malignancy unless curatively treated with no evidence of disease for ≥ 2 years except: adequately treated non-melanoma skin cancer, curative treated *in situ* cancer of the cervix, ductal carcinoma in situ (DCIS), stage 1 grade 1 endometrial carcinoma; or low risk-disease per discretion of the PI.

6. A history of allergic reactions attributed to compounds of similar chemical or biologic composition to olaparib, pembrolizumab, carboplatin, or other agents used in the study.

7. Has received prior therapy with an anti-PD-1, andti-PD-L1, or anti PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX 40, CD137).

8. Has received prior radiotherapy within 2 weeks of start of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

9. Concomitant use of known strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (e.g., ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting olaparib is 2 weeks.

10. Concomitant use of known strong CYP3A inducers (e.g. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, and St. John's wort) or moderate CYP3A inducers (e.g., bosentan, efavirenz, modafinil). The required

washout period prior to starting olaparib is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.

11. Resting ECG indicating uncontrolled, potentially reversible cardiac conditions as judged by the investigator (e.g., unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation > 500 ms, electrolyte disturbances, etc.) or patients with congenital long QT syndrome.

12. Diagnosis of myelodysplastic syndrome/acute myeloid leukemia or with features suggestive of MDS/AML.

13. Major surgery within 2 weeks of starting study treatment; must have recovered from any effects of major surgery.

14. Has a diagnosis of immunodeficiency or is receiving chronic systemic corticosteroid therapy (in doses exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of treatment.

15. Received a live vaccine or live-attenuated vaccine within 30 days prior to the first dose of pembrolizumab. Administration of killed vaccines is allowed. 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.

16. Considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease, or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on high resolution computed tomography (HRCT) scan or any psychiatric disorder that prohibits obtaining informed consent.

17. Unable to swallow orally administered medication or with gastrointestinal disorder likely to interfere with absorption of study medication.

18. Pregnant and/or breastfeeding. A WOCBP who has a positive urine pregnancy test within 72 hours of first dose of treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

    Female patients who are expecting to conceive or Male patients who are expecting to father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of trial treatment.

19. Prior organ or allogeneic stem cell transplant or double umbilical cord blood transplantation.

20. Has an active autoimmune disease (i.e. rheumatoid arthritis, lupus, Sjogren's syndrome) that has required IV or subcutaneous systemic treatment in the past 2 years (excluding Rituxan). Replacement therapy (i.e. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

21. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. Note: no testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

22. History of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.

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

3.3 Inclusion of Women and Minorities

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

3.4 Lifestyle Restrictions

It is prohibited to consume grapefruit juice while on olaparib therapy.

Pembrolizumab may have adverse effects on a fetus in utero. Refer to Appendix E 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).

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed

1. The registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

4.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (if applicable).

4.5 Strategies for Recruitment and Retention

Patients will be screened and recruited from existing clinic patients and referrals made to the head and neck cancer program. Patients will undergo the consent process in the clinic.

5.0 TREATMENT PLAN

5.1 Premedication Administration

Prevention of nausea and vomiting with relation to carboplatin should be managed with palonosetron 0.25 mg IV + fosaprepitant 150 mg IV at treatment start time. **Avoid corticosteroids such as dexamethasone.** Please refer to the product label or local standards of care for additional carboplatin supportive measures.

There are no premedications for pembrolizumab or olaparib.

5.2 Study Intervention Description

Olaparib is a PARP inhibitor currently approved for ovarian cancer.

Pembrolizumab is an immunotherapy that blocks the PD-L1 pathway and is FDA-approved for first- and subsequent-line treatment of RM-HNSCC.

Carboplatin is a platinum coordination compound and is commercially available for RM-HNSCC per NCCN guidelines.

5.3 Study Intervention Administration

For the first 6 cycles of treatment, participants will receive olaparib, pembrolizumab, and carboplatin on a 21-day cycle. For the remaining cycles of treatment (up to 29), participants will receive olaparib and pembrolizumab.

During the first 6 cycles, olaparib will be taken at a dose of 200 mg twice daily by mouth on Days 1 through 10 of each 21-day cycle. For the remaining 29 cycles, olaparib will be taken at a dose of 300 mg twice daily by mouth on Days 1 through 21. Olaparib tablets should be taken at the same times each day, approximately 12 hours apart with one glass of water. The tablets should be swallowed whole and not chewed, crushed, dissolved, or divided. Olaparib tablets can be taken with or without food. Participants will be asked to complete a medication diary (Appendix D) and bring it with them to each treatment visit. It does not matter if olaparib is taken before or after pembrolizumab (or carboplatin).

Pembrolizumab (200 mg) will be given intravenously over 30 minutes (-5/+10 minutes) on an outpatient basis on Day 1 of each 21-day cycle, for a maximum of 35 cycles. During the first 6 cycles (when given with carboplatin), carboplatin will be given first, followed by pembrolizumab.

Carboplatin AUC 5 will be given intravenously over 30 minutes on an outpatient basis on Day 1 of each 21-day cycle for the first 6 cycles of treatment only.

5.4 Definitions of Evaluability

All patients who receive any study treatment are evaluable for toxicity. Patients are evaluated for toxicity from first receiving study treatment until a 30-day follow up after the conclusion of treatment or death.

All patients who are given at least one dose of study drug, regardless of if they undergo a disease response assessment, are evaluable for disease response. Patients given at least one dose of study drug who later withdraw, are removed from the trial, or die, and have not undergone a disease response assessment will be considered as a progression event.

All patients who are given at least one dose of study drug are evaluable for DoR, PFS and OS.

5.5 Concomitant Therapy and Supportive Care Guidelines

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. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

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.

5.5.2 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase 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 (eg, FluMist®) are live attenuated vaccines and are not allowed.
- **Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology related to pembrolizumab. In these cases, a prednisone daily dose ≤20 mg is an acceptable criterion to re-implement pembrolizumab if the treating physician deems that clinically appropriate.**

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. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

The use of any natural/herbal products or other traditional remedies should be discouraged.

5.5.2.1 Medications that may NOT be administered

Prohibited medication/class of drug:	
Anticancer therapy: Chemotherapy Immunotherapy Hormonal therapy* Radiotherapy (except palliative) Biological therapy Other novel agents	Not permitted while the patient is receiving study medication
Live virus vaccines Live bacterial vaccines	Not permitted while the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.

*Hormone Replacement Therapy (HRT) is acceptable

5.5.2.2 Restricted concomitant medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed):
Strong CYP3A inhibitors: itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir Moderate CYP3A inhibitors: ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil	Strong or moderate CYP3A inhibitors should not be taken with olaparib. If there is no suitable alternative concomitant medication, then the dose of olaparib should be reduced for the period of concomitant administration. The dose reduction of olaparib should be recorded in the CRF with the reason documented as concomitant CYP3A inhibitor use. • Strong CYP3A inhibitors – reduce the dose of olaparib to 150 mg twice daily, days 1-5, for Cycles 1-6; to 200 mg twice daily for Cycles 7+ for the duration of concomitant therapy with the strong inhibitor and for 5 half-lives afterwards. • Moderate CYP3A inhibitors - reduce the dose of olaparib by 50 mg (to 150 mg bid, days 1-10, for Cycles 1-6; to 250 mg bid for Cycles 7+) for the duration of concomitant therapy with the moderate inhibitor and for 3 half-lives afterwards. • After the washout of the inhibitor is complete, the olaparib dose can be re-escalated.
Strong inducers: phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort Moderate CYP3A inducers: bosentan, efavirenz and modafinil	Strong or moderate CYP3A inducers should not be taken with olaparib. If the use of any strong or moderate CYP3A inducers are 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 then they must be monitored carefully for any change in efficacy of olaparib.
• CYP3A4 substrates: hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine • CYP2B6 substrates: bupropion, efavirenz • OATP1B1substrates: bosentan, glibenclamide, repaglinide, statins and valsartan • OCT1, MATE1 and MATE2K substrates: metformin • OCT2 substrates: serum creatinine • OAT3 substrates: furosemide, methotrexate	Effect of olaparib on other drugs: Based on limited *in vitro* data, olaparib may increase the exposure to substrates of CYP3A4, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. Based on limited *in vitro* data, olaparib may reduce the exposure to substrates of 2B6. Caution should be observed if substrates of these isoenzymes or transporter proteins are co-administered.

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed):
Anticoagulant therapy	Patients who are taking warfarin may participate in this trial; however, it is recommended that international normalized ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin and low molecular weight heparin are permitted.
Palliative radiotherapy	Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the investigator does not feel that these are indicative of clinical disease progression during the study period. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.
Administration of other anti-cancer agents	Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates or denosumab for bone disease and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning study treatment.

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

5.5.3 Rescue Medications and 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 6.0. 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 Section 6.0 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 Duration of Therapy

If at any time, the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue for 35 cycles (2 years) or until one of the following criteria applies:

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unable to receive further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious non-compliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center (SCC) decides to close the study

In the event that the study is closed by SCC, adequate notification will be provided so that appropriate adjustments to participant treatment can be made.

Patients who prematurely discontinue treatment for any reason will still be followed as indicated in the study calendar.

5.7 Duration of Follow-up

Patients will be seen approximately 30 days after the last dose of study treatment. Then, patients will be followed every 3 months until death or study completion. Patients who came off study for an event other than progression (if coming off for AEs, etc.), will be assessed every 6 weeks (42 ± 7 days) by radiologic imaging if in Cycles 1-6 or every 12 weeks (+/- 1 week) if in Cycles 7-35 to monitor disease status. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Patients who come off study because they completed all 35 cycles of treatment will be assessed every 3 months (12 weeks +/- 1 week) by radiologic imaging to monitor disease status.

Patients who come off study will be followed for AEs (for at least 30 days), disease status (if appropriate), subsequent lines of anticancer treatment (number of lines of therapy and cancer drugs given in each line) and survival status.

Patients will be followed by review of the medical records.

5.8 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for three scheduled visits and is unable to be contacted by the study team.

The following actions must be taken if the participant fails to return to clinic for a required study visit:

- The study team will attempt to contact the participant and reschedule the missed visit within 1 week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

6.0 DOSE DELAYS/DOSE MODIFICATIONS

6.1 Olaparib Dose Modifications

For guidance on dose reductions when concomitant strong or moderate CYP3A inhibitors cannot be avoided, refer to Section 5.5.2.

When dose reduction is necessary in Cycles 1-6, patients will take: dose reduction 1= one 150 mg tablet twice daily (days 1-10) or dose reduction 2= one 150 mg tablet twice daily (days 1-5).

When dose reduction is necessary in Cycles 7+, patients will take: dose reduction 1= one 150 mg tablet and one 100 mg tablet twice daily, or dose reduction 2= two x 100 mg tablets twice daily, or dose reduction 3= one 150 mg tablet twice daily, or dose reduction 4= one 100 mg tablet twice daily.

If patients were dose reduced in Cycles 1-6, they will start olaparib in Cycle 7 at the full dose of 300 mg twice daily, as the toxicity profile changes with the removal of carboplatin.

In case a dose reduction is necessary, olaparib will be administered as follows:

Dose reductions for study treatment to manage adverse events

Cycle	Initial Dose	Following re-challenge post interruption: Dose reduction 1	Dose reduction 2	Dose reduction 3	Dose reduction 4
1-6	200 mg twice daily, days 1-10	150 mg twice daily, days 1-10	150 mg twice daily, days 1-5	Not applicable	Not applicable
7+	300 mg twice daily	250 mg twice daily	200 mg twice daily	150 mg twice daily	100 mg twice daily

Any toxicity observed during the course of the study could be managed by interruption of t he dose of study treatment or dose reductions. Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer, the study team must be informed.

Once dose is reduced, escalation is not permitted (except following concomitant treatment with CYP3A4 inhibitors – see Section 5.5.2).

For guidance on dose reductions when concomitant strong or moderate CYP3A inhibitors cannot be avoided, see Section 5.5.2.2.

6.1.1 Management of hematological toxicity

Management of anemia

Hemoglobin (Hb)	Action to be taken
Hb < 10 *but* ≥ 8 g/dl (CTCAE Grade 2)	**First occurrence:** Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib with supportive treatment (e.g., transfusion) *or* interrupt dose for a maximum of 4 weeks. Study treatment can be restarted if Hb has recovered to > 9g/dl. **Subsequent occurrences:** If Hb**< 10** *but* **≥ 9 g/dl** investigator judgement to continue olaparib with supportive treatment (e.g., transfusion) *or* dose interrupt (for max of 4 weeks) and upon recovery dose reduction may be considered (in Cycles 1-6 to **150 mg twice daily, days 1-10** as a first step and to **150 mg twice daily, days 1-5** as a second step; in Cycles 7+ to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step). If Hb**< 9** *but* **≥ 8 g/dl**, investigator judgement to continue olaparib with supportive treatment (e.g., transfusion) *or* dose interrupt (for max of 4 weeks) until Hb ≥ 9 g/dl and upon recovery dose reduction may be considered (in Cycles 1-6 to **150 mg twice daily, days 1-10** as a first step and to **150 mg twice daily, days 1-5** as a second step; in Cycles 7+ to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step).

Hemoglobin (Hb)	Action to be taken
Hb < 8 g/dl (CTCAE Grade 3)	Give appropriate supportive treatment (e.g. transfusion) and investigate causality. Investigator judgement to continue olaparib with supportive treatment (e.g. transfusion) *or* interrupt olaparib for a maximum of 4 weeks until improved to Hb ≥ 9 g/dl. Upon recovery dose reduce (in Cycles 1-6 to **150 mg twice daily, days 1-10** as a first step and to **150 mg twice daily, days 1-5** as a second step; in Cycles 7+ to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step) in the case of repeat Hb decrease.

Common treatable causes of anemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases, management of anemia may require blood transfusions. For cases where patients develop prolonged hematological toxicity (≥2 week interruption/delay in study treatment due to CTCAE grade 3 or worse anemia and/or development of blood transfusion dependence), refer to guidance later in this section for management.

Management of neutropenia, leukopenia and thrombocytopenia

Toxicity	Study treatment dose adjustment
CTCAE Grade 1-2	Investigator judgement to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation
CTCAE Grade 3-4	Dose interruption until recovered to CTCAE grade 1 or better for a maximum of 4 weeks. If repeat CTCAE grade 3-4 occurrence, dose reduce olaparib (in Cycles 1-6 to **150 mg twice daily, days 1-10** as a first step and to **150 mg twice daily, days 1-5** as a second step; in Cycles 7+ to **250 mg twice daily** as a first step, to **200 mg twice daily** as a second step, to **150 mg twice daily** as a third step, and to **100 mg twice daily** as a fourth step).

Adverse events of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow up and interruption of study drug if CTCAE grade 3 or worse neutropenia occurs.

Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary.

Platelet transfusions, if indicated, should be done according to local hospital guidelines.

For cases where patients develop prolonged hematological toxicity (≥2 week interruption/delay in study treatment due to CTCAE grade 3 or worse), refer to guidance later in this section for management.

Management of prolonged hematological toxicities while on study treatment
If a patient develops prolonged hematological toxicity such as:

- ≥2 week interruption/delay in study treatment due to CTCAE grade 3 or worse anaemia and/or development of blood transfusion dependence
- ≥2 week interruption/delay in study treatment due to CTCAE grade 3 or worse neutropenia (ANC < 1 x 10^9/L)
- ≥2 week interruption/delay in study treatment due to CTCAE grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (Platelets < 50 x 10^9/L)

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice. Study treatment should be discontinued if blood counts do not recover to CTCAE grade 1 or better within 4 weeks of dose interruption.

Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE and full reports must be provided by the investigator to Merck. Olaparib treatment should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

6.1.2 Management of non-hematological toxicity

Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer than this, Merck must be informed. Where toxicity reoccurs following re-challenge with study treatment, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue study treatment.

Study treatment can be dose reduced (in Cycles 1-6 to **150 mg twice daily, days 1-10** as a first step and to **150 mg twice daily, days 1-5** as a second step; in Cycles 7+ to **250 mg twice daily** as a first step, to **200 mg twice daily** as a second step, to **150 mg twice daily** as a third step, and to **100 mg twice daily** as a fourth step). Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the investigator considers to be related to administration of study treatment.

6.1.3 Management of new or worsening pulmonary symptom

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further diagnostic workup (including a high resolution CT scan) should be performed to exclude pneumonitis.

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Study Physician.

6.1.4 Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. These events are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

Patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Alternatively, olaparib can be taken with a light meal/snack (i.e. 2 pieces of toast or a couple of crackers).

6.1.5 Interruptions for intercurrent non-toxicity related events

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the principal investigator.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF.

Study treatment should be stopped at least 3 days prior to planned surgery. After surgery, study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any needle biopsy procedure.

Study treatment should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Because the AEs related to olaparib may include asthenia, fatigue and dizziness, patients should be advised to use caution while driving or using machinery if these symptoms occur.

6.1.6 Renal impairment

If subsequent to study entry and while still on study therapy, a patient's estimated CrCl falls below the threshold for study inclusion (≥51 ml/min), retesting should be performed promptly.

Dose reduction for study treatment if patient develops moderate renal impairment

Cycle	Initial Dose	Moderate renal impairment (calculated creatinine clearance by Cockcroft -Gault equation or based on a 24 hour urine test between 31 and 50 ml/min): Dose reduction
1-6	200 mg twice daily, days 1-10	150 mg twice daily, days 1-10
7+	300 mg twice daily	250 mg twice daily

Because the CrCl determination is only an estimate of renal function, in instances where the CrCl falls to between 31 and 50 mL/min, the investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted.

Olaparib has not been studied in patients with severe renal impairment (creatinine clearance $\leq$ 30 ml/min) or end-stage renal disease; if patients develop severe impairment or end stage disease is it recommended that olaparib be discontinued.

6.2 Carboplatin Dose Modifications

Guidance for dose modifications or delays and treatment of AEs attributed to carboplatin will be guided based on the package insert. If carboplatin is omitted or stopped, patients will continue to receive olaparib and pembrolizumab.

6.3 Pembrolizumab Dose Modifications

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

modification and toxicity management guidelines for irAEs associated with pembrolizumab/combination treatment are provided in the table below.

6.3.1 Attribution of Toxicity

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to the combination, to olaparib alone, or to pembrolizumab alone, for adverse events listed in the table below, both interventions must be held according to the criteria in the table.

6.3.2 Holding Study Interventions

When study interventions are administered in combination, if the AE is considered immune-related, both interventions should be held according to recommended dose modifications.

6.3.3 Restarting Study Interventions

Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in the table below.

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions.
- If the toxicities do resolve and conditions are aligned with what is defined in the table below, the combination of olaparib and pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to olaparib alone, re-initiation of pembrolizumab as a monotherapy may be considered at the principal investigator's discretion.

Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab monotherapy and combination therapy

General instructions:

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

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 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) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)

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

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

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

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

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

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

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

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM)

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

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.

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 intervention**	Participant may be premedicated 1.5h (± 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:	**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.	No subsequent dosing

Life-threatening; pressor or ventilatory support indicated	Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug intervention.**	
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

If pembrolizumab is omitted or stopped, patients will continue to receive olaparib (and carboplatin if in Cycles 1-6).

7.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. Please refer to Appendix B for definitions and Appendix C for a grid of reporting timelines.

Adverse events will be tracked from start of treatment through 30 days post treatment. Any SAE of MDS/AML or new primary malignancy occurring after the 30-day follow-up period should be reported to Merck regardless of the investigator's assessment of causality. All adverse events must be recorded on the toxicity tracking case report form (CRF) with the exception of:

- Baseline adverse events, which shall be recorded on the medical history CRF

Refer to the data submission schedule in Section 11 for instructions on the collection of AEs in the EDC.

Reporting requirements for Washington University study team may be found in Section 11.1.

7.1 Sponsor-Investigator Reporting Requirements

7.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

7.1.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The Sponsor Investigator is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO.

(Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

7.1.3 Reporting to Merck

SAEs including cancer and overdose must be reported to Merck within 2 business days but no longer than 3 calendar days of learning of the event.

Events of clinical interest (refer to Appendix B for definitions) must be reported if potential drug-induced liver injury (DILI) or require regulatory reporting within 2 business days but no longer than 3 calendar days of learning of the event.

7.1.3.1 Pregnancy Reporting

Pregnancy/lactation exposure must be reported to Merck within 2 business days but no longer than 3 calendar days of learning of the event.

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study intervention(s). 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.

7.2 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 7.1 include:

- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

8.0 PHARMACEUTICAL INFORMATION

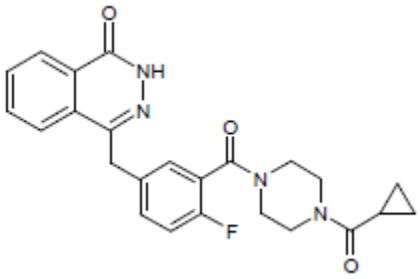
8.1 Olaparib

8.1.1 Olaparib Description

Olaparib (AZD2281, KU-0059436) is a potent inhibitor of PARP developed as a monotherapy as well as for combination with chemotherapy, ionizing radiation and other anti-cancer agents including novel agents and immunotherapy.

Chemical Name: 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2H)-one

Molecular Formula: $C_{24}H_{23}FN_4O_3$
Molecular Weight: 434.46



8.1.2 Clinical Pharmacology

The mechanism of action for olaparib activity as a single agent has been proposed to involve the trapping of inactivated PARP onto the single-strand breaks preventing their repair and generating a potential block for cellular DNA replication.

8.1.3 Pharmacokinetics and Drug Metabolism

The poor solubility of olaparib means advanced drug delivery technologies are required to deliver adequate bioavailability. The initially developed capsule formulation of olaparib consists of 50 mg dosing units with a monotherapy dosing schedule of 400 mg bid. The tablet formulation consists of dosing units up to 150 mg olaparib with a monotherapy dosing schedule of 300 mg bid. Given the different drug delivery technologies in the capsule and tablet, the formulations cannot be considered to be bioequivalent.

A formal bioequivalence study has not been conducted for the tablet and capsule formulations.

Based on the totality of the efficacy, safety/tolerability profile and the patient

convenience of a bd dosing schedule, the 300 mg bd tablet dose was chosen as the recommended Phase III monotherapy dose (Study D0810C00024).

The relative bioavailability of the capsule and tablet formulations was investigated in a 2-period crossover design at 3 single dose levels (n=6 per dose level), in patients with advanced solid tumors (Study D0810C00024 [Study 24]). Table 9 shows the derived PK parameters from Cohorts 1 to 3 in Study 24. The AUC ratio for tablet to capsule, normalized to the therapeutic dose level for tablet formulation (300 mg) shows that the tablet formulation appeared to give 31% higher exposure to olaparib compared to capsule formulation:

300 mg tablet/400 mg capsule: 63.0/57.9 * 300/250=1.31.

Table 10 Comparison of steady state olaparib exposure for the capsule and tablet formulations

Parameter	Summary statistic	Capsule 400 mg bd	Tablet 300 mg bd	Tablet 300 mg bd
		Pooled population PK analysis (Olaparib-MS-06)	Pooled population PK analysis (Olaparib-MS-06)	OlympiAD population PK analysis (Olaparib-MS-05)
$C_{max,ss}$ (µg/mL)	n	48	227	36
	Gmean (range)	6.18 (2.06-14.5)	7.67 (3.35-23.5)	6.41 (2.16-17.7)
AUC_{ss}(µg.h/mL)	n	48	227	36
	Gmean (range)	43.5 (9.11-128)	49.0 (16.5-183)	41.2 (17.6-140)
C_{min} (µg/mL)	n	48	227	36
	Gmean (range)	1.86 (0.19-8.11)	1.57 (0.25-10.0)	1.17 (0.11-8.00)

AUC_{ss} Area under the plasma concentration-time curve at steady state; bd Twice daily; $C_{max,ss}$ Concentration maximum (plasma) at steady state; C_{min} Minimum plasma concentration; Gmean Geometric mean; PK pharmacokinetic.
Data Source: Table 8 Olaparib-MS-06 and Table 4 Olaparib-MS-05.

8.1.4 Supplier

Olaparib will be supplied by Merck & Co.

8.1.5 Dosage Form and Preparation

Olaparib is available as either capsules or tablets; however, only tablets are being provided for this trial.

8.1.6 Storage and Stability

The product should be stored in the pack provided and used according to the instructions on the label.

8.1.7 Administration

Olaparib should be taken twice daily approximately 12 hours apart. Each dose

should be taken with a glass of water, with or without food.

8.2 Pembrolizumab

8.2.1 Description

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and 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 being advanced for clinical development as an IV immunotherapy for advanced malignancies.

8.2.2 Supplier

Pembrolizumab will be supplied by Merck & Co.

8.2.3 Dosage Form and Preparation

Pembrolizumab is provided as a liquid drug product.

8.2.4 Storage and Stability

Pembrolizumab should be stored under refrigerated conditions (2°C - 8°C).

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.

8.2.5 Administration

Pembrolizumab will be given as per standard of care, that is, intravenously over the course of 30 minutes (-5 min/+10 min) on an outpatient basis.

8.3 Carboplatin

8.3.1 Carboplatin Description

Carboplatin is supplied as a sterile, pyrogen-free, 10 mg/mL aqueous solution of carboplatin. Carboplatin is a platinum coordination compound. The chemical name for carboplatin is platinum, diamine [1,1-cyclobutane-dicarboxylato(2-)- 0,0']- ,(SP-4-2). It has a molecular formula of C6H12N2O4Pt and a molecular weight of 371.25. It is soluble in water at a rate of approximately 14 mg/mL, and the pH of a 1% solution is 5 to 7. It is virtually insoluble in ethanol, acetone, and dimethylacetamide.

8.3.2 Supplier

Carboplatin is commercially available.

8.3.3 Dosage Form and Preparation

Carboplatin aqueous solution is a premixed aqueous solution of 10 mg/mL carboplatin. It can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water (D5W) or 0.9% Sodium Chloride Injection, USP. It is supplied as follows: 50 mg/5 mL aqueous solution in multidose vials 150 mg/15 mL aqueous solution in multidose vials 450 mg/45 mL aqueous solution in multidose vials 600 mg/60 mL aqueous solution in multidose vials.

Note: aluminum reacts with carboplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

8.3.4 Storage and Stability

Unopened vials of carboplatin solution are stable for the life indicated on the package when stored at controlled room temperature and protected from light. The multidose vials of carboplatin aqueous solution are reported to maintain microbial and chemical stability at room temperature for up to 14 days following multiple needle entries.

8.3.5 Administration

Carboplatin will be administered over 30 minutes. Dosing will be AUC5.

Hypersensitivity to carboplatin has been reported in 2% of patients. These allergic reactions have been similar in nature and severity to those reported with other platinum-containing compounds, i.e., rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. Anaphylactic reactions have been reported as part of postmarketing surveillance. These reactions have been successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

9.0 CORRELATIVE STUDIES

9.1 Archived Tumor Tissue

9.1.1 Collection of Specimen

Ten slides from most recent tumor specimen preferably collected from the relapsed

setting (excluding cytology) will be requested. This may be archival tissue from a previous pre-treatment diagnostic biopsy or resection, tissue collected under HRPO# 201102323 ("Analysis of Histological, Genomic, Molecular, and Clinical Factors in Head and Neck Cancer: The Tissue Acquisition Protocol (TAP)") to which participants in this study will be encouraged to enroll, or tissue collected under the auspices of this protocol should archival or previously banked tissue be unavailable. If biopsies are performed as part of this protocol, collection will be performed as follows: tissue samples will be obtained by simple excision (1-2 cm^3 portion of tissue) or 4 mm or greater dermatology biopsy punch and specimens should be fixed in 10% buffered formalin.

9.1.2 Handling of Specimen

Archived tissue should be delivered to the study team.

Tumor tissue will be sent for Tempus-xT648 genome sequencing and PD-L1 CPS.

9.2 Peripheral Blood

9.2.1 Collection of Specimen(s)

Fifty mL of anticoagulated blood will be collected in 3 EDTA purple top tubes and 1 red top tube at the following time points:

- baseline (Cycle 1 Day 1)
- Cycle 2 Day 1 – drawn before carboplatin administration, irrespective of timing of olaparib dose
- disease progression

Peripheral blood will be collected by standard venous phlebotomy. The sample should be spun and processed for peripheral white blood cells. Residual red blood cells will be removed by hypotonic lysis. Nucleated cells will be washed in phosphate buffered saline, divided into approximately 20 x 10^6 cells/aliquot, spun down, and the supernatant removed. Cell pellets for potential correlative genomics will be labeled with a unique specimen ID number, snap frozen in liquid nitrogen, and stored under liquid nitrogen vapor in an inventoried storage unit at the Siteman Cancer Center TPC until analysis. The remaining peripheral blood samples will be spun and the serum and plasma stored for potential correlative circulating tumor related protein or biomarker studies.

9.2.2 Handling of Specimen(s)

Samples may be analyzed for T-, B-, and NK-cell subsets, cytokines, and/or tumor DNA.

9.3 Future Research

Archived tumor tissue and peripheral blood may be evaluated for potential correlative studies if the primary endpoint is met.

10.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form Medical History Form	Prior to starting treatment
Treatment Form	Every cycle
Toxicity Form	Continuous
Correlatives Form	Baseline, C2D1, time of progression
Treatment Summary Form	Completion of treatment
Follow Up Form	Every 3 months
Tumor Measurement Form	Baseline, end of every even numbered cycle for first 6 cycles, then every 4^{th} cycle, and end of treatment. For patients who complete every 35 cycles, every 3 months.
Progression Form	Time of disease progression
Death Form	Time of death
MedWatch Form	See Section 7.0 for reporting requirements

10.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 7.0) must be captured in the Toxicity Form. Baseline AEs should be captured on the Medical History Form.

Participant death due to disease progression should be reported on the Toxicity Form as grade 5 disease progression. If death is due to an AE (e.g. cardiac disorders: cardiac arrest), report as a grade 5 event under that AE. Participant death must also be recorded on the Death Form.

11.0 MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Immune-Related RECIST (iRECIST) Criteria[30]

11.1.1 Definitions

Evaluable for Adverse Events. All patients will be evaluable for adverse event evaluation from the time of their first treatment.

Evaluable for Response. All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of Cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below.

Response and progression will be evaluated in this study using the revised international criteria (RECIST version 1.1) proposed by the RECIST committee as well as the modified iRECIST guidelines. Investigators should note the different requirements for confirmatory scans as well as follow up for the two criteria.

11.1.2 RECIST 1.1 Response and Evaluation Endpoints

Measurable Disease. Measurable tumor lesions (nodal, subcutaneous, lung parenchyma, solid organ metastases) are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with chest X-ray and as ≥10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥10 mm by CT scan). Malignant lymph nodes must be ≥15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

Non-Measurable Disease. All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

Target Lesions. When more than one measurable tumor lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions

and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and be those that lend themselves to reproducible repeated measurements. Note that pathological nodes must meet the criterion of a short axis of ≥15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

Non-Target Lesions. All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered non-target lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent."

11.1.3 Response Criteria

All patients will have their best response from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): Disappearance of target and non-target lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures <10 mm (Note: continue to record the measurement even if <10 mm and considered CR). Residual lesions (other than nodes <10 mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases [*Eur J Ca* 45:228-247, 2009]) before CR can be accepted. Confirmation of response is only required in non-randomized studies.

Partial Response (PR): At least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non-target lesions must be non-PD. Confirmation of response is only required in non-randomized studies.

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

Progressive Disease (PD): At least a 20% increase in the sum of diameters of

measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥5 mm. Appearance of new lesions will also constitute PD (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment or where the tumor burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Integration of target, non-target, and new lesions into response assessment

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response For This Category Also Requires
Target lesions ± non target lesions				
CR	CR	No	CR	Normalization of tumor markers, tumor nodes <10 mm
CR	Non-CR/non-PD	No	PR	Normalization of tumor markers, tumor nodes <10 mm
CR	Not all evaluated	No	PR	
PR	Non-PD/not all evaluated	No	PR	
SD	Non-PD/not all evaluated	No	SD	Documented at least once ≥4 weeks from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Non target lesions ONLY				
No Target	CR	No	CR	Normalization of tumor markers, tumor nodes <10 mm
No Target	Non-CR/non-PD	No	Non-CR/ non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes*	PD	

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

*Investigators should record all new lesions. If the new lesion is felt to be equivocal, treatment may be continued pending further assessments.

11.1.4 iRECIST Response Assessment

Overall response will also be assessed using iRECIST. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression.

Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix. iRECIST time-point and best overall responses will be recorded separately.

Confirming progression: Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks, after iUPD.

iCPD is confirmed if further increase in tumor burden, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued increase in tumor burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease, or new lesions.
    - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum.
    - Continued unequivocal progression in non-target disease with an increase in tumor burden.
    - Increase in size of previously identified new lesion(s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- RECIST 1.1 criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR, or iCR if those criteria are met compared to baseline). The prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that iCPD is not documented at the next assessment after iUPD (*Lancet Oncol* 18:e143-e152, 2017 - Table 2).

New lesions:
New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis

[or 15 mm in short axis for nodal lesions]), and recorded as New Lesions - Target (NLT) and New Lesion - Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case record form.

PD is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions.

Time-point (TP) iResponse

Target Lesions*	**Non-Target Lesions***	**New Lesions***	**Time Point Response**	
			No prior iUPD**	**Prior iUPD**, *****
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD.
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD).
iUPD	Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in SOM of at least 5 mm, otherwise remains iUPD.

Time-point (TP) iResponse

Target Lesions*	Non-Target Lesions*	New Lesions*	Time Point Response	
			No prior iUPD**	Prior iUPD**, ***
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: • previously identified T lesion iUPD SOM ≥5 mm and/or • NT lesion iUPD (prior assessment - need not be unequivocal PD)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: • previously identified T lesion iUPD ≥5 mm and/or • previously identified NT lesion iUPD (need not be unequivocal) and/or • size or number of new lesions previously identified
Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on increase in size or number of new lesions previously identified.
* Using RECIST 1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR, and SD would be the same. ** in any lesion category. *** previously identified in assessment immediately prior to this TP.				

All patients will have their iBOR from the start of study treatment until the end of treatment classified as outlined below.

iRECIST best overall response (iBOR)

TPR 1	TPR 2	TPR 3	TPR 4	TPR 5	iBOR
iCR	iCR, iPR, iUPD, NE	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR

iRECIST best overall response (iBOR)

TPR 1	TPR 2	TPR 3	TPR 4	TPR 5	iBOR
iUPD	iPR, iSD, NE	iCR	iCR, iPR, iSD, iUPD, NE	iCR, iPR, iSD, iUPD, iCPD, NE	iCR
iUPD	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	PR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, iCPD, NE	iPR
iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, ICPD, NE	iSD
iUPD	iCPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD

Table assumes a randomized study where confirmation of CR or PR is not required.

- NE = not evaluable that cycle.
- Designation "I" for BOR can be used to indicate prior iUPD to aid in data interpretation.
- For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation.

11.1.5 Response and Stable Disease Duration (RECIST 1.1 and iRECIST)

Response duration will be measured from the time measurement criteria for CR/PR or iCR/iPR (whichever is first recorded) are first met until the first date that recurrent or PD is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

Stable disease duration will be measured from the time of start of treatment until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

11.1.6 Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (*e.g.*, 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm

should be assigned. For lesions which fragment/split, add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion."

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm as assessed using calipers (*e.g.*, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.*, for body scans). Other specialized imaging or other techniques may also be appropriate for individual case (*Eur J Ca* 45:228-247, 2009). For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

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

Tumor Markers. Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in CR.

Cytology, Histology. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (*e.g.*, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment

when the measurable tumor has met criteria for response or stable disease is advised to differentiate between response or SD and PD.

12.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least one patient has been enrolled) or one year after accrual has opened (if no patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

13.0 STATISTICAL CONSIDERATIONS

13.1 Statistical Hypotheses

This is an open-label, single-arm phase 2 trial. The primary objective is to determine the objective response rate (ORR) for recurrent or metastatic HNSCC to olaparib,

pembrolizumab, and carboplatin. The primary hypothesis is that olaparib, pembrolizumab, and carboplatin will result in an ORR higher than the historical ORR observed with pembrolizumab, platinum and 5-FU reported in the KEYNOTE-048 trial. Secondary objectives are to determine the duration of response (DoR), PFS, OS, AEs, HR and *PTEN* gene status, PD-L1 CPS status, and HPV status. Simon's two-stage design[31] will be used for the primary objective.

13.2 Sample Size Determination

The primary endpoint is ORR. The sample size calculation is based on the primary endpoint only. The previous study (KEYNOTE-048) showed that the ORR for the patients with pembrolizumab, carboplatin, and 5-FU was 36%. A Simon optimal two-stage design[31] will test the null hypothesis that the true ORR is less than or equal to 36% versus the alternative hypothesis that it exceeds 36% at the type I error rate of 10%. In the first stage, 13 patients will be accrued. If the study continues, 16 additional patients will be accrued. The null hypothesis will be rejected if 14 or more responses are observed in these 29 patients. This design will have 90% power to reject the null hypothesis when the true ORR is 62%.

13.3 Stopping Rules

An assessment of dose delivery of olaparib will be performed across the first 2 cycles of treatment. After enrollment of the first 13 patients, an assessment of dose delivery of olaparib will be performed across the first two cycles of treatment. We target for 80% or more of patients to receive the planned 10 days of olaparib per cycle during the first two cycles of treatment.[18] If this target is met, enrollment will be continued. If not, the study will be paused to determine the next step.

In the first stage, 13 patients will be accrued. If five or fewer patients have an objective tumor response, the study will be stopped and the alternative hypothesis will be rejected. Otherwise, 16 additional patients will be accrued, for a total of 29 patients.

13.4 Accrual

At Washington University, we estimate 40 patients/year will be eligible for this trial. We anticipate enrollment of approximately 3 patients per month.

13.5 Statistical Analyses

13.5.1 Patient Disposition

The number of patients discontinued, the reasons for discontinuation, and the amount of therapy administered will be summarized by patient and by reason for discontinuation.

13.5.2 Protocol Deviations

All significant deviations will be summarized by patient and type of deviation.

13.5.3 Demographics and Baseline Characteristics

Subject demographic and clinical characteristics will be summarized to characterize the treatment population. Descriptive summaries will include means, standard deviations, medians, ranges for continuous variables and frequency and percentage for categorical variables.

13.5.4 Endpoint Analysis

For Aim 1, ORR and its associated 95% confidence interval will be calculated assuming a binomial distribution. DoR will be summarized by dose using the minimum, 25^{th} percentile, median, 75^{th} percentile, and maximum values. PFS is defined as the time from date of study enrollment to disease progression or death from any cause, whichever occurs first. The patients alive, without progression, are censored at the last disease assessment. OS is defined as the time from the date of first treatment to the date of death, or censored at the last follow-up alive. The Kaplan-Meier method will be used to calculate the probability of PFS and OS.

Data on the tolerability and toxicity of treatment (AEs and SAEs) will be collected for each subject, including frequency, type, and severity of adverse events.

HR and *PTEN* gene status was altered (defined as the presence of an alteration in one or more HR genes or *PTEN*) or not altered. PD-L1 CPS status included CPS $\geq$20 or CPS 0-19. The correlation between HR and *PTEN* gene status, PD-L1 CPS status, or HPV status with efficacy endpoints (ORR, PFS, and OS) will be investigated by Chi-Square or log-rank tests, as appropriate.

The descriptive statistics of peripheral blood collected at baseline, after cycle 2 and at progression will be provided. The mixed models will be considered to evaluate changes over time. The logistic and Cox regression models will be used to test the correlation with efficacy endpoints.

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APPENDIX A: ECOG Performance Status Scale

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.

APPENDIX B: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse event

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

G. Events of Clinical Interest

Selected nonserious and SAEs are also known as ECIs and must be reported to Merck.

Events of clinical interest for this study include:

1. MDS/AML
2. New primary malignancy (other than MDS/AML
3. Pneumonitis
4. An overdose of pembrolizumab that is not associated with clinical symptoms or abnormal laboratory results. 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.
5. Hy's law: 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.

APPENDIX C: Reporting Timelines

Expedited Reporting Timelines			
Event	**HRPO**	**QASMC**	**Merck**
Serious adverse events (including cancer and overdose)			Report within 2 business days but no longer than 3 calendar days of learning of the event.
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment	
Events of clinical interest			Report within 2 business days but no longer than 3 calendar days of learning of the event.
Pregnancy/lactation exposure			Report within 2 business days but no longer than 3 calendar days of learning of the event.
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.		
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.		
Protocol exception	Approval must be obtained prior to implementing the change		
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.		
Breach of confidentiality	Within 10 working days.		

Expedited Reporting Timelines			
Event	**HRPO**	**QASMC**	**Merck**
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.		

Routine Reporting Timelines			
Event	**HRPO**	**QASMC**	**Merck**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report, which is typically due every 6 months.	
Minor deviation	Report summary information at the time of continuing review.		
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.		
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.		

APPENDIX D: PATIENT'S MEDICATION DIARY

Today's Date: _____ Agent: olaparib Cycle: _____

Patient Name: _____ Study ID#: _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each month. Take _____mg (___tablets) of olaparib daily in the morning, one hour after a light breakfast at approximately the same time each day. Take the olaparib with a glass of water and drink the glass of water in as little time as possible. Swallow the tablets whole and do not chew the tablets.
2. Record the date, the number of tablets taken, and when you took them.
3. If you forgot to take your first dose of olaparib dose before 6:00PM, then do not take a second dose that day. Restart taking the olaparib the next day.
4. If you have any questions or notice any side effects, please record them in the comments section. Record the time if you should vomit.
5. Please return the forms to your physician or your study coordinator when you go to your next appointment. Please bring your unused study medications and/or empty bottles with you to each clinic visit so that a pill count can be done.
6. Avoid St. John's Wort, Seville oranges, grapefruit, grapefruit juice, grapefruit hybrids, pummelos, and exotic citrus fruits from 7 days before you start taking olaparib and throughout the entire study.

Day	Date	What time was dose taken?	# of tablets taken	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				

APPENDIX E: Contraceptive Guidance and Pregnancy Testing

Women of childbearing potential are required to have a negative serum pregnancy test within 72 hours prior to the first dose of study treatment.

A woman is considered fertile following menarche and until become post-menopausal unless permanently sterile. Women in the following categories are not considered women of childbearing potential:

- 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.

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following:

- 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 the Table below 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 patients (along with their male partners) are required to use two forms of highly effective contraception in combination, beginning with the signing of the informed consent document and continuing during participation in the study and for at least 1 month following the last dose of study treatment. Male patients must use a condom during treatment and for 3 months after the last dose of olaparib when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients should also use a highly effective form

of contraception if they are of childbearing potential. Male patients should not donate sperm throughout the period of taking olaparib and for 3 months following the last dose of olaparib.

Acceptable non-hormonal birth control methods include:

- Total/true abstinence: When the patient refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the trial and for at least 1 month after the last dose of study drug for female patients and for 3 months after last dose for male patients. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a trial) and withdrawal are not acceptable methods of contraception]
- Vasectomized sexual partner PLUS male condom with participant assurance that partner received post-vasectomy confirmation of azoospermia
- Tubal occlusion PLUS male condom
- IUD PLUS male condom provided coils are copper-banded

Acceptable hormonal methods:

- Normal and low dose combined oral pills PLUS male condom
- Cerazette (desogestrel) PLUS male condom. Cerazette is currently the only highly efficacious progesterone based pill.
- Hormonal shot or injection (e.g., Depo-Provera) PLUS male condom
- Etonogestrel implants (e.g., Implanon, Norplant) PLUS male condom
- Norelgestromin / EE transdermal system PLUS male condom
- Intrauterine system [IUS] device (e.g., levonorgestrel releasing IUS -Mirena®) PLUS male condom
- Intravaginal device (e.g., EE and etonogestrel) PLUS male condom

If a patient is suspected to be pregnant, olaparib, pembrolizumab and carboplatin should be immediately discontinued. In addition, a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing. 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). Refer to Section 7.1.3 for further reporting guidance.

If a female patient or female partner of a male patient becomes pregnant during therapy or within 6 months after the last dose of olaparib, pembrolizumab, carboplatin, the investigator must be notified in order to facilitate outcome follow-up.

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] ○ Oral ○ Intravaginal

○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b] ○ 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] ● Intrauterine hormone-releasing system (IUS) ● 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 locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.