

A Phase II study of induction SBRT and olaparib followed by
combination pembrolizumab/olaparib in gastric and
gastroesophageal junction (GEJ) cancers

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Principal Investigator: Sunnie Kim, MD
University of Colorado Comprehensive Cancer Center
Mail Stop 8117, Research One South
12801 E. 17th Avenue, Room 8116
Aurora, CO 80045
Telephone (303) 724-2520
Fax (303) 724-3889
Email: *sunnie.kim@CUAnschutz.edu*

**Coordinating Center
and Lead Principal
Investigator:** Sunnie Kim, MD
University of Colorado Comprehensive Cancer Center

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PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.	02.10.2021		Initial Submission
2	6.28.2022	Correction to SAE section, Correction to Schema, correction to schedule of events footnote for imaging intervals	General clarifications in conjunction with Pembrolizumab IB update
3	10.04.2022	Added language pertaining to timing of EOT scans	Clarification
4	12.09.2022	Removed conflicting language in con-meds section	Clarification
5	10.11.2023	Added language to define evaluable patients	Clarification
6	04.09.2024	Expanded Olaparib dosing window	Clarification
7	10.25.2024	Harmonized AE procedures	Discrepancy Resolution
8	04.01.2025	Minor edits to I/E, prohibited therapy, conmeds, rescue medicine, participant discount, AESI, appendix 6, and table 10	New Merck template language

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STATEMENT OF COMPLIANCE

This is an investigator-initiated study. The principal investigator (PI), Sunnie Kim, MD, is conducting the study and acting as the sponsor. As the sponsor-investigator, both the legal/ethical obligations of a PI and those of a sponsor will be followed.

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by applicable United States (US) laws and applications, including but not limited to 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), as applicable.

The PI will assure that no changes to the protocol will take place without documented approval from the Institutional Review Board (IRB). All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Sponsor-Principal Investigator: _____
Print/Type Name

Signature: _____ **Date:** _____

Site Principal Investigator: _____
Print/Type Name

Signature: _____ **Date:** _____

LIST OF ABBREVIATIONS

SBRT	Stereotactic Beam Radiation Therapy
GEJ	Gastroesophageal Junction
ORR	Objective Response Rate
OS	Overall Survival
PFS	Progression Free Survival
DOR	Duration of Response
DCR	Disease Control Rate
HRD	Homologous Recombination Deficiency
HR	Homologous Recombination
PD-L1	Programmed Death Ligand 1
MMR	Mismatch Repair
MSI	Microsatellite Instability
TMB	Tumor Mutational Burden
ctDNA	Circulating Tumor DNA
PD-1	Programmed Death-1
PARP	Poly (ADP-ribose) polymerase
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
HER-2	human epidermal growth factor receptor 2)
MRI	Magnetic Resonance Imaging
CT	Computed Tomography
ECOG	human epidermal growth factor receptor 2)
CD8	cluster of differentiation 8
PBMC	peripheral blood mononuclear cells
IgG4	Immunoglobulin G4
mAb	Monoclonal Antibody
PD-L2	Programmed Death ligand 2
SSB	Single Strand Break
DSB	Double Strand Break
T2DM	Type 2 Diabetes Mellitus
NGS	Next Generation DNA Sequencing
Q3W	Every 3 weeks
Q2W	Every 2 weeks
PK	Pharmacokinetics

NSCLC	Non-Small Cell Lung Cancer
TMDD	target-mediated drug disposition
RP2D	Recommended Phase 2 Dose
WOCBP	Women of Child Bearing Potential
ANC	Absolute Neutrophil Count
ULN	Upper Limit of Normal
GFR	Glomerular Filtration Rate
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
DLT	Doses Limiting Toxicity
PR	Partial Response
CR	Clinical Response
SD	Stable Disease

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol Title: A Phase II study of induction SBRT and olaparib followed by combination pembrolizumab/olaparib in gastric and gastroesophageal junction (GEJ) cancers

Objectives:

Primary Objective:

- To assess the anti-tumor efficacy of combined therapy as determined by measurement of objective response rate (ORR)

Secondary Objectives:

- To assess the anti-tumor efficacy of combined therapy as determined by measurement of overall survival (OS), progression free survival (PFS), duration of response (DOR) and disease control rate (DCR) as a total cohort and HRD (Homologous Recombination Deficiency) versus HR (Homologous Recombination) proficient.
- To evaluate the safety and tolerability of radiotherapy added to olaparib.

Tertiary/ Exploratory Objective:

- To define the effect of HRD on combination SBRT (Stereotactic Beam Radiation Therapy), olaparib, and pembrolizumab on immunomodulation as measured by immune cell infiltration and activation in plasma/serum assays and tissue.

Endpoint:

Primary Endpoint:

- Objective Response Rate of unirradiated tumors (ORR per RECIST 1.1)

Secondary Endpoints:

- Overall Survival (OS) from the initiation of therapy to the date of death or to the date of last follow-up.
- Progression Free Survival (PFS) from the initiation of therapy to the date of progression or to the date of last follow-up.
- Duration of response (DoR) defined as the time from documentation of tumor response to disease progression.

- Disease control rate (DCR) defined as the sum of partial response (PR), complete response (CR) and stable disease (SD).
- Treatment-emergent adverse events (AEs), serious adverse events (SAEs) of combination SBRT and olaparib

Tertiary/ exploratory:

- Immune changes in tumor tissue and plasma at baseline compared to after combination SBRT/olaparaib and after Olaparib/pembrolizumab
- Assess response based on HRD status, PD-L1 expression, MMR (Mismatch Repair)/MSI (Microsatellite Instability), and TMB (Tumor Mutational Burden) in tumor
- Changes in cytokines, ctDNA in plasma/serum
- Abscopal effect based on irradiated disease site

Population:

Sample size

- *Maximum number of participants that can be enrolled is 32 (allow for screen failures)*
- *Minimum number of participants to be enrolled 26 (between two cohorts: 13 in the HR deficient cohort, 13 in the HR proficient cohort) (number of participants needed to answer scientific question/aims)*

Phase:

II

Participating Sites:

University of Colorado Hospital (UCHealth Metro and Highlands Ranch Hospital)
 Memorial Hospital (UCHealth South)

Description of Study Intervention:

Concurrent SBRT with Olaparib followed by combination Olaparib and Pembrolizumab

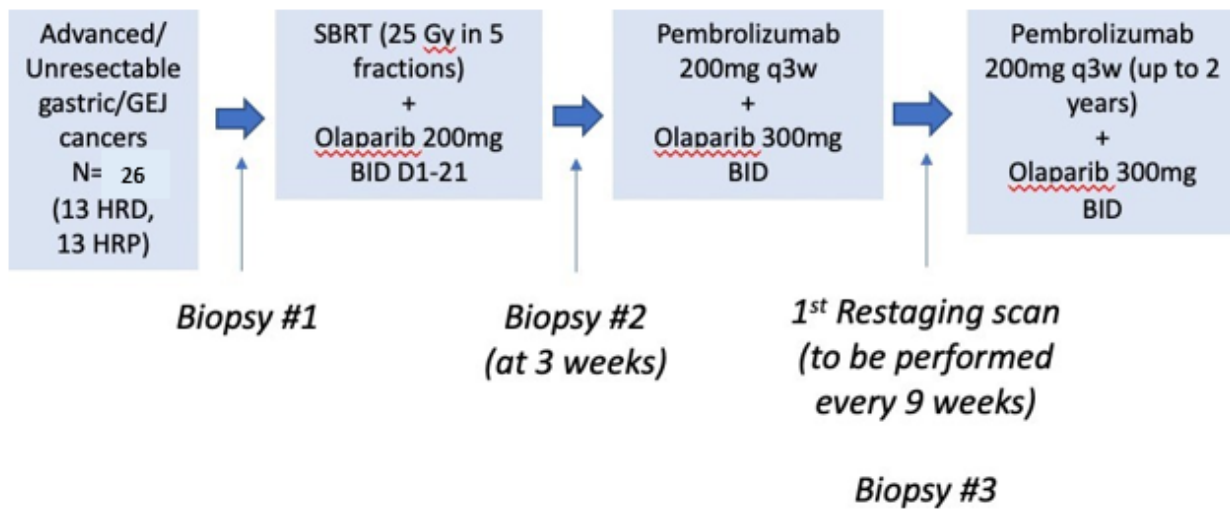
Study Duration:

Enrollment will last approximately 3 years. Total length of study is 4 years. Enrollment is anticipated at 8 per year

Participant Duration:

1 year from study initiation

1.2 STUDY SCHEMA



1.3 SCHEDULE OF EVENTS

Trial Period:	Screening Phase	Treatment Cycles ^a					End of Treatment	Post-Treatment	
Treatment Cycle/Title:	Study Screening	Day 1 Cycle 1 ^a	Day 8 Cycle 1	Day 15 Cycle 1	Day 1 Cycle>1 ^e	Every 9 weeks	Discontinue ^b	30 Day Safety Follow Up ^k	Follow Up
Scheduling Window (Days):	-28 to -1		+/- 1	+/- 1	± 7	± 3	At time of Discontinuation (+/- 7)	+7	Q12W (+/- 7)
Administrative Procedures									
Informed Consent	x								
Inclusion/Exclusion Criteria	x								
Demographics and Medical History ^j	x								
Prior and Concomitant Medication Review	x	x	x	x	x		x	x	
Radiation ^p		x							
Olaparib ^o		x	x	x	x				
Pembrolizumab					x				
Clinical Procedures/Assessments									
Review Adverse Events		x	x	x	x		x	x	
Full Physical Examination	x								
Directed Physical Examination		x	x	x	x		x	x	
Vital Signs and Weight ^f	x	x	x	x	x		x	x	
ECOG Performance Status ⁱ	x	x	x	x	x		x	x	
Survival Status								x	x
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory^m									
Pregnancy Test – Urine or Serum β-HCG ^c	x	x			x				
PT/INR and aPTT	x	x			x		x		
CBC with Differential	x	x	x	x	x		x		
Comprehensive Serum Chemistry Panel	x	x	x	x	x		x		
Urinalysis	x	x			x		x		
Total T3, FT4 and TSH	x				x ^g		x		
ECG ^l	x								
Efficacy Measurements									
Tumor Imaging ^h	x					x	x ^s		x ⁿ

Trial Period:	Screening Phase	Treatment Cycles ^a					End of Treatment	Post-Treatment	
Treatment Cycle/Title:	Study Screening	Day 1 Cycle 1 ^a	Day 8 Cycle 1	Day 15 Cycle 1	Day 1 Cycle>1 ^e	Every 9 weeks	Discontinue ^b	30 Day Safety Follow Up ^k	Follow Up
Scheduling Window (Days):	-28 to -1		+/- 1	+/- 1	± 3	± 3	At time of Discontinuation (+/- 7)	+7	Q12W (+/- 7)
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood									
Biopsy Tissue Collection ^d	x				x				
Correlative studies blood collection ^d	x				x		x		

^a For Cycle 1 only, patient will be seen weekly. All other cycles as listed in schedule of events

^b All patients with clinically significant abnormal laboratory results at treatment completion or study drug discontinuation (EOT) visit are to be followed until the results return to normal (or patient's baseline), or until a valid reason, other than a drug- related effect, is identified. Patients with an unresolved AE or SAE event at treatment completion or study drug discontinuation will be contacted by the investigator or his or her designee to determine the status of the event until the event is resolved or stabilized, the patient is lost to follow up, or it has been determined that the study treatment or participation is not the cause of the event. If the post-trial visit occurs less than 30 days after the last dose of study treatment, a subsequent follow-up phone call should be made at 30 days post the last dose of study treatment to determine if any adverse events have occurred since the post-trial clinic visit

^c Pregnancy test on blood or urine samples will be performed for pre-menopausal women of childbearing potential one within 28 days prior to the start of study treatment and the other on Day 1 of the study prior to commencing treatment. Tests will be performed by the hospital's local laboratory. If results are positive the patient is ineligible/must be discontinued from the study. In the event of a suspected pregnancy during the study, the test should be repeated.

^d First biopsy and correlative bloodwork to be collected prior to C1D1 (within 14 days of starting therapy). For baseline biopsy only, available archived tumor tissue of a metastatic tumor collected up to 28 days prior to registration is acceptable. Second biopsy and correlative bloodwork to be collected within 5 days prior to C2D1, before treatment with olaparib/pembrolizumab. Third biopsy and correlative bloodwork to be collected within 5 days prior to C4D1, before starting treatment with olaparib/pembrolizumab. Correlative bloodwork only within 5 days of EOT.

^e Cycle 2 Day 1 should start within two weeks of completing combination olaparib and radiation.

^f Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

^g Perform on Day 1 of every cycle starting from Cycle 2 and at EOT

^h Tumor imaging is strongly preferred to be acquired by computed tomography (CT). For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when local practice mandates it. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

ⁱ Evaluation of ECOG at screening is to be performed within 14 days prior to the date of treatment.

^j Medical history will include all active conditions and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator

^k The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the participant will move into survival follow-up. If the post-trial visit occurs less than 30 days after the last dose of study treatment, a subsequent follow-up phone call should be made at 30 days post the last dose of study treatment to determine if any adverse events have occurred since the post-trial clinic visit

^l ECGs are required within 7 days prior to starting study treatment

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

ⁿ In participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on study treatment (every 12 weeks \pm 7 days) until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

^o Drug diaries will be collected and reviewed at the end of each cycle for Olaparib compliance. Additionally, patients should bring any bottles dispensed for the previous cycle with them to each clinic visit (starting at Day 1 cycle 2) for compliance.

^p The simulation planning scan needs to be completed prior to treatment start date. A radiation oncology assessment will occur at least once during the SBRT course as per standard of care. At 2 weeks post-SBRT, a radiation oncology nurse will call patient to assess for any further toxicities. See section 4.3 for additional radiation details.

^q Only Concomitant Medications related to the treatment of AE or SAE, and other medical conditions deemed necessary by the PI will be recorded.

^r For patients who come off treatment for reasons other than progression, follow up scans will be recorded every 12 weeks. Participants who experience confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-Up Phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first. Patients will be followed for 5 years for survival

^s EOT scans are only required if a scan has not been performed within 8 weeks prior to the EOT visit

2 INTRODUCTION

2.1 STUDY BACKGROUND

Gastric and esophageal cancers account for approximately 10% of cancers diagnosed annually worldwide. In the United States (US), the 5-year survival remains poor, at approximately 30% for gastric cancer and 18% for esophageal cancer. In the advanced setting, platinum agents (oxaliplatin and cisplatin) and fluoropyrimidines (5-fluorouracil, capecitabine) are generally employed first-line, with a median overall survival of only 9 to 11 months in the US and Europe [Cunningham et al., 2008]. Therefore, new treatment strategies are in high demand.

2.2 RATIONALE

Combination Checkpoint Inhibition and PARP Inhibition

Immunotherapy has shown activity in the treatment of advanced gastric and esophageal cancers. The KEYNOTE-012 study, which was a Phase 1b trial assessing the activity of the programmed cell death 1 (PD-1) inhibitor, pembrolizumab, in advanced gastric cancer showed an objective response rate (ORR) of 22% and mOS of 11.4 months [Muro et al., 2016]. The phase III trial of single agent nivolumab vs placebo in advanced gastric cancer further demonstrated an improvement in overall survival (OS) (5.3 vs 4.1 months, hazard ratio [HR], 0.63; 95% confidence interval [CI], 0.50-0.78; $p < 0.0001$) and ORR (11.2% vs 0%) [Kang et al., JCO 2017]. KEYNOTE-059 showed an ORR of 11.6% in patients with gastric and gastroesophageal junction (GEJ) cancers after at least two lines of therapy, leading to the approval of pembrolizumab in the third line setting for programmed cell death ligand 1 (PD-L1) positive gastric and GEJ adenocarcinomas [Fuchs et al., 2018]. Most recently, KEYNOTE-590 and CheckMate-649 both showed an overall survival benefit when a PD-1 inhibitor was added to 1L chemotherapy versus chemotherapy alone (12.4 mo vs 9.8 mos and 14.4 mos vs. 11.1 mos, respectively) [Kato et al, 2020, Moehler et al, 2020]. These positive findings led to FDA approvals for both nivolumab and pembrolizumab to 1L chemotherapy. There is an urgent need to develop clinical trials for gastric and esophageal cancers refractory to prior immune checkpoint inhibition.

Combination therapies with other agents to improve response are actively being investigated. Gastric cancers have been a promising target for PARP inhibition. Gastric cancer has also been with microsatellite instability (MSI) raising the possibility that this cancer type might be enriched for responders to poly ADP ribose polymerase (PARP) inhibition based therapy. An analysis of olaparib single agent activity in 14 gastric cancer cell lines demonstrated that approximately 50% were very sensitive (with IC₅₀ values <500 nM). A comparatively high

percentage of gastric tumor samples have been reported to have low *ATM* protein expression levels, between 21 and 65% in Eastern patients [Kang et al., 2008; Kim et al., 2013]. *ATM*, which is a tumor suppressor gene found on human chromosome 11q22-23 encodes a large protein kinase that is important in the cellular response to DNA double-strand breaks, inducing cell cycle arrest via p53 and facilitating repair through phosphorylation of numerous downstream targets [Weber et al., 2015]. A phase II trial of *ATM* low advanced gastric cancer patients reported a significant improvement in survival with olaparib plus paclitaxel vs paclitaxel alone [Bang et al., 2015]. These data provide the first clinical data to support enhanced olaparib activity in a non-*BRCA* DNA repair deficient tumor background. This survival advantage was not appreciated in the phase III GOLD trial, but the trial may not have been sufficiently enriched for patients with homologous recombination deficient tumors for whom PARP inhibition was most likely to benefit [Bang et al., 2016].

Combination therapy is currently under investigation to determine if immune priming or other immunomodulation can be induced to allow for a response to checkpoint blockade. PARP inhibitors may stimulate antigen presentation via increased T cell cytotoxic activity. In preclinical models, PARP inhibition with anti-PD-L1 therapy compared with each agent alone significantly increased the therapeutic efficacy, and PARP inhibitors combined with anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) therapy in *BRCA1*-deficient ovarian tumor models induced long-term survival [Jiao et al., 2017; Higuchi et al., 2015]. Multiple combinations of PARP inhibitors with immunotherapy are currently being studied, including a phase II study of durvalumab with olaparib in metastatic castrate-resistant prostate cancer (GU ASCO 2017: demonstrated tolerability and partial responses in 4 of 6 heavily pretreated patients), and a phase I/II trial of durvalumab with olaparib and/or cediranib in advanced solid tumor malignancies (ASCO 2016: demonstrated tolerability and a 67% disease control rate (DCR) in the durvalumab + olaparib arm) [Karzai et al., 2017; Lee et al., 2017]. Recently, a Phase I/II clinical trial showed that combination niraparib and pembrolizumab resulted in a 25% ORR in platinum resistant ovarian cancer, which surpasses the ORR with pembrolizumab or PARP inhibition alone (11% versus 5%) [Konstantinopoulos et al., SGO 2018].

One group that may particularly benefit from this approach are tumors with germline or somatic mutations in the homologous recombination (HR) DNA damage repair pathway – including *BRCA1/2*, *PALB2*, *ATM*, and the *FANC* family of genes. *BRCA1/2* mutated ovarian tumors contain more tumor-infiltrating lymphocytes as compared to HR proficient ovarian tumors, and a significantly higher neoantigen load has been appreciated in *BRCA1/2* mutated and otherwise HR-deficient ovarian cancers [Strickland et al., 2015; Strickland et al., 2016].

Combining Radiation, PARP inhibition and PD-1 Inhibition

Ionizing radiation (IR) is a promising combination strategy to augment the action of combination

PARP and PD-1 inhibition.

To support use of combination PARP inhibition and radiation, IR has been shown to activate and recruit PARP1 to damaged DNA. In pre-clinical models, combination radiotherapy and PARP inhibition inhibited tumor growth in murine lung cancer models significantly longer than radiotherapy or PARPi alone [Albert et al., 2007]. Evidence for sequencing PD-1 based therapy after combination PARP inhibition and IR is seen in colorectal cancer cell lines (CT26 and MC38), in which PARP inhibition with veliparib and IR increased tumor surface PD-L1 localization more than IR alone [Seyedin et al., 2020]. Sequencing of PD-1 inhibition after local tumor irradiation has been shown to induce abscopal antitumor immune responses in addition to expansion of polyfunctional intratumoral CD8+ T cells, a decrease in intratumoral dysfunctional CD8+ T cells, and expansion of reprogrammable CD8+ T cells [Wei et al, 2021]. Tumor antigen expression (i.e. MHC-1 surface localization) was significantly higher when colorectal cancer cell lines were treated with veliparib and radiation doses of 4 and 8 Gy compared to control ($p < 0.05$ for both). In murine models, veliparib and sub-ablative high-dose IR followed by anti-PD-1 therapy produced complete responses (4/9, 44%) in CT26 and MC38 flank tumors. In comparison, treatment with IR and PD-1 inhibition trended to prolong tumor growth delay longer than IR alone and resulted in fewer complete tumor responses (2/7, 28.5%) [Seyedin et al., 2020].

Pre-clinical work found that when comparing subablative hypofractionated radiation versus ablative single fraction SBRT, a dose of >10 to 12Gy resulted in increased immunosuppression due to upregulation of DNA exonuclease Trex1, which leads to decreased production of cyclic GMP-AMP and subsequently, decreased immune gene transcription [Vanpouille-Box C et al., 2017]. In addition, doses >10 Gy caused vascular damage which led to reduced effector T-cell recruitment to the tumor [Park HJ et al., 2012]. In contrast, a moderate subablative dose of 8 Gy x 3 has been shown to increase tumor immunogenicity and increase of abscopal effect [Ko EC et al., 2018; Park HJ et al., 2012]. A phase 1 dose-escalation study evaluated five different dose levels of SBRT with neoadjuvant chemotherapy in patients with HER2 negative breast cancer. The pathological complete response rate (pCR) was 36%, and none were seen in the first 2 dose levels and did not increase with dose escalation beyond dose level 3 (25.5 Gy over 3 consecutive days). This study suggested that 25.5 Gy is the optimal dose for preoperative SBRT to elicit tumor responses [Bondiau PY et al., 2013]. However, the optimal dosing with radiation and PARP inhibitor combination remains a question. There is an ongoing study in triple negative breast cancer evaluating radiation dosing and scheduling in this range with PARP and PD-1 inhibition (NCT NCT04837209).

We therefore propose a trial combining induction ionizing radiation and PARP inhibition to prime tumors for improved response to combined PARP and PD-1 inhibition in advanced gastric and GEJ adenocarcinomas (HR proficient and HR deficient) after at least one line of therapy.

The objective is to produce an abscopal effect which will be measured by the ORR of the unirradiated disease sites. The immunomodulatory role of PARP inhibition and IR followed combined PD-1 and PARP inhibition remains an unanswered question.

To that end, we will obtain serial biopsies for exploratory immunomodulation research including but not limited to the following: changes in intratumoral T cell clonality and inflammatory gene signature; changes in immune subsets, tumor antigen specific T cells, and inflammatory gene signatures in peripheral blood mononuclear cells (PBMCs); and changes in cytokine activity in plasma/serum.

2.3 PEMBROLIZUMAB BACKGROUND

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD1. 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.

Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, 2010]. 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 Tcells/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 [Dudley et al., 2005; Hunder et al., 2008].

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 Tcells 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 CTLA-4 that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PDL1 and/or PD-L2) [Greenwald et al., 2005; Okazaki et al., 2001].

The structure of murine PD-1 has been resolved [Zhang et al., 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable-type (IgVtype)

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 (CD3 ζ), protein kinase C-theta (PKC θ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki et al., 2001; Chemnitz et al., 2004; Sheppard et al., 2004; and Riley, 2009]. The mechanism by which PD-1 down-modulates Tcell 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]. As a consequence the PD1/PD-L1 pathway is an attractive target for therapeutic intervention in gastric and gastroesophageal junction adenocarcinomas.

2.4 OLAPARIB BACKGROUND

Olaparib (AZD2281, KU-0059436) is a potent Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation (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. 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. 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. BRCA1 and BRCA2 defective tumors are intrinsically sensitive to PARP inhibitors, both in animal models [Hay et al., 2009; Rottenberg et al., 2008] and in the clinic [Fong et al., 2009]. The mechanism of action for olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair [Helleday, 2011; Murai et al., 2012]. Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by HR repair. Olaparib has been shown to inhibit selected tumor cell lines in vitro and in xenograft and primary explant models as well as in genetic BRCA knock-out models, either as a stand-alone treatment or in combination with established chemotherapies. Patients will be treated with olaparib 200 mg q12hrs each day of a 21-day cycle in tablet formulation until disease progression, unacceptable toxicity, withdrawal of

consent or death. Tablet formation is preferred over capsule formulation based on recent work demonstrating equivalent efficacy with a reduced pill burden [Mateo et al, 2016].

Pre-clinical experience

The pre-clinical experience is fully described in the current version of the olaparib Investigator's Brochure.

Toxicology and safety pharmacology summary

The toxicology and safety pharmacology is fully described in the current version of the olaparib Investigator's Brochure.

2.5 RISK/BENEFIT ASSESSMENT

2.5.1 KNOWN POTENTIAL RISKS

Risks of radiation include the following acute toxicities:

- Generalized fatigue, malaise, anorexia
- Skin changes
- Site specific toxicities include difficulty swallowing, shortness of breath, loss of appetite, nausea/vomiting, bowel cramping, loose stool or diarrhea.
- Late toxicities of GI ulceration or obstruction, esophageal stricture, pneumonitis, renal toxicity, liver toxicity, bone weakening.

Risks of olaparib include the following acute toxicities:

- Generalized effect on energy level
- Hematological toxicity (neutropenia, leukopenia, anemia, thrombocytopenia)
- Gastrointestinal toxicity (nausea, vomiting, diarrhea)
- Pulmonary toxicity (dyspnea, infection)
- Renal toxicity

Risks of pembrolizumab include the following toxicities:

- Pneumonitis
- Diarrhea/Colitis
- AST/ALT elevation or increased bilirubin
- Type 1 diabetes mellitus (T2DM) or Hyperglycemia
- Hypophysitis
- Hyperthyroidism
- Hypothyroidism
- Nephritis and renal dysfunction

- Myocarditis

These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously.

2.5.2 KNOWN POTENTIAL BENEFITS

The potential benefit of the regimen is to improve treatment efficacy in refractory gastric and gastroesophageal junction adenocarcinomas with a non-chemotherapy option. Gastric/GEJ adenocarcinomas that harbor homologous recombination deficiency do not have any approved

2.5.3 ASSESSMENT OF POTENTIAL BENEFITS

therapies. This treatment could potentially address a biomarker driven tumor.

The risks to participants are reasonable in relation to the anticipated benefits to participants and/or society, and in relation to the importance of the knowledge that may reasonably be expected to result, thereby falling in favor of performing the study:

- **To Participant:** Benefit of possible increased and/or sustained disease response.
- **To Society:** Improved understanding of the efficacy and mechanism of action of this treatment regimen in gastric/GEJ adenocarcinoma.
- **Justify the importance of the knowledge gained:** The knowledge gained will help determine future clinical trial directions in homologous recombination deficient and proficient gastric/GEJ adenocarcinoma.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To assess the anti-tumor efficacy of combined therapy as determined by measurement of objective response rate (ORR)	Objective Response Rate (ORR per RECIST 1.1) of unirradiated tumors	Objective Response Rate is an established clinical endpoint for gastric and gastroesophageal junction adenocarcinomas. ORR of unirradiated tumors is to evaluate for an abscopal effect.
Secondary		
To assess the anti-tumor efficacy of combined therapy	Overall Survival (OS) from the initiation of therapy to the	Although the study is not designed or powered to

<p>as determined by measurement of overall survival (OS), progression free survival (PFS), duration of response (DOR) and disease control rate (DCR) as a total cohort and HRD versus HR proficient.</p> <p>To evaluate the safety and tolerability of radiotherapy added to Olaparib.</p>	<p>date of death or to the date of last follow-up.</p> <p>Progression Free Survival (PFS) from the initiation of therapy to the date of progression or to the date of last follow-up.</p> <p>Duration of response (DoR) defined as the time from documentation of tumor response to disease progression.</p> <p>Disease control rate (DCR) defined as the sum of partial (PR), complete response (CR) and SD.</p> <p>Treatment-emergent adverse events (AEs), serious adverse events (SAEs),</p>	<p>compare overall survival and progression free survival with other regimens, OS and PFS will provide preliminary data regarding efficacy of the regimen. DOR and DCR will also provide preliminary efficacy data.</p> <p>Toxicity will be assessed according to NCI CTCAE v5.0</p>
Tertiary/Exploratory		
<p>To define the effect of HRD on combination SBRT, olaparib, and pembrolizumab on immunomodulation as measured by immune cell infiltration and activation in plasma/serum assays and tissue.</p>	<p>Immune changes in tumor tissue and plasma at baseline compared to after combination SBRT/olaparaib and after olaparib/pembrolizumab</p> <p>Assess response based on HRD status, PD-L1 expression, MMR/MSI, and TMB in tumor</p> <p>Changes in cytokines, ctDNA in plasma/serum</p> <p>Abscopal effect based on irradiated disease site</p>	<p>This endpoint will demonstrate exploratory data to evaluate key immune and DNA Damage Response and Repair pathway biomarkers that may predict for treatment response.</p>

4 STUDY DESIGN

4.1 OVERALL DESIGN

This study is an open-label, phase II study with a safety lead-in to assess the response rate of induction olaparib and stereotactic beam radiotherapy (SBRT) followed by combination olaparib/pembrolizumab in patients with metastatic gastric and GEJ cancers after at least one of therapy. The secondary endpoint is combined therapy in tumors with evidence of both homologous recombination deficiency (by germline or somatic Next-generation DNA sequencing [NGS]), as well as homologous recombination proficiency. Exploratory endpoints will assess the impact of homologous recombination deficiency and proficiency on response to radiation, PARP inhibition and PD-1 blockade.

4.2 JUSTIFICATION FOR DOSE

4.2.1 PEMBROLIZUMAB

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 7.5fold 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 all pembrolizumab protocols.

4.2.2 OLAPARIB

4.2.2.1 COMBINATION WITH RADIATION

Pre-clinical work found that when comparing subablative hypofractionated radiation versus ablative single fraction SBRT, a dose of >10 to 12Gy resulted in increased immunosuppression due to upregulation of DNA exonuclease Trex1, which leads to decreased production of cyclic GMP-AMP and subsequently, decreased immune gene transcription [Vanpouille-Box C et al., 2017]. In addition, doses >10 Gy caused vascular damage which led to reduced effector T-cell recruitment to the tumor [Park HJ et al., 2012]. In contrast, a moderate subablative dose of 8 Gy x 3 has been shown to increase tumor immunogenicity and increase of abscopal effect [Ko EC et al., 2018; Park HJ et al., 2012]. A phase 1 dose-escalation study evaluated five different dose levels of SBRT with neoadjuvant chemotherapy in patients with HER2 negative breast cancer. The pathological complete response rate (pCR) was 36%, and none were seen in the first 2 dose levels and did not increase with dose escalation beyond dose level 3 (25.5 Gy over 3 consecutive days). This study suggested that 25.5 Gy is the optimal dose for preoperative SBRT to elicit tumor responses[Bondiau PY et al., 2013].

4.2.2.2 COMBINATION WITH PEMBROLIZUMAB

A phase I study evaluating durvalumab with olaparib in recurrent ovarian, cervical and triple negative breast cancers determined the RP2D as olaparib 300mg twice daily [Lee et al., 2017]

4.3 RADIATION DETAILS

The treating radiation oncologist will select 1 site of disease (metastatic or primary) to target with radiation. Sites of disease planned to be biopsied should not be radiated.

Guidance on choosing site for irradiation:

- A single site (metastasis or primary lesion) will be chosen for irradiation
- Disease site planned to be biopsied should not be radiated
- There should be a measurable lesion apart from the irradiated lesion
- A disease site causing clinical symptoms that would benefit from palliative radiation should be prioritized (e.g. pain, obstruction, bleeding, etc). If there are no areas causing significant clinical symptoms, radiation oncology can choose the disease site for radiation per their discretion.

Simulation and treatment may be performed with the patient in the supine or prone position with appropriate immobilization devices for the specific tumor location at the discretion of the treating radiation oncologist. The CT should extend cephalad ≥ 5 cm above the tumor to be treated, and ≥ 5 cm caudad. External skin localizing marks, which may include permanent tattoos, are recommended for radiation daily localization and set-up accuracy. The radiation oncologist will contour a gross tumor volume (GTV) and internal target volume (ITV) when 4D CT simulation is obtained. No additional expansion will be added for a clinical target volume (CTV) in most cases. GTV (or ITV) to planning target volume (PTV) expansion of 3-7 mm will be applied and can be modified around organs at risk at the discretion of the treating radiation oncologist. Dose should be prescribed to the PTV. Greater than 95% of the PTV should be covered by greater than 95% of the prescription dose, but it is allowable to compromise PTV coverage to meet OAR constraints. Maximum point dose within the PTV may up to 130% of the prescribed dose, but effort should be made to minimize hot spots $>110\%$ of the prescribed dose that fall outside the GTV. Intratumoral fiducial markers and/or respiratory gating techniques are not required, but can be utilized at the discretion of the treating radiation oncologist, when determined to be appropriate and technically feasible. 3D conformal or Intensity Modulated Radiation Therapy (IMRT) techniques are acceptable for treatment planning, although IMRT is preferred. Volumetric Modulated Arc Therapy (VMAT) and static IMRT are both acceptable. Image guidance modality and frequency is at the discretion of the treating radiation oncologist.

All patients will be treated with 5 Gy per fraction for a total of 5 fractions totaling 25 Gy. Radiation treatment will be delivered daily and to be completed within 2 weeks in case course falls over weekend or there are other logistical issues (i.e. machine downtime issues).

Protocol radiation dosing regimen is outlined in the table below:

Regimen [†]	Dose per fraction	Number of fractions	Total dose	EQD2 ₁₀ /EQD2 ₃
A	5 Gy	5	25 Gy	31.25/40

Organ at risk dose constraints are provided below and all provided constraints must be met. Constraints have been adapted from institutional dose constraints, the widely accepted and utilized Timmerman dose constraints, and appropriate clinical studies when applicable. Most constraints have been adapted to be more conservative. No constraints have been made more lenient for this study.

5-fraction OAR constraints

OAR	Volumetric constraint(s) (if applicable)	Max point dose (if applicable)
Brachial plexus	-	26.0 Gy
Spinal cord*	V15<0.35 cc	22.5 Gy
Cauda equina	V21<5 cc	25.5 Gy
Esophagus**	V17.7<5 cc	25.2 Gy
Heart	V24<15 cc	30.0 Gy
Great vessels	V39<10 cc	45.0 Gy
Large airways	V25.8<5 cc	30.0 Gy
Chest wall	V30<30 cc	-
Lung (ipsilateral-ITV)	Mean<9 Gy	-
Lung (total-ITV)	V11<35%	-
Liver	At least 700 cc < 12 Gy	-
Stomach	V30<1 cc	33.0 Gy
Duodenum	V30<1 cc V20<5 cc	33.0 Gy
Small bowel (bowel bag)	V20<10 cc	27.0 Gy
Large bowel and rectum	V20<5 cc	30.0 Gy
Kidney (each hilum)	V19.5<15 cc	-
Kidney (bilateral cortex)	V14.7<1/3 volume	-
Bladder	V17<15 cc	33.0 Gy
Femoral heads	V24<10 cc	-

* For spine SBRT, MR or CT-myelogram imaging is required to define the cord for OAR avoidance.

**Avoid circumferential irradiation

4.4 END OF STUDY DEFINITION

The study will be completed once 26 patients are evaluable for the primary endpoint, and the last patient enrolled has been evaluated for objective response rate (ORR). Evaluable is defined as patients who have received at least 1 dose of the treatment, SBRT + Olaparib and Olaparib + Pembrolizumab, and have had baseline imaging.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

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

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision to sign and date the consent form.
2. Participant must be ≥ 18 years of age
3. Histologically confirmed metastatic gastric or GEJ adenocarcinoma that is amenable to biopsy either at primary or metastatic site.
4. Patient must consent at initiation of study to serial tumor biopsies during study.
Irradiated lesions will not be considered for biopsy. For baseline biopsy, available archived tumor tissue of a metastatic tumor collected up to 28 days prior to registration is acceptable. If, after patient consent, the tumor is deemed inaccessible, the biopsy is not in the subject's best interest per investigator discretion, or the patient refuses biopsy during course of the study, patients will be allowed to remain on study.
5. Participant must have a primary tumor or a single metastatic site amenable to radiation in: the stomach, esophagus, liver, lungs, pancreas, thoracic/abdominal LNs, or soft tissues.
Of note - sites of disease planned to be biopsied should not be radiated.
6. Participant must have at least one radiographically-confirmed index lesion that will not undergo RT and is measurable based on RECIST v1.1.
7. Homologous recombination deficiency cohort: pre-identified presence of somatic or germline deleterious mutation, as determined by NGS only, in at least one gene critical to DNA repair through homologous recombination, including but not limited to: *ARID1A*, *ATM*, *ATR*, *MRE11A*, *NBN*, *PTEN*, *RAD50/51/51B*, *BARD1*, *BLM*, *BRCA1*, *BRCA2*, *BRIP1*, *FANCA/C/D2/E/F/G/L*, *PALB2*, *WRN*, *CHEK2*, *CHEK1*, *BAP1*, *FAM175A*, *SLX4*, *MLL2* or *XRCC*.
 - a. All patients must undergo NGS testing in a CLIA certified, CAP tested and bioinformatics-validated testing lab PRIOR to protocol treatment, to determine

which cohort they are eligible for – HRD versus HR proficient. The testing may have been done at any time prior to enrollment.

- b. For patients within whom a deleterious mutation in the homologous recombination pathway is found, the determination of a deleterious mutation must be supported in the documentation included in the testing, and should include clinical, or pre-clinical literature to support the finding that a specific mutation results in impaired function of the gene, and thus impaired DNA repair through homologous recombination. Variants of unknown significance will not be eligible.
 - c. Patients with germline deleterious mutations may have been identified at any time point prior to inclusion in the protocol and do NOT need to have this genetic testing repeated regardless of time frame and intervening therapy.
8. Participants must have received at least one line of therapy including a fluoropyrimidine and platinum drug. For participants with HER2+ tumors, they must have received trastuzumab. Adjuvant therapy does not count toward first-line therapy unless patient recurs within 6 months of completion.
 9. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
 10. Participants must have the ability to swallow whole pills and liquids at the Screening Visit and, in the investigator's judgement, for the duration of the study.
 11. Have adequate organ function as defined in Table 1

Table 1: Adequate Organ Function Laboratory Values:

System:	Laboratory Value:
Hematological	
Absolute neutrophil count (ANC)	$\geq 1500/\mu\text{L}$
Platelets	$\geq 100\,000/\mu\text{L}$
Hemoglobin	$\geq 9.0\text{ g/dL}$ or $\geq 5.6\text{ mmol/L}^a$
Renal	
Creatinine <u>OR</u> Measured or calculated ^b creatinine clearance (GFR can also be used in place of creatinine or CrCl)	$\leq 1.5 \times \text{ULN}$ <u>OR</u> $\geq 30\text{ mL/min}$ for participant with creatinine levels $> 1.5 \times \text{institutional ULN}$
Hepatic	
Total bilirubin	$\leq 1.5 \times \text{ULN}$ OR direct bilirubin $\leq \text{ULN}$ for participants with total bilirubin levels $> 1.5 \times \text{ULN}$
AST (SGOT) and ALT (SGPT)	$\leq 2.5 \times \text{ULN}$ ($\leq 5 \times \text{ULN}$ for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	$\leq 1.5 \times \text{ULN}$ unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

^a Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

^b Creatinine clearance (CrCl) should be calculated per institutional standard.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

12. Participant receiving corticosteroids, for reasons other than radiation related toxicities, may continue as long as their dose is stable (meaning no increase or on tapering dose) for least 4 weeks prior to initiating protocol therapy.
13. Female participants are eligible if they are: not pregnant (within 28 days prior to start of study treatment - see Appendix 3), not breastfeeding, and at least one of the following conditions applies:
 - a.) Not a woman of childbearing potential (WOCBP) as defined in Appendix 3
 - OR
 - b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least 120 days after the last dose of study treatment.
14. Male participants must agree to use a contraception as detailed in Appendix 3 of this protocol during the treatment period and for at least 120 days after the last dose of study treatment and refrain from donating sperm during this period.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Has received prior systemic anti-cancer therapy within 4 weeks or 5 half-lives (whichever is shorter) and has not recovered to grade ≤ 1 or baseline from AE associated with anticancer therapy prior to allocation.
 - a. Note: Participants must have recovered from all AEs due to previous therapies to \leq Grade 1 or baseline. Participants with \leq Grade 2 neuropathy may be eligible.
 - b. Note: If participant received major surgery within 4 weeks, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.
2. Has received prior radiotherapy within 2 weeks of start of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids specifically for radiation toxicities, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to non-CNS disease.
3. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella,

varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed. Note: Vaccines for SARS CoV-2 will be permitted before and during the course of study.

4. Is currently participating in, or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment. Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.
5. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.
6. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded
7. Has known active CNS metastases and/or carcinomatous meningitis that requires ongoing treatment or are found to be progressing. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e. without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.
8. Has severe hypersensitivity (\geq Grade 3) to pembrolizumab or olaparib and/or any of its excipients.
9. Participant must not have impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
10. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
11. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
12. Has an active infection requiring systemic therapy.
13. Has a known history of Human Immunodeficiency Virus (HIV).

14. Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or 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.
15. Has active tuberculosis. Note: no testing for tuberculosis is required unless mandated by local health authority.
16. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's ability to cooperate with the requirements of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
- .
17. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of trial treatment.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 MEALS AND DIETARY RESTRICTIONS

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting. It is not recommended to consume grapefruit juice while on olaparib therapy.

5.3.2 CONTRACEPTION

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

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

5.3.3 PREGNANCY

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab and olaparib, it will be recorded as an AE and the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck within 2 working days if the outcome is a serious adverse

experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to Merck as an AE and followed as described in Section 8.4.7.

5.3.4 USE IN NURSING WOMEN

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

5.4 SCREEN FAILURES

Subject may be re-screened for eligibility with documented approval from the PI.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The volume of patients currently seen at the recruiting sites is sufficient to support required study volume. Physicians in medical oncology, radiation oncology, and surgery at each study site will be contacted via email to promote awareness of study recruitment.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

Potential trial patients will be pre-identified at participating centers into two cohorts:

- (1) germline or somatic deleterious mutation involving genes critical to the DNA repair through homologous recombination deficiency (HRD), as demonstrated by Next-generation DNA sequencing in a CLIA certified, CAP tested and bioinformatics-validated testing lab prior to enrollment. This could include, but not be limited to one of the following genes: *ARID1A*, *ATM*, *ATR*, *MRE11A*, *NBN*, *PTEN*, *RAD50/51/51B*, *BARD1*, *BLM*, *BRCA1*, *BRCA2*, *BRIP1*, *FANCA/C/D2/E/F/G/L*, *PALB2*, *WRN*, *CHEK2*, *CHEK1*, *BAP1*, *FAM175A*, *SLX4*, *MLL2* or *XRCC* and
- (2) no evidence of HR deficiency.

If a pathogenic mutation in the HR pathway is confirmed and not listed above, the study PI will determine if the patient is eligible based on available clinical or pre-clinical literature.

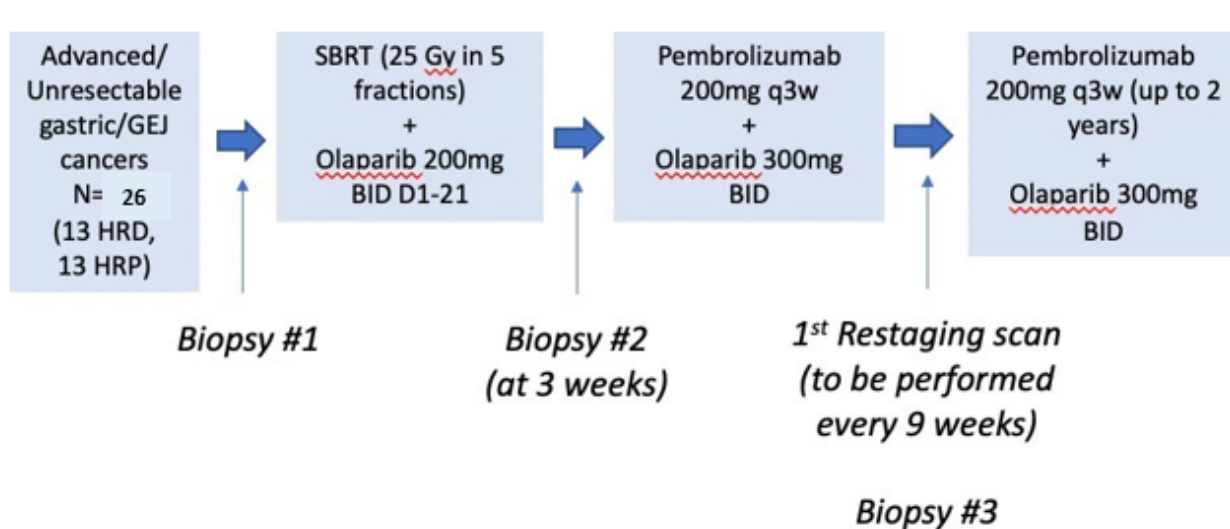
The determination of a deleterious mutation must be supported in the documentation included in the testing, and should include clinical, or pre-clinical literature to support the finding that a

specific mutation results in impaired function of the gene, and thus impaired DNA repair through homologous recombination. Mutations and deletions will be evaluated against the Human Gene Mutation database and other online databases (ClinVar, Breast Cancer Information Core, PubMed) to evaluate the functional relevance, and to make a determination on the likelihood of the mutation resulting in defective homologous recombination-dependent DNA repair. Variants of unknown significance will not be eligible.

The testing may have been done at any time prior to enrollment.

Starting C1D1, olaparib 200mg PO BID will be given concurrently with radiation (25 Gy in 5 fractions). Each cycle is 21 days. Starting on C2D1, Pembrolizumab 200mg IV will be administered on Day 1 every 3 weeks with olaparib 300mg PO BID (12 hours apart). There is no specification regarding the sequence in which the drugs should be given on days when they are administered together. For Cycle 1, patients will be evaluated weekly for 3 weeks with blood tests, clinic visits, and physical exams. Starting Cycle 2, patient will be evaluated every 3 weeks on Day 1 of each cycle.

Patients will undergo serial tumor biopsies as depicted in the Trial Diagram below. Restaging will occur every 9 weeks. If at first restaging there is no evidence of progressive disease (PD), as determined by RECIST v1.1 and immune-related RECIST (irRECIST) criteria, and the patient is tolerating therapy, then patient will continue with study therapy, with clinic visits and lab work on Day 1 of future cycles and restaging imaging every 9 weeks. Patients will continue to remain on study as long as there is no evidence of PD (according to RECIST v1.1 and irRECIST criteria) and the therapy is adequately tolerated. For patients who demonstrate a response beyond 2 years of trial therapy, they will continue with olaparib treatment alone.



Serial tumor biopsies and blood samples will be taken to assess immune changes in tumor tissue and plasma at baseline compared to after combination SBRT/olaparib and after olaparib/pembrolizumab, assess response based on HRD status, PD-L1 expression, MMR/MSI, and TMB in tumor, changes in cytokines, ctDNA in plasma/serum

Patients will undergo the treatment and biopsy schedule as detailed above. However, in the event that tumor is inaccessible, the biopsy is not in the subject's best interest, or the patient refuses biopsy during course of the study, this will be documented and patients will be allowed to remain on study. Additionally, patients will continue to remain on study as long as there is no evidence of PD (according to RECIST v1.1 criteria and irRECIST) and the therapy is adequately tolerated. Interim analyses to assess secondary endpoints of OS and PFS will be scheduled to occur at 12 months and 24 months. For patients who demonstrate a response beyond 2 years of trial therapy, they will continue with olaparib treatment alone.

We plan to enroll 26 patients (13 HR deficient, 13 HR proficient).

6.1.1 SAFETY LEAD-IN

Safety Lead-In

During the safety lead-in portion of the study, 6 evaluable patients will be enrolled regardless of HR status, to ensure safety of combination radiation and olaparib in gastric/GEJ adenocarcinoma. Patients will be enrolled in a staggered fashion with 10 days minimum between each patient enrolled. The goal of the safety evaluation for the combination is to determine if there are any increased or unexpected toxicities due to combination of agents that would not be expected with either agent alone. Patients in the safety lead-in portion will be included in total planned enrollment.

DLTs:

The DLT evaluation period will be defined as the period from the first dose of combination radiation and olaparib to Cycle 2 Day 21.

A dose-limiting toxicity (DLT) is defined as a drug-related (or at least possibly related) clinically significant adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications and meeting CTCAE Grade 3 or 4.

If there are no dose limited toxicities, as defined above, we will proceed with the remaining portion of the trial. If $>2/6$ patients experience a DLT attributable to the investigational agents, we will not proceed with the rest of the study.

Once determined that the combination of radiation and olaparib is safe, an additional 20 patients will be enrolled with a planned total enrollment of 13 patients each in the HR deficient and proficient cohorts, respectively. Based on the estimate that 35% of gastric and GEJ cancers will exhibit HR deficiency, we anticipate that the HR proficient cohort will accrue more rapidly than the HR deficient cohort.

6.1.2 DOSING AND ADMINISTRATION

The treatment to be used in this trial is outlined below:

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle (excluding Cycle 1)	Experimental
Olaparib*	200mg PO BID	daily	PO	Daily during Radiation D1-21	Experimental
Olaparib*	300mg PO BID	daily	PO	Daily Post-Radiation	Experimental
SBRT	25Gy in 5 fractions	daily M-F	N/A	5 days starting Day 1	Experimental

*During radiation portion, Olaparib dose will be 200mg PO BID. When combined with pembrolizumab, Olaparib dose will be 300mg PO BID.

Trial treatment should begin on the day of treatment (Combination SBRT and Olaparib)

6.1.3 TIMING OF DOSE ADMINISTRATION

6.1.3.1 OLAPARIB

Trial treatment with olaparib should be administered starting on Day 1 of a 21-day cycle. Olaparib tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each dosing container will contain sufficient medication for at least 21 days plus overage. Olaparib will be dispensed to patients on Day 1 and every 21 days thereafter until the patient completes the study, withdraws from the study, or closure of the study. Study treatment is available as a green film-coated tablet containing 100mg or 150mg of olaparib. Patients will be administered olaparib orally twice daily at 200 mg BID concurrently with radiation and 300mg continuously when combined with pembrolizumab. Olaparib tablets should be taken at the same time each day, approximately 12 hours apart with one glass of water. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be

taken with or without food. Trial treatment may be administered up to 7 days before or after the scheduled Day 1 of each cycle (after Cycle 1) due to administrative reasons.

If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (e.g., because of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

6.1.3.2 PEMBROLIZUMAB

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks starting with Cycle 2. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

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

All trial treatments will be administered on an outpatient basis.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

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

Pembrolizumab will be provided by Merck as summarized under 6.2.2.

Olaparib will be provided by Astrazeneca as summarized under 6.2.2. However, shipments will be handled by Merck.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/ 4mL	Solution for Injection
Olaparib 200mg and 300mg*	Oral tablet

*Separate doses for different treatment periods. Please refer to Table 6.1.2 for more information.

Supplies will be labeled in accordance with regulatory requirements.

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

6.2.3 PRODUCT STORAGE AND STABILITY

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

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

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

6.2.4 PREPARATION

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

6.3 STUDY INTERVENTION COMPLIANCE

Since pembrolizumab is given intravenously, and patients must be present at the treatment machine for all radiotherapy, compliance will be confirmed by documentation of pembrolizumab administered as per medical oncology, and radiotherapy treatments documented in the record and verify system as per standard of care.

Drug diaries will be collected at each cycle to confirm Olaparib compliance. Additionally, patients should bring any bottles dispensed for the previous cycle with them to each clinic visit so that treatment compliance can be assessed.

6.4 PROHIBITED THERAPY

6.4.1 PEMBROLIZUMAB

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

Antineoplastic systemic chemotherapy or biological therapy

- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab or olaparib
- Live vaccines within 30 days prior to the first dose of study treatment, while participating in the study, and for 30 days after the last dose of study intervention. 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.
- Vaccines for SARS CoV-2 will be permitted
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of glucocorticoids is allowed as long as the dose is stable (meaning no increase or on tapering dose) for at least 4 weeks prior to initiating protocol therapy. Other uses may be approved after consultation with the Sponsor-Investigator.

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

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

There are no prohibited therapies during the Post-Treatment Follow-up Phase. If a new therapy is started by participants in the post-treatment follow-up phase they will only be followed for survival.

6.4.2 OLAPARIB

General Concomitant Medication and Supportive Care Guidelines

There is a potential for interaction of olaparib with other concomitantly administered drugs, but only concomitant medications related to AE or SAE treatment, and other medical conditions deemed necessary by the PI will be recorded on the case report form (CRF). The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team

should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of.

The use of any natural/herbal products or other traditional remedies should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the case report form (CRF) if related to AE or SAE treatment, and other medical conditions deemed necessary by the PI.

Medications that may NOT be administered

No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy (Hormone replacement therapy (HRT) is acceptable), radiotherapy, biological therapy or other novel agent) is to be permitted while the patient is receiving study medication. Live virus and live bacterial vaccines should not be administered 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.

Restricted concomitant medications

Strong or Moderate CYP3A inhibitors

- Known strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) should not be taken with olaparib. If there is no suitable alternative concomitant medication then the dose of olaparib 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 100mg bd for the duration of concomitant therapy with the strong inhibitor and for 5 half lives afterwards.
- Moderate CYP3A inhibitors - reduce the dose of olaparib to 150mg bd 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 or Moderate CYP3A inducers

- Strong (e.g., phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort) and moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil) of CYP3A 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 or inhibitor then they must be monitored carefully for any change in efficacy of olaparib.

P-gp inhibitors

It is possible that co-administration of P-gp inhibitors (eg amiodarone, azithromycin) may increase exposure to olaparib. Caution should therefore be observed.

Effect of olaparib on other drugs

Based on limited in vitro data, olaparib may increase the exposure to substrates of CYP3A4, P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K.

Based on limited in vitro data, olaparib may reduce the exposure to substrates of CYP3A4, CYP1A2, 2B6, 2C9, 2C19 and P-gp. The efficacy of hormonal contraceptives may be reduced if co administered with olaparib. Caution should therefore be observed if substrates of these isoenzymes or transporter proteins are co-administered.

Examples of substrates include:

- CYP3A4 – hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine
- CYP1A2 – duloxetine, melatonin
- CYP2B6 – bupropion, efavirenz
- CYP2C9 – warfarin
- CYP2C19 - lansoprazole, omeprazole, S-mephenytoin
- P-gp - simvastatin, pravastatin, digoxin, dabigatran, colchicine
- OATP1B1 - bosentan, glibenclamide, repaglinide, statins and valsartan
- OCT1, MATE1, MATE2K – metformin
- OCT2 - serum creatinine
- OAT3 -furosemide, methotrexate

Anticoagulant Therapy

Patients who are taking warfarin may participate in this trial; however, it is recommended as standard of care 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, low molecular weight heparin and novel oral anticoagulants (NOACs) are permitted.

Grapefruit juice

It is not recommended to consume grapefruit juice while on olaparib therapy

6.5 CONCOMITANT THERAPY

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 participants' primary physician.

6.5.1 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. Only concomitant medications related to AE or SAE treatment, and other medical conditions deemed necessary by the PI will be recorded on the case report form (CRF). If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. If a participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. All concomitant medications administered during SAEs or AESIs are to be recorded. AESIs are defined in Section 8.4.

6.5.1.1 PRIOR MEDICATIONS

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

6.5.2 RESCUE MEDICINE

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs associated with study intervention are outlined along with the dose modification guidelines in Appendix 6, Table 10. 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 or olaparib.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab or olaparib, the Investigator does not need to follow the treatment guidance. Refer to Appendix 6, Table 10 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.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION (STOPPING RULES)

The Sponsor-Investigator has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Quality or quantity of data recording is inaccurate or incomplete
- Poor adherence to protocol and regulatory requirements
- Plans to modify or discontinue the development of the study drug

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

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM STUDY

Participants are free to withdraw from participation in the study at any time upon request.

In addition, the investigator has the right to withdraw a patient from the study at any time should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 8.1.4.1.

A participant must be discontinued from study treatment but continue to be monitored in the study and moved to survival follow-up for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment
- Confirmed radiographic disease progression outlined in Section 8.1.2.6
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment

Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (excluding carcinoma in situ of the bladder) who have undergone potentially curative resection do not have to discontinue study intervention.

- Unacceptable adverse experiences as described in Appendix 5 and Appendix 6.
- The participant has a medical condition or personal circumstance which, in the opinion of the treating investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- Sponsor-Investigator determines it is in the best interest of the patient
- Patient non-compliance with the study treatment or procedure as determined by the treating investigator
- The participant has a confirmed positive serum pregnancy test
- Recurrent Grade 2 pneumonitis
- Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving 2 cycles of the combination including 2 doses of pembrolizumab and at least 80% of the planned doses of olaparib and pembrolizumab beyond the date when the initial CR was declared. These participants may be eligible for second course treatment described in Appendix 7.
- Administrative reasons

Every effort should be made to obtain information on the primary reason for withdrawal from the study or study drug discontinuation, and should be documented in the appropriate eCRF.

7.3 LOST TO FOLLOW-UP

A subject 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 staff. The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- Site will attempt to contact the subject and reschedule the missed visit, as well as advise subject on importance of maintaining assigned visit schedule.
- Before a subject is deemed lost to follow-up, the delegated study staff will make every effort to regain contact with the subject with 3 required contact attempts. These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, he or she will be considered lost to follow up and withdrawn from the study. No additional data/survival status will be collected from then on.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 STUDY PROCEDURES

The Schedule of Events - **Section 1.3** summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

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

8.1.1 ADMINISTRATIVE PROCEDURES

8.1.1.1 INFORMED CONSENT

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

General Informed Consent

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

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

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

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

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

8.1.1.2 MEDICAL HISTORY

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

8.1.1.3 DISEASE DETAILS AND TREATMENTS

8.1.1.3.1 DISEASE DETAILS

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

8.1.1.3.2 PRIOR TREATMENT DETAILS

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

8.1.1.3.2 SUBSEQUENT ANTI-CANCER THERAPY STATUS

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

8.1.1.3.2 RESTING 12-LEAD ECG

ECGs are required within 7 days prior to starting study treatment and when clinically indicated.

Twelve-lead ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes in each case. The Investigator or designated physician will review the paper copies of each of the 12-lead ECGs on each of the study days when they are collected.

ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding, the Investigator will record it as an AE on the eCRF. The original ECG traces must be stored in the patient medical record as source data.

8.1.2 CLINICAL PROCEDURES/ASSESSMENTS

8.1.2.1 ADVERSE EVENT (AE) MONITORING

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the Schedule of Events and more frequently if clinically indicated.

Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0 (see Appendix 2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 8.4 for detailed information regarding the assessment and recording of AEs.

8.1.2.2 FULL PHYSICAL EXAM

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

8.1.2.3 DIRECTED PHYSICAL EXAM

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

8.1.2.4 VITAL SIGNS

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment, at treatment discontinuation and follow-up as specified in the Schedule of Events (Section 1.3). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

8.1.2.5 EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE SCALE

The investigator or qualified designee will assess ECOG status (see Appendix 1) at screening, prior to the administration of each dose of trial treatment, discontinuation of trial treatment, and at 30 day Safety Follow-up as specified in the Schedule of Events.

8.1.2.6 TUMOR IMAGING AND ASSESSMENT OF DISEASE

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

8.1.2.6.1 INITIAL TUMOR IMAGING

Initial tumor imaging at Screening must be performed within 28 days prior to the date of allocation. The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1.

Tumor Imaging During the Study

The first on-study imaging assessment should be performed at 9 weeks (63 days \pm 7 days) from the date of allocation. Subsequent tumor imaging should be performed every 9 weeks (63 days \pm 7 days) or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the Investigator.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging every 9 weeks, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

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

8.1.2.6.2 END OF TREATMENT AND FOLLOW-UP TUMOR IMAGING

In participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (\pm 7 days). If previous imaging was obtained within

8 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. In participants who discontinue study treatment due to documented disease progression and the Investigator elects not to implement iRECIST, this is the final required tumor imaging.

In participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging every 12 weeks to monitor disease status until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

8.1.2.6.3 SECOND COURSE (RETREATMENT) TUMOR IMAGING

Tumor imaging must be performed within 14 days prior to restarting treatment with pembrolizumab. Local reading (Investigator assessment with site radiology reading) will be used to determine eligibility.

The first on-study imaging assessment should be performed at 9 weeks (63 days \pm 7 days) after the restart of treatment. Subsequent tumor imaging should be performed every 9 weeks (63 days \pm 7 days) or more frequently, if clinically indicated.

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

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

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

In participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 9 weeks (63 days \pm 7 days) until either the start of a new anticancer treatment, disease progression, pregnancy, death, or the end of the study, whichever occurs first.

8.1.2.6.4 RECIST 1.1 ASSESSMENT OF DISEASE

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study treatment). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, the Sponsor-Investigator allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

8.1.2.6.5 IRECIST ASSESSMENT OF DISEASE

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. When clinically stable, participants should not be discontinued

until progression is confirmed by the Investigator, working with local radiology, according to the rules below. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response.

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

Table 2: Imaging and Treatment after First Radiologic Evidence of Progressive Disease

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

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

8.1.3 LABORATORY PROCEDURES/ASSESSMENTS

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

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 3

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

Table 3: Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β -human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β -hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam (<i>If abnormal</i>)	Total triiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count	(<i>CO₂ or biocarbonate</i>)	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		PK
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin (<i>If total bilirubin is elevated above the upper limit of normal</i>)		
	Total protein		
	Blood Urea Nitrogen		

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

‡ If considered standard of care in your region.

8.1.4 OTHER PROCEDURES

8.1.4.1 WITHDRAWAL/DISCONTINUATION

When a participant discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4. Participants who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Appendix 7. After discontinuing treatment following assessment of CR, these participants should return to the site for a Safety Follow-up Visit (described in Section 8.3) and then proceed to the Follow-Up Period of the study (described in Section 8.3).

8.1.4.2 SCREENING

Screening procedures may be repeated after consultation with the PI.

8.1.4.3 POST-TREATMENT VISITS

Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of study treatment or before the initiation of a new anti-cancer treatment, whichever comes first. If the post-trial visit occurs less than 30 days after the last dose of study treatment, a subsequent follow-up phone call should be made at 30 days post the last dose of study treatment to determine if any adverse events have occurred since the post-trial clinic visit. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Participants with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment will also be followed and recorded. Participants who are eligible for retreatment/crossover with pembrolizumab (as described in Appendix 7) may have up to two safety follow-up visits, one after the Initial Treatment Period and one after the Second Course Treatment.

Follow-Up Visits

Participants who discontinue study treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (42 ± 7 days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of the study or if the participant begins retreatment with pembrolizumab as detailed in Appendix 7. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Appendix 7 will move from the follow-up phase to the Second Course Phase when they experience disease progression.

Survival Follow up

Participants who experience confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-Up Phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first. Patients will be followed for 5 years for survival.

8.2 CORRELATIVE LABORATORY EVALUATION (RESEARCH)

The University of Colorado Pathology Shared Resource, GI Translational Lab/Pitts Laboratory, and Human Immune Monitoring Shared Resource (HIMSR) will coordinate and process the sample collection of tissue and blood samples for research related testing at central laboratories. Instruction manuals and supply kits will be provided for all central laboratory assessments.

Exploratory PD-L1 analysis will be conducted by Merck through Qualtek.

Please see lab protocols and forms for instructions.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant

adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product, is also an adverse event.

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

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

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs, including lab work, characterized as intermittent require documentation of onset and duration of each episode.

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

- All AEs from the time of treatment through 30 days following cessation of study treatment must be collected by the delegated study team. AEs that have an onset greater than 30 days after the last dose of study drug will not be collected.
- All pregnancies and exposure during breastfeeding, from the time of treatment through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Serious adverse event or serious suspected adverse reaction. An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, 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, or a congenital anomaly/ birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization

may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

All AEs, meeting serious criteria from the time of study treatment through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be collected by the delegated study staff.

Refer to Table in Section 8.4.3.1 for additional details regarding each of the above criteria.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. The following table will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE (v5.0).

V5.0 CTCAE Grading	
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4	Life threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE

NCI CTCAE □ National Cancer Institute Common Terminology Criteria for Adverse Events. Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

If an event is assessed as a "significant medical event," it must be reported as a serious adverse event.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

The clinician's assessment of an AE's relationship to study agent (drug, biologic, device) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to the study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be Related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration

of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- **Not Related** – The AE is completely independent of study drug administration, and/ or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

Expectedness will only be documented for SAEs. Study Principal Investigator with collaboration with the Sponsor will be responsible for determining whether an SAE is expected or unexpected. An SAE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/ stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UAPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events during the designated protocol specified timelines according to Section 8.4.1. SAEs will be followed until resolution or stabilization. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit.

8.3.5 ADVERSE EVENT REPORTING

The investigator must record non-serious adverse events and report to DSMC and IRB according to timetable for reporting specified in section 10.1.5.

8.3.5.1 DEFINITION OF AN OVERDOSE FOR THIS PROTOCOL AND REPORTING OF OVERDOSE TO THE SPONSOR-INVESTIGATOR AND TO MERCK

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

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours via SAE form to the Sponsor-Investigator and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The Sponsor-Investigator must notify FDA and all participating PIs in an IND safety report of potential serious risks as soon as possible, but in no case later than 15 calendar days after the Sponsor-Investigator determines that the information qualifies for reporting. (21 CFR 312.32(c)(1))

The Sponsor-Investigator must notify FDA of any unexpected fatal or life-threatening adverse reactions as soon as possible, but in no case later than 7 calendar days after the Sponsor-Investigator’s initial receipt of the information. (21 CFR 312.32(c)(2)).

All SAEs will be followed until satisfactory resolution or until the site PI deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the sponsor-investigator and should be provided as soon as possible.

The Sponsor-Investigator will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the Sponsor-Investigator's initial receipt of the information.

All SAEs will be reported using the FDA 3500A Mandatory MedWatch report form. SAE form can be found at:

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf>

To submit an SAE, email as follows within 24 hours of becoming aware of the event:

To: Sunnie.Kim@cuanschutz.edu

CPDM.IIT@cuanschutz.edu

Subject: 21-4129 SAE Report Form

Attach: SAE form completed and signed by the Investigator

Body of Email: List the following information as assessed by the Investigator

- Whether the event is expected or unexpected
- Causality of events in relation to all study medications
- Whether the SAE is related to disease progression
- CTCAE grade

Reporting of AEs, SAEs, and Other Reportable Safety Events to Merck

Individual AE reports including SAEs and other relevant safety information are to be reported via Merck Safety Reporting Portal available at this link: <https://safetyreporting.merck.com>.

In the event the Safety Portal is experiencing technical difficulties, and the AE information cannot be uploaded, or the acknowledgement was not received, the AE information should be faxed to the Merck GPV facsimile number: 215-661-6229, or toll-free fax 1-800-547-5552. If fax confirmation is not received within one (1) business day, Principal Investigator/Institution will contact Merck to determine if the original report needs to be re-sent. It should be noted that the Safety Portal should only be used for individual adverse event reporting. Principal Investigator/Institution will maintain a record of the confirmation.

The investigator must record all serious adverse events and report to DSMC and IRB according to timetable for reporting specified in section 10.1.5. Per institutional policy, all serious adverse

events occurring at UCCC/UCHealth will be entered into OnCore according to timetable for reporting specified in section 10.1.5.

The study clinician will complete an SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the Merck within 2 working days.
- Other SAEs, regardless of relationship, will be submitted to the Sponsor-Investigator within 24 hours of site awareness and within 2 days to Merck via fax number listed.

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

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the Merck product, must be reported within 24 hours to the Sponsor-Investigator and within 2 working days to Merck Global Safety.

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

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

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215-661-6229) at the time of submission to FDA.

Follow-up of unresolved serious adverse events

Any SAEs that are unresolved at the time of the initial report submission should be followed up by the investigator for as long as medically indicated, and an updated SAE report submitted at the

time new information regarding the event becomes available.

8.3.6.1 ADVERSE EVENT OF SPECIAL INTEREST (AESI)

Selected non-serious and serious adverse events are also known as Adverse Events of Significant Interest (AESI) and must be reported via FDA 3500A Mandatory MedWatch form within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).

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

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any AESI, or follow up to an AESI, whether or not related to Merck product, must be reported within 2 working days to Merck Global Safety.

Adverse events of special interest for this trial include:

1. An overdose of Merck product, as defined in Section 8.4.5.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor-Investigator, that is not associated with clinical symptoms or abnormal laboratory results.
2. All Potential DILI events meeting biochemical criteria of Hy's law will be reported regardless of suspected etiology to the Sponsor as a SAE, within 2 business days but no longer than 3 calendar days, with other medical event (OME) criteria in the absence of other SAE criteria. Potential DILI/DILI events are defined as:

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.

8.3.7 REPORTING OF PREGNANCY AND LACTATION TO THE SPONSOR- INVESTIGATOR AND TO MERCK

Pregnancies and infant exposures during breastfeeding that occur after the consent form is

signed but before treatment allocation/randomization must be reported by the investigator if they cause the participant to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and infant exposures during breastfeeding that occur from the time of treatment allocation/randomization through 120 days following cessation of investigational therapy, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator as an Adverse Event. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as SAEs (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor-Investigator and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UAP)

The Office of Human Research Protection (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of UAP.

8.4.2 REPORTING OF UNANTICIPATED PROBLEMS

Incidents or events that meet the OHRP criteria for UAPs require the creation and completion of a UAP report. It is the Site PI’s responsibility to report UAPs to their IRB. The Lead PI is

responsible for reporting the UAP to the IRB and the UCCC DSMC. The UAP report will include the following information:

- Protocol-identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents a UAP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UAP.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Endpoint:

- Objective Response Rate (ORR per RECIST 1.1) of unirradiated tumors

Secondary Endpoints:

- Overall Survival (OS) from the initiation of therapy to the date of death or to the date of last follow-up.
- Progression Free Survival (PFS) from the initiation of therapy to the date of progression or to the date of last follow-up.
- Duration of response (DoR) defined as the time from documentation of tumor response to disease progression.
- Disease control rate (DCR) defined as the sum of partial (PR), complete response (CR) and SD.
- Treatment-emergent adverse events (AEs), serious adverse events (SAEs)

Exploratory Endpoints:

- Immune changes in tumor tissue and plasma at baseline compared to after combination SBRT/olaparaib and after Olaparib/pembrolizumab
- Assess response based on HRD status, PD-L1 expression, MMR/MSI, and TMB in tumor
- Changes in cytokines, ctDNA in plasma/serum
- Abscopal effect based on irradiated disease site

9.2 SAMPLE SIZE DETERMINATION

This is a one arm single-stage Phase II clinical trial. The null hypothesis that the ORR is 0.25 will be tested against the one-sided alternative that the ORR is 0.45. Total of 26 patients yields a

type I error rate of 0.1 when the null hypothesis is true and power of 0.8 when the alternative hypothesis is true.

9.3 POPULATION FOR ANALYSES

All eligible patients who has received any level of the target treatment will be included in the analyses for all preliminary, secondary and safety analysis except for the duration of response analysis. The analysis for duration of response will only include the patients who has responded.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Summary descriptive statistics will be calculated and presented for all primary, secondary outcomes for all participants, and for stratifications defined by participants demographic characteristics. The demographic characteristics of the participants will be presented with descriptive statistics also. The means, medians and the 95% confidence intervals will be calculated for continuous variables; the frequencies, estimated rates, and the exact 95% confidence intervals will be calculated for the binary and categorical variables.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

One-sided proportion test will be conducted for the ORR, with significant level 0.1. The cumulative frequency, estimated proportion and the exact 95% confidence interval will be reported.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

No formal hypothesis tests will be conducted for the secondary endpoints. Descriptive summarize statistics will be presented. The cumulative frequency, estimated proportion and the exact 95% confidence interval will be reported for the Disease control rate. For OS, PFS and DOR, the survival probability (Kaplan-Meier survival curve) will be calculated by the Kaplan-Meier method, the survival curve and the median survival time will be reported with the corresponding 2-sided 95% Brookmeyer-Crowley's Confidence Interval if feasible.

9.4.4 ANALYSIS OF THE EXPLORATORY ENDPOINTS

Exploratory immune analyses will be conducted to evaluate anti-tumor immune responses. The exploratory objectives are intended to collect data for use in planning future scientific investigations or clinical research. Each of the exploratory analyses are expected to be performed only using descriptive techniques, reporting descriptive statistics including confidence intervals when appropriate. Any statistical tests performed for evaluation of exploratory objectives will be done without formal adjustment for multiple comparisons, but in the context of the number of tests performed. A subject will be considered evaluable for immune response if they receive at least one dose of treatment, SBRT + Olaparib and Olaparib + Pembrolizumab,. The magnitude of immune responses will be described.

9.4.5 SAFETY ANALYSES

Safety Assessments

The safety of Olaparib, SBRT and pembrolizumab will be assessed by evaluating study drug exposure, adverse events, serious adverse events, oncology-related events, all deaths, as well as changes in laboratory determinations and vital sign parameters.

Duration of Study Drug

A summarization of the number of days and/or cycles subjects were exposed to study drug will be provided.

Adverse Events

Analyses of adverse events (and serious adverse events) will include only "treatment-emergent" events, i.e., those that have an onset on or after the day of the first dose of study drug. Analyses will not include those that have an onset greater than 30 days after the last dose of study drug. Treatment emergent adverse events will be summarized by system organ class and preferred term according to the MedDRA adverse event coding dictionary. The percentage of subjects experiencing an adverse event at a given severity, NCI CTCAE toxicity grade, and relationship to study drug will be provided.

Deaths

The number of subject deaths will be summarized (1) for deaths occurring while the subject was still receiving study drug in this study, (2) for deaths occurring off treatment within 30 days after the last dose of study drug, and (3) for all deaths in this study regardless of the number of days after the last dose of study drug. The relatedness of the deaths to the study drugs will also be provided.

9.4.6 BASELINE DESCRIPTIVE STATISTICS

The baseline characteristics of all enrolled subjects will be summarized. Subject's age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while gender,

race and other categorical variables will be provided using frequency tabulations. Selected medical history data will be summarized using frequency tabulations.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/ administering study product.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent process will be initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families.

Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study.

The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The study allows the inclusion of non-English speaking and non-reading participants. Witnesses to these consent processes will be individuals not associated with the trial and will not have a conflict of interest.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

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

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

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

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the Sponsor-Investigator(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor-Investigator.

The study monitor, other authorized representatives of the Sponsor-Investigator, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Colorado Cancer. This will not include the participant's contact or identifying information. Rather, individual participants and

their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the University of Colorado Cancer Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the University of Colorado Cancer Center.

10.1.4 FUTURE USE OF STORED SPECIMENS OR DATA

- **Intended Use:** Samples and data collected under this protocol may be used to study outcomes and any secondary endpoints broadly related to gastric and GEJ cancers. No genetic testing will be performed. Samples will be used to investigate exploratory endpoints of: immune changes in tumor tissue and plasma at baseline compared to after combination SBRT/olaparaib and after Olaparib/pembrolizumab, to assess response based on HRD status, PD-L1 expression, MMR/MSI, and TMB in tumor, and to look at changes in cytokines, ctDNA in plasma/serum. If consented to, leftover samples will be stored for banking for use in other studies.
- **Storage:** Access to stored samples will be limited using the University of Colorado Pathology Shared Resource, GI Translational Lab/Pitts Laboratory, and Human Immune Monitoring Shared Resource (HIMSR) and Merck via Qualtek. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.
- **Tracking:** Data will be tracked using OnCore and REDCap.
- **Disposition at completion of the study:** All stored samples will be sent to University of Colorado Pathology Shared Resource, GI Translational Lab/Pitts Laboratory, and Human Immune Monitoring Shared Resource (HIMSR). Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking. Leftover samples will be optional to consent to banking with the University of Colorado Pathology Shared Resource for use in other studies.

Data collected for this study will be analyzed and stored at the University of Colorado Cancer Center. After the study is completed, the de-identified, archived data will be transmitted to and stored at the University of Colorado Pathology Shared Resource, GI Translational Lab/Pitts Laboratory, and Human Immune Monitoring Shared Resource (HIMSR) for use by other researchers including those outside of the study. Permission to transmit data to these facilities will be included in the informed consent.

With the participant's approval and as approved by local IRBs, de-identified biological samples will be stored at the University of Colorado Pathology Shared Resource, GI Translational

Lab/Pitts Laboratory, and Human Immune Monitoring Shared Resource (HIMSR) with the same goal as the sharing of data with these facilities. These samples could be used for research into understanding how to improve treatments for patients with gastric/gastropharyngeal junction cancers. These facilities will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the masking of the identity of the participant.

During the conduct of the study, and individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage will not be possible after the study is completed.

When the study is completed, access to study data and/ or samples will be provided through the University of Colorado Pathology Shared Resource, GI Translational Lab/Pitts Laboratory, and Human Immune Monitoring Shared Resource (HIMSR)

10.1.5 SAFETY OVERSIGHT

The Sponsor-Investigator will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial including any specimens collected, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and study participant safety for all clinical studies at the CU Cancer Center, which is the coordinating institution of this trial. A summary of the DSMC's activities is as follows:

- Conduct of internal audits
- Ongoing review of all serious adverse events (SAEs) and unanticipated problems (UAPs)
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs and UAPs are reported to the DSMC, IRB and the Sponsor-Investigator per protocol. All SAEs and UAPs are to be reported to the DSMC within 7 (for fatal or life-threatening events) or 15 (non-life-threatening events) calendar days of the Sponsor-Investigator receiving notification of the occurrence.

Each subject's treatment outcomes will be discussed by the site PI and appropriate staff at regularly scheduled meetings. Data regarding number of subjects, significant toxicities, dose

modifications, and treatment responses will be discussed and documented in the meeting's minutes.

The sponsor investigator is responsible for organizing and conducting regularly scheduled teleconferences with all participating sites. The sponsor investigator will also be responsible for including data from all the participating sites to include the minutes from these regularly scheduled teleconferences between the sponsor investigator and the sites within the overall trial's DSM progress report.

The sponsor investigator will provide a DSM progress report to the CU Cancer Center DSMC on a recurring basis (either every six or twelve months based on DSMC vote). The DSM report will include a protocol summary, current enrollment numbers, summary of toxicity data to include specific SAEs, UAPs and AEs, any dose modifications, all protocol deviations, and protocol amendments. The DSM report submitted to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted. Results and recommendations from the review of this progress report by the DSMC will then be provided to the sponsor investigator in a DSMC review letter. The sponsor investigator is then responsible for ensuring this letter is submitted to the site's IRB of record at the time of IRB continuing review.

10.1.6 CLINICAL MONITORING

Clinical site monitoring will be conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/ amendment(s), with GCP, and with applicable regulatory requirement(s).

Monitoring for this study will be performed by a CU Cancer Center Clinical Monitor in accordance with the clinical monitoring plan (CMP), incorporated herein by reference. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of the monitoring reports.

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

Quality Control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/ resolution.

Following written SOPs, the study monitor will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial-related sites, source data/ documents, and reports for the purpose of monitoring and auditing by the DSMC audit team, and inspection by local and regulatory authorities.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.8.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of an investigational marketing application and until there are no pending or contemplated marketing

applications or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations or institutional policies. No records will be destroyed without the written consent of the sponsor-investigator, if applicable. It is the responsibility of the sponsor-investigator to inform the PI when these documents no longer need to be retained.

10.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or SOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH E6, sections:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3.
- 5.1 Quality Assurance and Quality Control, section 5.1.1.
- 5.20 Noncompliance, sections 5.20.1 and 5.20.2.

It is the responsibility of the study team to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents, reported to DSMC, COMIRB, and Merck. Protocol deviations must be sent to the local IRB per institutional guidelines. The site PI/ study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the - SOP and/or study procedures manual.

10.1.10 PUBLICATION AND DATA SHARING POLICY

This study will ensure that the public has access to the published results of this research.

As required, either for publication (the ICMJE or other publication policy), or according to U.S. regulations (Section 801 of the Food and Drug Administration Amendments Act of 2007) this clinical trial will be registered in a public trials registry including ClinicalTrials.gov, which is sponsored by the National Library of Medicine, and the NCI CTRP Registry for cancer clinical trials.

10.1.11 CONFLICT OF INTEREST POLICY

Independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed by the

University of Colorado Denver's (UCD) Office of Regulatory Compliance Conflict of Interest and Commitment Management (COIC) program. Persons with a perceived conflict of interest will have such conflicts managed in a way that is appropriate to their participation in the trial. Conflict of Interest management plans are project-specific and are reviewed at least annually. UCD has integrated the institutional conflict of interest management program with its existing program.

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12 APPENDICES

APPENDIX 1: ECOG PERFORMANCE STATUS

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

APPENDIX 2: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting. (<http://ctep.cancer.gov/reporting/ctc.html>)

APPENDIX 3: CONTRACEPTIVE GUIDANCE AND PREGNANCY TESTING

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

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

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

Contraception Requirements

Female patients of child bearing potential and male patients with partners of child bearing potential, who are sexually active, must agree to the use of two highly effective forms of contraception.

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame. This should be started from the signing of the informed consent and continue throughout period of taking study treatment and for 120 days after last dose of study drug

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 4 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
 - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception that has a low user dependency consistently and correctly as described in Table 4.

Table 4: Highly Effective Contraceptive Methods That Have Low User Dependency

Highly Effective Methods That Have Low User Dependency <i>Failure rate of <1% per year when used consistently and correctly.</i>
Progestogen- only contraceptive implant ^{a, b} Intrauterine hormone-releasing system (IUS) ^b Intrauterine device (IUD) Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation.

Pregnancy Testing

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

Following initiation of treatment additional pregnancy testing will be performed at monthly intervals during the treatment period and at 120 days after the last dose of study treatment and as required locally.

Pregnancy testing will be performed per the protocol calendar, and whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

APPENDIX 4: DESCRIPTION OF THE IRECIST PROCESS FOR ASSESSMENT OF DISEASE PROGRESSION

Assessment at Screening and Prior to RECIST 1.1 Progression

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

Assessment and Decision at RECIST 1.1 Progression

In participants who show evidence of radiological PD by RECIST 1.1 the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management (see Table 2). This decision by the Investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

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

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

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

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

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

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

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

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters

of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

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

Confirmation of Progression

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

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

Persistent iUPD

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

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

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

Resolution of iUPD

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

- None of the progression-confirming factors identified above occurs, AND

- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

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

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

Management Following the Confirmatory Imaging

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

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

Detection of Progression at Visits After Pseudo-progression Resolves

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

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

- Previously identified non-target lesions show any significant growth

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

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

Additional details about iRECIST are provided in the iRECIST publication [Seymour et al, 2017].

APPENDIX 5: DOSE MODIFICATION AND TOXICITY MANAGEMENT FOR OLAPARIB

Any toxicity observed during the course of the study could be managed by interruption of the 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. Study treatment can be dose reduced to 250 mg twice daily as a first step and to 200 mg twice daily as a second step. If the reduced dose of 200 mg twice daily is not tolerable, no further dose reduction is allowed and study treatment should be discontinued. Once dose is reduced, escalation is not permitted.

RENAL IMPAIRMENT

If after 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.

A dose reduction is recommended for patients who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation of between 31 and 50 ml/min) for

any reason during the study: the dose of olaparib should be reduced to 200mg 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 ≤ 30 mL/min) or end-stage renal disease; if patients develop severe impairment or end stage disease is it recommended that olaparib be discontinued

MANAGEMENT OF HEMATOLOGICAL TOXICITY

Management of anemia

Table 5: Management of anemia

Anemia	Management/Next Dose for olaparib
\leq Grade 1 Grade 2	Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib with supportive treatment (eg transfusion) <i>or</i> interrupt dose for a maximum of 4 weeks. If repeat Hb < 10 but ≥ 8 g/dl , dose interrupt (for max of 4 weeks) until Hb ≥ 10 g/dl and upon recovery dose reduction to 250 mg twice daily as a first step and to 200 mg twice daily as a second step may be considered.
Grade 3 Grade 4	Give appropriate supportive treatment (e.g. transfusion) and investigate causality. Interrupt olaparib for a maximum of 4 weeks. until improved to Hb ≥ 10 g/dl. Upon recovery dose reduce 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.

*Patients requiring a delay of >4 weeks should go off protocol therapy. The Study Principal Investigator should be consulted for possible resumption of treatment at a lower dose for patients who showed disease response.

**Patients requiring > two dose reductions should go off protocol therapy.

Management of neutropenia, leukopenia, and thrombocytopenia

Table 6: Management of neutropenia, leukopenia and thrombocytopenia

Neutropenia/leukopenia/thrombocytopenia	Management/Next Dose for <i>olaparib</i>
≤ Grade 1 Grade 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
Grade 3 Grade 4	Dose interruption until recovered to CTCAE gr 1 or better for a maximum of 4 weeks. If repeat CTCAE grade 3-4 occurrence, dose reduce olaparib to 250 mg twice daily as a first step and 200 mg twice daily as a second step

*Patients requiring a delay of >4 weeks should go off protocol therapy. The Study Principal Investigator should be consulted for possible resumption of treatment at a lower dose for patients who showed disease response.

**Patients requiring > two dose reductions should go off protocol therapy.

Adverse event 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 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 Section 5.2.2.3.3

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 anemia 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 10⁹/L)

- ≥ 2 week interruption/delay in study treatment due to CTCAE grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (Platelets $< 50 \times 10^9/L$)

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 gr 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 NCI CTEP. Olaparib treatment should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

MANAGEMENT OF NON-HEMATOLOGICAL TOXICITY

Management of new or worsening pulmonary symptoms

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 Principal Investigator.

Management of nausea, vomiting and diarrhea

Events of nausea and vomiting are known to be associated with olaparib treatment. In study D0810C00019 nausea was reported in 71% of the olaparib treated patients and 36% in the placebo treated patients and vomiting was reported in 34% of the olaparib treated patients and 14% in the placebo treated patients. 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.

No routine prophylactic anti-emetic treatment is required at the start of study treatment, however, 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 tablets can be taken with a light meal/snack (ie 2 pieces of toast or a couple of biscuits).

As per international guidance on anti-emetic use in cancer patients (ESMO, NCCN) generally a single agent antiemetic should be considered eg dopamine receptor antagonist, antihistamines or dexamethasone.

Table 7: Management of nausea

Nausea	Management/Next Dose for <i>olaparib</i>
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level
Grade 3	Hold* until <Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy

*Patients requiring a delay of >4 weeks should go off protocol therapy. The Study Principal Investigator should be consulted for possible resumption of treatment at a lower dose for patients who showed disease response.

**Patients requiring > two dose reductions should go off protocol therapy.

Table 8: Management of vomiting

Vomiting	Management/Next Dose for <i>olaparib</i>
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level
Grade 3	Hold* until <Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy

*Patients requiring a delay of >4 weeks should go off protocol therapy. The Study Principal Investigator should be consulted for possible resumption of treatment at a lower dose for patients who showed disease response.

**Patients requiring > two dose reductions should go off protocol therapy.

Table 9: Management of diarrhea

Diarrhea	Management/Next Dose for <i>olaparib</i>
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level

Grade 3	Hold* until <Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy

*Patients requiring a delay of >4 weeks should go off protocol therapy. The Study Principal Investigator should be consulted for possible resumption of treatment at a lower dose for patients who showed disease response.

**Patients requiring > two dose reductions should go off protocol therapy.

Recommended management: Loperamide antidiarrheal therapy

Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours)

Adjunct anti-diarrheal therapy is permitted and should be recorded when used.

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 Study 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.

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.

APPENDIX 6: DOSE MODIFICATION AND TOXICITY MANAGEMENT FOR IMMUNE-RELATED AES ASSOCIATED WITH PEMBROLIZUMAB

AEs associated with pembrolizumab exposure, including coadministration with additional compounds may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab 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, administration of corticosteroids and/or other supportive care.

For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes.

Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 10.

Table 10: Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:				
<ol style="list-style-type: none"> 1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks. 2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks. 3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids. 				
Immune-related AEs	Toxicity grade or conditions (CTCAEv5.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	<ul style="list-style-type: none"> • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper 	<ul style="list-style-type: none"> • Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	<ul style="list-style-type: none"> • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper 	<ul style="list-style-type: none"> • Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with \geq 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.
	Grade 4	Permanently discontinue		
AST / ALT elevation or	Grade 2	Withhold	<ul style="list-style-type: none"> • Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper 	<ul style="list-style-type: none"> • Monitor with liver function tests (consider weekly or more frequently until liver

Increased bilirubin	Grade 3 or 4	Permanently discontinue	<ul style="list-style-type: none"> Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper 	enzyme value returned to baseline or is stable
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β -cell failure	Withhold	<ul style="list-style-type: none"> Initiate insulin replacement therapy for participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia 	<ul style="list-style-type: none"> Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	<ul style="list-style-type: none"> Administer corticosteroids and initiate hormonal replacements as clinically indicated. 	<ul style="list-style-type: none"> Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue ¹		
Hyperthyroidism	Grade 2	Continue	<ul style="list-style-type: none"> Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate 	<ul style="list-style-type: none"> Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue ¹		
Hypothyroidism	Grade 2	Continue	<ul style="list-style-type: none"> Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care 	<ul style="list-style-type: none"> Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue		
Nephritis and Renal dysfunction	Grade 2	Withhold	<ul style="list-style-type: none"> Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper. 	<ul style="list-style-type: none"> Monitor changes of renal function
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of	Withhold	<ul style="list-style-type: none"> Based on severity of AE administer corticosteroids 	<ul style="list-style-type: none"> Ensure adequate evaluation to confirm etiology and/or exclude other causes

	myocarditis (which was previously myocarditis Grade 1 using CTCAE v4.0)			
	Grade 2, 3 or 4	Permanently discontinue		
	Intolerable/persistent Grade 2	Withhold	<ul style="list-style-type: none"> Based on type and severity of AE administer corticosteroids 	<ul style="list-style-type: none"> Ensure adequate evaluation to confirm etiology and/or exclude other causes
All other immune-related AEs	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

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

NOTE:

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

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

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 11.

Table 11: 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	<p>Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics</p> <p>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.</p> <p>Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment</p>	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

<p>Grades 3 or 4</p> <p>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)</p> <p>Grade 4: Life-threatening; pressor or ventilatory support indicated</p>	<p>Stop Infusion.</p> <p>Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids</p> <p>Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated.</p> <p>**In cases of anaphylaxis, epinephrine should be used immediately.</p> <p>Participant is permanently discontinued from further study drug treatment.</p>	<p>No subsequent dosing</p>
<p>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</p>		

Other allowed dose interruption for pembrolizumab

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

APPENDIX 7: SECOND COURSE FOR PEMBROLIZUMAB

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

Either

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

OR

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

AND

- Experienced an investigator-determined radiographic disease progression by RECIST 1.1 after stopping initial treatment, and
 - Upon unblinding at the time of centrally verified disease progression were found to have received pembrolizumab, and
 - No new anticancer treatment was administered after the last dose of study treatment, and
 - The participant meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
 - The study is ongoing

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

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